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FACOLTÀ DI SCIENZE DEL FARMACO
Department of Pharmaceutical Sciences
PhD Course in Pharmaceutical Sciences
XXIX Cycle

SUSTAINABLE CHEMISTRY FOR THE PREPARATION OF NITROGENATED POLYHETEROCYCLIC SYSTEMS OF BIOLOGICAL INTEREST

Tutor: Prof.ssa Egle M. Beccalli
Coordinator: Prof. Marco De Amici

MAZZA Alberto
R10576

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Abbreviation list

BINAP: 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene

Bn: benzyl

Boc: *tert*-butoxycarbonyl

CPT: camptothecin

DIAD: diisopropyl azodicarboxylate

dba: dibenzylideneacetone

DMF: dimethylformamide

dppf: 1,1′-ferrocenediyl-bis(diphenylphosphine)

LDA: lithium diisopropylamide

m-CPBA: 3-chloroperbenzoic acid

MW: microwave

NMP: 1-methyl-2-pyrrolidinone

PG: protecting group

PTSA: p-toluenesulfonic acid

TBA-HSO_4: tetrabutylammonium hydrogensulfate

THF: tetrahydrofuran

Topo I: topoisomerase I

Topo II: topoisomerase II

TPT: topotecan

Ts: tosyl

GI_{50}: growth inhibition (50%)

1,10-Phen: 1,10-phenanthroline

Chapter 1

Introduction

1.1 Relevance of nitrogen (poly)heterocycles in pharmaceutical field

Nitrogen heterocycles are among the most significant structural components of pharmaceuticals. For instance, an analysis of the database of U.S. FDA approved drugs reveals that 59% of unique small-molecule drugs contain a nitrogen heterocycle. Six-membered rings are the most frequently used, followed by five-membered and fused rings.[1] Also nitrogen-containing heterocycles are central to the chemical reactions that occur in all organisms. The metabolic transformation of amino acids into five, six, and seven-member heterocycles reveals the chemical logic and enzymatic machinery for shunting primary metabolites into bioactive heterocyclic nitrogen scaffolds.[2] Among the five-membered ring fused with an aromatic ring benzoxazole and benzimidazole derivatives are occupying a remarkable ranking. The scaffold of benzoxazole is a constituent of several natural products and often incorporated in drug design. In particular 2-substituted benzoxazoles is often found in ligands targeting a plethora of receptors and enzymes.[3,4] Furthermore, the pharmacological applications of benzimidazole derivatives include antitumor, antibacterial and antiviral activity, and analgesic, antiiflammatory, and antipyretic properties.[5] Also benzoxazines and quinoxalines, among the six-membered ring fused are scaffolds with a promising employments in pharmaceutical field. E.g. dihydrobenzoxazine derivatives have showed both thrombin inhibitory and glycoprotein IIb/IIIa (GPIIb/IIIa) receptor antagonistic activities[6], while quinoxaline derivatives has received particular attentions as promising anticancer agents.[7] At the end, nitrogen polycyclic scaffolds, such as pyrroloacridines, physostigmines, camptothecin and oxazinoindole derivatives are very relevant pharmaceutical classes in anticancer research. (Figure 1)

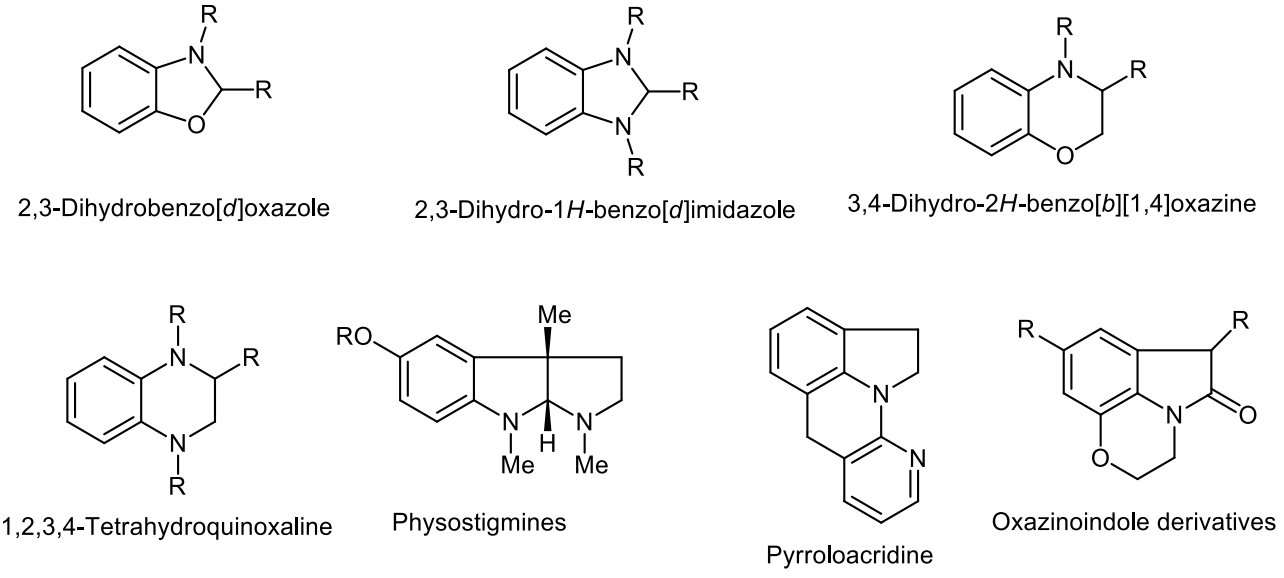


Figure 1
Nitrogen polyheterocycles

1.2 Transition metal-catalysis: advantages in nitrogen heterocycles synthesis

In the field of synthesis of nitrogen heterocycles, transition-metal catalyzed reactions perform a prominent role, especially considering the new perspectives of sustainable chemistry. Among the transition metal-catalysts used in organic synthesis palladium is certainly the most exploited and the most versatile. In recent years, the interest for palladium-catalyzed C-N bond-forming reactions has been strongly increased, as documented by the number of reviews with high impact.[8,9,10,11,12,13] Both Pd(0) and Pd(II) oxidation state are exploited as catalysts in the organic synthesis, and they are exploited in many different reactions such as Buchwald-Hartwig reaction, hydroamination and amination to achieve the C-N bonds formation. Moreover the interest was broadened considering the metal-catalyzed domino processes, the carboamination, aminohalogenation, aminooxygenation and diamination reactions that lead to the formation of two or more bonds in the same synthetic step.

Among the transition-metals, also platinum-catalyst was increasingly used in this field of C-N bond formations. Recent publications on the hydroamination reactions of alkenes[14] and alkynes.[15] report the use of platinum catalysts. Both platinum and palladium always require the presence of a ligand, especially phosphines, that modulate the reactivity of the metal center. (Figure 2)

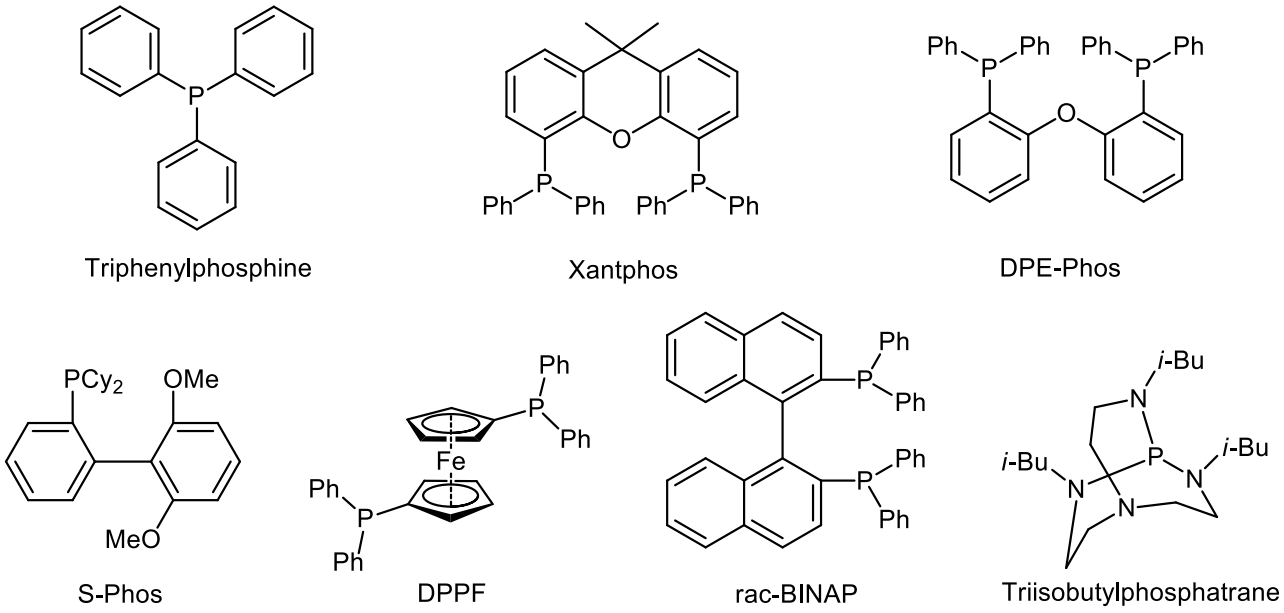
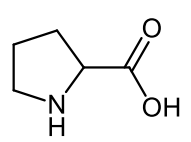


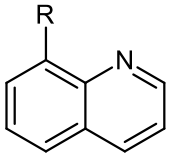
Figure 2
Phosphine ligands for palladium and platinum catalysis

This ligand permit fine tuning of the coordinated species allowing the properties of the complex at different steps of a catalytic cycle to be enhanced.[16] The choice of phosphine depends on the features of the substrates: e.g. in the palladium-catalyzed cross-coupling of amines and aryl halides, the electron donation of aryl substituent is the key to the stability of the amido complex with respect to reductive elimination. Using the class of ligands such as S-Phos, the reductive elimination step occurs readily for more nucleophilic amines such as *N*-alkyl anilines, *N,N*-dialkyl amines, and primary aliphatic amines.[17] Furthermore, ligands promote the solubility and prevent the 'clusterization' when the mechanism involves the formation of M(0) at the resting-state.

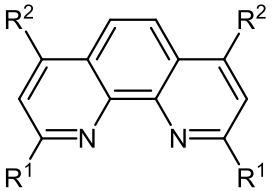
Also copper catalysis will be considered in this thesis. The use copper-catalyzed Buchwald-type reactions has many advantages in the field C-N bond formation, such as the lower cost of the copper catalysts compared to the more expensive palladium complexes. Another advantage of copper catalysis is that in many cases, copper-catalysed reactions work well without ligand, and, when required, the ligands are usually structurally quite simple and inexpensive respect to palladium and platinum ligands. Instead of phosphines, cheaper *N,O*, *N,N* or *O,O*-ligands as amino acid, compounds with a rigid backbone such as quinolone derivatives and aliphatic diketones have been reported to be effective in copper-catalyzed reaction.[18] (Figure 3) The role of the ligand was not clear, it was probably involved in the stabilization of the copper(I) active species, the increase of solubility, or the avoidance of aggregation of the copper species.[19] At the end, it was proposed that the advantage of bidentate ligands would be to facilitate the reaction by blocking two adjacent coordination sites, so that the aryl donor and the nucleophile could be close enough to couple easily.[20] Furthermore, the copper complexes tolerate better the atmospheric oxygen compared to the palladium and platinum catalysts that often are air-sensitive and require inert atmosphere. [21,22]



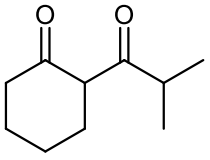
Proline



R = OH: 8-hydroxyquinoline;
R = NH_2: 8-aminoquinoline



R^1 = R^2 = H: 1,10-Phenanthroline;
R^1 = Me; R^2 = Ph: Bathocupreoine



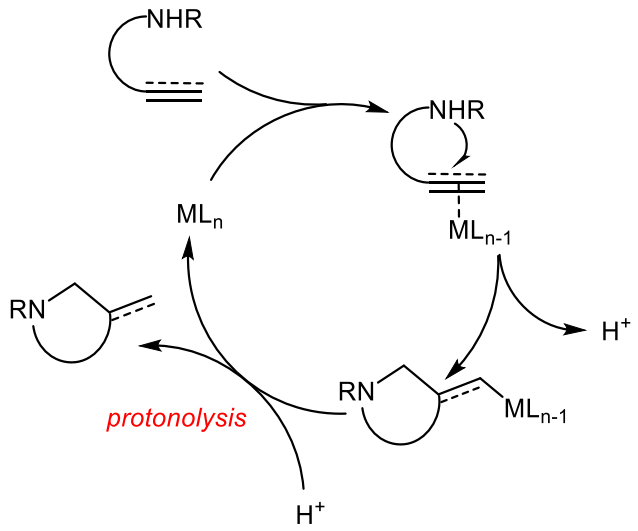
2-isobutyrylcyclohexanone

Figure 3
Ligands for copper catalysis

1.3 Hydroamination reaction

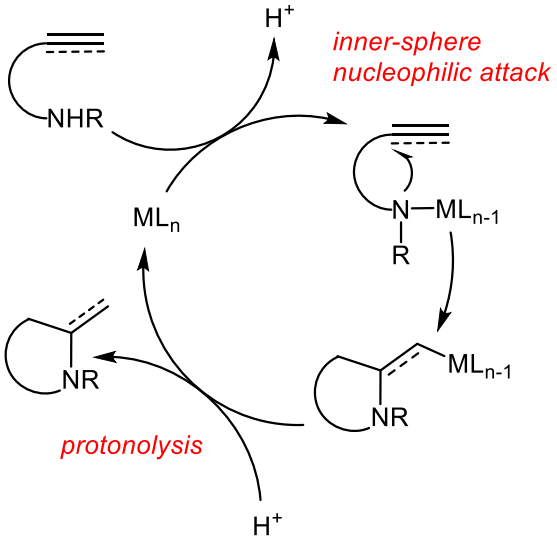
The hydroamination reaction is an atom-efficient pathway to add a nucleophilic nitrogen to a carbon-carbon unsaturated bonds. Intramolecular hydroamination of unactivated alkynes, alkenes or allenes bearing an amino group is one of the simplest methods to obtain nitrogen heterocycles. Generally, the hydroamination of alkenes is more difficult compared to the hydroamination of alkynes due to the lower reactivity and electron density of the double bonds.[23] Many efforts have been made toward the exploitation of this methodology in the field of natural products synthesis. Various metal complexes are used, in general metals with high Lewis acidity. Several studies to identify the most active transition-metal catalysts and to optimize the reaction conditions have been developed[24,25,26,27,28,29,30,31,32,33,34,35,36,37,38]. Good results have been obtained with the palladium complexes, but different metal catalysts may be used, such as platinum. The choice is depending on the substrates. For example, palladium(II) complexes catalyze the intramolecular oxidative amination of unactivated olefins with arylamines[39] and amides[40,41,42] but are not compatible with alkylamines.[43] Conversely, examples of intramolecular hydroamination of γ- and δ-amino olefins with secondary alkylamines under platinum(II) catalysis are reported.[14]

The reaction mechanisms can be quite different depending on the unsaturated substrates and the transition metals involved. Two potential mechanisms are commonly accepted. The first hypothesis considers the outer-sphere attack by a protic nucleophile NuH to a C-C unsaturated bond activated by the coordination with an electrophilic metal center. The newly formed M-C bond is then cleaved by protonolysis to regenerate the catalyst. (Scheme 1)



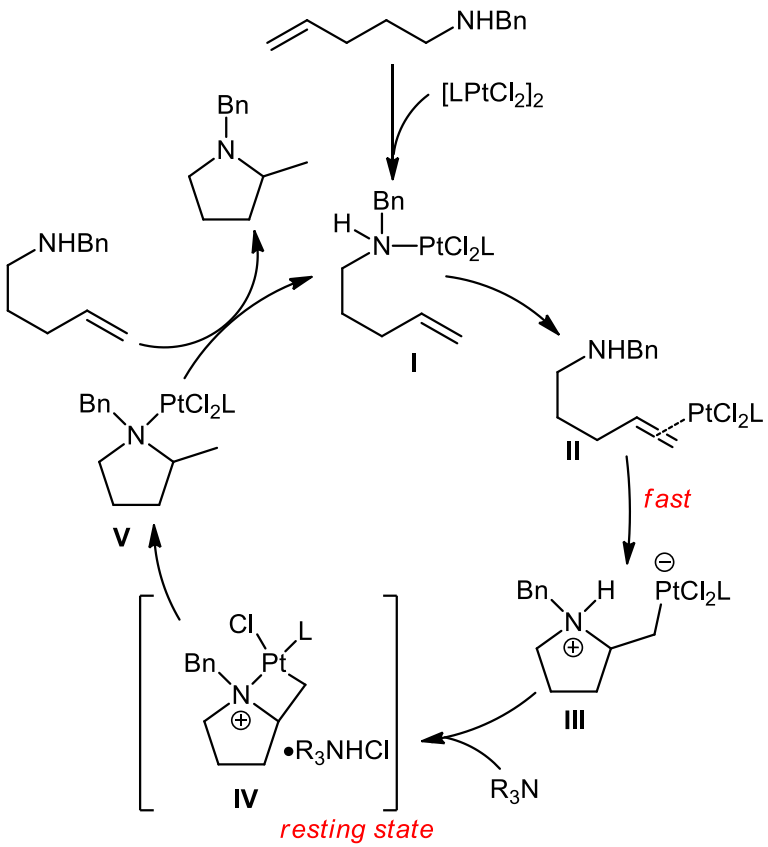
Scheme 1
Outer-sphere mechanism

An alternative mechanism regards the inner-sphere nucleophilic attack. In this case, the first step involves the oxidative addition of the metal to the NuH followed by alkene/alkyne insertion into the M-Nu bond. The resulting M-C bond is cleaved by a C-H reductive elimination or by protonolysis. (Scheme 2)



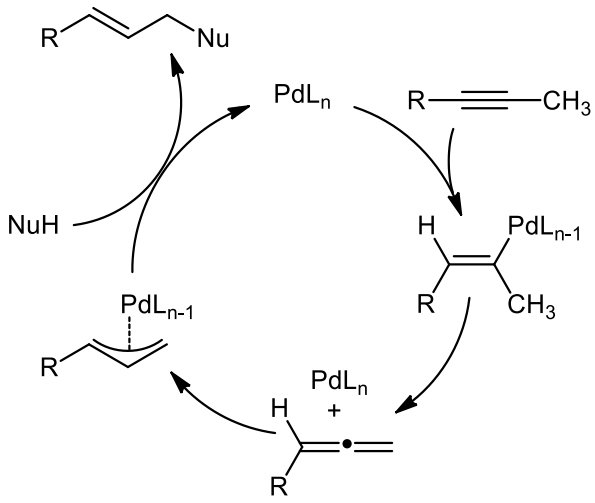
Scheme 2
Inner-sphere mechanism

Mechanistic studies, both experimental and theoretical, have demonstrated that both pathways can be operative. While this latter is generally preferred for more electron-rich metals such as rhodium and iridium, several studies suggest that palladium and platinum-catalyzed addition of N-H or O-H nucleophiles is more likely to run by the outer-sphere electrophilic activation mechanism.[44] A recent study of Widenhoefer's group, regarding the mechanism of platinum-catalyzed hydroamination of olefin, would seem to confirm this hypothesis. The first step can be the formation the nitrogen-bound platinum-amine complex **I** and this complex undergoes an intramolecular ligand exchange, forming the platinum alkene complex **II**, followed by the fast formation of the zwitterionic platinamethylpyrrolidinium complex **III** via rapid outer-sphere C−N bond formation. This complex reacts with free amine (that can be the starting secondary amine or the tertiary amine of the product) and the deprotonation restitutes the azaplatinacyclobutane complex **IV**. The complex **IV** represents the catalyst resting state and is consumed via turnover-limiting intramolecular protonolysis. Associative ligand exchange of **V** with the starting amine would release the product and regenerate the nitrogen-bound platinum-amine complex **I**.[45] (Scheme 3)



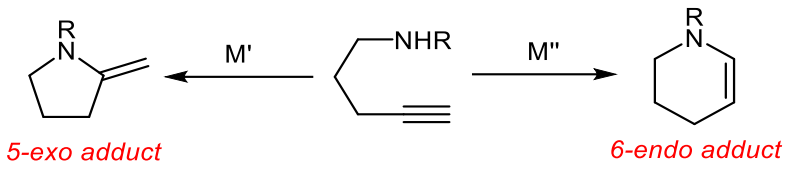
Scheme 3
Platinum catalyzed hydroamination: mechanism

Starting from non-terminal alkynes, in some cases the formation of allene intermediate is proposed followed by the formation of the π-allyl-metal complex which undergoes the attack of the nucleophile to give allyl derivatives.[46,47,48] (Scheme 4)



Scheme 4
Allene intermediate in hydroamination of non-terminal alkynes

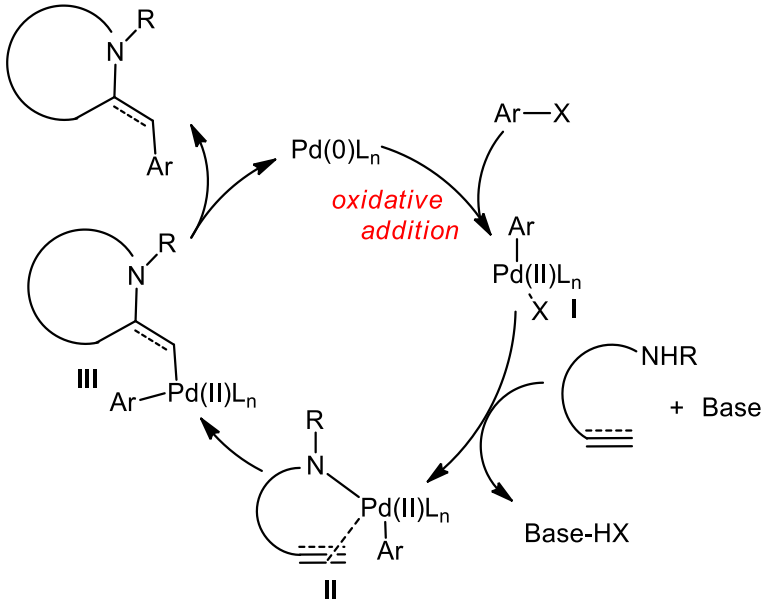
A particular mention regards the impact of the transition-metal catalysis on the regioselectivity. For example, *5-endo-dig*-cyclization process or *6-exo-dig* regioselectivity is observed starting from alkynylamines in the presence of different transition-metals catalysts. Regioselectivity can also be addressed changing reaction conditions or choosing different protecting group on the nitrogen involved as nuchleophile.[49] (Scheme 5)



Scheme 5
Regioselectivity in intramolecular hydroamination

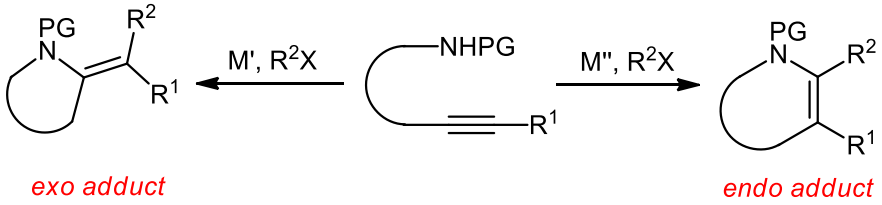
1.4 Carboamination reaction

The carboamination reactions consist of a domino process involving the formation of both C-C and C-N bonds. This reaction involves alkynes, alkenes or allenes-tethered amines and aryl halides as coupling partner. Carboamination reactions, and the analogous carboetherification (C-C and C-O bonds formation) reported in literature are relatively rare.[50,51,52,53,54,55,56,57,58,59,60,61,62] This domino process occurs in presence of palladium(0) complex as catalyst and require the presence of a base. The mechanism of the process consists in the oxidative addition of the Pd(0) to the aryl halide resulting in the formation of Pd(II) complex **I**. The base intervenes in the formation of the amido complex **II** between the amine and the Pd(II) complex **I**. The subsequent *syn*-aminopalladation restitute the intermediate **III**, and the subsequent reductive elimination affords the product.[63] (Scheme 6)



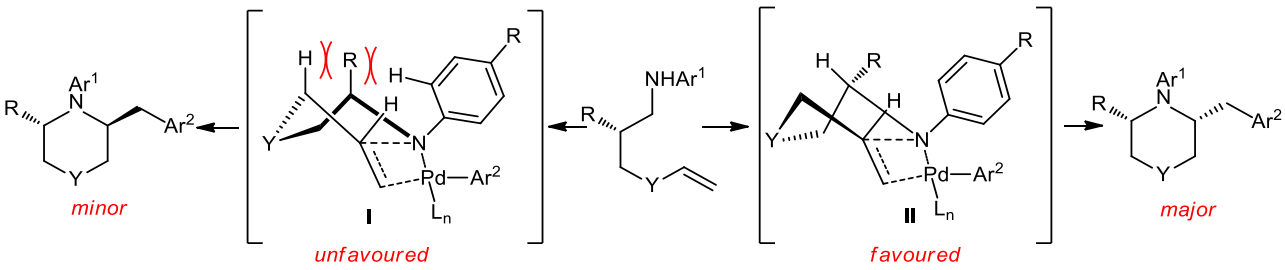
Scheme 6
Carboamination reaction: mechanism

Also the carboamination process can occour as *endo-dig* or *exo-dig* cyclization-step. The regioselectivity can be influenced by the reaction conditions, the *N*-protecting group or the different electron availability of the substrates.[64,65] (Scheme 7)



Scheme 7
Regioselectivity in carboamination reactions

In some cases, starting from chiral substrates, the reaction could be stereoselective, also without employing chiral ligand. This could be due to the particular conformation of the intermediate. The unfavourable transition state **I** contains a severe steric interaction between the H-substituent in C5 and the R-group, and also suffers from significant strain between the R-group in C2 and the *N*-aryl group justifying the improbable cyclization via this transition state. The products are obtained with good to excellent yield and 95–99% *ee*.[63] (Scheme 8)



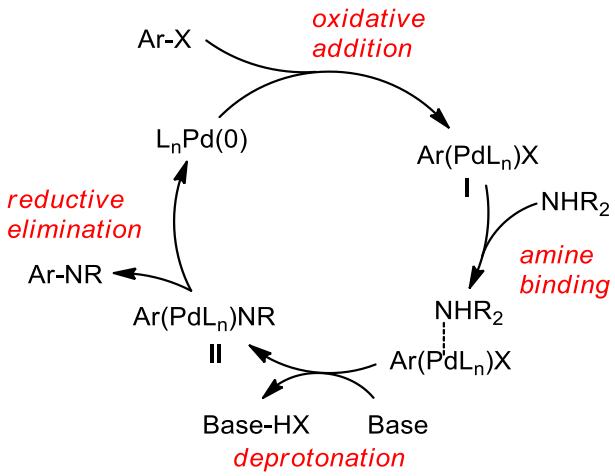
Scheme 8
Proposed boat-like transition state model in stereoselective carboaminations

1.5 Buchwald-Hartwig reaction

In 1995 Buchwald and Hartwig independently discovered an important amination/alkoxylation process based on the reaction between an aryl halide or pseudohalide (as triflate) and NH or OH functional groups able to react as a nucleophile.[66,67]

This process is realized under palladium catalysis and requires the presence of phosphine ligands and a stoichiometric amount of base, the choice of which are of great influence on the products formation. Many kinds of phosphines has been synthesized in the last years with different steric and electronic properties resulting in a large possibility of applications of this reaction with different nucleophiles and various aryl halides.[68] The best catalyst is palladium acetate due to the low cost and easy handling in the presence of chelating phosphines BINAP or dppf as ligands (Figure 2). Toluene is the preferred solvent. The intramolecular version of the Buchwald-Hartwig reaction affords heterocyclic systems.

The mechanism involves the oxidative addition of the palladium to the aryl halide giving the palladium complex **I**, followed by the coordination of the amine to the palladium. The base intervenes in the deprotonation of nucleophile, leading to the formation of the amido complex **II.** Reductive elimination produces the final aryl amine and regenerates the catalyst.[16] (Scheme 9)

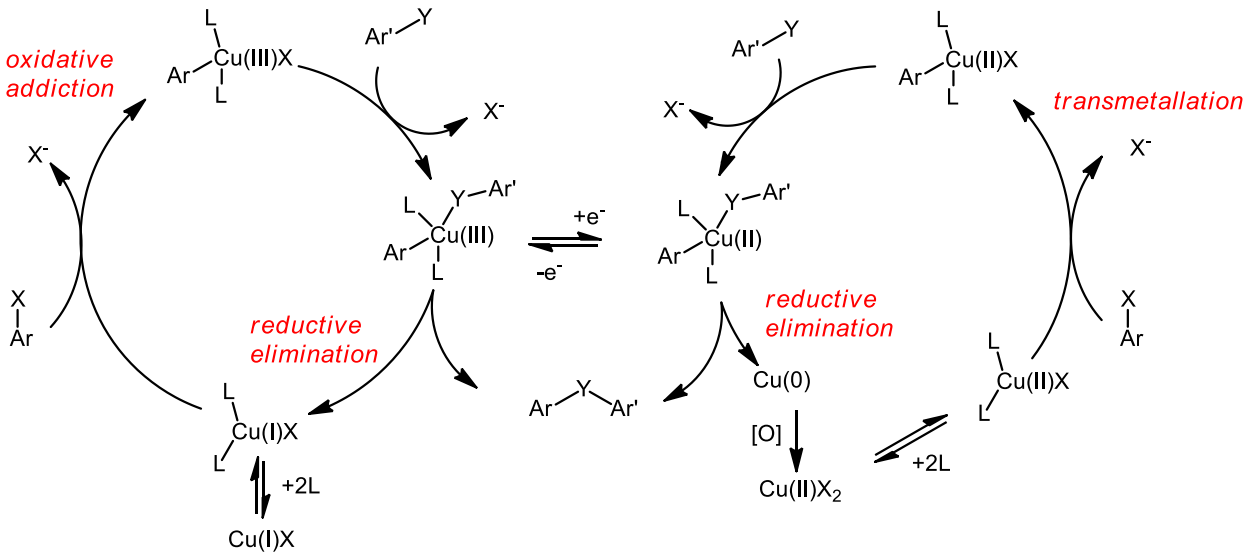


Scheme 9
Buchwald-Hartwig reaction mechanism

1.6 Ullmann-type reaction

The copper-mediated formation of C-N bonds (Ullmann condensation) is a well-known method, discovered more than a century ago, for the synthesis of *N*-aryl amines.[69] The initial reaction conditions were very harsh, using high-boiling polar solvents and stoichiometric amount of copper. In recent year new studies report the fundamental role of ligands in copper-catalyzed reactions and give a breakthrough in this coupling reaction (in term of copper loading, mild reaction conditions, substrate tolerance, yields obtained) leading to a renewed interest in Ullmann-type reactions. Compared to palladium, copper catalysis shows some interesting advantages, first of all, it is cheaper and has attracted recently high interest from the industry. The range of nucleophiles suitable for Ullmann arylations has become wider with time, and nowadays N-, O-, S-, P- and C-aryl bonds formation are easily accessible through these processes.[22]

The reaction can be catalyzed by both copper(I) or copper(II) catalysts. Some investigations seemed to demonstrate that the active catalyst are copper(I) species, but the initial copper source remained not very important for the outcome of the reaction, due to oxidation/reduction processes leading to copper(I) in all the cases during the reaction.[70] Moreover radical scavenge experiments have shown that radicals are involved in some steps. In the case of copper(I) the reaction mechanism considers the oxidative addition with formation of copper(III) intermediate as first step and the subsequent reductive elimination that regenerates the catalyst. In the case of copper(II) catalyst the first step is a transmetallation. The reductive elimination produce copper(0) that can be easily reoxidized in atmospheric conditions.[71] (Scheme 10)



Scheme 10
Copper catalyzed coupling reaction: proposed mechanism

1.7 Aim of the thesis

Having a survey of literature regarding the transition-metals catalyzed reactions applied to the C-N bonds formation, we intend to study the intramolecular reactions of unsaturated systems (alkynes, alkenes and allenes) tethered to a nucleophile with particular attention to the regioselectivity. Among different transition metals, palladium and platinum have been identified for their characteristics of reactivity, compatibility with different functional groups, easily to handle.

The aim of the thesis is to apply in particular the hydro- and carbamination reactions on aminophenol and diaminobenzene derivatives devoted to the preparation of nitrogen benzofused heterocycles, comparing the results with different catalysts.

In a separate chapter we show specific applications of two particular processes the Buchwald-Hartwig and Ullmann-type reactions. The cross-coupling reaction of amines and heteroaryl halides through amination process allows the synthesis of particular class of heteropolycyclic systems endowed with pharmacological properties as anticancer. In particular the C-N bond formation was the key step between tryptamines and 2-chloroquinolines to obtain the designed skeleton.

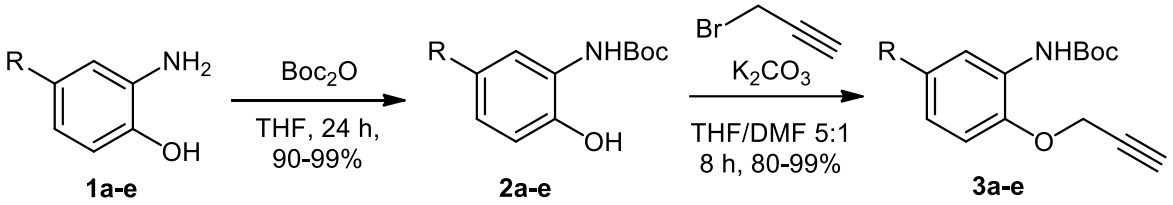
On a different application, the Ullmann-type reaction was used to afford oxazinoindole scaffold exploiting the intramolecular C-O bond formation starting from *N*-hydroxyethyl-isatin derivatives. The choice of the copper-catalyzed reaction stems from the low cost of the copper catalysts and their tolerance toward many reactive functional groups, and the reactions do not require rigorously anaerobic and anhydrous conditions. These features strongly support the development of this procedure for C−O (and also C−N) bond forming reactions.

Chapter 2

Hydroamination and carboamination reactions on unsaturated aminophenols and diaminobenzene derivatives

2.1 Hydroamination reactions: palladium catalysis

The first reaction devoted to the synthesis of heterocycles considered in this thesis is the hydroamination of terminal alkynes. *O*-propargyl ether of 2-aminophenol was the convenient substrate to obtain dihydrobenzo[1,4]oxazine, a scaffold with many interesting applications in pharmaceutical field.[72] The substrates were synthesized starting from commercially available 4-substituted 2-amino-phenols, protected at the nitrogen atom with *tert*-butoxycarbonyl. The subsequent reaction with propargyl bromide has provided the suitable substrates for the hydroamination reaction in two simple steps and good yield. (Scheme 11)



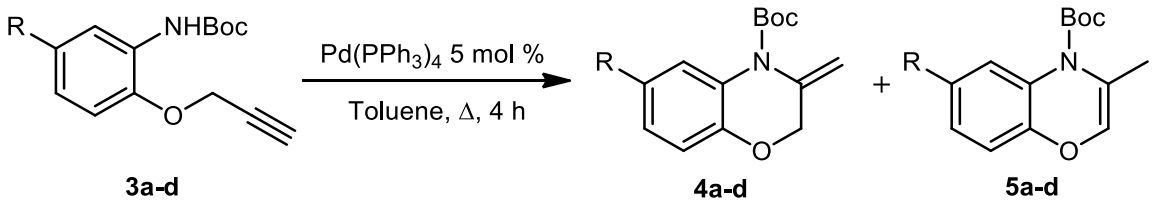
1a-e **2a-e** **3a-e**

a: R = H **b**: R = NO_2 **c**: R = Cl;
d: R = Me **e**: R = OMe

Scheme 11

Substrates synthesis

At first we have tested the hydroamination reactions, following the reactions conditions previously developed in our research group, using tetrakis(triphenylphosphine)palladium(0) as catalyst, in toluene under microwave irradiation.[73] We have noted that there were no significant differences carrying out the reaction in toluene at reflux and we have chosen to extend the reaction scope exploiting the traditional heating. As expected, the reaction was occurred with a *6-exo-dig* cyclization process and 3-methylene-dihydrobenzo[1,4]oxazines (**4a-d**) were achieved in good yields. During the chromatography we have observed a partial isomerization of these products and 3-methyl-benzo[1,4]oxazines (**5a-d**) were found beside **4**, probably due also to electron-withdrawing effect of the *tert*-butoxycarbonyl group on nitrogen. (Scheme 12, Table 1)



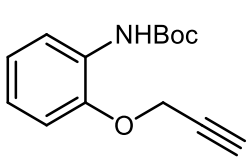
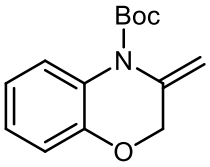
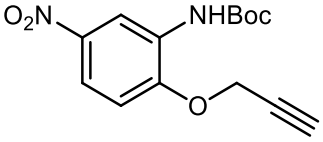
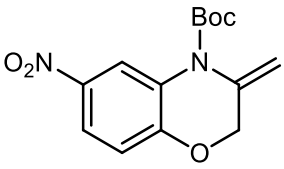
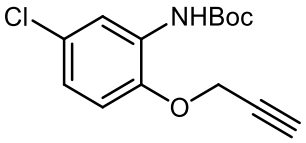
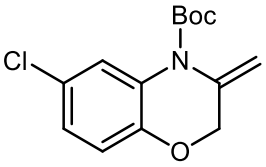
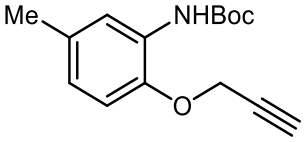
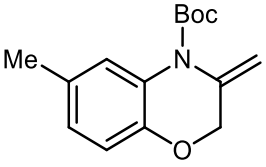
3a-d **4a-d** **5a-d**

a: R = H **b**: R = NO_2
c: R = Cl **d**: R = Me

Scheme 12

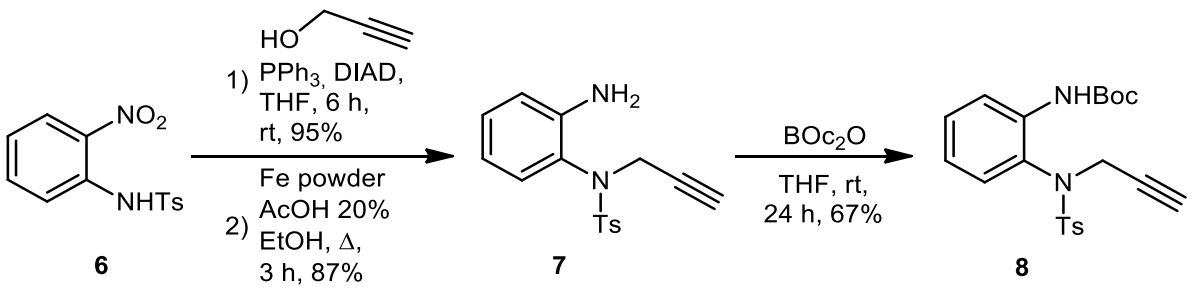
Palladium catalyzed hydroamination on *O*-propargyl derivatives

Table 1
Palladium catalyzed hydroamination on *O*-propargyl derivatives

	Substrate	Product	Yield (%)[a]
1	 **3a**	 **4a**	95 (58)
2	 **3b**	 **4b**	82 (76)
3	 **3c**	 **4c**	87 (45)
4	 **3d**	 **4d**	88 (70)

[a] Conversion calculated by NMR of the crude mixture. In parenthesis yield after chromatography.

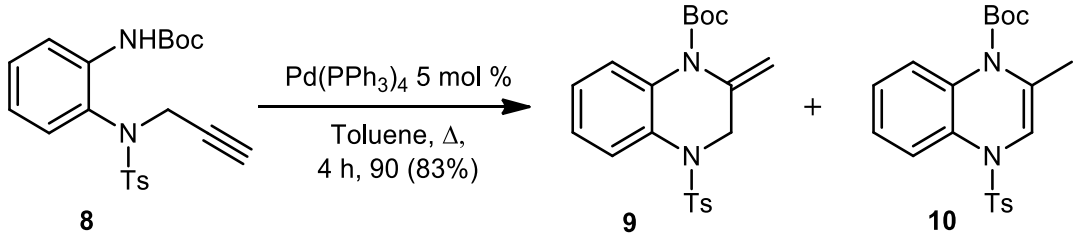
The hydroamination reaction was extended to the *N*-propargyl derivative of *o*-diaminobenzene. This substrate was obtained in a similar synthetic pathway. (Scheme 13).



6 **7** **8**

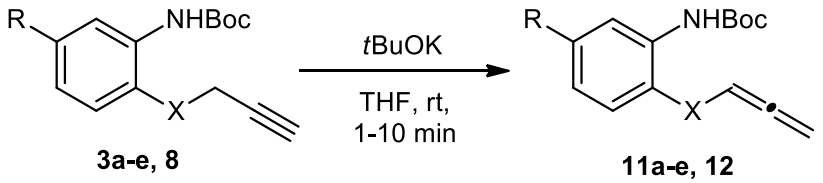
Scheme 13
Substrate synthesis

The 2-methylenedihydroquinoxaline **9** was obtained in good yield, reporting the same problem of isomerization of the exocyclic double bond. Also in this case, the 2-methylquinoxaline **10** was isolated after chromatography. (Scheme 14)



Scheme 14
Palladium catalyzed hydroamination on *N*-propargyl derivative

Having in mind the hypothesis in which the formation of allene is proposed as possible intermediate of hydroamination reaction on triple bond[46,47,48] (Chapter 1, Scheme 4), we have explored this procedure on the allenyl derivatives. The allene derivatives was easily achieved starting from the propargyl derivatives **3a-e** and **8** using potassium *tert*-butoxide as base in THF as solvent. The reaction occurs in 1 minutes starting from *O*-propargyl ethers and in 10 minutes at 0 °C with a lower yield working on *N*-propargyl derivative. (Scheme 15) Furthermore, these allenes are stable and can be purified through silica gel column chromatography.



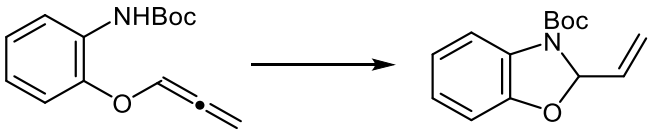
Scheme 15
Allene fomation

The reported reaction conditions on the allenyl derivative **11a** afforded the 2-vinyl-2,3-dihydrobenzoxazole **13a** in moderate yield, arising from a *5-exo*-allylic cyclization.[74] This result excludes the formation of the allene as intermediate in hydroamination reaction on terminal alkynes.

The reaction conditions were optimized to obtain *5-exo*-allylic cyclization, and the best conditions were found using an excess of triphenylphosphine respect to the catalyst. (Table 2) Although the exact role of the triphenylphosphine is not clear at present, we believe that the added phosphine might act as a Brønsted base helping to promote the initial hydropalladation step.[75] Regard to the

reaction mechanism we can hypothesize that π-allyl–Pd(II) complex intermediate is involved in the crucial step.[30,31]

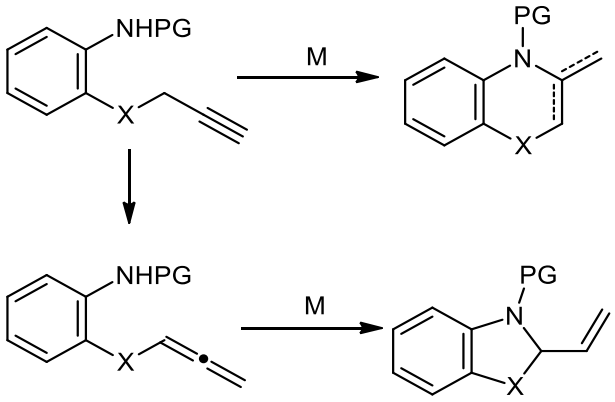
Table 2
Palladium catalyzed hydroamination on allenes: optimization of reaction conditions



11a **13a**

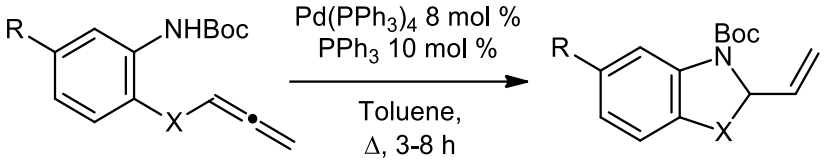
	Catalyst	Additive	Solvent	Temp [°C]	Time (min)	Yield (%)
1	$Pd(PPh_3)_4$ (8 mol %)	-	toluene	100	240	22
2	$Pd(PPh_3)_4$ (8 mol %)	-	toluene	120 (MW)	40	50
3	$Pd(PPh_3)_4$ (8 mol %)	-	MeCN	120 (MW)	40	34
4	$Pd(PPh_3)_4$ (8 mol %)	-	THF	120 (MW)	40	42
5	$Pd(PPh_3)_4$ (8 mol %)	-	DMF	120 (MW)	40	38
6	$PdCl_2(MeCN)_2$ (5 mol %)	-	MeCN	120 (MW)	40	48
7	$Pd(PPh_3)_4$ (8 mol %)	PPh3 (10 mol %)	toluene	120 (MW)	60	76
8	$Pd(PPh_3)_4$ (8 mol %)	PPh3 (10 mol %)	toluene	110	240	94

Then, starting from propargyl substrates, through an isomerization of the unsaturated bond, it is possible to achieve different regioselectivity obtaining different cyclization products. (Scheme 16)



Scheme 16
Divergent regioselectivity between propargyl and allene derivatives

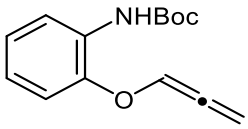
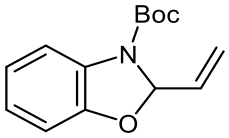
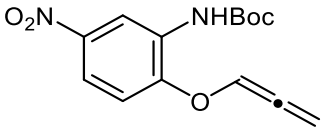
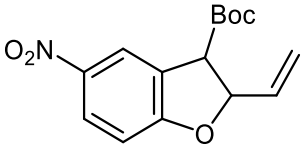
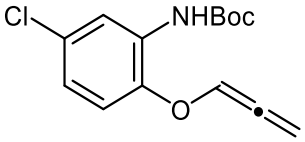
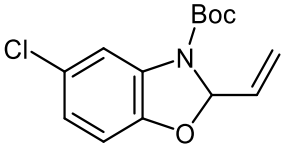
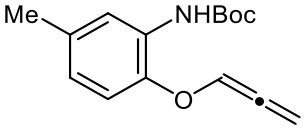
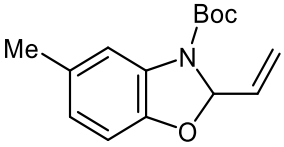
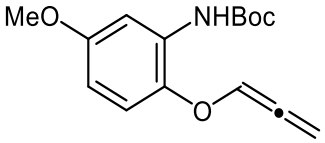
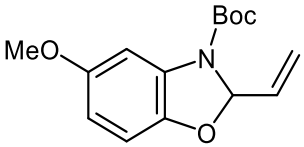
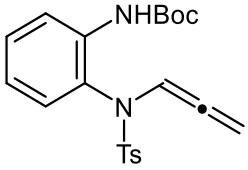
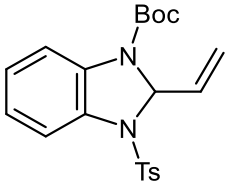
The optimized procedure was extended to a different substituted substrates with analogous results in moderate to good yields. (Scheme 17, table 3)



11a-e, 12 **13a-e, 14**

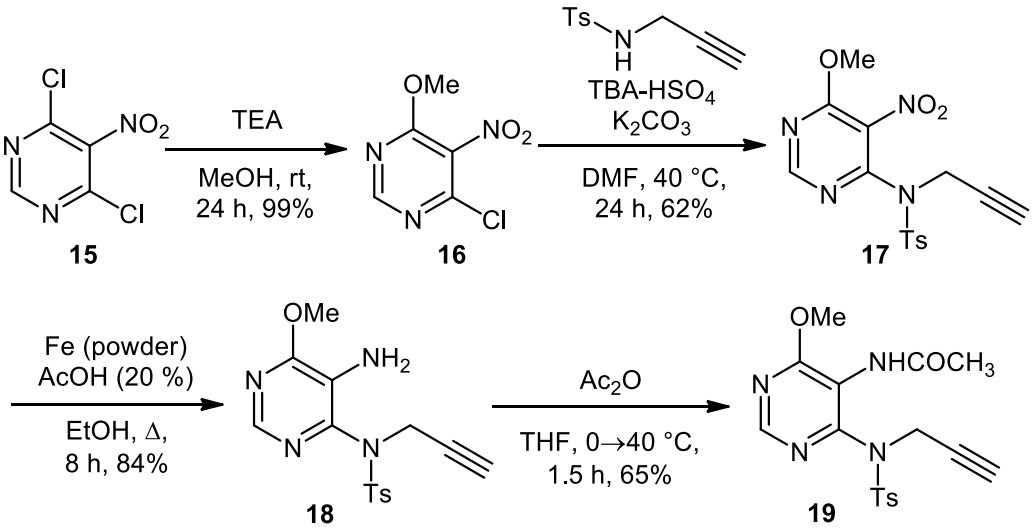
Scheme 17
Palladium catalyzed hydroamination on allenes: scope of reaction

Table 3
Palladium catalyzed hydroamination on allenes: scope of reaction

	Substrate	Product	Yield (%)
1	 **11a**	 **13a**	94
2	 **11b**	 **13b**	51
3	 **11c**	 **13c**	71
4	 **11d**	 **13d**	74
5	 **11e**	 **13e**	75
6	 **12**	 **14**	60

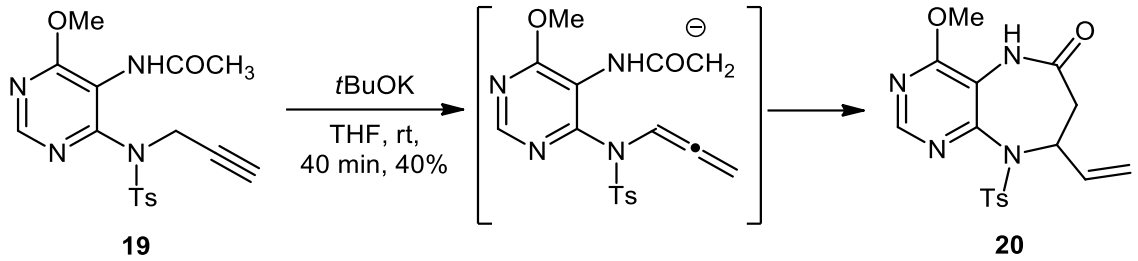
Going on in this study we have planned to test this methodology using allene tethered to an electron-poor heterocycles, such as pyrimidine and pyridine derivatives. The possibility to achieve dihydro-purine and dihydro-deazapurine respectively has encouraged our effort. Besides, commercially available 4,6-dichloro-5-nitropyrimidine (**15**) and 4-chloro-3-nitropyridine (**23**) have been identified as suitable substrates. As previously described for diaminobenzene, tosyl group was used as protecting group for the nitrogen bearing the unsaturated residue.

The first step of the synthetic pathway starting from **15** was the substitution of one the two chlorine atoms with an inert methoxy group. The remaining chlorine was exploited for a nucleophilic aromatic substitution with *N*-tosyl-propargylamide giving the unsaturated derivative **17**. The reduction of the nitro group afforded the compound **18**, and *tert*-butoxycarbonyl group was initially chosen for the protection of the nitrogen acting as nucleophile. Unfortunately the hydroamination reaction failed in different conditions, also with tosyl protecting group, then we have explored the *N*-acetyl derivative (**19**). (Scheme 18)



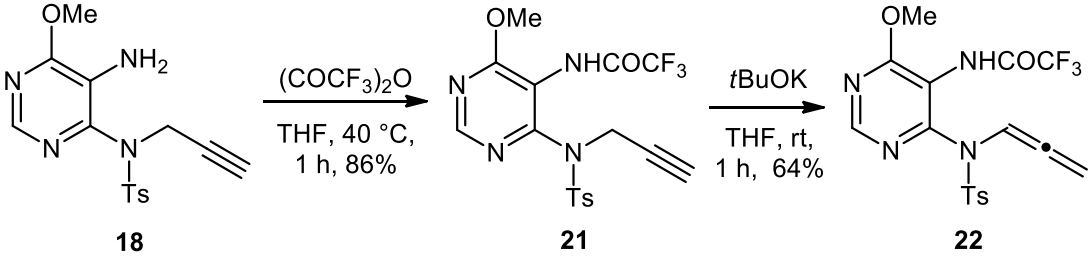
Scheme 18
Synthesis of pyrimidine derivative

In this case, the allene preparation with potassium *tert*-butoxide gave simultaneous deprotonation of the acetyl group with consequent intramolecular attack on the allenyl residue affording the 8-vinyl-dihydro-pyrimidodiazepinone (**20**) in moderate yield. (Scheme 19)



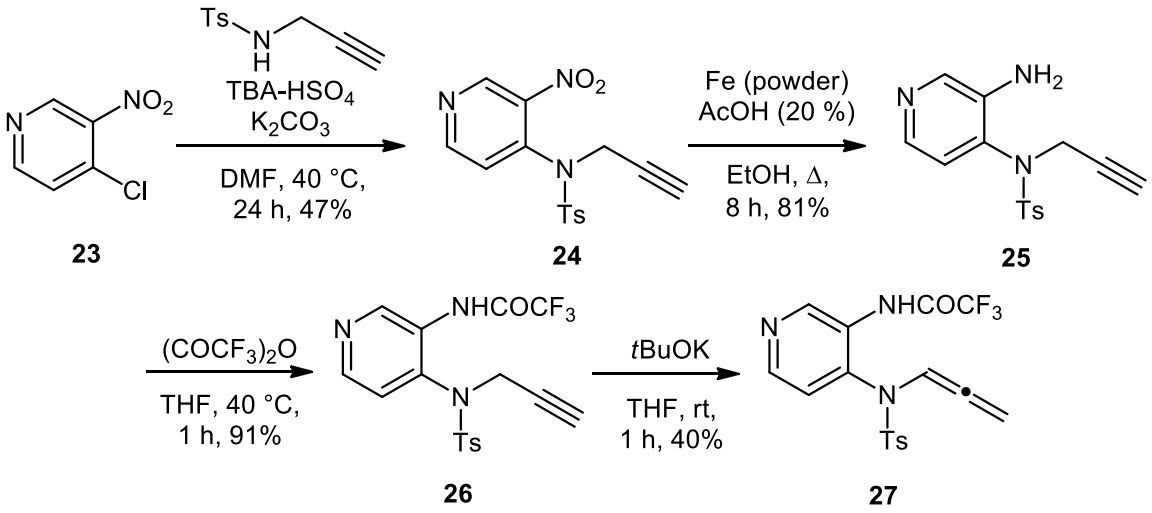
Scheme 19
Preparation of allene tethered diaminopyrimidine

To avoid the presence of acid hydrogens able to react with the allene we have chosen as protecting group the trifluoroacetyl group. On compound **21** the isomerization of the triple bond proceeded slowly: one hour was required to obtain the allene instead of 1 minute as reported for the analogue propargyl derivatives tethered to the benzene ring. (Scheme 20)



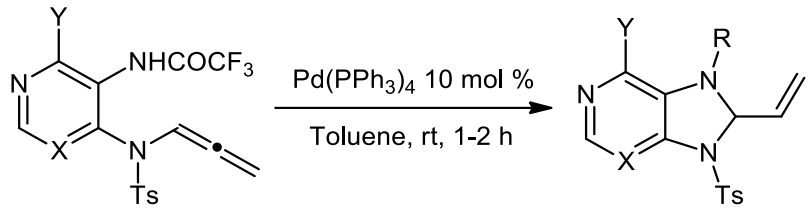
Scheme 20
Synthesis of allene-tethered diaminopyrimidine

The same synthetic pathway was repeated starting from the pyridine substrate **23**. (Scheme 21)



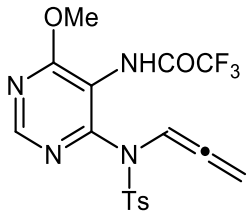
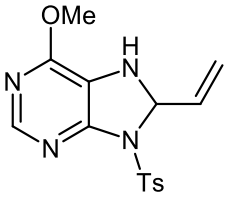
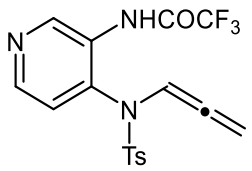
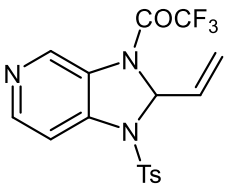
Scheme 21
Synthesis of allene-tethered diaminopyridine

The hydroamination reactions afforded the desired purine and deazapurine **28** and **29**, but the different electronic availability of these substrates has enforced different reaction conditions. Indeed, high temperature was detrimental, inducing the decomposition of substrates. Best yield was achieved at room temperature. Furthermore, less time was needful for the complete consumption of the starting material. Tetrakis(triphenylphosphine)palladium(0) remained the best catalyst, but in this case the excess of triphenylphosphine has not induced a significative yield improvement. Working on the *N*-allenyl-pyrimidine **22** it is noteworthy the loss of the trifluoroacetyl protecting group. (Scheme 22, table 4)



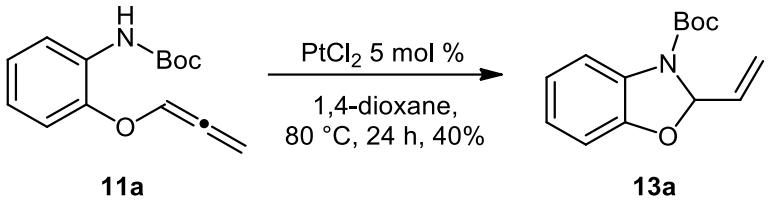
Scheme 22
Palladium catalyzed hydroamination on allene-tethered pyrimidine and pyridine

Table 4

Substrate	Product	Yield (%)
 **22**	 **28**	73
 **27**	 **29**	64

2.2 Hydroamination reactions: platinum catalysis

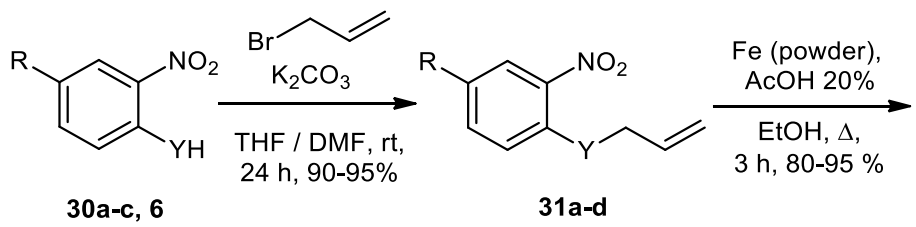
In order to verify the regioselectivity in the hydroamination process the allene derivative **11a** was also tested under platinum catalysis. Using platinum(II) chloride without ligand in dioxane as solvent, no different regioselectivity was observed and the dihydrobenzoxazole **13a** was obtained in lower yield respect to the palladium catalysis, beside the 15% of dealkylated starting material. (Scheme 23)



11a **13a**

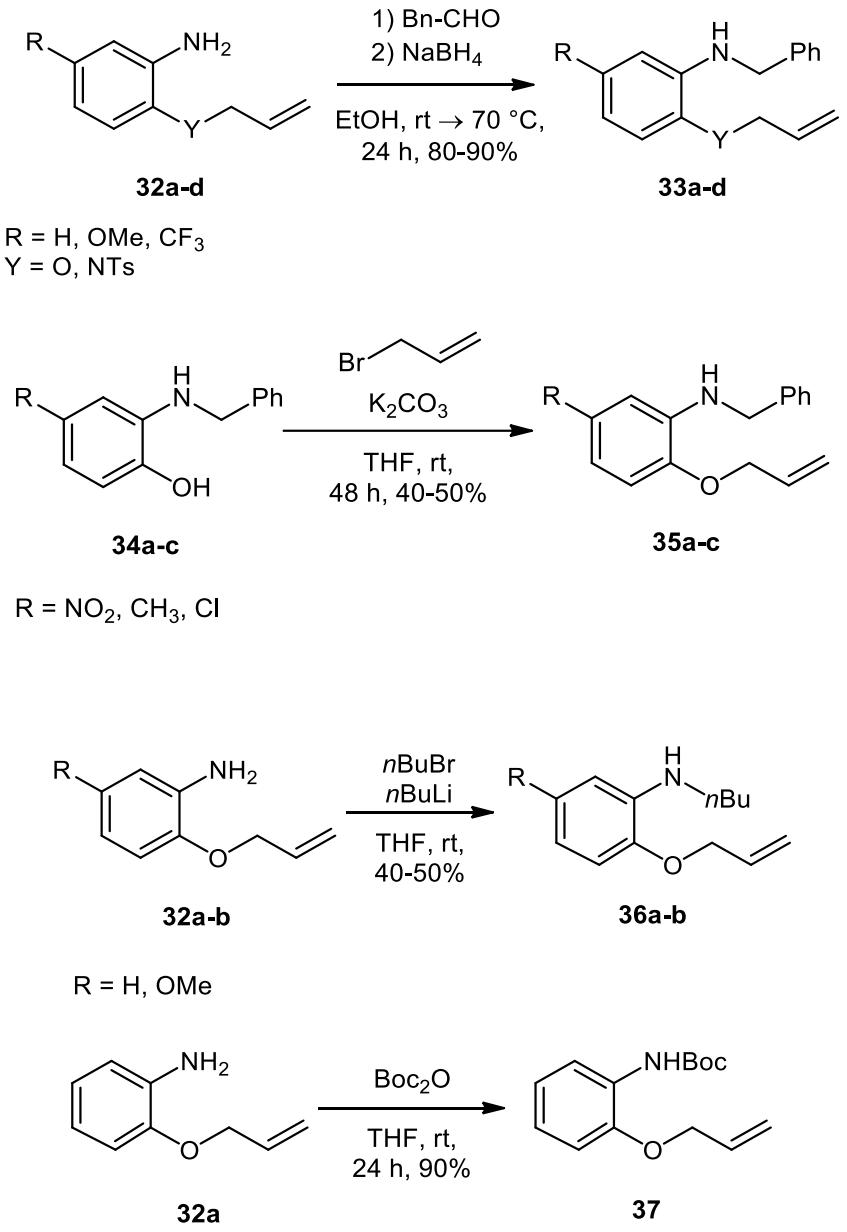
Scheme 23
Platinum catalyzed hydroamination on allene

The alkenes are cheaper and easier handling than alkynes and allenes. Moreover, intramolecular hydroamination of unactivated alkenes is one of the simplest methods to obtain nitrogen heterocycles. Continuing to explore platinum catalysis in hydroamination reactions and considering the hydroamination reactions reported in literature on the unactivated olefins,[14,15] we decided to study the reactivity of substituted *O*-allyl ethers and *N*-allyl amide, arising respectively from 2-aminophenols and *o*-diaminobenzene. The substrates were prepared as shown in scheme 25 following different synthetic pathways depending on the substituents. We synthesized different derivatives having the nucleophilic nitrogen substituted with benzyl group (**33a-d** and **35a-c**), alkyl residue (**36a-b**) and *tert*-butoxycarbonyl group (**37**), with the aim to investigate the influence of the substituent on the nucleophilic nitrogen. (Scheme 24)



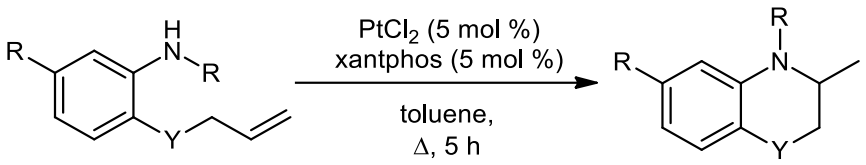
30a-c, 6 **31a-d**

R = H, OMe, CF_3
Y = O, NTs



Scheme 24
Substrates synthesis

The cyclization reactions were carried out with platinum(II) chloride as catalyst, Xantphos as ligand in toluene at reflux. The reaction resulted as a *6-exo-trig*-cyclization, leading to the formation of 3-methyl-3,4-dihydrobenzo[1,4]oxazine (**38a-i**). (Scheme 25) The best result was achieved when the nucleophilic nitrogen was substituted whit a benzyl group, while the presence of an alkyl residue, as the butyl, gave lower yield and required more reaction time for the complete consumption of starting material. On the allyl derivative of *o*-diaminobenzene the yield was lower. No result was obtained on the substrate protected with an electron withdrawing group.

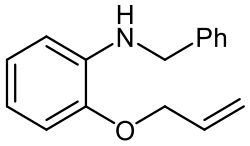
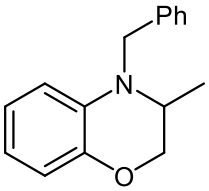
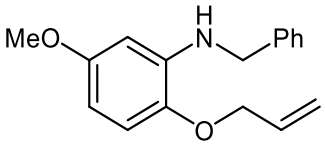
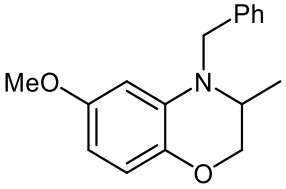
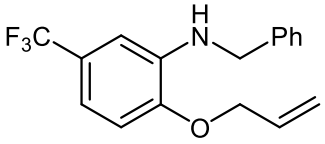
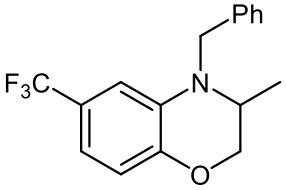
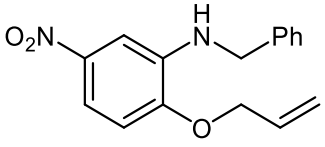
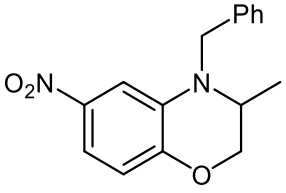


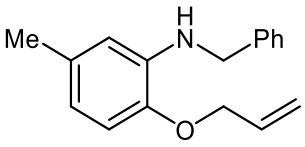
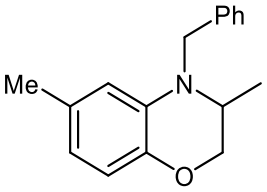
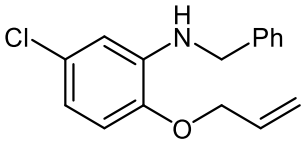
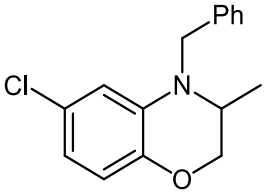
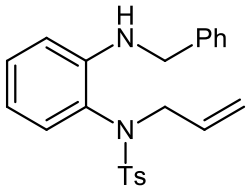
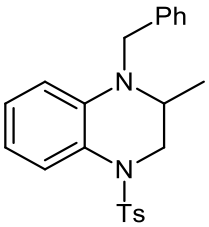
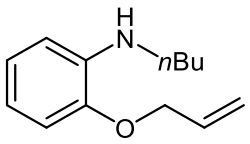
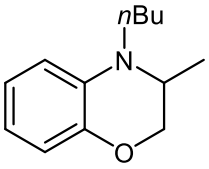
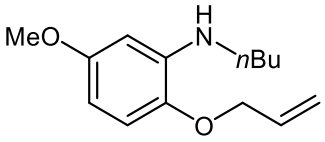
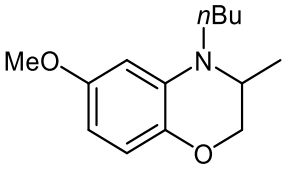
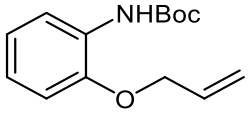
33a-d, 35a-c, 36a-b, 37 **38a-i**

Scheme 25

Hydroamination reaction on allyl derivatives

Table 5

	Substrate	Product	Yield (%)
1	 **33a**	 **38a**	90
2	 **33b**	 **38b**	60
3	 **33c**	 **38c**	88
4	 **35a**	 **38d**	70

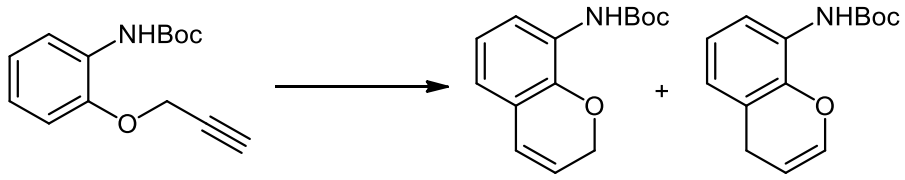
5	 **35b**	 **38e**	87
6	 **35c**	 **38f**	97
7	 **33d**	 **38g**	30 [a]
8	 **36a**	 **38h**	10 [a]
9	 **36b**	 **38i**	35 [a]
10	 **37**	-	0 [b]

[a] Reaction time was 10 h; [b] reaction time was 24 h.

2.3 Unexpected hydroarylation reactions: platinum catalysis

To complete our screening on aminophenols derivatives, we have explored the platinum catalysis on *O*-propargyl derivative **3**, with the aim to achieve a different regioselectivity in hydroamination reactions, encouraged by some examples in literature on alkynylamides[76,77,78,79,80,81], reporting a *7-endo-dig* cyclization. The substrate **3a** showed a different reactivity, where no hydroamination process was observed but a hydroarylation reaction involving the aromatic ring was reported. The benzopyran **39a** was formed as major product beside the isomerized compound **40a.** The isomerization of the double bond was probably due to the reaction mechanism. Different reaction conditions have been tested and the best result was found using platinum(II) chloride, without ligand in toluene at 80 °C. The use of ligand was detrimental, increasing the formation of dealkylated product. As well as, the use of platinum(IV) chloride reported lower yield, though this catalyst allowed the occurrence of reaction at lower temperature. (Table 6)

Table 6
Hydroarylation reaction conditions



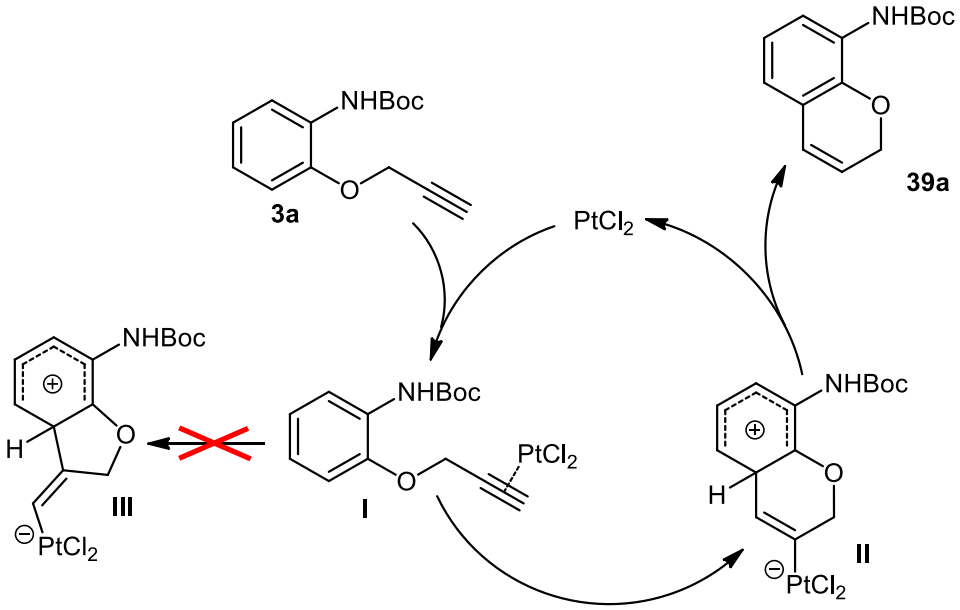
3a **39a** **40a**

	Catalyst	Ligand	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]
1	$PtCl_2(MeCN)_2$	-	toluene	110	6	40 (10)
2	$PtCl_2(MeCN)_2$	PPh_3	1,4-dioxane	100	3	30 (-)
3	$PtCl_2$	-	toluene	80	3	50 (10)
4	$PtCl_2$	Xantphos	MeCN	80	5	30 (-)
5	$PtCl_2$	-	1,4-dioxane	100	2	30 (20)
6	$PtCl_2$	JohnPhos	1,4-dioxane	70	2	25 (10)
7	$PtCl_2$	-	MeCN	80	3	40 (10)
8	$PtCl_2$	-	MeOH	65	3	20 (-)
9	$PtCl_4$	-	toluene	80	8	-
10	$PtCl_4$	-	1,2-dichloroethane	20	2	35 (5)

[a] In parenthesis yield of compound **40a**

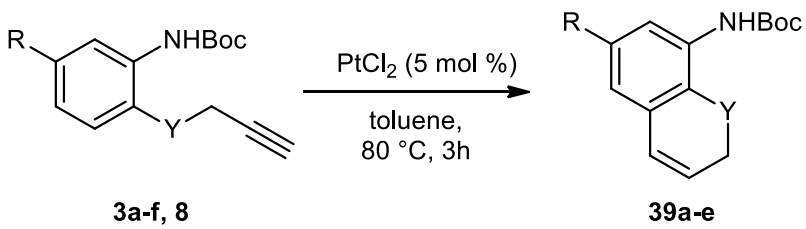
The mechanism usually proposed is based on a Friedel–Crafts alkenylation reaction, in fact electron-donating substituents facilitate the hydroarylation process.[82] Thus, coordination of platinum(II) chloride to **3a** affords **I**, which undergoes an electrophilic aromatic substitution to give the Wheland-type intermediate **II**, following an anti-Markovnikov process. This intermediate gives **39a** probably by a formal 1,3-H shift. The competitive 5-*exo-dig* cyclization with the formation of a five-membered ring **III** appears unlikely. Computational studies regarding the high energy of the

distorted structure of intermediate shows a kinetic and thermodynamic preference for *6-endo-dig* versus *5-exo-dig* cyclization.[83] (Scheme 26)



Scheme 26
Proposed Platinum catalyzed hydroarylation mechanism

The method was extended to different substituted *O*-propargyl derivatives. The best yields were achieved on substrates bearing electron-donor residues on the aromatic ring. The nature of these substituents influenced the yields as well as the formation of the isomerized product. The presence of an electron-withdrawing group, as the nitro was detrimental and no product was achieved. To clarify if this result was due to the electron disposability of substrate or is due to the ability of nitro group to chelate the catalyst we have synthesized a compound with a strong electron-withdrawing substituent, unequivocally unable to coordinate the platinum, as the trifluoromethyl group (**3f**). Also in this case, no result was obtained, confirming the importance of electron disposability of the aromatic ring for the success of this reaction. Bad result was obtained using the *N*-propargyl derivative of diaminobenzene, only trace of product was found in the crude mixture. (Scheme 27, Table 7)

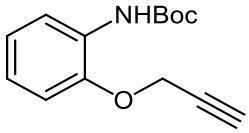
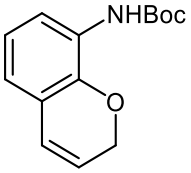
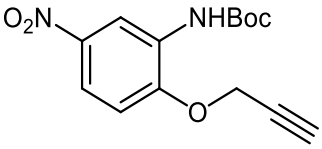
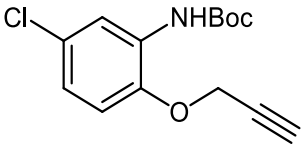
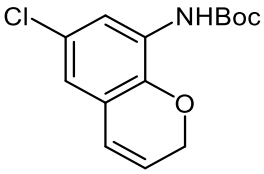
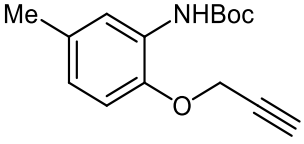
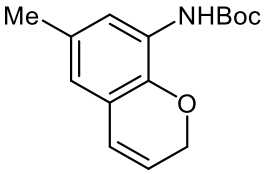
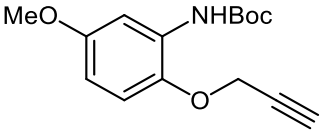
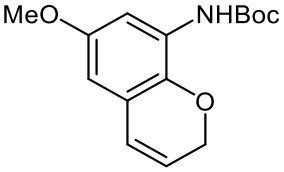
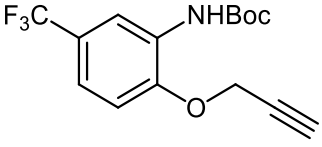


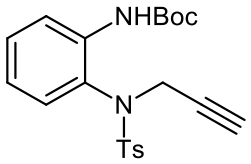
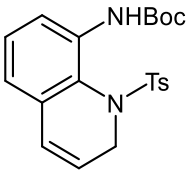
3a-f, 8 **39a-e**

Scheme 27
Hydroarylation reaction

Table 7

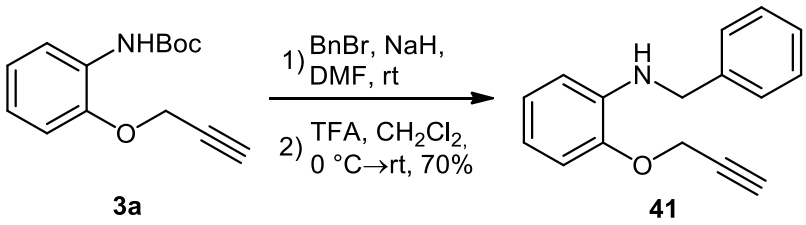
Hydroarylation reaction

	Substrate	Product	Yield (%)[a]
1	 **3a**	 **39a**	50 (10)
2	 **3b**	**-**	-
3	 **3c**	 **39b**	20 (5)
4	 **3d**	 **39c**	60 (5)
5	 **3e**	 **39d**	65 (-)
6	 **3f**	-	-

7	 **7**	 **39e**	traces (-)

[a] In parenthesis yield of isomerized product.

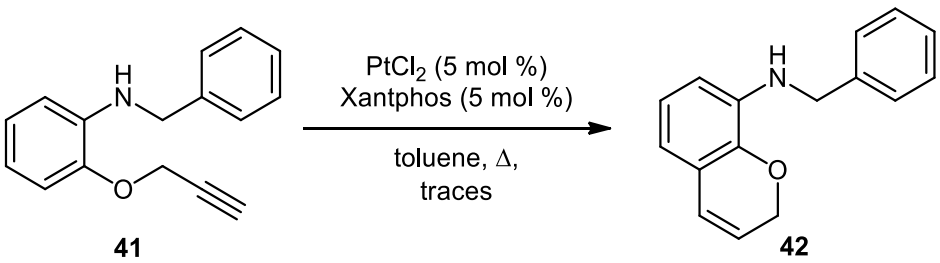
Considering that the trials on propargyl derivatives were carried out on *N*-Boc protected derivatives and the good results on allyl derivatives were achieved on *N*-benzyl derivatives, we have thought to synthesize the 2-*N*-benzyl-*O*-propargyl-phenol **41,** starting from **3a**, using sodium hydride as base and benzyl bromide in DMF. The *tert*-butoxycarbonyl protecting group was removed using trifluoroacetic acid in methylene chloride. (Scheme 28)



3a **41**

Scheme 28
Synthesis of substrate

Working on **41** no result was obtained as hydroamination product and poor result in hydroarylation reaction. (Scheme 29)

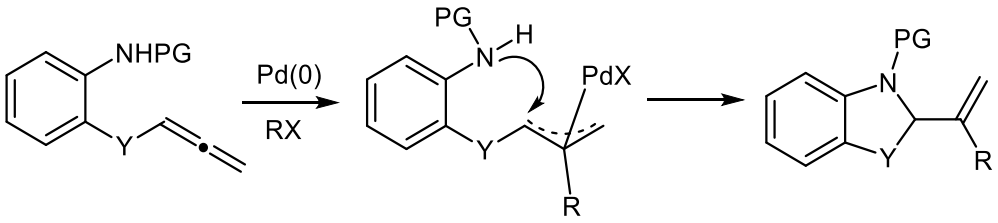


41 **42**

Scheme 29
Hydroamination versus hydroarylation reactions

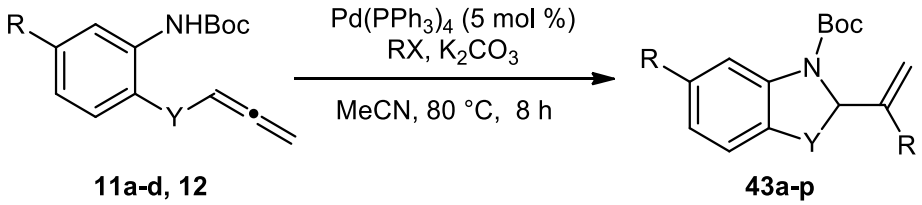
2.4 Carboamination reactions on allenes: palladium catalysis

Considering the good result achieved in the hydroamination reaction carried out on allenyl derivatives we thought to explore the carboamination reactions with the aim of having a styryl substituent at C-2 of the heterocyclic ring that would permit further functionalization. The allenyl derivatives **3a-e** were treated with aryl- or heteroaryl iodides, following the conditions previously used by our research group, in the presence of tetrakis(triphenylphosphine)palladium(0), potassium carbonate as base in acetonitrile at reflux.[73] The carboamination process proceed with complete regioselectivity resulting in the formation of five-membered ring products. The hypothesized mechanism occurs *via* the formation of a π-allyl palladium complex intermediate, accessible by the carbopalladation of the allene moiety followed by nucleophilic addition of the nitrogen atom. (Scheme 30)



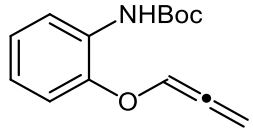
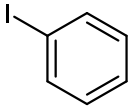
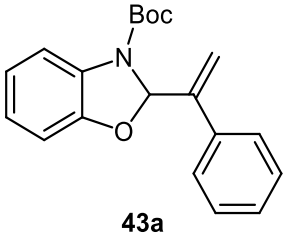
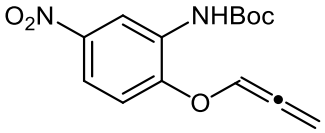
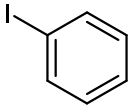
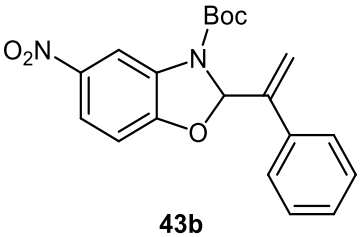
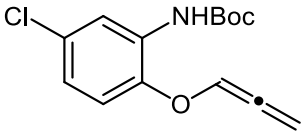
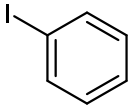
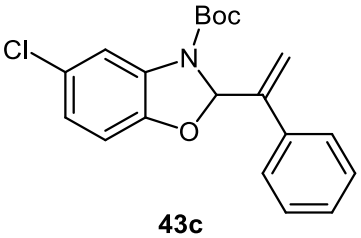
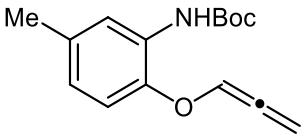
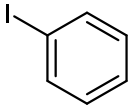
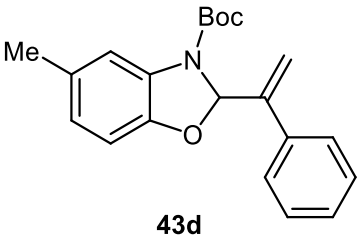
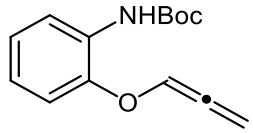
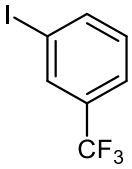
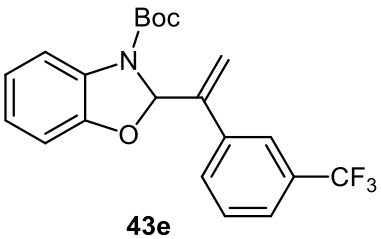
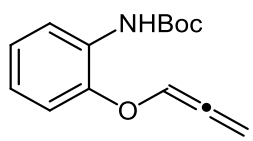
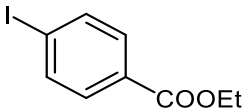
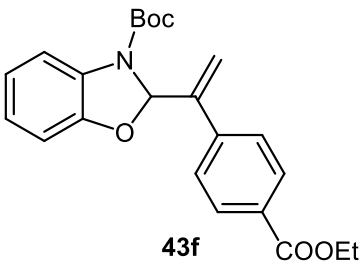
Scheme 30
Carboamination proposed mechanism

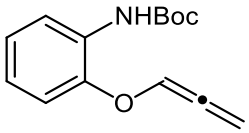
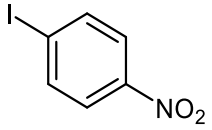
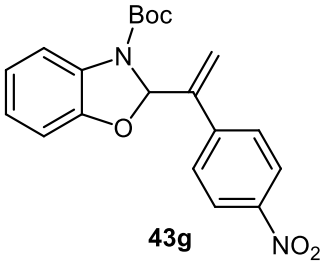
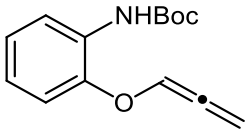
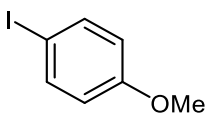
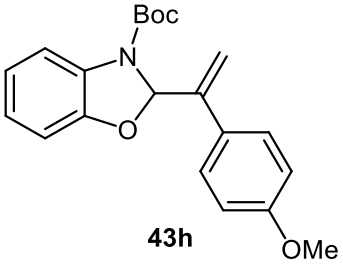
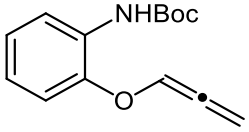
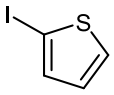
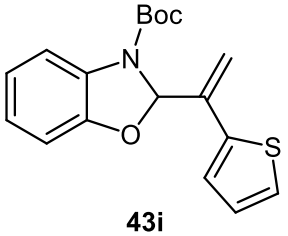
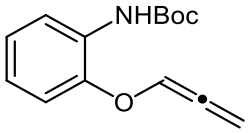
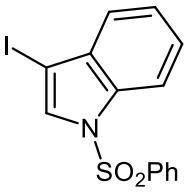
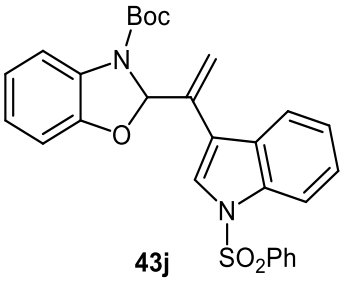
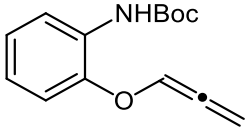
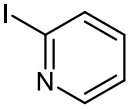
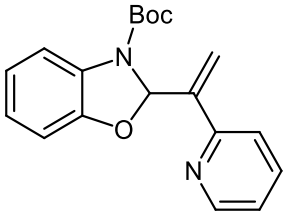
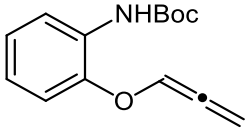
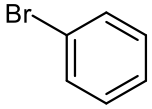
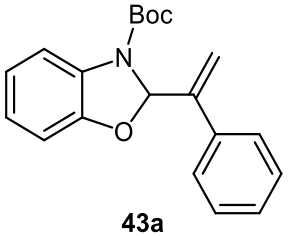
The process, which involves sequential C–C and C–N bond formation, occurred with a variety of electron-poor as well as electron-rich aryl iodides. The scope of the reaction was also successfully extended to different heteroaryl iodides, ranging from electron-rich, such as 2-iodothiophene and *N*-phenylsulfonyl-3-iodoindole, to electron-poor, such as 2-iodopyridine, to give the corresponding heteroaryl-substituted dihydrobenzazoles in moderate-to-good yields. Bromobenzene was also tested; the corresponding coupling product **43a** was obtained albeit in a lower yield (Table 8, entry 12). Moreover, it should be noted that the reaction of **11a** with allyl bromide provided 2-(1,4-pentadienyl)-dihydrobenzoxazole (**43p**) in 65 % yield. (Scheme 31, Table 8, entry 17)

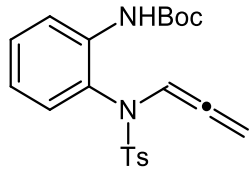
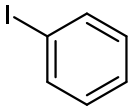
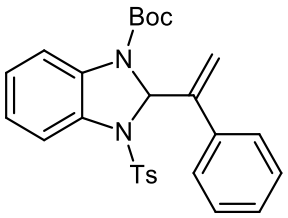
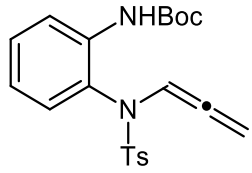
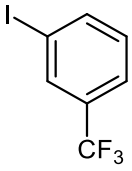
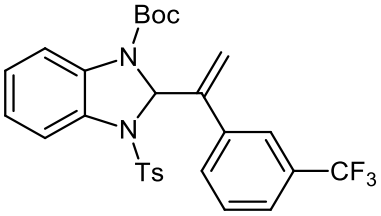
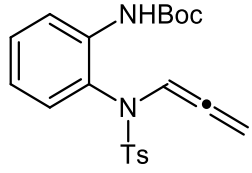
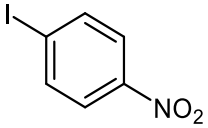
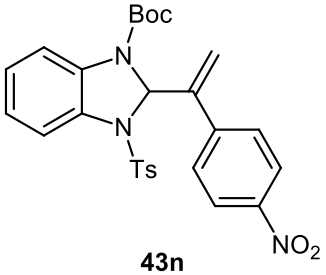
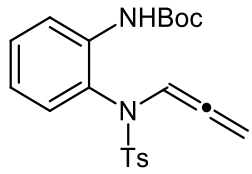
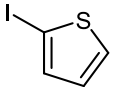
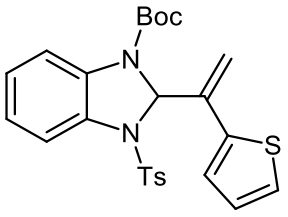
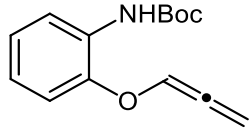
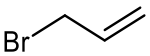
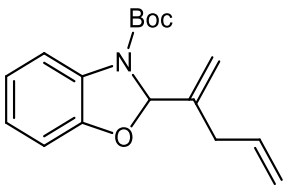


Scheme 31
Carboamination of allenes: scope of reaction

Table 8

	Substrate	RX	Product	Yield (%)
1	 **11a**		 **43a**	76
2	 **11b**		 **43b**	62
3	 **11c**		 **43c**	54
4	 **11d**		 **43d**	48
5	 **11a**		 **43e**	57
6	 **11a**		 **43f**	78

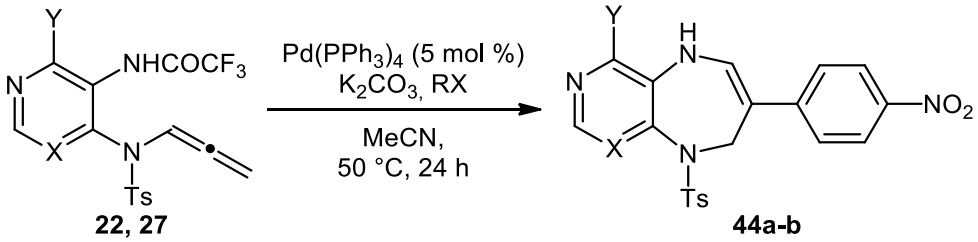
7	 **11a**		 **43g**	71
8	 **11a**		 **43h**	65
9	 **11a**		 **43i**	64
10	 **11a**		 **43j**	67
11	 **11a**		 **43k**	86
12	 **11a**		 **43a**	50

13	 **12**		 **43l**	86
14	 **12**		 **43m**	70
15	 **12**		 **43n**	65
16	 **12**		 **43o**	46
17	 **11a**		 **43p**	65

As in the case of hydroamination, we tried to extend this method to allenyl derivatives of electron-poor heterocycles as pyrimidine and pyridine. The cyclization required the trifluoroacetyl as protecting group on the nucleophilic nitrogen. Compared to the aryl substrate (*o*-diaminobenzene), the most relevant remark was the different regioselectivity in the C-N bond formation obtaining the pyrimido[4,5]diazepine (**44a**) through the *7-endo*-cyclization process. The

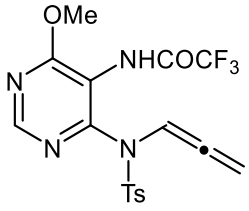
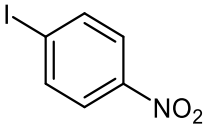
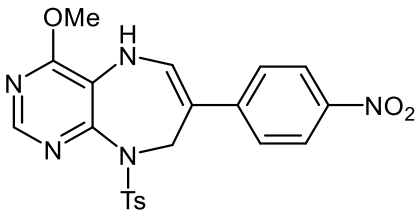
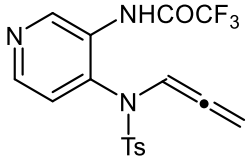
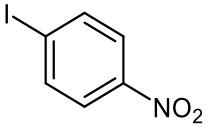
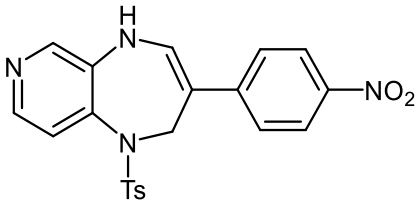
reaction conditions required lower temperature respect to the electron-rich substrates, no carboamination products were obtained with different aryl- or heteroaryl iodides.

Starting from the substituted pyridine **27, t**he same regioselectivity was reported in the cyclization step, affording 3-(4-nitrophenyl)-pyrido[3,4-*b*]diazepine (**44b**) in comparable yield. (Scheme 32)

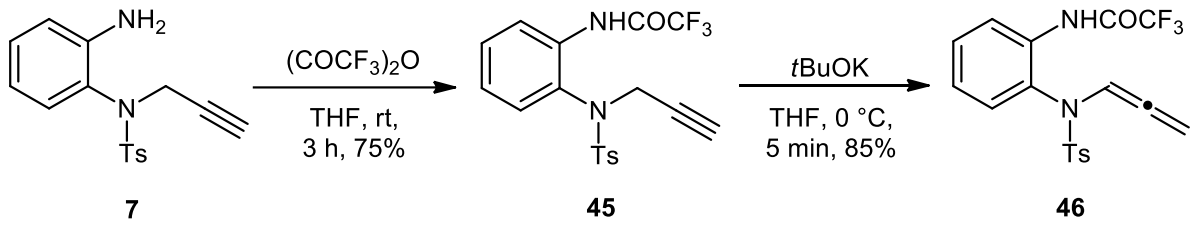


Scheme 32
Carboamination of allene tethered pyridine and pyrimidine

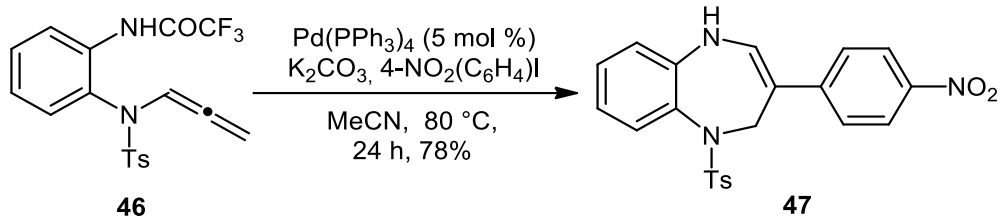
Table 9

	Substrate	RX	Product	Yield (%)
1	 **22**		 **44a**	35
2	 **27**		 **44b**	42

To identify the factors that could have influenced the different regioselectivity, we have tried, at first, the same reaction conditions on the allenyl derivative of diamino-benzene (**46**), protected with strong electron-withdrawing trifluoroacetyl group on the nucleophilic nitrogen. (Scheme 33) Also in this case, we reported the *7-endo*-cyclization leading the formation of 1,4-benzodiazepine (**47**) in good yield. On the same substrate we have tested different aryl-iodide but surprisingly no *7-endo*-cyclization has occurred and only the corresponding heteroaryl-substituted dihydrobenzazoles (**43**) was found in the crude mixture. (Scheme 34)

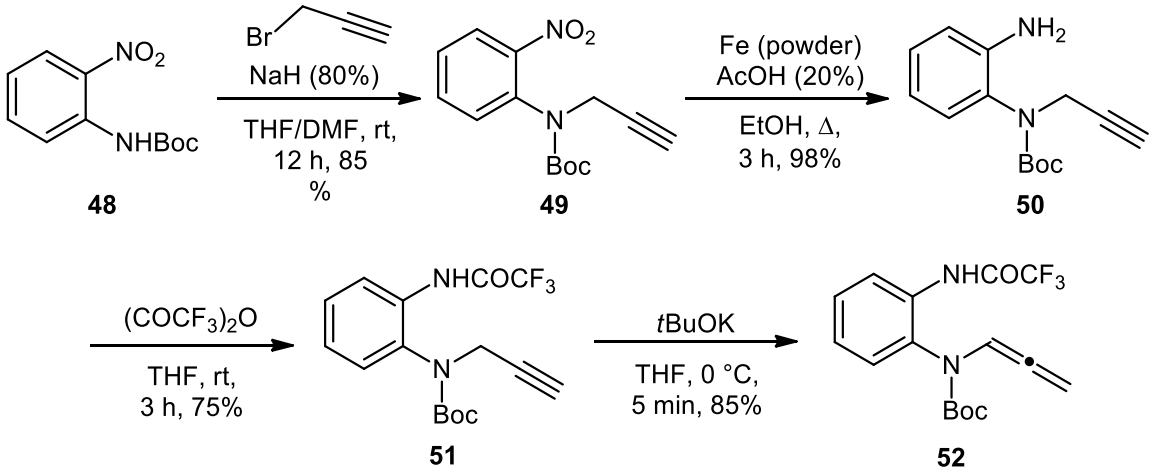


Scheme 33
Substrate synthesis



Scheme 34
Carboamination of allene tethered *o*-diaminobenzene

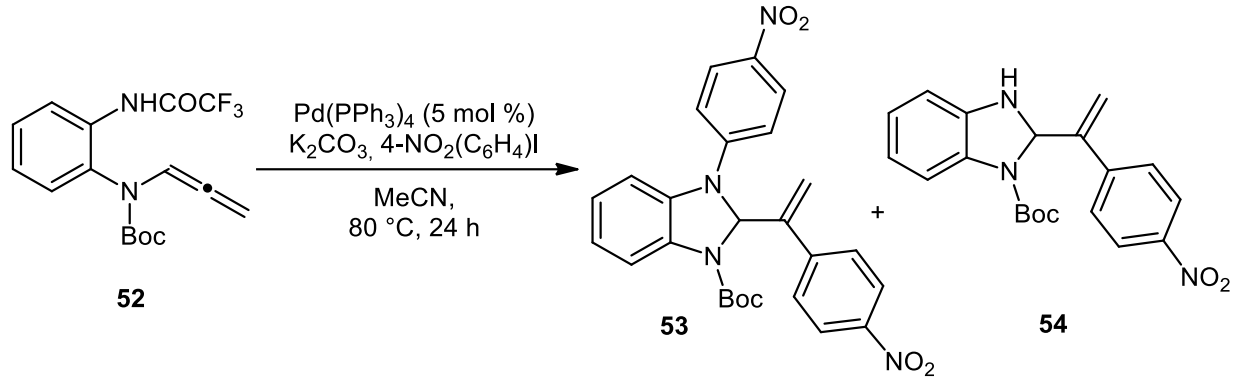
At last, we have changed the protecting group on the nitrogen bearing the allenyl moiety, leaving unchanged the protecting group on the nucleophilic nitrogen. The compound (**52**) was synthesized from *tert*-butyl *N*-(2-nitrophenyl)-carbamate (**48**), following a synthetic pathway seen above for the preparation of the *N*-tosyl derivatives. (Scheme 35)



Scheme 35
Substrate synthesis

In this case the presence of the quite labile trifluoroacetyl group afforded a five-membered dihydrobenzimidazole following a 5-*exo*-cyclization process with loss of the trifluoroacetyl group

and concomitant *N*-aryl functionalization (**53**), obtained in a mixture with the non-isolated NH derivative (**54**). (Scheme 36)



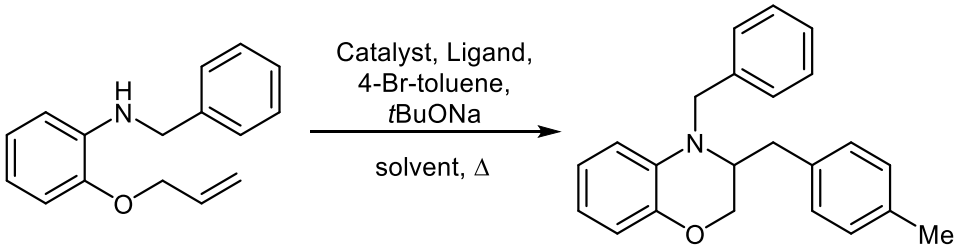
Scheme 36

Carboamination of allene tethered *o*-diaminobenzene: influence of protecting group

2.5 Carboamination reaction on alkenes: palladium catalysis

The carboamination reactions was also tried on *O*-allyl derivative of aminophenol, exploiting aryl bromide as coupling reactant. The first trial was carried out on *N*-*tert*-butoxycarbonyl protected derivative **37** but no result was obtained. A domino process was achieved using *N*-benzyl derivative **33a**. The best reaction conditions were found exploiting tris(dibenzylideneacetone)dipalladium(0) as pre-catalyst, xantphos as ligand and sodium *tert*-butoxide as base in toluene. (Table 10)

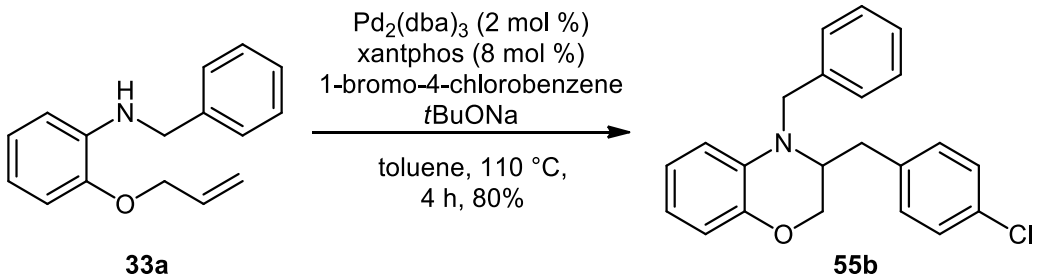
Table 10
Carboamination reactions on *O*-allyl ether: reaction conditions



33a **55a**

	Catalyst	Ligand	Solvent	Time (h)	Yield (%)
1	$Pd(OAc)_2$ (5 mol %)	DPE-Phos (5 mol %)	toluene	24	46
2	$Pd_2(dba)_3$ (2 mol %)	xantphos (8 mol %)	toluene	4	70
3	$Pd_2(dba)_3$ (2 mol %)	xantphos (8 mol %)	THF	48	20
4	$Pd_2(dba)_3$ (2 mol %)	P(*o*-tol)$_3$ (8 mol %)	toluene	48	-
5	$Pd_2(dba)_3$ (2 mol %)	xantphos (8 mol %	toluene	2	50

As expected, using a more activate bromide, such as 1-bromo-4-chlorobenzene, higher yield was achieved. (Scheme 37) In this process a new stereocenter was formed and the next challenge will be to obtain stereoselective ciclization reaction.



33a **55b**

Scheme 37
Carboamination reactions on *O*-allyl ether

Chapter 3

Synthesis of polyheterocyclic systems of biological interest through transition-metal catalysis

3.1 Design, synthesis and biological evaluation of a new scaffold of topoisomerase I inhibitors[84]

Inhibition of topoisomerases activities, essential enzymes for vital cellular processes, is lethal and leads to cell death, thus establishing topoisomerases as a promising target for cancer treatment.[85] Recently, a series of 2,3-heteroaryl substituted maleimides and heterofused imides as well the corresponding bis-derivatives were prepared by our research group and their antiproliferative effects on human cells (NCI-H460 lung carcinoma) and rat aortic smooth muscle cells (SMC's), as well as their ability to stabilize the DNA-intercalator-topoisomerase II ternary complex were evaluated. The compounds of these series showed IC_{50} values comparable to those observed for the leading molecule Elinafide. They affected G1/S phase transition of the cell cycle, showed in vitro DNA intercalating activity and in vivo antitumor activity.[86,87] Continuing the researches having topoisomerases as biological target, our interest is now addressed to topoisomerase I (Topo I). The interest in topoisomerase I as a therapeutic target promoted various efforts to identify other chemotypes effective as topoisomerase inhibitors and chemical/modelling efforts to rationally design specific analogs among known inhibitors. Their screening with purified Topo I and isolated DNA substrates led to the discovery of various Topo I inhibitors belonging to the different chemistry families.

3.2 DNA topoisomerases: mechanism and role in cancer treatment

The topoisomerases are ubiquitous enzymes essential for the vital cellular processes as involved in different steps of DNA replication, transcription and recombination. In particular topoisomerase I and topoisomerase II play a key role binding to the DNA double helix inducing temporary single (Topo I) or double strand break (Topo II) allowing relaxation of the DNA for replication.

The catalytic mechanism of topoisomerases in all cases consists in a nucleophilic attack of a DNA phosphodiester bond by a catalytic tyrosyl residue of the enzyme. The resulting covalent attachment of the tyrosine to the DNA phosphate is either at the 3′-end of the broken DNA in the case of topoisomerase I enzymes or at the 5′-end of the broken DNA for the topoisomerase II. Topoisomerase I are the only that operates through covalent link with the 3′-end of the broken DNA while generating a 5′-hydroxyl end at the other end of the break. Topo I relaxation mechanism consists in “controlled rotation”: the enzyme relaxes DNA by letting the 5′-hydroxyl end swivel around the intact strand. This processive reaction does not require ATP or divalent metal binding (Mg^{2+}), which is different from the case of Topo II enzymes.[88] (Figure 4)

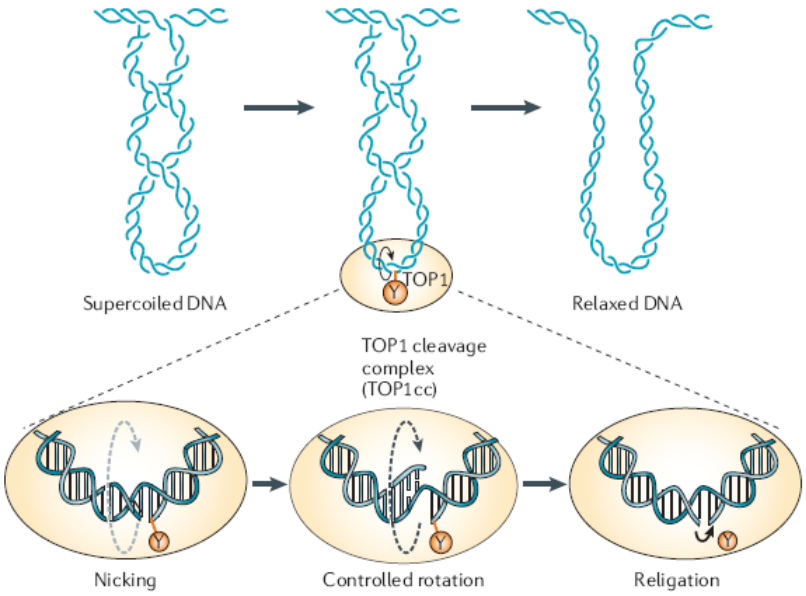


Figure 4
Topo I establishes a covalent bond to the DNA, creating a nick that allows for rotation of the DNA about the remaining, intact DNA strand; at last the DNA has been religated.[89]

Topoisomerases are required for both normal and cancer cells, but are overexpressed in cancer cells due to the high level of DNA metabolism and intrinsic defects in DNA repair and checkpoints, which are the landmarks of cancer cells. The inhibition of these enzymes lead to the cell apoptosis. Thus DNA topoisomerases I and II are established molecular targets of anticancer drugs.

3.3 Camptothecin and synthetic Topo I inhibitors

Camptothecin was first isolated from the bark of the Chinese tree, *Camptotheca acuminata*. (Figure 5) It was discovered and was tested clinically in the mid 1970's and showed anticancer activity, but was discontinued because of its side effects.

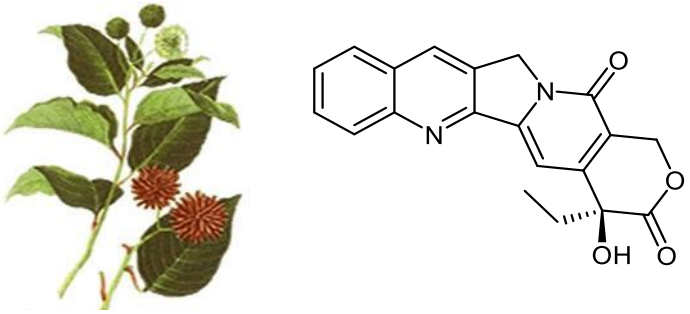


Figure 5
Camptotheca acuminate and camptothecin

Besides the major limitation of camptothecins is the instability at physiological pH. They are inactivated within minutes by lactone E ring opening. (Figure 6a). Two approaches have been taken to overcome this problem: addition of a methylene group in the E ring whit the synthesis of homocamptothecins, as Diflomotecan and conversion of the E ring to a five-membered ring. The first approach limits E ring opening but, once this happens, they become irreversibly. In the second approach, conversion of the E ring to a five-membered ring completely stabilizes the drug. The complete stabilization of the E-ring has been successfully achieved with the removal of the lactone. The α-keto derivatives, as S39625.51, are highly potent synthetic compounds against Topo I.[85] (Figure 6b)

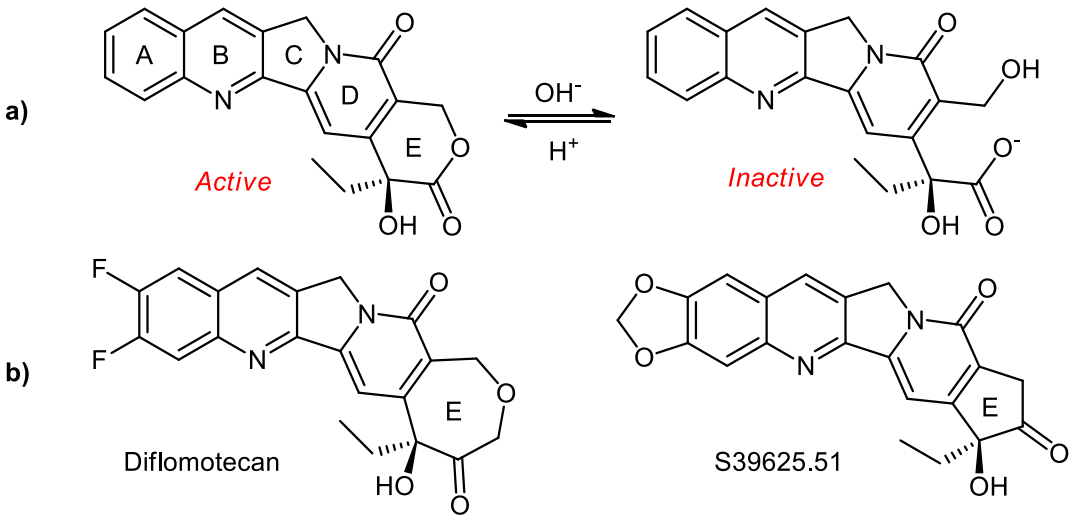


Figure 6

a) E-ring lactone opening; b) synthetic approach to overcome the E-ring opening

The other drawback in the use of camptothecins is their low solubility in water. After the discovery that Topo I is the cellular target of camptothecin, the water-soluble derivatives of camptothecin, Topotecan and Irinotecan, were successfully developed. Unlike the first, Irinotecan is a prodrug: the bis-piperidine residue is removed in liver by carboxylesterase.[89] (Figure 7)

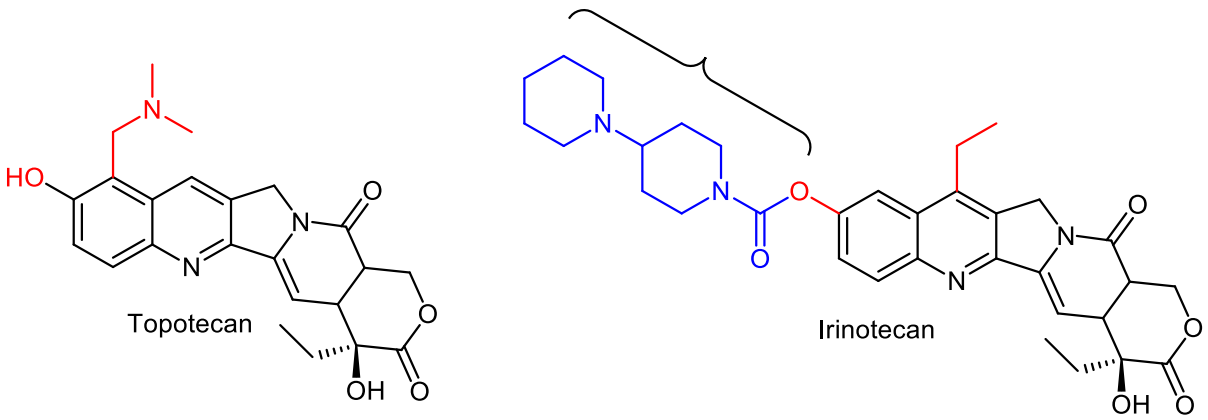


Figure 7

Topotecan and Irinotecan

3.4 Noncamptothecin Topo I Inhibitors

Since camptothecins have several limitations in therapeutic employ (instability and low solubility, as said above, but also resistance and severe side-effects), noncamptothecin Topo I inhibitors have been developed in the last years. Three important chemical families are indenoisoquinolines[90] and indolocarbazoles[91] and phenantridines.[92] (Figure 8)

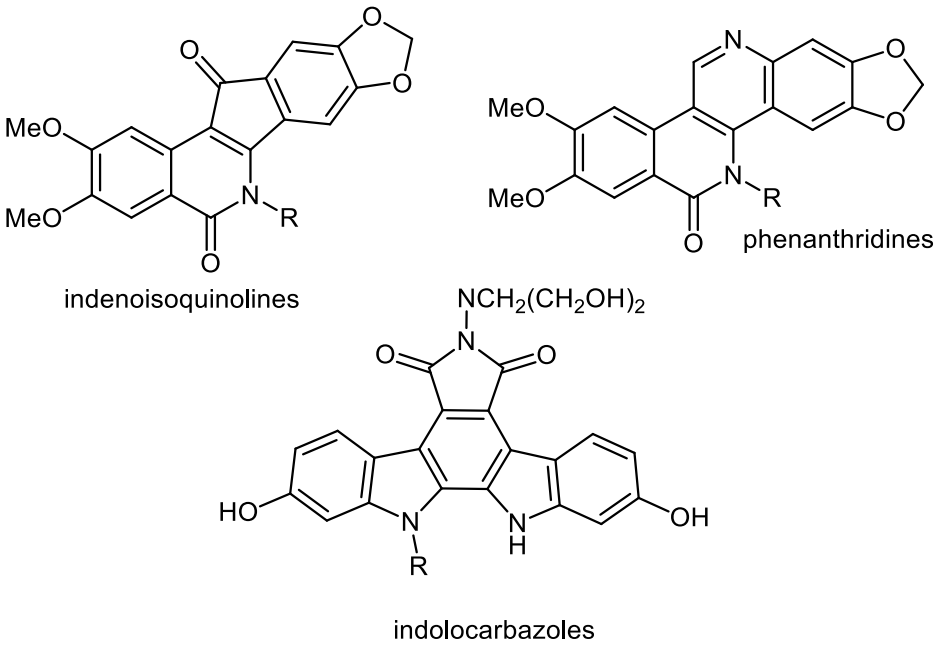


Figure 8
Noncamptothecin Topo I Inhibitors families

The indolocarbazoles were the first introduced but appear to hit other cellular targets besides Topo I. The indenoisoquinolines are chemically stable and their antiproliferative activity is similar to or greater than that of camptothecins (NCI60 cell lines). They selectively target Topo I, but they trap the enzyme at differential sites from camptothecins. They are not substrates for the ABC membrane transporters which suggests an ability to overcome resistance to camptothecins. The phenanthridine derivatives share many of the same advantages as the indenoisoquinolines, which is not surprising considering the chemical similarities between the two families.

3.5 Mechanism of action of Topo I inhibitors

From a mechanistic point of view, agents that inhibit topoisomerase I can be grouped into two classes: poisons and suppressors. Both inhibit the catalytic activity of the enzyme, nevertheless poisons stabilize a covalent intermediate complex, called cleavable complex, thus producing single-stranded DNA breakages. Otherwise, suppressors interfere with other steps of the catalytic

cycle without stabilize the cleavable complex, for example through a direct interaction with the enzyme or the formation of a molecular complex with DNA. The cytotoxicity of Topo I inhibitors is due to the trapping of Topo I rather than a real inhibition of catalytic activity, thus camptothecins are defined as Topo I poison. As said above the Topo I acts through cutting of a single DNA strand thus allowing a controlled rotation of the DNA-Topo I complex around the unbroken strand.

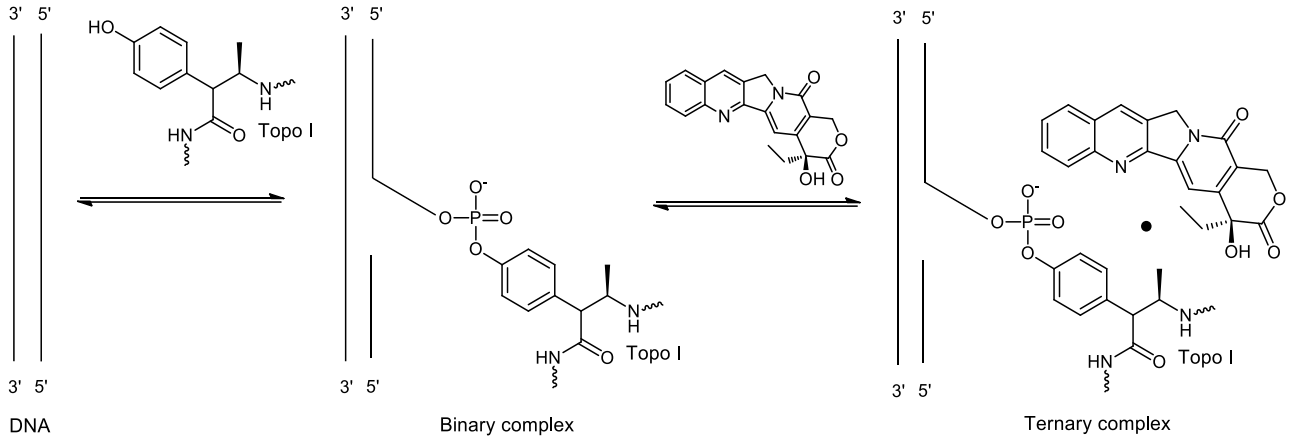
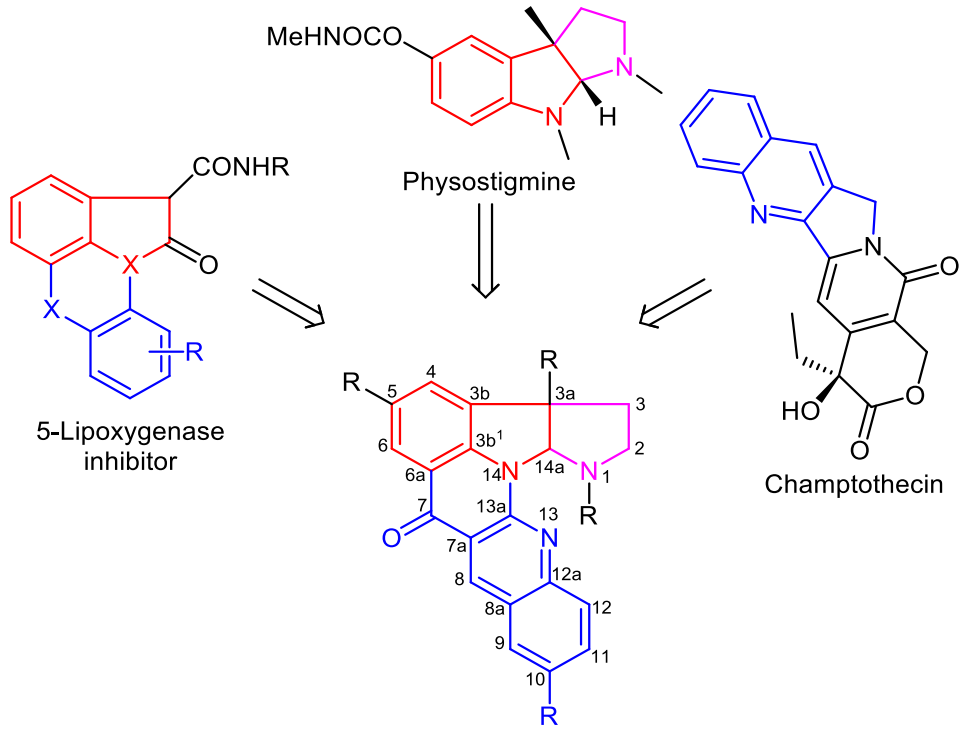


Figure 9
Ternary complex formation

The early interaction between Topo I and DNA leads to the formation of a complex binary complex. The camptothecins show affinity for the binary complex rather than either Topo I or DNA alone. The interaction of the drug with the binary complex generate the ternary complex. (Figure 9) The stabilization of the cleavage ternary complex is the result of specific inhibition of the religation, the most critical step in the catalytic cycle. The ternary complex is potentially reversible and non lethal, but the collision of this complex with the replication fork leads the cell apoptosis. The ternary complex is stabilized by an array of hydrogen bonding and hydrophobic interactions between the drug and both the enzyme and the DNA.[85,88,**Errore. Il segnalibro non è definito.**]

3.6 Scaffold, design and retrosynthetic pathway

Our efforts were addressed to realize a new heteropolycyclic scaffold, having Topo I as biological target. The general structure has been designed considering some structural analogies among the 5-lipooxygenase inhibitors, physostigmine derivatives and camptothecins.[84] (Scheme 41)

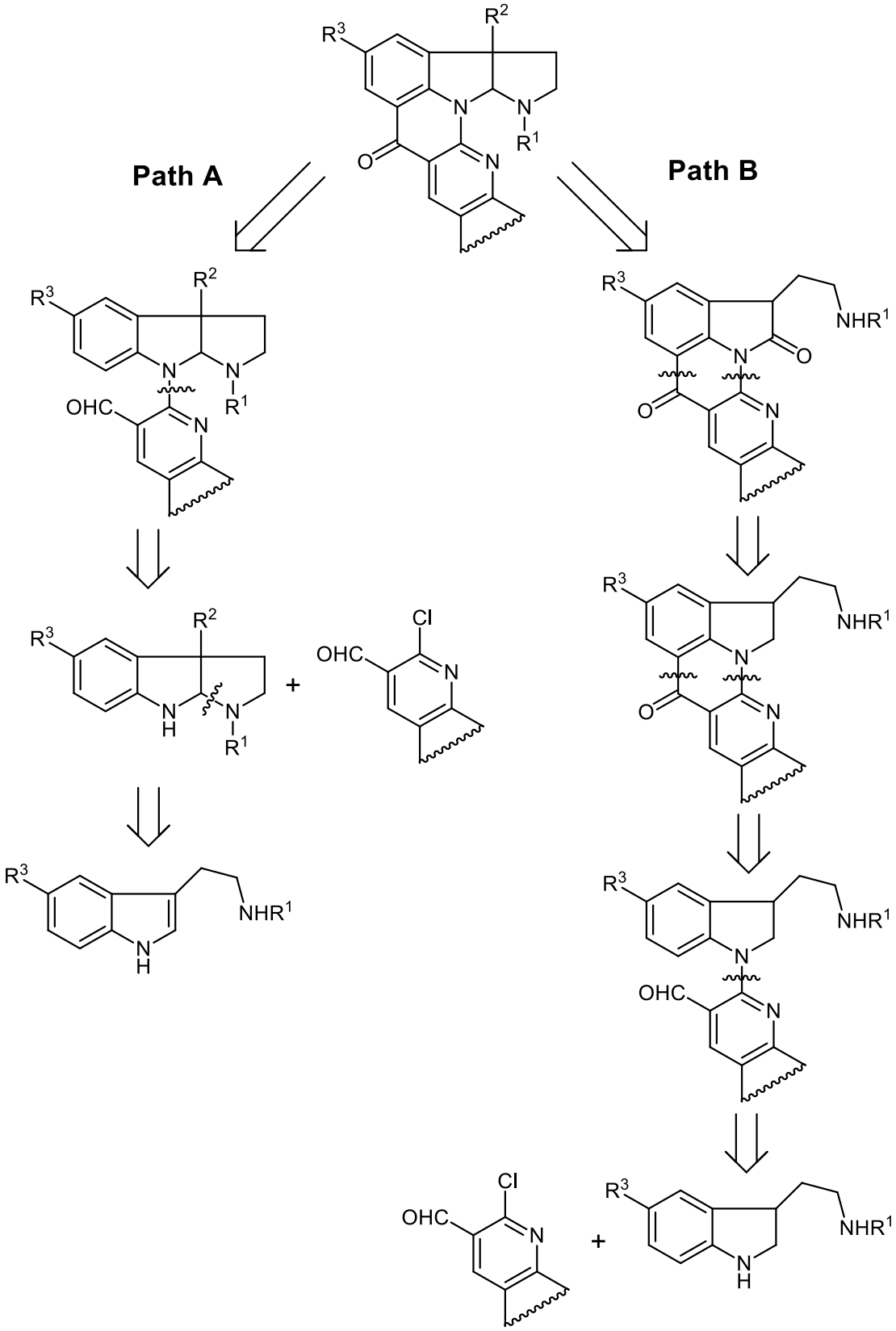


Scheme 41
Scaffold design

3.7 Scaffold synthesis

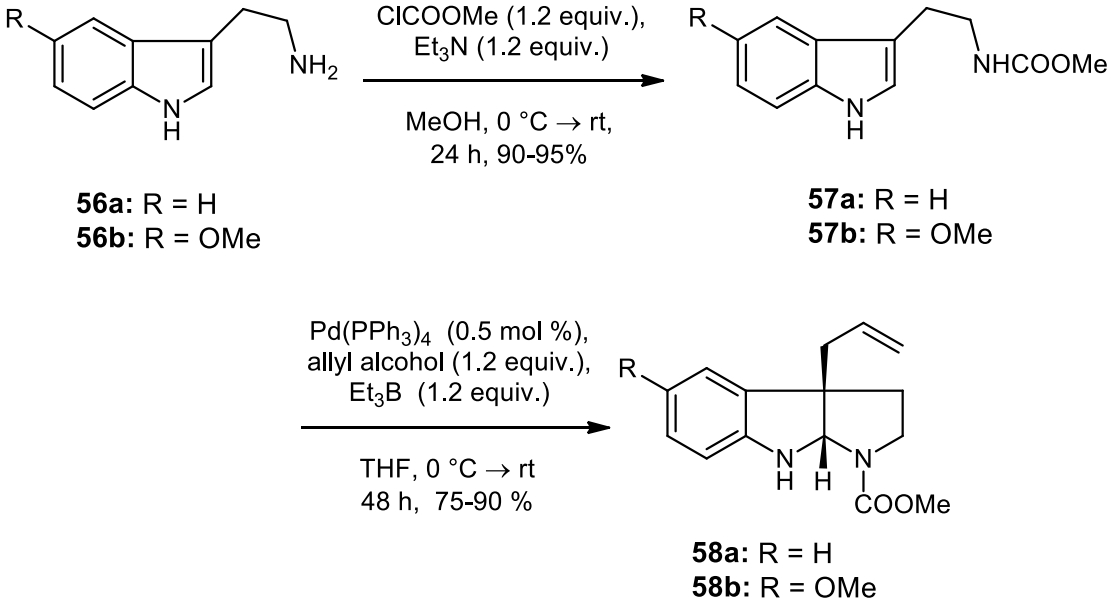
Two possible retrosynthetic pathways were initially identified to obtain the scaffold: path A, starting from triptamine and path B starting from 3-substituted indoline, in both cases followed as a key steps by a sequence of *N*-arylation/aromatic acylation. The minor steps prompted us to follow path A. (Scheme 38)

Starting from substituted tryptamines (**56**), the first step provided the formation of the tricyclic tetrahydropyrrolo[2,3-*b*]indoles (**58**) through the intramolecular reaction of the carbamates (**57**) under the catalysis of Pd-complex/Lewis acid ($Pd(PPh_3)4/Et_3B$) in THF as solvent at r.t.[93] The alkylative amination step was performed in the presence of allyl alcohol as electrophile resulting the concomitant insertion of the allyl substituent in position 3a. Both Pd-complex and Et_3B Lewis acid were necessary to obtain allylation. The intramolecular amination was stereoselective giving only the *cis* isomer in the junction of the B and C rings, as stated by ^1H NMR NOESY experiments (Scheme 39).



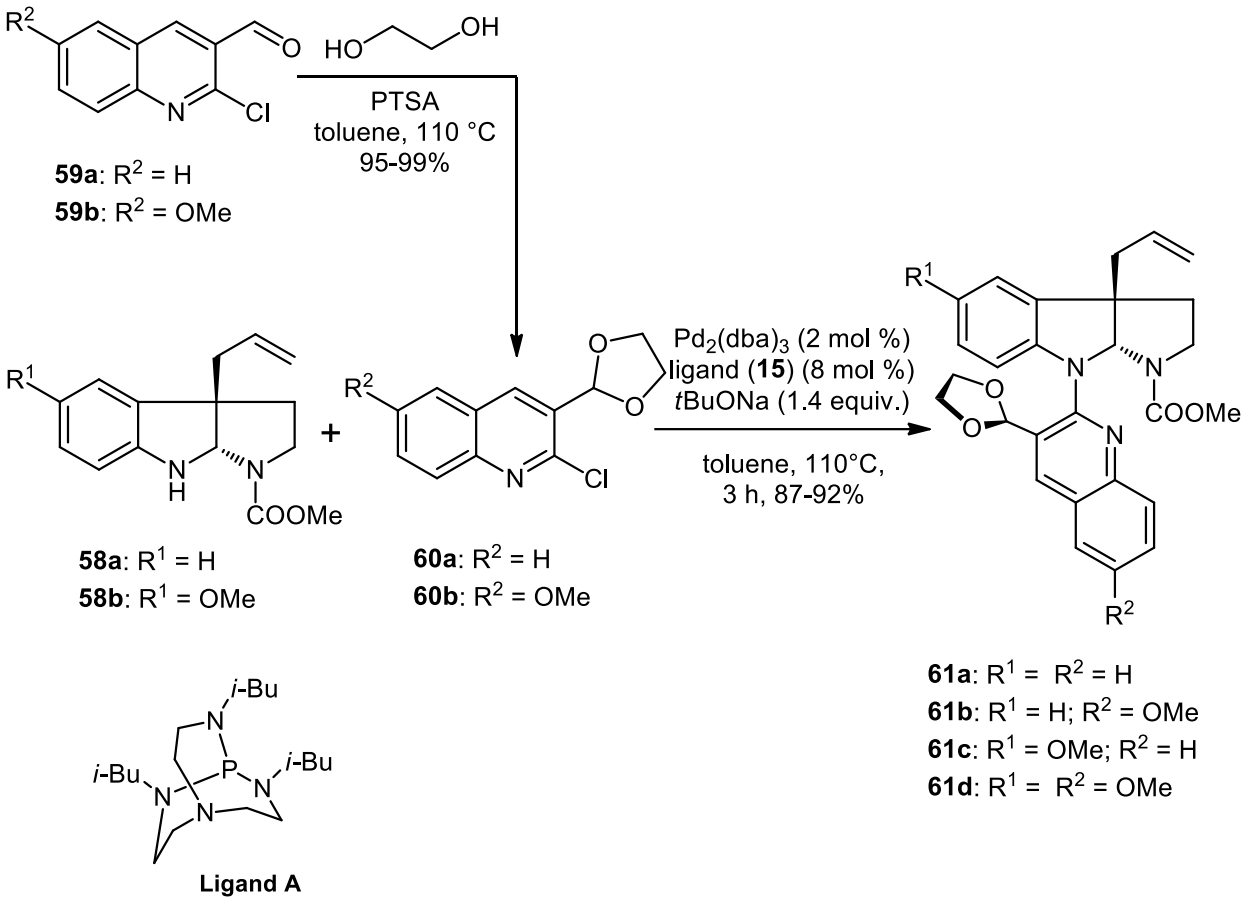
Scheme 38
Retrosynthetic pathway

The tricyclic systems (**58**) were in all the cases obtained as enantiomers mixture. Attempts to separate the isomers as diastereoisomers by using chiral carbamate derivatives of the triptamine (S)-(-)-2-methylbutyl carbamate, (1S)-(+)-menthyl carbamate, (1R)-(-)-myrtenol carbamate) gave unsatisfactory results or failed in the cyclization step.



Scheme 39
Synthesis of tetrahydropyrrolo[2,3-b]indoles

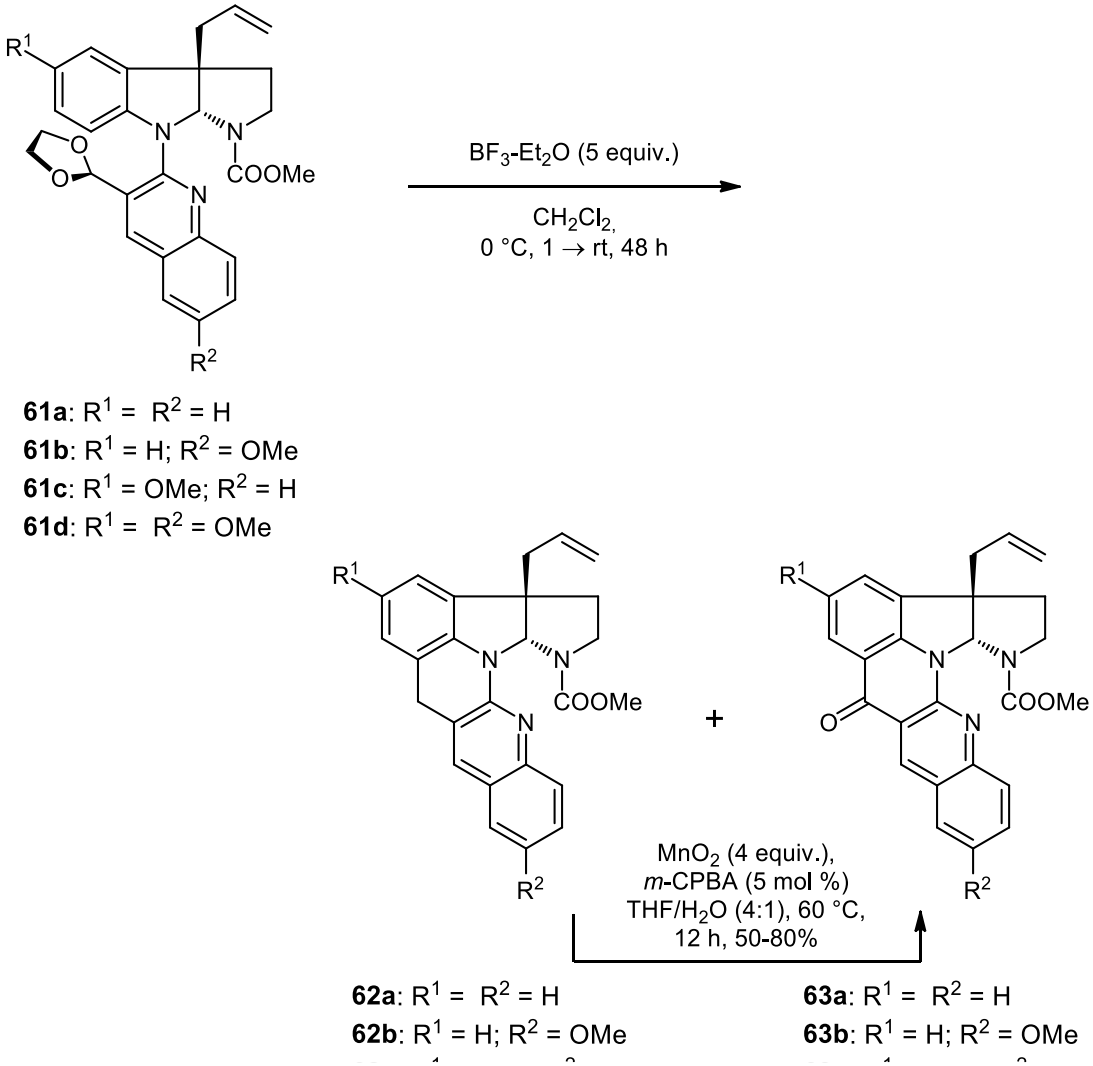
The subsequent step consist in the substitution of the indolic nitrogen with an opportune aryl halide, the 2-chloroquinoline-3-carbaldehydes (**59**). No result was obtained attempting the SNAr reaction using LDA. Thus a Pd-catalyzed Buchwald-Hartwig *N*-arylation has been attempted, using the conditions reported in literature. At first we used palladium acetate as catalyst, BINAP as ligands and Cs_2CO_3 base in toluene at 110 °C. The reaction condition was after optimized as reported in Table 1. The best conditions employed tris(dibenzylideneacetone)dipalladium(0) as pre-catalyst, triisobutylphosphatrane (**A**) as ligand and sodium *tert*-butoxide as base in toluene at 110°C. The reaction required the protection of the formyl substituent as acetal (**60**) (Scheme 40, table 11) The subsequent step was the intramolecular Friedel-Crafts reaction of the intermediate **61** using the BF_3-Et_2O as Lewis acid and carrying out the reaction on the protected formyl group directly. The polyheterocyclic alkylated derivative was obtained as a mixture of two products **62** and **63**, one of which was the oxidized form in position 7. (Scheme 41) This is due to the particular mechanism of the reaction, which occurs through an oxido-reductive path.[94] (Scheme 42) The treatment of the mixture with oxidants manganese(IV) oxide and *m*-CPBA resulted in the complete transformation of compound **62** in **63**.



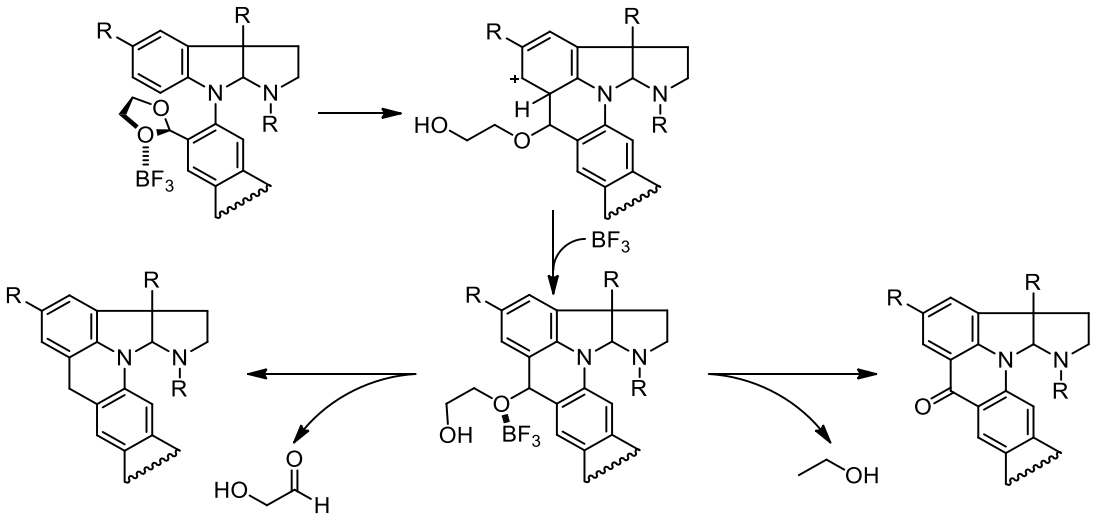
Scheme 40
Buchwald-Hartwig reaction

Table 11
Buchwald-Hartwig reaction optimization

	Catalyst	Ligand	Base	T °C	Time (h)	Yield (%)
1	$Pd(OAc)_2$ (2 mol %)	BINAP (2 mol %)	Cs_2CO_3	110	24	10
2	$Pd(OAc)_2$ (2 mol %)	dppf (2 mol %)	*t*BuOK	110	24	5
3	$Pd(OAc)_2$ (2 mol %)	Ligand **A** (4 mo l%)	Cs_2CO_3	110	24	25
4	$Pd_2(dba)_3$ (5 mol %)	BINAP (10 mol %)	*t*BuONa	110	24	60
5	$Pd_2(dba)_3$ (5 mol %)	BINAP (10 mol %)	Cs_2CO_3	100	24	70
6	$Pd_2(dba)_3$ (1 mol %)	Ligand **A** (4 mol %)	*t*BuONa	100	24	75
7	$Pd_2(dba)_3$ (0.5 mo l%)	Ligand **A** (2 mol %)	K_2CO_3	100	24	75
8	$Pd_2(dba)_3$ (2 mol %)	Ligand **A** (8 mol %)	*t*BuONa	110	3	85



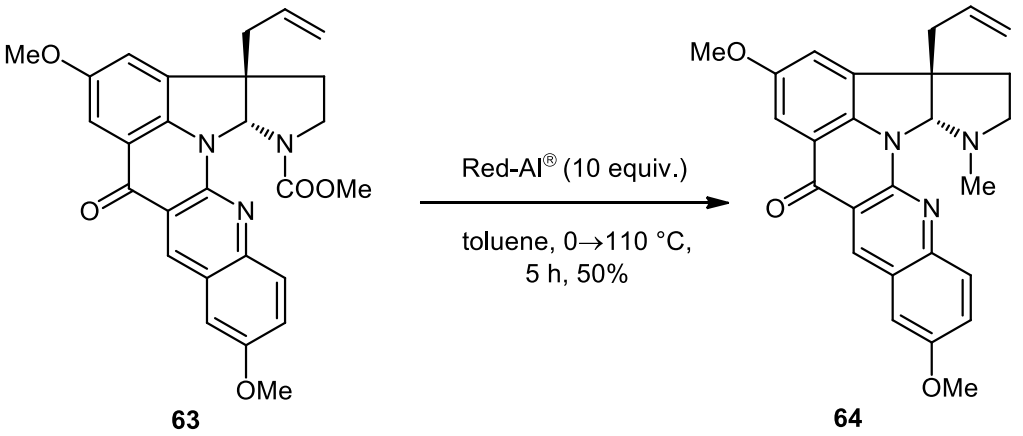
Scheme 41
Friedel-Crafts intramolecular reaction



Scheme 42
Proposed mechanism for Friedel-Crafts intramolecular reaction

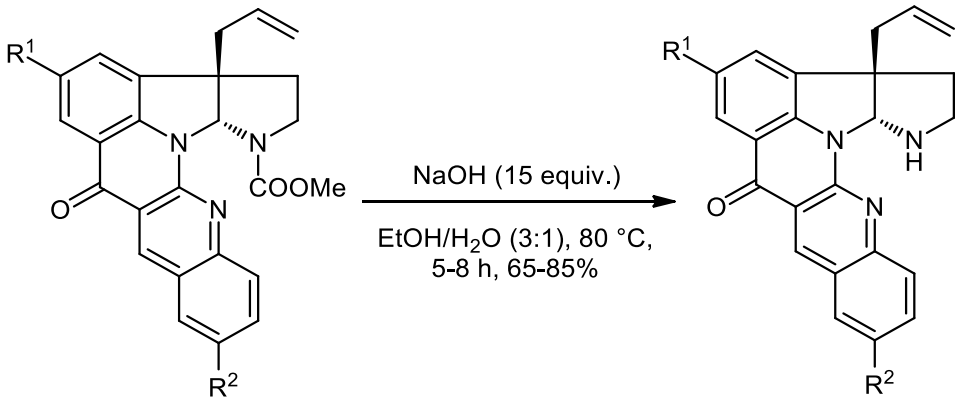
3.8 Functionalization of the scaffold

The insertion of different substituents on the polycyclic scaffold has been realized with the aim to evaluate changes in the biological activity, in fact the presence of polar groups may have strong interaction with the enzyme. The functionalization in position 1 may be obtained from **63** by reduction of the carbomethoxy group using sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) in toluene to give compound **64**. (Scheme 43) or by basic hydrolysis obtaining derivatives **65a-d**. (Scheme 44)



63 **64**

Scheme 43
Reduction of carbomethoxy group in position 1

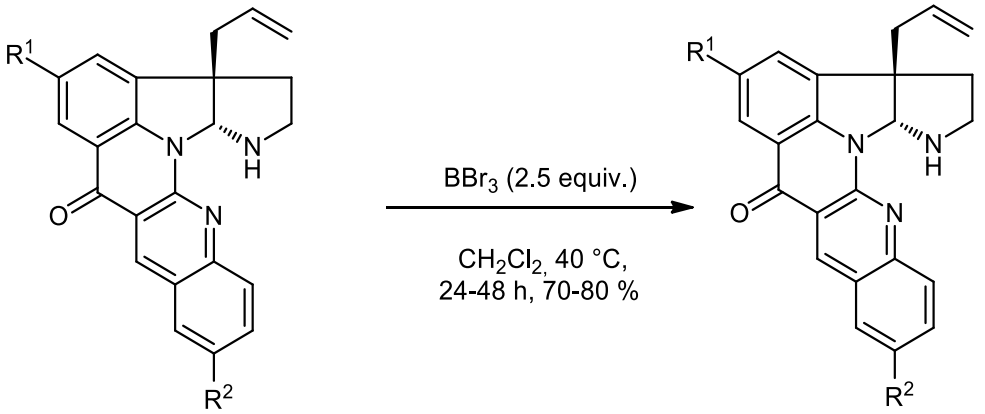


63a: R^1 = R^2 = H
63b: R^1 = H; R^2 = OMe
63c: R^1 = OMe; R^2 = H
63d: R^1 = R^2 = OMe

65a: R^1 = R^2 = H
65b: R^1 = H; R^2 = OMe
65c: R^1 = OMe; R^2 = H
65d: R^1 = R^2 = OMe

Scheme 44
Hydrolysis of carbomethoxy group in position 1

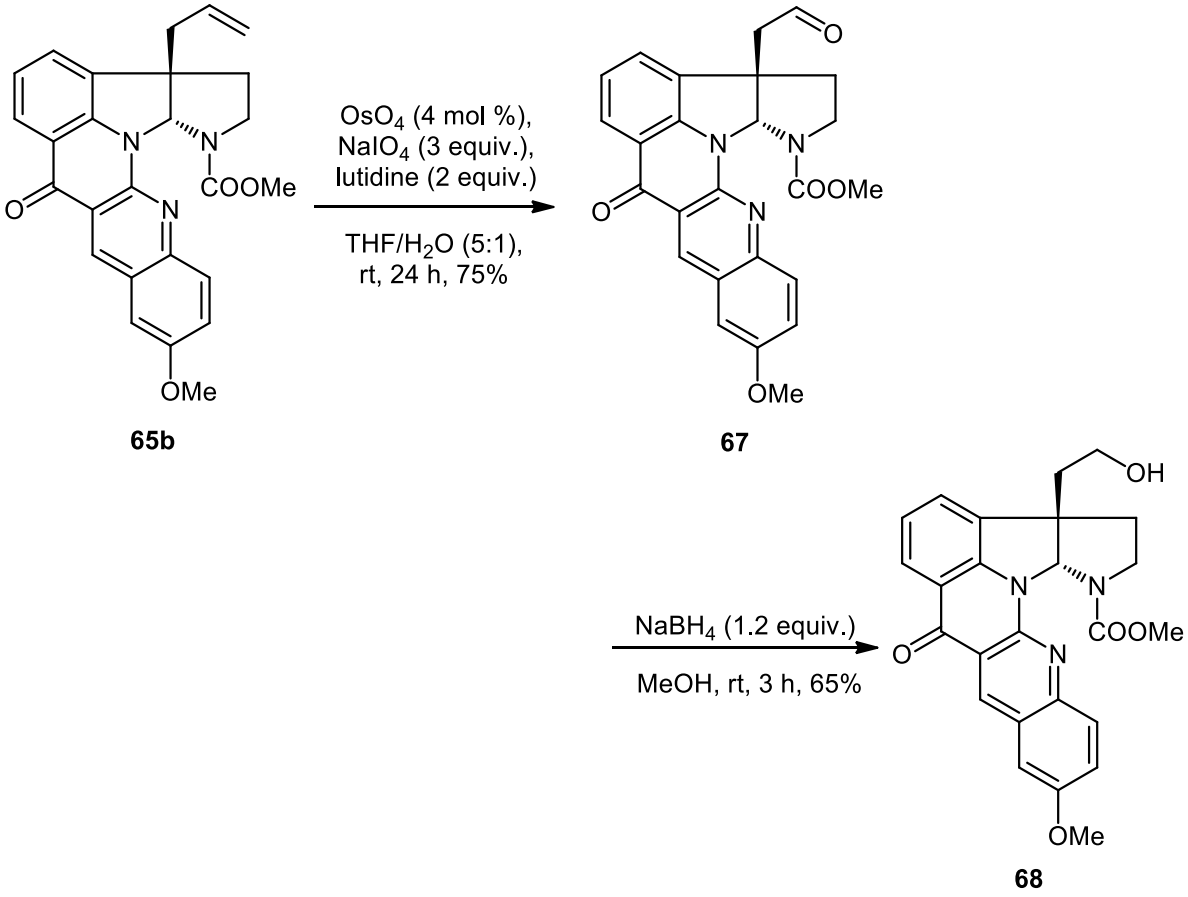
The methoxy substituents may be present in positions 5 and 10, the reaction with BBr_3 in dichloromethane of the intermediates **65b** and **65d** resulted in the formation of the phenolic derivatives **66a-b**. (Scheme 45)



65b: R^1 = H; R^2 = OMe
65d: R^1 = R^2 = OMe

66a: R^1 = H; R^2 = OH
66b: R^1 = R^2 = OH

Scheme 45
Hydrolysis of methoxy substituents



65b

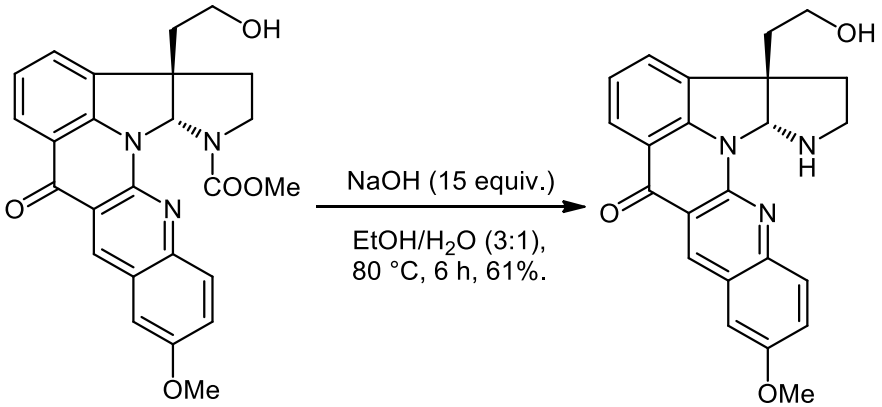
67

68

Scheme 46
Modification of allyl residue in 3a position

The 2-hydroxyethyl substituent selected as polar branch, was formed in position 3a from the allyl substituent through the sequence oxidation and reduction. The first attempt using ozone failed, probably due to instability of the tetrahydropyrroloindole portion under ozonolysis conditions. Thus, osmium tetroxide and sodium periodate was employed to obtain the aldehyde derivative **67**, followed by the reduction with sodium borohydride achieving the hydroxyethyl residue **68**. (Scheme 46)

The hydrolysis of the compound **68** carried out in basic conditions afforded in satisfactory yield the free amine derivative **69**. (Scheme 47)

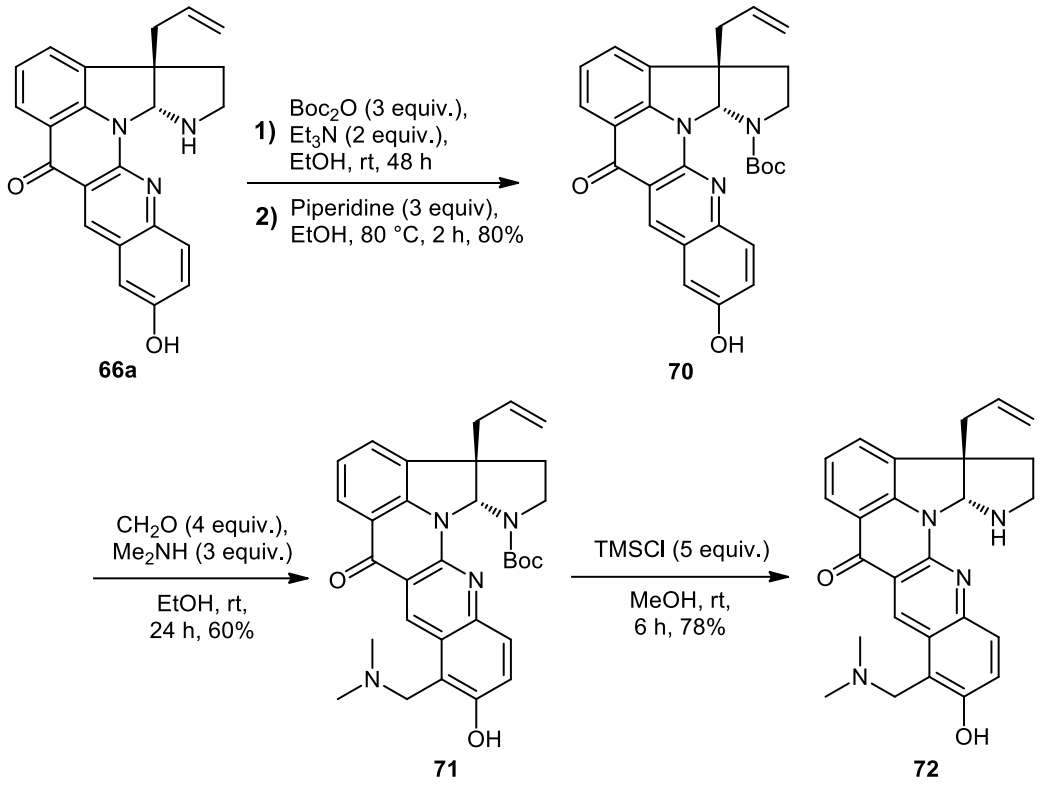


68 **69**

Scheme 47
Hydrolysis of carbomethoxy group in position 1

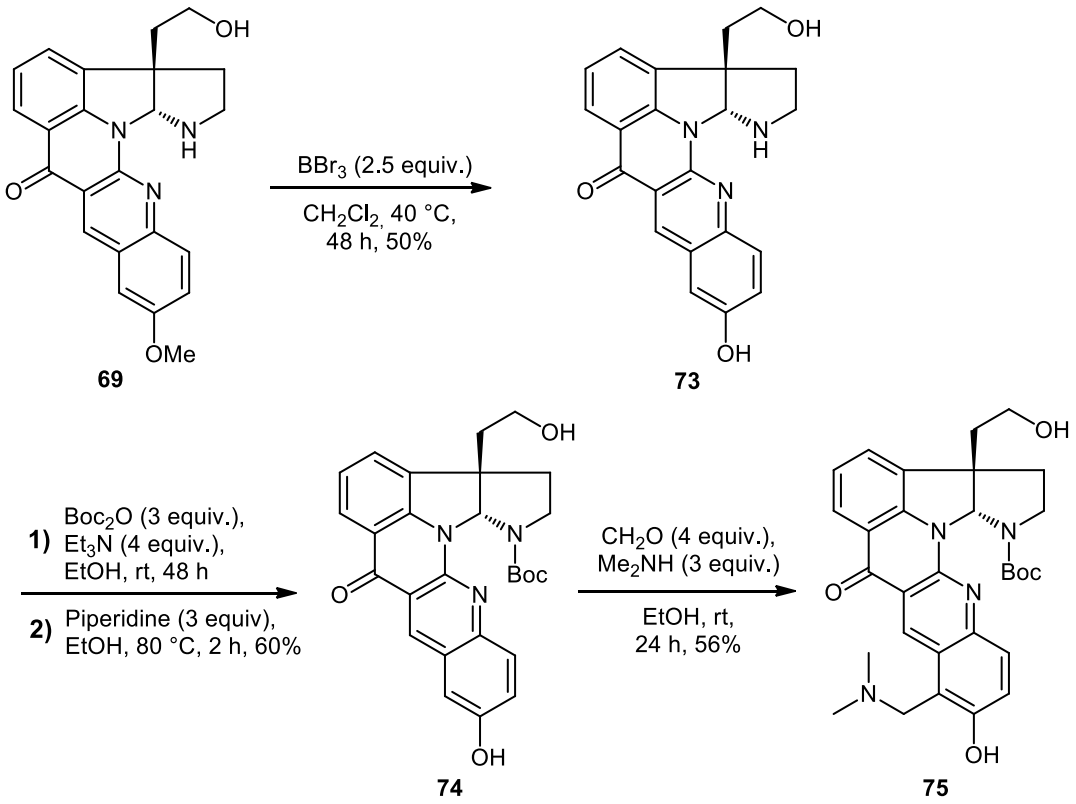
The projected decoration of the scaffold involved the insertion of a dimethylaminomethyl group, present also on the TPT, synthetic derivative of CPT. The product was obtained through a Mannich reaction but to have the product it is required the presence of both hydroxy group in position 10 and the protection on the amine in position 1. The Mannich reaction was carried out on compound **70**, protected with *tert*-butoxycarbonyl group in position 1, obtained from **66a** with di-*tert*-butyl dicarbonate. The Mannich product was achieved using aq. formaldehyde and dimethylamine, in ethanol at room temperature. The *N*-protecting group was at last removed using chlorotrimethylsilane, giving the compound **72**. (Scheme 48)

The same synthetic pathway was repeated starting from the compound **69**. In this case the first step was the hydrolysis of the methoxy group in position 10. The last step has to be also in this case the deprotection of the amine in position 1, but the compound **75** is unstable under the reaction conditions. Different deprotection procedures were tried, but in all case with unsatisfactory results. (Scheme 49)



Scheme 48

Insertion of dimethylaminomethyl group in position 9



Scheme 49

Insertion of dimethylaminomethyl group in position 9

This synthetic pathway allowed the synthesis various derivatives, diversified each other by the presence of different substituents in position 1, 3a, 5, 9 and 10 of the hexacyclic scaffold. (Figure 10, table 11)

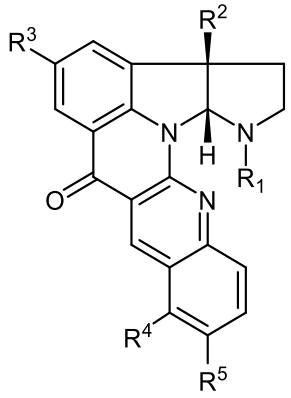


Figure 10
Different substituents on the hexacyclic scaffold

Table 11

	R¹	**R²**	**R³**	**R⁴**	**R⁵**
64	Me	Allyl	OMe	H	OMe
65a	H	Allyl	H	H	H
65b	H	Allyl	H	H	OMe
65c	H	Allyl	OMe	H	H
65d	H	Allyl	OMe	H	OMe
66a	H	Allyl	H	H	OH
66b	H	Allyl	OH	H	OH
69	H	$(CH_2)_2OH$	H	H	OMe
70	Boc	Allyl	H	H	OH
74	Boc	$(CH_2)_2OH$	H	H	OH
71	Boc	Allyl	H	CH_2NMe_2	OH
75	Boc	$(CH_2)_2OH$	H	CH_2NMe_2	OH
72	H	Allyl	H	CH_2NMe_2	OH

3.9 Biological evaluation: antiproliferative activity

The ability of new derivatives to inhibit cell growth was investigated by an in vitro assay on three human tumor cell lines, H460 (large cell lung carcinoma), MSTO-211H (human biphasic mesothelioma) and HeLa (cervix adenocarcinoma). The results, expressed as GI_{50} indicate for all tested derivatives a detectable antiproliferative activity, with values in the micromolar range. Among the new synthesized compounds, the most active is **69**, characterized by the 2-hydroxyethyl substituent in position 3a and a methoxy group in 10, which shows GI_{50} values in the low micromolar range in all considered cell lines. For **65b** and **66b**, GI_{50} values lower that 10 μM are obtained in two cell lines (H460 and MSTO-211H). For all other compounds the cytotoxicity is lower and indeed GI_{50} values ranging from 13.0 to 35.2 μM can be observed. All results, expressed as GI_{50} values, are shown in Table 2. The camptothecin was used as reference compound.

Table 12
Cell growth inhibition in the presence of tested compounds (CPT as reference compound)

	GI_{50}[a] (μM)		
	H-460	**MSTO-211H**	**HeLa**
64	› 50	34.2 ± 7.9	18.3 ± 1.2
65a	14.4 ± 0.9	13.0 ± 2.1	16.5 ± 1.0
65b	8.9 ± 1.4	7.8 ± 1.0	14.8 ± 1.5
65c	32.2 ± 4.7	14.4 ± 3.3	30.7 ± 4.8
65d	18.6 ± 0.3	13.5 ± 2.6	16.6 ± 3.8
66a	› 50	18.7 ± 0.6	19.0 ± 0.5
66b	4.8 ± 1.0	7.0 ± 0.9	15.3 ± 0.8
69	0.85 ± 0.09	1.9 ± 0.3	1.4 ± 0.3
70	32.7 ± 0.8	24.1 ± 1.6	30.5 ± 1.8
74	26.8 ± 2.0	13.7 ± 0.9	13.0 ± 2.2
71	17.8 ± 1.7	22.8 ± 2.4	35.2 ± 1.6
75	16.4 ± 1.4	20.0 ± 1.6	13.0 ± 1.0
75	26.2 ± 1.2	29.1 ± 1.9	29.3 ± 5.6
CPT	0.0020 ± 0.0002	0.0021 ± 0.0001	0.0054 ± 0.0002

[a] Mean values ±SD of at least three independent experiments are reported

On the basis of these data, some preliminary structure-activity relationships could be drawn. In particular, the presence of the 2-hydroxyethyl chain in **69** seems to be determinant for the biological activity. Indeed, the presence of the allyl substituent (**65b**) induces a significant decrease in cytotoxicity, especially in H460 and HeLa cells where an increase of about of one order of magnitude can be observed. Nevertheless, the effectiveness of the 2-hydroxyethyl is considerably dampened by the presence of Boc in position 1 and hydroxyl in position 10 and/or a dimethylaminomethyl side chain in position 9 as suggested by the comparison between **69** and **74** or **71**. It is noteworthy that the presence of a substituent in position 1 (methyl or Boc) appears detrimental for the occurrence of the cytotoxic capacity in all compounds (**64**, **70**, **74**, **71** and **75**) and indeed they show high GI_{50} values.

3.10 Biological evaluation: interaction with DNA

The interesting antiproliferative effect exerted by the most biologically active compound **69** and in particular, the presence of a wide planar heteropolycyclic scaffold, suggested an investigation on the ability to form a molecular complex with DNA through an intercalative mode of binding. For this purpose flow linear dichroism (LD) experiments were performed with DNA solutions in the absence and in the presence of **69** and the corresponding allyl derivative **65b**. The obtained LD spectra are shown in Figure 11, the UV-vis absorbance spectra of the test compounds (A) are also reported as reference.

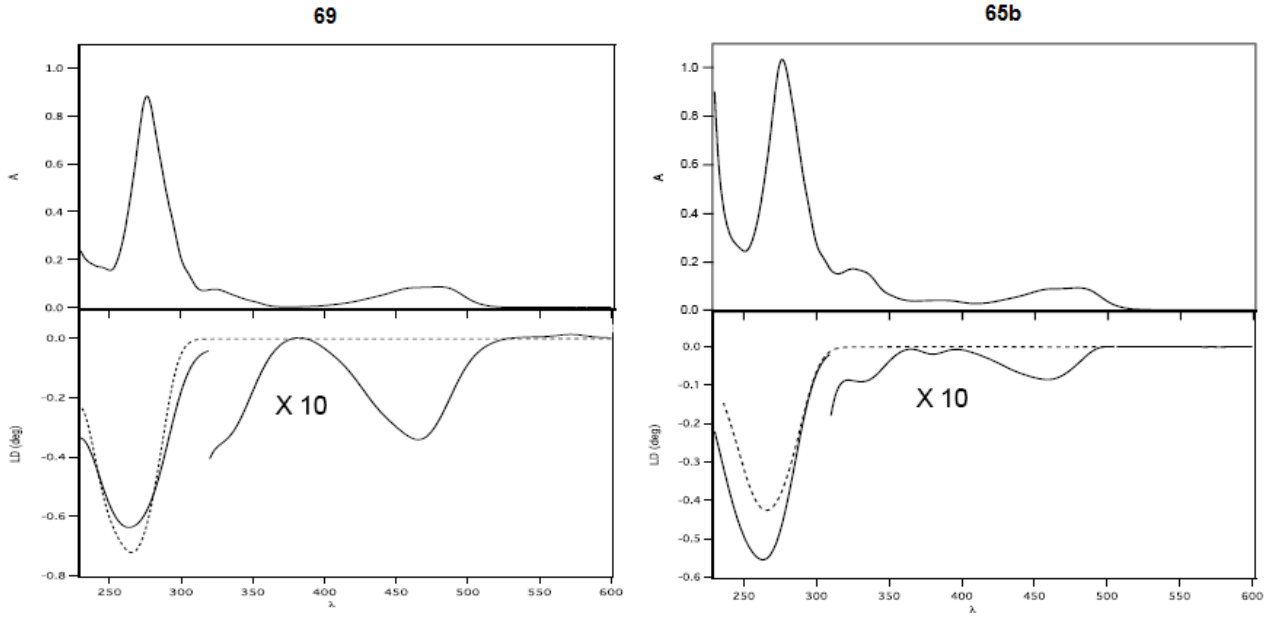


Figure 11
Absorbance spectra (A) for compounds **69** and **65b** at 1.2 X 10^{-5} M. Linear flow dichroism spectra (LD) for compounds **69** and **65b** at different [compound]/[DNA] ratios: dotted line ¼ 0; continuous line ¼ 0.08. [DNA] ¼ 1.9 X 10^{-3} M

Both LD spectra show an evident negative signal at 260 nm, typical of the macromolecule and due to the strong absorption of DNA base pairs at this wavelength. Moreover, interestingly, in the presence of the considered derivative (continuous lines) a further dichroic signal appears at higher wavelengths (380e520 nm). Because no contribution from the macromolecule exists in this latter spectral region, the occurrence of the signal has to be attributed to the added chromophore, which, otherwise, absorbs at these wavelengths (see absorption spectra, A). Since small molecules, such as **69** and **65b**, cannot become oriented in the flow field, the occurrence of the LD signal has to be attributed to the formation of a molecular complex with DNA that permit them the orientation. Moreover, the negative sign of the LD signal, as the strong band at 260 nm, indicate a parallel orientation of the planar hexacyclic system of new derivatives with respect to the plane of the purine and pyrimidine base pairs. This means that **69** and **65b** form a complex with DNA via an intercalative mode of binding.

3.11 Biological evaluation: effect on topoisomerase

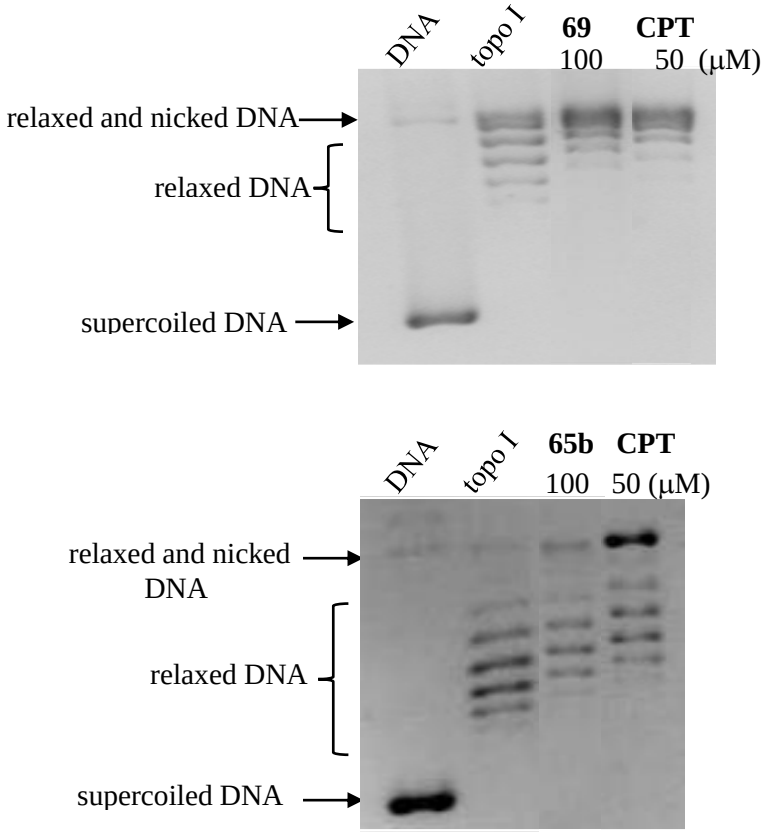


Figure 12
Effect of compounds **69** and **65b** on relaxation of supercoiled pBR322 DNA mediated by topo I

At this point the ability of the most active derivative **69** and **65b** to affect the catalytic activity of Topo I were investigated. Figure 12 shows the effect of the test compounds on the relaxation of supercoiled DNA mediated by Topo I. The enzyme removes supercoils from pBR322 plasmid

DNA (lane DNA) giving rise to a population of relaxed DNA topoisomers that migrates differently depending on their linking number (lane Topo I). The results shown in figure 12 indicate that both **69** and **65b** affects the relaxation activity of the enzyme and indeed they induce both a decrease in the number of topoisomers and an increase in the intensity of the band corresponding to the relaxed plus nicked DNA. This behavior, similar to that observed for CPT, a well-known topoisomerase I poison, demonstrate the capacity of test compounds to interfere with the catalytic activity, but does not allow to establish if it is due to a poisoning effect.

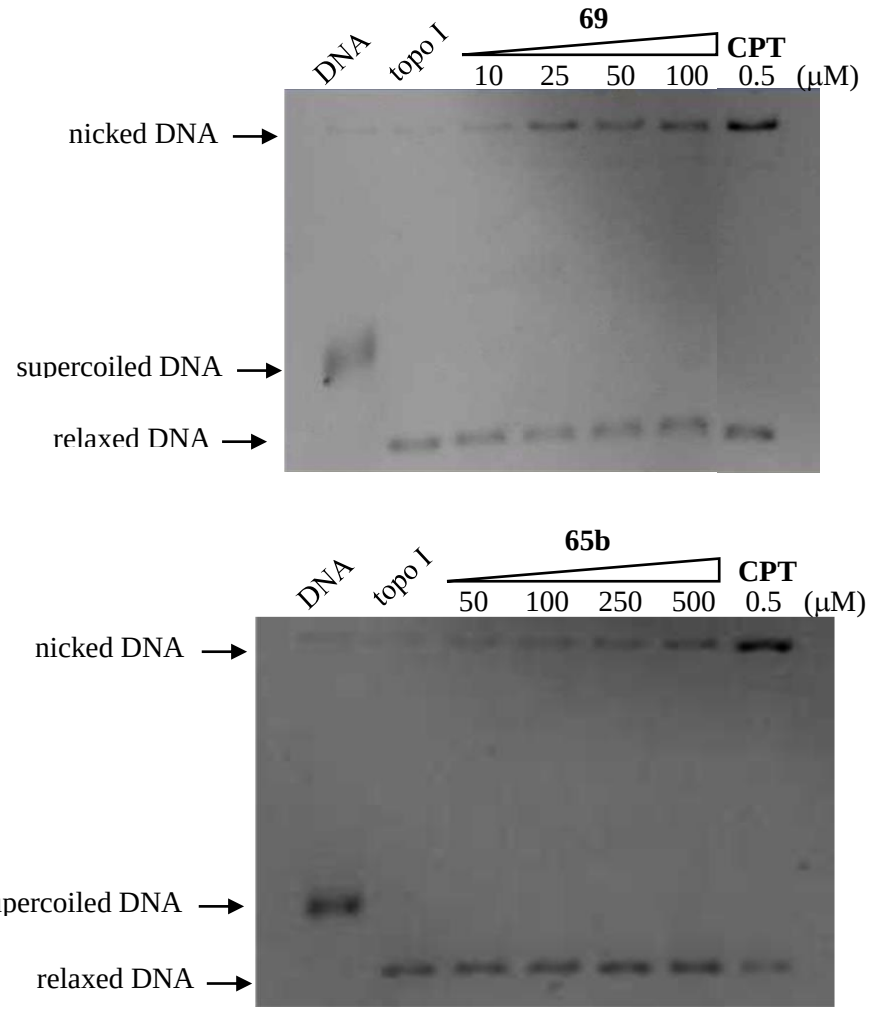


Figure 13
Effect of compounds **24** and **20b** on the stabilization of covalent-DNA Topo I complex

Therefore, to discriminate between a specific poisoning action and other possible nonspecific effects, due for example to DNA intercalation, the experiments were performed with agarose gel containing ethidium bromide and the results are showed in figure 13, in comparison with champtothecin. Indeed, in these latter experimental conditions the DNA species moving toward the anode become progressively saturated by the intercalative effect of ethidium and this influences significantly their rate of migration. Otherwise, the electrophoretic mobility of the band

corresponding to the nicked DNA, resulting from the stabilization of the cleavable complex, is unaffected by the presence of ethidium bromide and thus can be easily detected.

The results obtained by incubating DNA and enzyme in the presence of increasing concentrations (from 10 to 100 μM) of **69** indicate for this compound the ability to induce the formation of the cleavable complex as from 25 μM. For the analogue **65b** a lower poisoning effect emerges from the experiments reported in Figure 13. Indeed, for this latter derivative, a concentration of 500 μM has to be used to detect a significant increase in the band corresponding to the nicked DNA. For the well-known poison champtothecin, as expected, a notable amount of nicked DNA is formed already at 0.5 μM concentration. It is interestingly to note that these results are in agreement with cytotoxicity data reported in Table 12. Indeed, **69** demonstrates an antiproliferative effect clearly higher with respect to **65b**, with GI_{50} values from 4 to 11 times lower, depending on the cell line taken into consideration. As regard CPT, its cytotoxicity is notably higher with respect to both new derivatives and indeed

GI_{50} even in the nanomolar range are obtained (Table 12). Thus, it can be concluded that a correlation can be drawn between the poisoning effect and the antiproliferative ability.

3.12 Analysis of the binding mode

The binding mode of the most interesting compounds **69** and **65b** was analyzed by docking calculations and compared to that of the reference crystallographic compound topotecan (Figure 14). The docked conformation of reference compound topotecan is in excellent accord with the crystallographic structure (Figure 15), providing support to the following discussion. Moreover, the binding energies computed for topotecan, **69** and **65b** are -129.4, -128.4 and -128.2 kcal/mol, respectively, thus the docking software correctly ranks the three compounds.

The binding mode predicted for **69** and **65b** (Figure 12, panels A, C and D) shows that the tetracyclic planar moiety is in both cases well packed in-between the two DNA bases pairs made by deoxycytidine 599 and deoxyguanosine 576 (corresponding to the 50 terminus of the cleaved DNA strand) and by deoxyadenosine 600 and thymidine 575, which is covalently bound to Tyr523 through its 30 phosphate group.

The benzonaphthyridinone group of **69** and **65b** (rings A-C) are partially overlaid with the pyrroloquinoline group of topotecan (rings A-C), with the scaffold of the former compounds being slightly shifted toward the a-helix formed by residues Thr518 Tyr523. This shift allows compounds **69** and **65b** to form a moderately strong H-bond involving the nitrogen atom of ring B and the guanidine group of Arg164 (N···H distance = 2.47 and 2.42 Å; N···HeN angle = 170.8 and 169.0 deg. for compounds **69** and **65b**, respectively). The difference in antiproliferative activity (Table

12) and in Topo I poisoning (Figures 12 and 13) observed for compounds **69** and **65b** are reasonably due to the substituent at C-3a. Indeed, the allyl chain of **65b** is not apparently involved in any interaction with either topoisomerase or DNA. Conversely, a rather strong H-bond is observed between the hydroxyethyl substituent and the acidic group of Asp333 (H···O=C distance = 1.65 Å; O-H···O=C angle = 175.5 deg.).

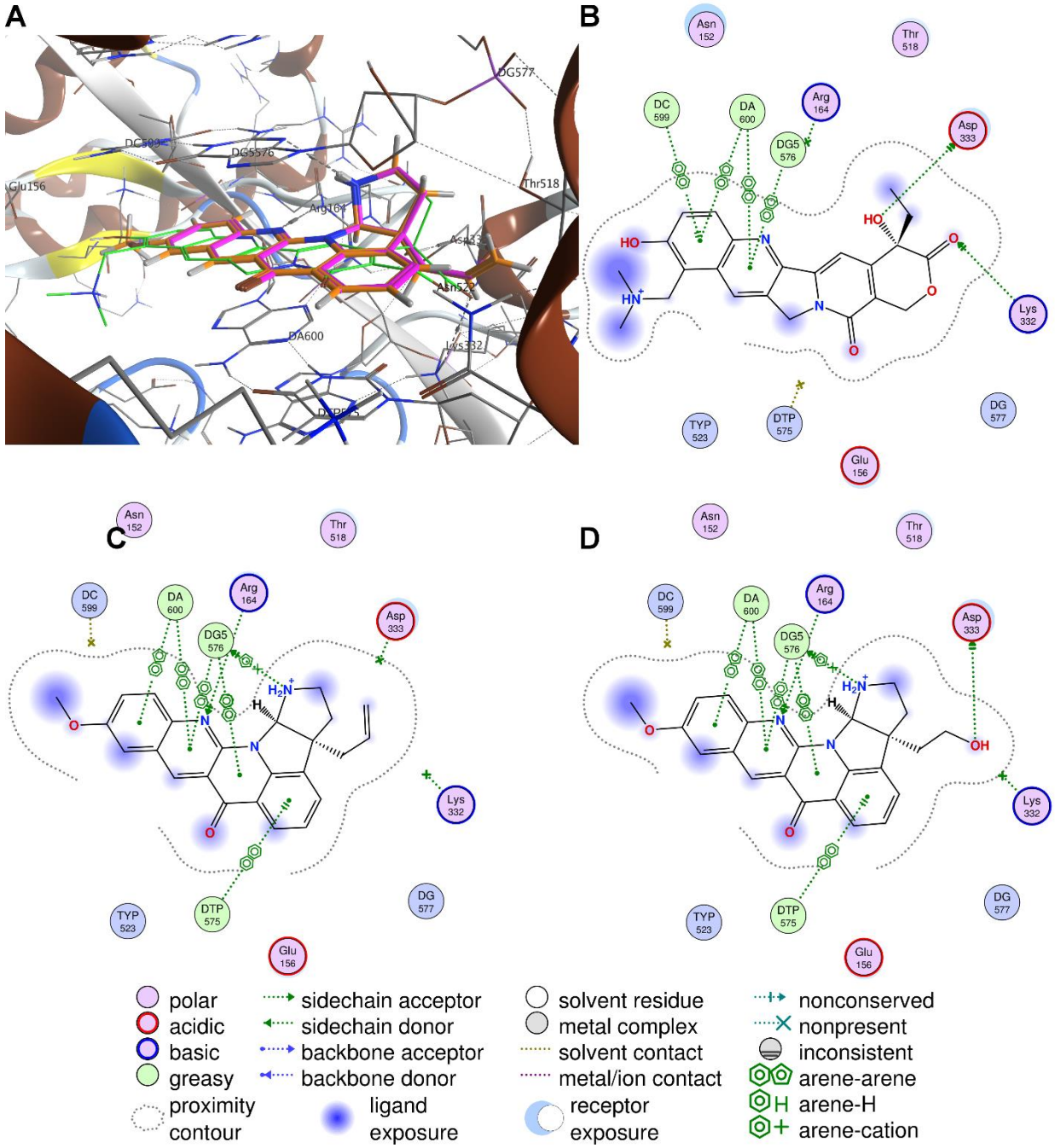


Figure 14

Panel A: Predicted binding mode for compounds **69** (carbon atoms coloured in magenta) and **65b** (carbon atoms coloured in orange). The crystallographic structure of topotecan (PDB code: 1K4T; carbon atoms coloured in green) is also reported as a reference. Panels B, C and D: diagram reporting all ligand interactions for topotecan and compounds **65b** and **69**, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

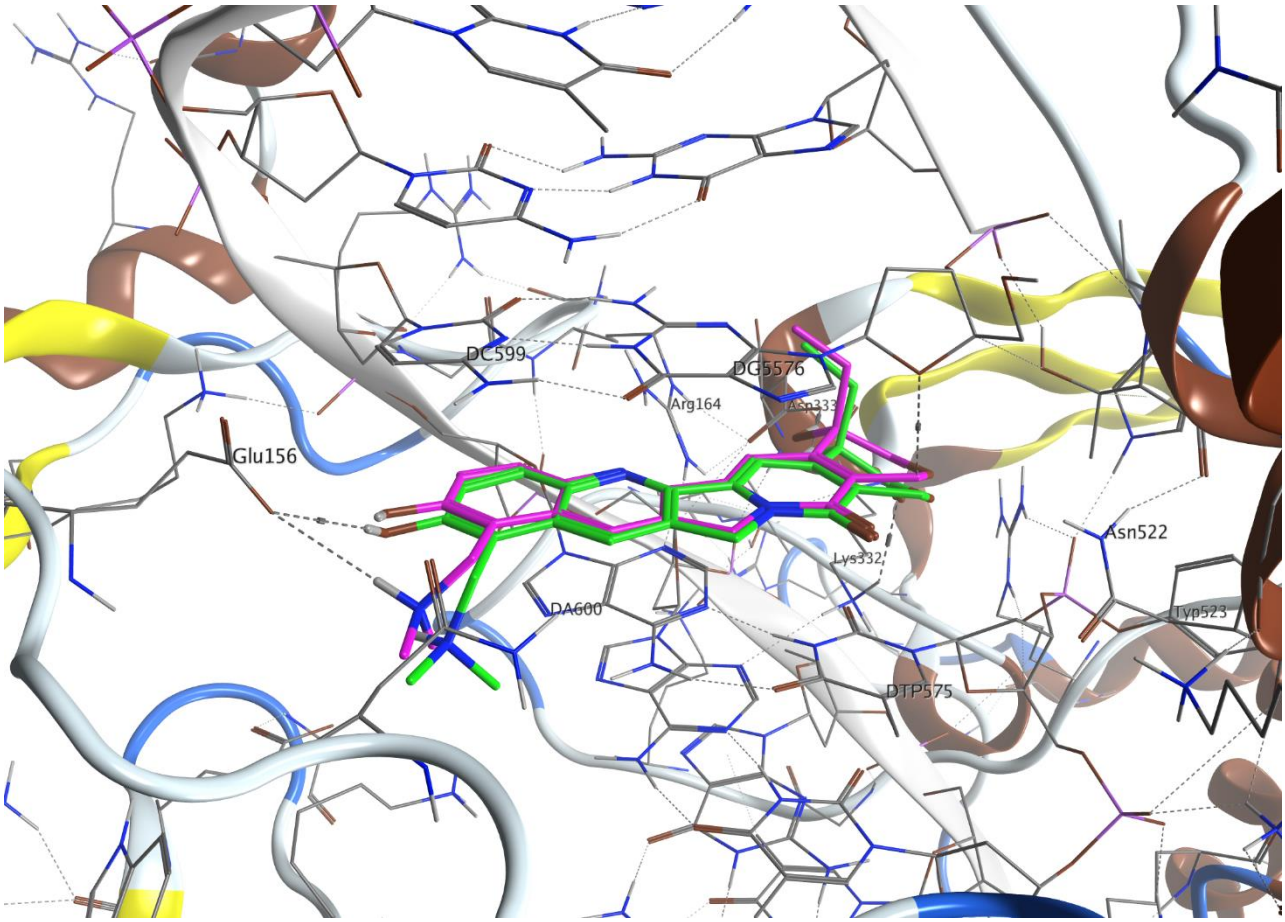


Figure 15
Comparison between the binding pose of topotecan obtained by docking (carbon atoms colored in magenta) and the crystallographic structure (1K4T.pdb, carbon atoms colored in green).

3.13 Synthesis of new oxazino[2,3,4-*hi*]indole derivatives

Different scaffold endowed with inhibitory capacity against topoisomerases I and II and in particular showing no parallel cytotoxic activities was represented by pyrido[3,2,1-*kl*]phenoxazine derivatives as compound A-62176.[95] Recently, more evidence has been obtained that suggests that phyto-, endo- and synthetic cannabinoids could be useful in the treatment of cancer due to their ability to regulate cellular signaling pathways critical for cell growth and survival.[96] Among the cannabinoid derivatives, the chemical structure of WIN 55,212-2 involving the 1,4-oxazine ring fused with the indole skeleton exhibits anti-cancer effects in a variety of different cancerous cell lines including human prostate cancer,[97] human glioblastoma multiforme,[98] rat glioma[99] and B16 melanoma cells.[100] Moreover a series of 5,7-dibromo isatin derivatives exhibited in vitro anticancer activity on the human cancer cell lines including colon HT29. They were demonstrated efficient dual inhibitors of tubulin polymerization and the Akt (Protein kinase B) pathway.[101,102] (Figure 16)

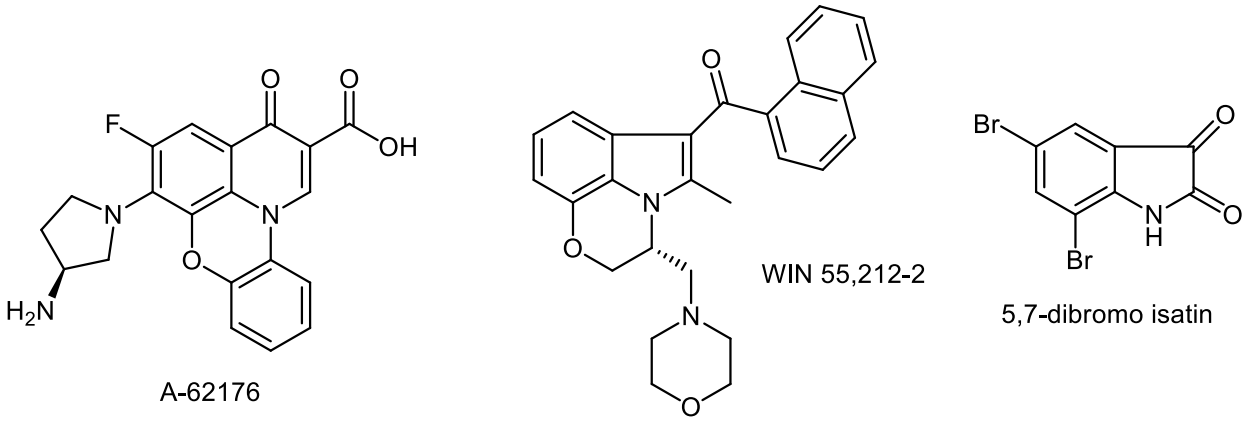


Figure 16
Cytotoxic heterocycles

These considerations prompted us to design a heteropolycyclic system endowed with cytotoxic activity, based on scaffold hopping combining some of the structural features of pyridophenoxazine, oxazinoindole and dibromoisatin.[103] (Figure 17)

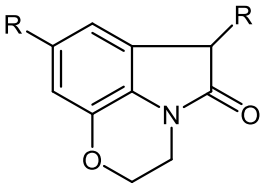


Figure 17
Designed scaffold

We have identified as key intermediate of the synthetic pathway the *N*-2-hydroxyethyl-5,7-dibromo isatin able to give a double functionalization through the transition-metal catalyzed reactions. (Figure 18)

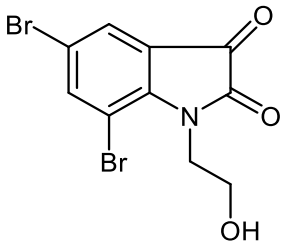
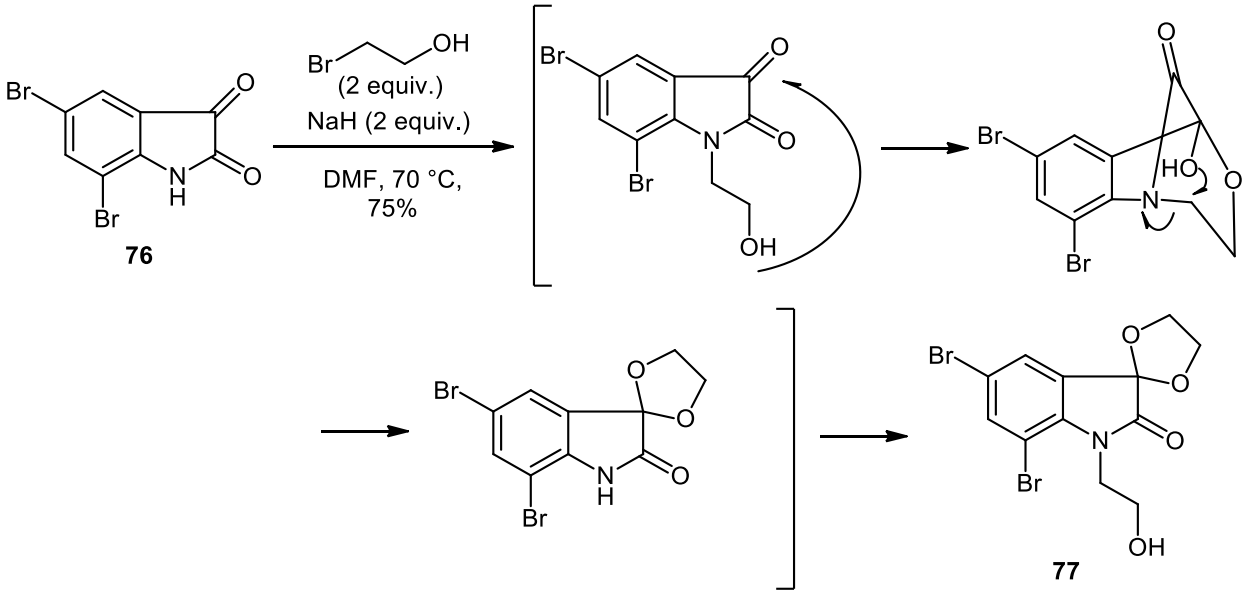


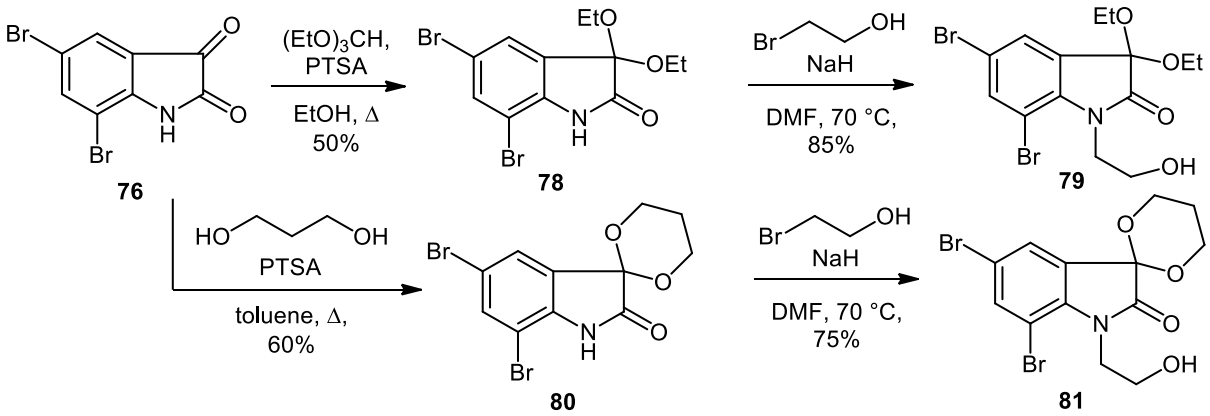
Figure 18
Designed substrate for double functionalization

The first trial for the synthesis of the scaffold, starting from 5,7-dibromoisatin and using 2-bromoethanol and sodium hydride as base in DMF as solvent failed. Indeed, the *N*-hydroxyalkyl intermediate was unstable and rearranged in basic condition leading the formation of spiroisatin.[104] Thus, we have exploited this reactivity to achieve *N*-hydroxyalkyl spiroisatin in one step, using two equivalent of 2-bromoethanol and sodium hydride. (Scheme 50)



Scheme 50
Synthesis of designed key intermediate

The subsequent desired cyclization didn't give product in different reaction conditions then we prepared dibromo isatins protected in position 3 with different acetals, exploiting similar synthetic pathways. (Scheme 51).



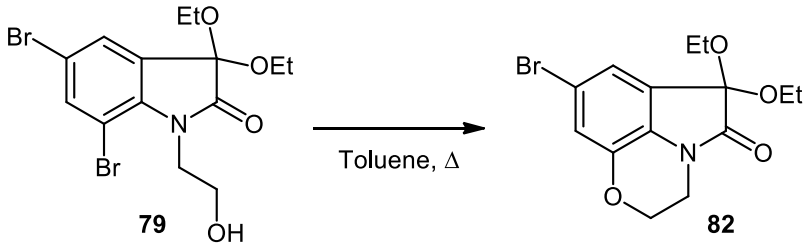
Scheme 51

Synthesis of substrates

The intermediate **79** was then cyclized through an intramolecular alkoxylation reaction in order to obtain the oxazinoindole scaffold. The C-O bond formation was achieved under copper catalysis, exploiting the Ullmann-type reaction. The use of oxygen nucleophile, compared to nitrogen, has remained a less explored area due to the diminished nucleophilicity of this atom and different reaction conditions were tested to achieve the cyclized product. The best reaction conditions used copper acetate as catalyst, in toluene as solvent in the presence of sodium hydride as base. (Entry 12) No reaction was obtained with different bases. (Table 13)

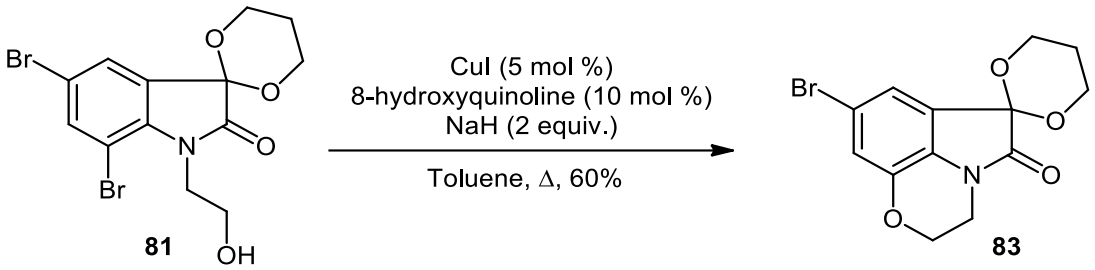
Table 13

Intramolecular Ullmann-type reaction condition



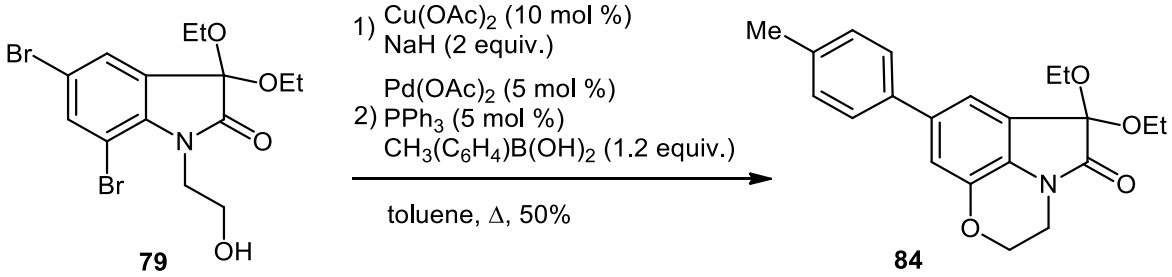
	Catalyst (mol %)	Ligand	Base	Yield
1	$Pd(OAc)_2$ (2.5 mol %)	JohnPhos (3 mol %)	Cs_2CO_3 (1.5 equiv.)	-.
2	$Pd_2(dba)_3$ (2 mol %)	BINAP (5 mol %)	NaH (2.5 equiv.)	-
4	$Pd_2(dba)_3$ (2 mol %)	*t*-BuDavePhos (7 mol %)	*t*-butONa (1.5 equiv.)	dimer
5	$Pd(OAc)_2$ (2.5 mol %)	*t*-BuDavePhos (7 mol %)	Cs_2CO_3 (1.5 equiv.)	-
6	$Pd(OAc)_2$ (2.5 mol %)	dppf (4 mol %)	*t*-butONa (1.2 equiv.)	dimer
8	CuI (10 mol %)	1,10-Phen (20 mol %)	Cs_2CO_3 (2 equiv.)	20 %
9	CuI (5 mol %)	8-OH-quinoline (10 mol %)	NaH (1.25 equiv.)	10 %
10	$Cu(OAc)_2$ (10 mol%)	-	NaH (2 equiv.)	80 %

Using spiro[1,3]dioxane derivative **81** the cyclization reaction was performed using copper(I) iodide as catalyst and 8-hydroxyquinoline as ligand. NaH as base and toluene as solvent have remained irreplaceable. (Scheme 52)



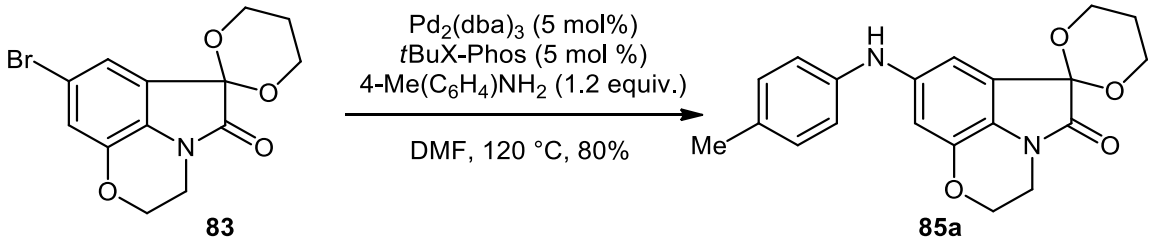
Scheme 52
Intramolecular Ullmann-type reaction

To afford the functionalized scaffold the bromine atom in position 5 was susceptible of a second nucleophilic substitution, exploiting tandem Cu/Pd catalyzed processes as alkoxyamination, alkoxyarylation, a double alkoxylation. The alkoxylation/arylation process (involving Suzuki-Miyaura reaction) starting from **79** and using the *p*-tolyl boronic acid afforded 5-tolyl oxazinoindole (**84**). The yield of the one-pot reaction was comparable with the overall yield of two reactions carried out with the isolation of the intermediate product. (Scheme 53)

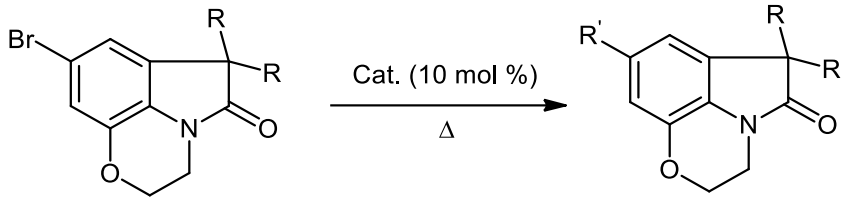


Scheme 53
One-pot alkoxylation/arylation reaction

The alkoxylation/amination (involving Buchwald-Hartwig reactions) using substituted anilines resulted in a 5-arylamino oxazinoindoles (**85a**). (Scheme 54) The same amination reactions, in lower yields, were obtained under copper catalysis (involving Ullmann-type reaction) (**85a-d**) (Scheme 55, table 14)



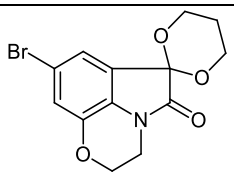
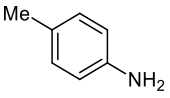
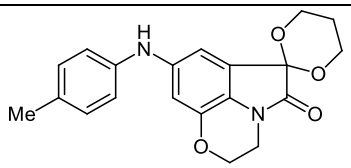
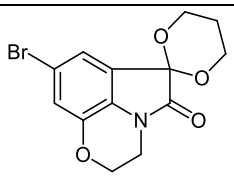
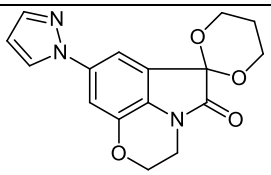
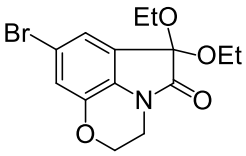
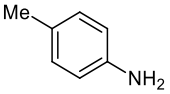
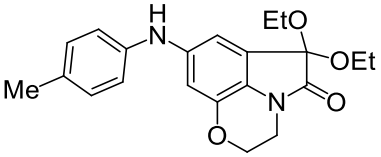
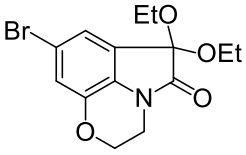
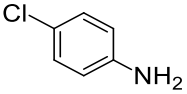
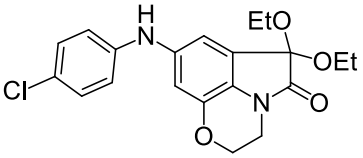
Scheme 54
Palladium catalyzed amination reaction



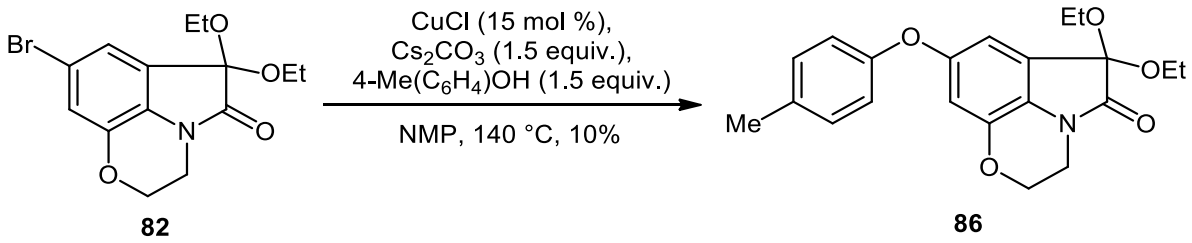
83,82 **85a-d**

Scheme 55
Copper catalyzed amination reactions

Table 14
Copper catalyzed amination reactions

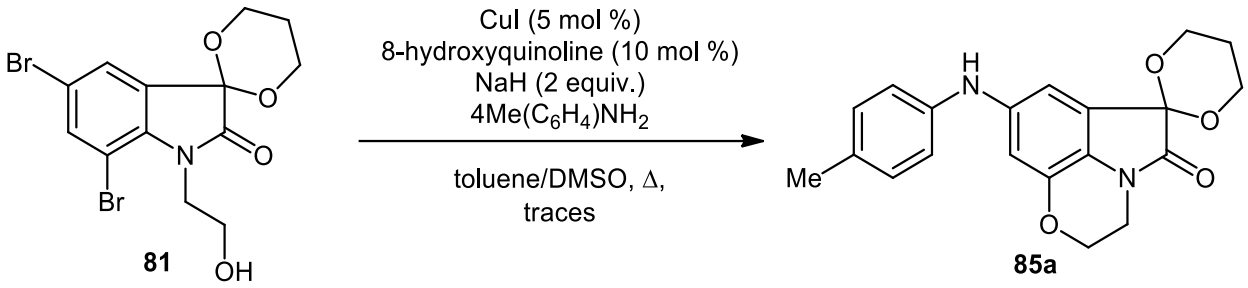
	Substrate	RNH_2	Cat.	Solvent	Product	Yield (%)
1	 **83**		CuI	DMSO	 **85a**	40
2	 **83**		Cu	MeCN	 **85b**	20
3	 **82**		CuI	DMSO	 **85c**	50
4	 **82**		CuI	DMSO	 **85d**	40

Alkoxylation using *p*-cresol, copper(I) chloride as catalyst in NMP as solvent, was obtained in lower yield, due to the less nucleophilicity of the oxygen. (Scheme 56)



Scheme 56
Double alkoxylation reaction

Then we explored the possibility to perform the alkoxyamination or the double alkoxylation in one step, starting from **81** under copper catalysis without the need of the isolation of intermediate **83**, as a cascade process. The development of cascade reactions is an important goal in organic synthesis from the viewpoint of operational simplicity and assembly efficiency. (Scheme 57)



Scheme 57
One step alkoxyamination reactions

The 5-bromoindolooxazines **82, 83** and the substituted derivatives **85** will be tested in order to evaluate the cytotoxicity. Preliminary results in collaboration with Catania University showed some activity of the *N*-alkylated-5,7-dibromoisatin derivatives but no anticancer activity for the oxazinoindole derivatives. A positive aspect was regarding the toxicity in primary cells, we observed that none of the compounds was toxic at the concentrations effective on cancer cells.

Chapter 4

Conclusion

In conclusion, different scaffolds were achieved exploiting palladium and platinum catalysis. Starting from the same or similar substrates substituted with alkynes, alkenes and allenes and using different protecting group we have obtained dihydrobenzoxazines, dihydroquinoxalines, dihydrobenzoxazole, dihydrobenzoimidazoles, benzopyrans and dihydroquinolines. Furthermore, dihydro-purine and dihydro-deazapurine, pyrimido- and pyridodiazepine was achieved starting pyridine and pyrimidine tethered with the same unsaturated residues. At the end, exploiting carboamination reactions we have achieved different scaffolds substituted with aryl moiety. (Figure 19)

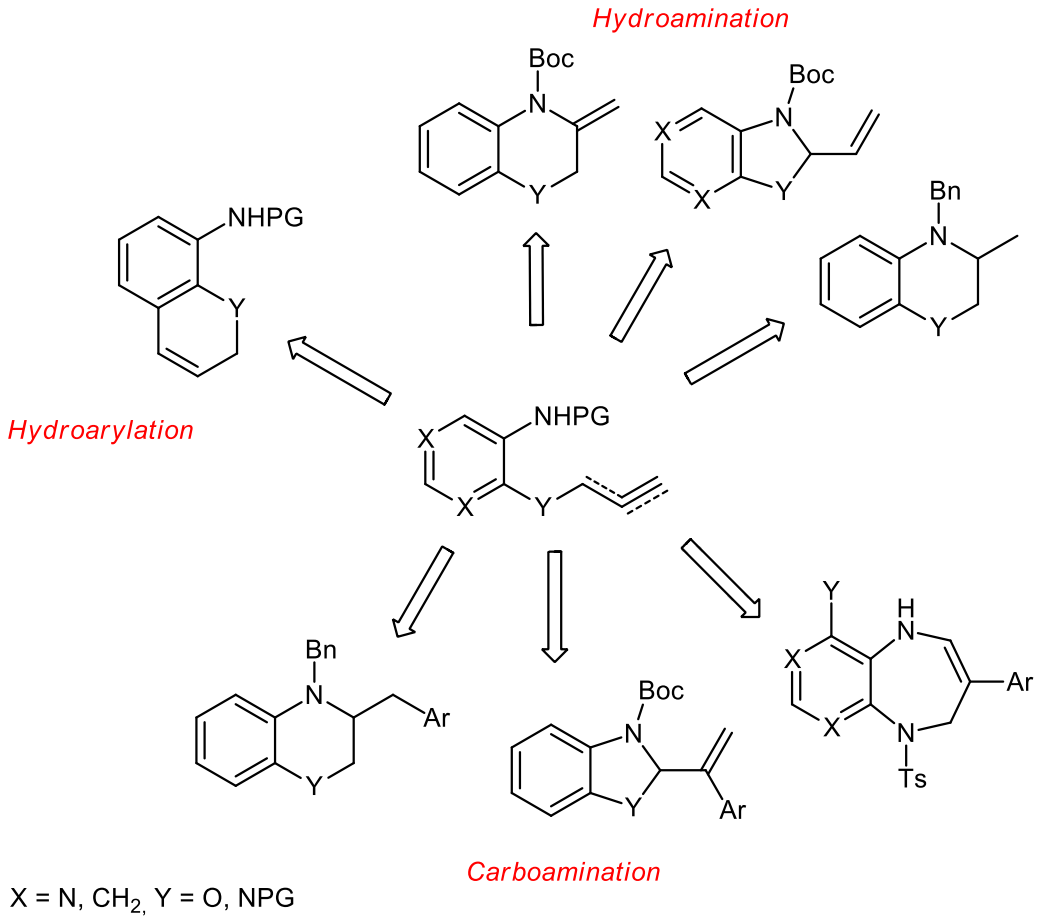


Figure 19
Hydroamination, hydroarylation and carboamination product

Furthermore, the preparation of a new scaffold starting from triptamines exploiting as a key step the sequential protocol palladium catalyzed *N*-arylation/intramolecular Friedel-Crafts alkylation. The antiproliferative activity of the derivatives due to the Topo I inhibition has been evaluated. Although the potency of the new derivatives is two orders of magnitude lower than that of CPT, all compounds resulted active on at least two of the three evaluated cell lines. A computational binding mode analysis has been performed on most active compound to provide insights possibly useful for designing decorations that might improve the activity of the scaffold.

At the end, the copper catalysis was exploited to achieve of new oxazino[2,3,4-*hi*]indole derivatives. The synthesis, starting from commercially available 5,7-dibromoisatin exploit a double sequential functionalization as alkoxyamination, alkoxyarylation, or double alkoxylation. The 5-bromoindolooxazines intermediate and the substituted derivatives will be tested in order to evaluate the cytotoxicity.

All the methodologies exploited in this thesis afforded heterocycles and heteropolycyclic systems obtained in good yields, performed with normal procedures not requiring particular conditions or apparatus. The different yields of the products are due to the different reactivity of the substrates used, the efficiency of the processes are in all the cases confirmed.

Acknowledgements

Funding for this work was provided by the Ministero dell'Università e della Ricerca (MIUR) (PRIN 2010e2011-prot. 20109Z2XRJ).

Chapter 5

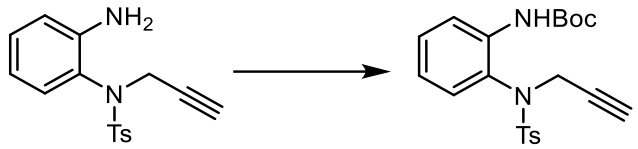
Experimental section

All NMR spectra regarding the third chapter are available in the Supporting Information (A. Mazza, E. M. Beccalli, A. Contini, A. N. Garcia-Argaez, L. Dalla Via, M. L. Gelmi, **A new scaffold of topoisomerase I inhibitors: design, synthesis and biological evaluation**, *Eur. J. Med. Chem*., **2016** (124) 326-339): http://dx.doi.org/10.1016/j.ejmech.2016.08.045

1. Chemisrty

General details: melting points were determined by the capillary method with a Büchi B-540 apparatus. IR spectra were recorded with a Jasco FT/IR 5300 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AVANCE 400 spectrometer at 400 and 100 MHz, a Varian Gemini 200 MHz spectrometer at 200 and 50 MHz and a Varian Oxford 300 MHz spectrometer at 300 and 75 MHz. Chemical shifts are given as δ values in ppm relative to residual solvent peaks (CHCl3) as the internal reference. ^{13}C NMR spectra were ^{1}H-decoupled and the multiplicities determined by the APT pulse sequence. Mass spectra were recorded with a LCQ Advantage Thermo Finningan spectrometer. Elemental analyses were executed with a Perkin–Elmer CHN Analyser Series II 2400. TLC separations were performed on pre-coated Merck silica-gel 60-F254. Preparative separations were performed by flash chromatography on Merck silica gel (0.035–0.070 mm).

tert-Butyl (2-(4-methyl-_N_-(prop-2-yn-1-yl)phenylsulfonamido)-phenyl)carbamate (8)



7 **8**

Boc_2O (1.2 equiv.) was added to a solution of *N*-tosyl-*N*-propargyl-2-aminoaniline **7** (1 equiv) in THF (60 mL) at room temperature. The reaction mixture was heated at reflux for 24 h. Every 8 h, further Boc_2O (1.2 equiv.) was added. The solvent was removed under reduced pressure, water was added to the residue and the solution was extracted with AcOEt (3 ×). The organic phases were dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the product.

Yield: 67%.

White solid; m.p.: 125 - 127 °C.

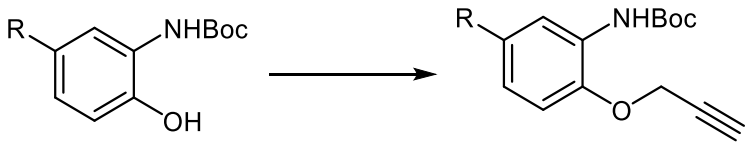
^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.14 (dd, *J* = 8.4, 1.3 Hz, 1 H), 7.59 (d, *J* = 8.4 Hz, 2 H), 7.40 (br. s, 1 H, exchange with D_2O), 7.25– 7.34 (m, 3 H), 6.82 (td, *J* = 8.0, 1.5 Hz, 1 H), 6.66 (dd, *J* = 8.0, 1.5 Hz, 1 H), 4.40 (br. s, 1 H), 4.34 (br. s, 1 H), 2.17 (t, *J* = 2.5 Hz, 1 H), 1.52 (s, 9 H), 2.44 (s, 3 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 153.0 (s), 144.6 (s), 138.5 (s), 134.8 (s), 130.1 (d), 129.6 (d), 128.8 (d), 128.7 (d), 127.6 (s), 122.6 (d), 120.7 (d), 80.9 (s), 77.6 (s), 74.3 (d), 41.9 (t), 28.6 (q), 21.8 (q), ppm.

IR: $\tilde{\nu}$ = 3395, 3266, 2999, 2968, 2930, 2120, 1722, 1525, 1445, 1338 cm^{-1}.

MS (ESI): m/z = 423.0 $[M+Na]^+$. ($C_{21}H_{24}N_2O_4S$).

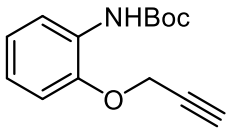
General procedure for the preparation of *O*-propargyl ethers



2a-e **3a-e**

Under N_2, K_2CO_3 was added (1.2 equiv.) to a stirred solution of the corresponding commercially available *tert*-butyl (2-hydroxyphenyl)carbamate (1 equiv.) in THF/DMF (3 mL/1 mL/mmol) at room temperature. The mixture was cooled to 0 °C and a solution of propargyl bromide (80% in toluene, 1.2 equiv.) was added dropwise. The resulting mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the mixture was extracted with AcOEt (3 ×) and then washed with brine. The organic phases were dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by crystallization or flash chromatography on silica gel.

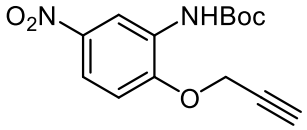
tert-Butyl (2-(prop-2-yn-1-yloxy)phenyl)carbamate (3a)



Yield: 97%.

Data are consistent with literature.[105]

tert-Butyl (5-nitro-2-(prop-2-yn-1-yloxy)phenyl)carbamate (3b)



Yield: 80%.

Yellow solid; m.p.: 111 - 113 °C.

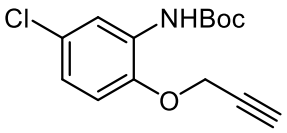
^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.03 (d, *J* = 2.9 Hz, 1 H), 7.90 (dd, *J* = 9.2, 2.9 Hz, 1 H), 7.10 (br. s, 1 H, exchange with D_2O), 7.04 (d, *J* = 9.2 Hz, 1 H), 4.86 (d, J = 2.6 Hz, 2 H), 2.61 (t, *J* = 2.6 Hz, 1 H), 1.54 (s, 9 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 152.3 (s), 149.9 (s), 142.7 (s), 129.3 (s), 118.4 (d), 113.8 (d), 110.9 (d), 81.8 (s), 77.6 (d), 76.9 (s), 57.0 (t), 28.5 (q) ppm.

IR: ṽ = 3361, 3258, 2993, 2939, 2120, 1706, 1594, 1535, 1345, 1278 cm^{-1}.

MS (ESI): m/z = 315.0 $[M+Na]^+$. ($C_{14}H_{16}N_2O_5$)

tert-Butyl (5-chloro-2-(prop-2-yn-1-yloxy)phenyl)carbamate (3c)



Yield: 94%.

White solid; m.p.: 62 - 65 °C.

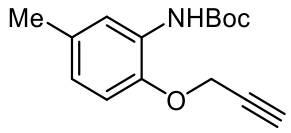
^{1}H NMR (200 MHz, CDCl3): δ = 8.17 (s, 1 H), 7.05 (br. s, 1 H, exchange with D_2O), 6.89–7.00 (m, 2 H), 4.73 (d, *J* = 2.6 Hz, 2 H), 2.55 (t, *J* = 2.6 Hz, 1 H), 1.53 (s, 9 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 152.5 (s), 144.2 (s), 129.9 (s), 127.6 (s), 121.8 (d), 118.6 (d), 112.9 (d), 81.1 (s), 78.6 (s), 76.3 (d), 57.0 (t), 28.5 (q) ppm.

IR: ṽ = 3436, 3299, 2980, 2933, 2125, 1729, 1598, 1520, 1273 cm^{-1}.

MS (ESI): m/z = 304.0 $[M+Na]^+$. ($C_{14}H_{16}ClNO_3$).

tert-Butyl (5-methyl-2-(prop-2-yn-1-yloxy)phenyl)carbamate (3d)



Yield: 97%.

White solid; m.p.: 58 - 60 °C.

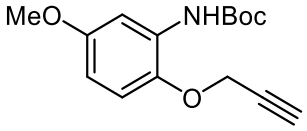
^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.95 (s, 1 H), 7.04 (br. s, 1 H, exchange with D_2O), 6.86 (d, *J* = 8.1 Hz, 1 H), 6.75 (ddd, *J* = 8.1, 2.0, 0.6 Hz, 1 H), 4.71 (d, *J* = 2.6 Hz, 2 H), 2.53 (t, *J* = 2.6 Hz, 1 H), 2.30 (s, 3 H), 1.53 (s, 9 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 153.0 (s), 144.7 (s), 132.0 (s), 128.6 (s), 122.7 (d), 119.4 (d), 112.1 (d), 80.5 (s), 78.6 (s), 76.0 (d), 56.9 (t), 28.5 (q), 21.3 (q) ppm.

IR: $\tilde{\nu}$ = 3408, 3276, 2980, 2930, 2129, 1731, 1532 cm^{-1}.

MS (ESI): m/z = 284.1 $[M+Na]^+$. ($C_{15}H_{19}NO_3$).

tert-Butyl (5-methoxy-2-(prop-2-yn-1-yloxy)phenyl)carbamate (3e)



Yield: 99%.

White solid; m.p.: 72 - 74 °C.

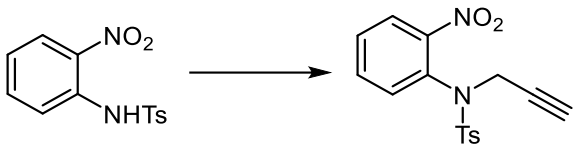
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (br. s, 1 H), 7.08 (br. s, 1 H, exchange with D_2O), 6.89 (d, *J* = 8.9 Hz, 1 H), 6.48 (dd, *J* = 8.9, 3.0 Hz, 1 H), 4.67 (d, *J* = 2.4 Hz, 2 H), 3.78 (s, 3 H), 2.52 (t, *J* = 2.4 Hz, 1 H), 1.52 (s, 9 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9 (s), 152.5 (s), 139.7 (s), 129.8 (s), 113.4 (d), 107.3 (d), 104.4 (d), 80.4 (s), 78.5 (s), 75.8 (d), 57.4 (t), 55.7 (q), 28.3 (q) ppm.

IR: $\tilde{\nu}$ = 3433, 3255, 2997, 2945, 2127, 1698, 1619, 1606, 1534 cm^{-1}.

MS (ESI): m/z = 300.3 $[M+Na]^+$. ($C_{15}H_{19}NO_4$).

4-Methyl-*N*-(2-nitrophenyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (6A)

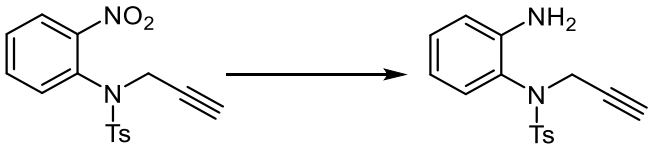


6 **6A**

A suspension of *N*-tosyl-2-nitroaniline (1 equiv.), prop-2-yn-1-ol (1.1 equiv.) and PPh_3 (1.5 equiv.) in anhydrous THF (6 mL/mmol) was stirred under N_2. The mixture was cooled to 0 °C and a solution of diisopropyl azodicarboxylate (1.5 equiv.) in THF (1 mL/mmol) was added dropwise over a period of 30 min. The reaction mixture was warmed to room temperature and stirred for 6 h. The solvent was removed under reduced pressure and the crude product was dissolved in CH_2Cl_2. Then it was washed sequentially with 2 M NaOH, 1 M HCl, saturated $NaHCO_3$ solution and brine. The organic phases were dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the product.

Yield: 95%.
Yellow solid; m.p.: 87 - 88 °C.
^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.85–7.89 (m, 1 H), 7.51–7.62 (m, 4 H), 7.34–7.38 (m, 1 H), 7.24–7.28 (m, 2 H), 4.60 (br. s, 2 H), 2.43 (s, 3 H), 2.26 (t, *J* = 2.5 Hz, 1 H) ppm.
^{13}C NMR (50 MHz, $CDCl_3$): δ = 149.9 (s), 144.5 (s), 136.2 (s), 133.3 (d), 133.1 (d), 131.8 (s), 130.2 (d), 129.8 (d), 128.1 (d), 125.4 (d), 78.3 (s), 74.6 (d), 41.3 (t), 21.8 (q) ppm.
IR: $\tilde{\nu}$ = 3436, 3277, 2921, 2123, 1728, 1599, 1532 cm^{-1}.
MS (ESI): m/z = 353.0 $[M+Na]^+$. ($C_{16}H_{14}N_2O_4S$).

***N*-(2-Aminophenyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (7)**



6A **7**

Fe powder (6 equiv.) was added to a suspension of **6A** (1 equiv.) in a mixture of AcOH (20% in H_2O, 2.5 ml/mmol), EtOH (5 ml/mmol). The resulting suspension was heated at reflux for 3 h. The reaction mixture was filtered through a pad of Celite using AcOEt to remove the iron excess. The filtrate was washed with $NaHCO_3$ sat. (3 ×), dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the product.

Yield: 87%.

Pale yellow solid; m.p.: 109 - 111 °C.

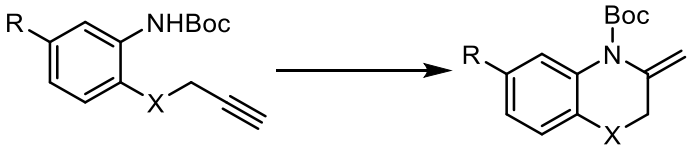
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.2 Hz, 2 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 7.14 (t, *J* = 7.6 Hz, 1 H), 6.85 (d, *J* = 7.6 Hz, 1 H), 6.64 (d, *J* = 7.6 Hz, 1 H), 6.58 (t, *J* = 7.6 Hz, 1 H), 4.57 (d, *J* = 16.1 Hz, 1 H), 4.33–4.46 (br. s, 2 H, exchange with D_2O), 4.26 (d, *J* = 16.1 Hz, 1 H), 4.26 (d, *J* = 16.1 Hz, 1 H), 2.18 (s, 1 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7 (s), 143.9 (s), 135.5 (s), 129.9 (d), 129.4 (d), 129.3 (d), 128.4 (d), 124.9 (s), 118.4 (d), 117.1 (d), 78.1 (s), 73.6 (d), 40.8 (t), 21.6 (q) ppm.

IR: $\tilde{\nu}$ = 3446, 3362, 3303, 2921, 1911, 1617, 1498, 1335 cm^{-1}.

MS (ESI): m/z = 322.9 $[M+Na]^+$. ($C_{16}H_{16}N_2O_2S$).

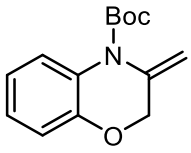
General procedure for the Pd-catalyzed hydroamination reactions on alkynyl derivatives



3a-d, 8 **4a-d, 9**

$Pd(PPh_3)_4$ (8 mol %) were added to a solution of the suitable propargyl derivative (1 equiv.) in toluene (10 mL/mmol) under nitrogen atmosphere. The reaction mixture was stirred at reflux at 90 °C for 4 h. The reaction mixture was filtered under reduced pressure through a Celite pad washing with AcOEt. The solvent was removed under reduced pressure and the crude was purified by silica gel chromatography.

***tert*-Butyl 3-methylene-2*H*-benzo[*b*][1,4]oxazine-4(3*H*)-carboxylate (4a)**



Yield: 58%.

Colourless oil.

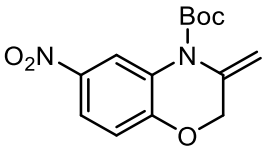
^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.01-6.76 (m, 4 H), 5.34 (s, 1 H), 5.13 (s, 1 H), 4.56 (s, 2H), 1.53 (s, 9 H).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 152.0 (s), 147.2 (s), 133.7 (s), 131.6 (s), 24.7 (d), 123.6 (d), 120.9 (d), 117.1 (d), 107.9 (t), 82.5 (s), 69.8 (t), 28.4 (q) ppm.

IR: ṽ = 3433, 3058, 2979, 2932, 2870, 1717, 1602, 1494 cm^{-1}.

MS (ESI): m/z = 270.1 [M+Na]+, 249.0 $[M]^+$. ($C_{14}H_{17}NO_3$).

***tert*-Butyl 3-methylene-6-nitro-2*H*-benzo[*b*][1,4]oxazine-4(3*H*)-carboxylate (4b)**



Yield: 76%.

Colourless oil.

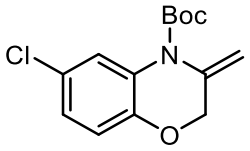
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 8.76 (d, *J* = 2.7 Hz, 1 H), 7.89 (dd, *J* = 9.0, 2.7 Hz, 1 H), 6.93 (d, *J* = 9.0 Hz 1 H), 5.43 (s, 1 H), 5.35 (s, 1 H), 4.66 (s, 2 H), 1.57 (s, 9 H) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$) δ = 152.4 (s), 151.6 (s), 143.0 (s), 134.0 (s), 129.6 (s), 120.3 (d), 119.6 (d), 117.3 (d), 111.5 (t), 81.8 (s), 69.7 (t), 28.5 (q) ppm.

IR: ṽ = 3436, 3128, 2986, 2923, 2851, 2626, 1926, 1721, 1588, 1513 cm^{-1}.

MS (ESI): m/z = 315.0 $[M+Na]^+$. ($C_{14}H_{16}N_2O_5$).

tert-Butyl 6-chloro-3-methylene-2_H_-benzo[_b_][1,4]oxazine-4(3_H_)-carboxylate (4c)



Yield: 45%.

Colourless oil.

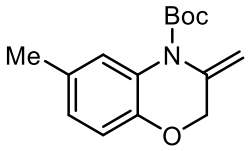
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 2.4 Hz, 1 H), 6.94 (dd, *J* = 8.7, 2.4 Hz, 1 H), 6.79 (d, *J* = 8.7 Hz 1 H), 5.35 (d, *J* = 0.5 Hz, 1 H), 5.19 (d, *J* = 0.5 Hz, 1 H), 4.54 (d, *J* = 0.5 Hz, 2 H), 1.54 (s, 9 H) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$) δ = 151.5 (s), 145.5 (s), 135.7 (s), 127.7 (s), 125.7 (s), 124.5 (d), 123.2 (d), 118.0 (d) 109.0 (t), 83.0 (s), 69.5 (t), 28.3 (q) ppm.

IR: ṽ = 3422, 3086, 2979, 2930, 2333, 1858, 1719, 1601 cm^{-1}.

MS (ESI): m/z = 281.0 $[M+H]^+$. ($C_{14}H_{16}ClNO_3$).

tert-Butyl 6-methyl-3-methylene-2H-benzo[_b_][1,4]oxazine-4(3_H_)-carboxylate (4d)



Yield: 70%.

Colourless oil.

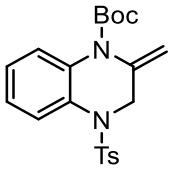
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 7.53 (s, 1 H), 6.95-6.67 (m, 2 H), 5.34 (s, 1 H), 5.15 (s, 1 H), 4.54 (d, *J* = 0.6 Hz, 2 H), 2.30 (s, 3 H), 1.54 (s, 9 H) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$) δ = 152.0 (s), 145.0 (s), 136.9 (s), 133.8 (s), 126.8 (s), 125.3 (d), 123.8 (d), 116.7 (d), 107.6 (t), 82.4 (s), 69.8 (t), 28.4 (q), 21.13 (q) ppm.

IR: ṽ = 3432, 3056, 2977, 2928, 1715 cm^{-1}.

MS (ESI): m/z = 284.0 $[M+H]^+$. ($C_{15}H_{19}NO_3$).

tert-Butyl 2-methylene-4-tosyl-3,4-dihydroquinoxaline-1(2_H_)-carboxylate (4e)



Yield: 83%.

Colourless oil.

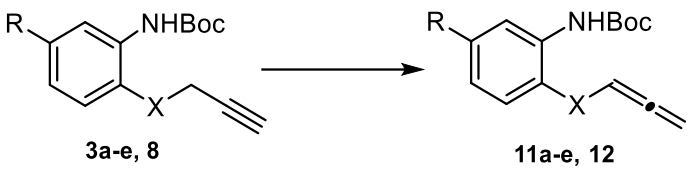
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 7.71-7.38 (m, 4 H), 7.26-7.13 (m, 4 H), 5.14 (, d, *J* = 0.8 Hz, 1 H), 4.53 (d, *J* = 0.8 Hz, 1 H), 4.36 (s, 2 H), 2.30 (s, 3 H), 1.34 (s, 9 H) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$) δ = 151.8 (s), 143.7 (s), 138.5 (s), 134.7 (s), 133.8 (s), 131.7 (s), 129.6 (d), 127.7 (d), 127.4 (d), 126.6 (d), 124.8 (d), 124.7 (d), 98.8 (t), 82.6 (s), 53.1 (t), 28.1 (q), 21.8 (q) ppm.

IR: $\tilde{\nu}$ = 3422, 2979, 2330, 1920, 1720 cm^{-1}.

MS (ESI): m/z = 423.0 $[M+Na]^+$. ($C_{21}H_{24}N_2O_4S$).

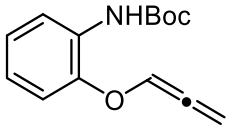
General procedure for the preparation of allenes



3a-e, 8 **11a-e, 12**

The corresponding *N*-Boc-*O*-propargyl ether **3a-e, 8** (1 equiv.) was dissolved in THF (12 mL/mmol) at room temperature. *t*BuOK (2.5 equiv.) was added to the solution in one portion and the mixture was stirred for 3 min. Water was then added and the mixture extracted with AcOEt (3 ×). The solvent was removed in vacuo and the crude was purified by flash chromatography on silica gel to afford the product.

***tert*-Butyl *N*-(2-(propa-1,2-dien-1-yloxy)phenyl)carbamate (11a)**



Yield: 84%.

Colourless oil.

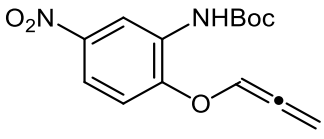
^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.5 Hz, 1 H), 6.91–7.09 (m, 4 H, 3 H after exchange with D_2O), 6.81 (t, *J* = 5.9 Hz, 1 H), 5.48 (d, *J* = 5.9 Hz, 2 H), 1.52 (s, 9 H), ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.7 (s), 152.8 (s), 145.4 (s), 129.6 (s), 123.7 (d), 122.4 (d), 119.1 (d), 118.4 (d), 115.7 (d), 90.4 (t), 80.7 (s), 28.6 (q) ppm.

IR: ṽ = 3440, 2980, 2931, 1965, 1732, 1602, 1522 cm^{-1}.

MS (ESI): m/z = 270.1 $[M+Na]^+$. ($C_{14}H_{17}NO_3$).

***tert*-Butyl *N*-(5-nitro-2-(propa-1,2-dien-1-yloxy)phenyl)carbamate (11b)**



Yield: 52%.

Yellow solid; m.p.: 117 - 118 °C.

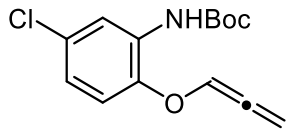
^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.06 (d, *J* = 2.6 Hz, 1 H), 7.88 (dd, *J* = 9.0, 2.6 Hz, 1 H), 7.10–7.15 (m, 2 H, 1 H after exchange with D_2O), 6.84 (t, *J* = 5.9 Hz, 1 H), 5.56 (d, *J* = 5.9 Hz, 2 H), 1.54 (s, 9 H), ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.6 (s), 152.3 (s), 149.7 (s), 143.5 (s), 129.7 (s), 118.2 (d), 116.7 (d), 114.2 (d), 113.8 (d), 91.2 (t), 81.9 (s), 28.5 (q) ppm.

IR: ṽ = 3435, 2974, 2928, 2002, 1733, 1541, 1343 cm^{-1}.

MS (ESI): m/z = 315.0 $[M+Na]^+$. ($C_{14}H_{16}N_2O_5$).

tert-Butyl _N_-(5-chloro-2-(propa-1,2-dien-1-yloxy)phenyl)carbamate (11c)



Yield: 66%

Colourless oil.

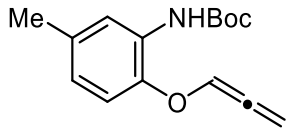
^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 2.0 Hz, 1 H), 7.01 (br. s, 1 H, exchange with D_2O), 6.87–6.95 (m, 2 H), 6.78 (t, *J* = 5.9 Hz, 1 H), 5.48 (d, *J* = 5.9 Hz, 2 H), 1.53 (s, 9 H), ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.4 (s), 152.5 (s), 143.7 (s), 130.5 (s), 129.0 (s), 122.0 (d), 118.9 (d), 118.3 (d), 116.6 (d), 91.0 (t), 81.3 (s), 28.5 (q) ppm.

IR: ṽ = 3438, 2980, 2933, 1967, 1732, 1600, 1520 cm^{-1}.

MS (ESI): m/z = 304.0 $[M+Na]^+$. ($C_{14}H_{16}ClNO_3$).

tert-Butyl _N_-(5-methyl-2-(propa-1,2-dien-1-yloxy)phenyl)carbamate (11d)



Yield: 70%

Colourless oil.

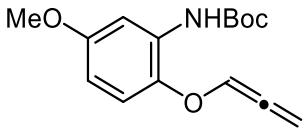
^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 1.3 Hz, 1 H), 6.98 (br. s, 1 H, exchange with D_2O), 6.93 (d, *J* = 8.1 Hz, 1 H), 6.79 (t, *J* = 5.9 Hz, 1 H), 6.75 (dd, *J* = 8.1, 1.3 Hz, 1 H), 5.45 (d, *J* = 5.9 Hz, 2 H), 2.30 (s, 3 H), 1.53 (s, 9 H), ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.6 (s), 152.9 (s), 143.2 (s), 133.6 (s), 129.2 (s), 122.8 (d), 119.5 (d), 118.9 (d), 115.8 (d), 90.6 (t), 80.7 (s), 28.6 (q), 21.4 (q) ppm.

IR: ṽ = 3441, 2978, 2928, 1965, 1730, 1602, 1530, 1467 cm^{-1}.

MS (ESI): m/z = 284.0 $[M+Na]^+$. ($C_{15}H_{19}NO_3$).

tert-Butyl _N_-(5-methoxy-2-(propa-1,2-dien-1-yloxy)phenyl)carbamate (11e)



Yield: 90%

White solid; m.p.: 41 - 43 °C.

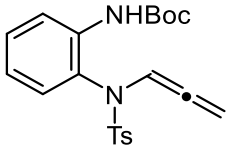
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (br. s, 1 H), 7.00 (br. s, 1 H, exchangewith D_2O), 6.94–6.99 (m, 1 H), 6.78 (t, *J* = 5.9 Hz, 1 H), 6.48 (dd, *J* = 8.8, 3.0 Hz, 1 H), 5.43 (d, *J* = 5.9 Hz, 2 H), 3.78 (s, 3 H), 1.52 (s, 9 H) ppm.

^{13}C NMR (100 MHz, CDCl3): δ = 202.0 (s), 155.9 (s), 152.5 (s), 138.8 (s), 130.4 (s), 119.6 (d), 117.4 (d), 107.6 (d), 104.1 (d), 90.7 (t), 80.6 (s), 55.7 (q), 28.3 (q), ppm.

IR: ṽ = 3437, 2982, 2934, 1959, 1715, 1607, 1540 cm^{-1}.

MS (ESI): m/z = 300.0 $[M+Na]^+$. ($C_{15}H_{19}NO_4$).

tert-Butyl _N_-(2-(4-methyl-N-(propa-1,2-dien-1-yl)phenylsulfonamido)phenyl)carbamate (12)



Yield: 40%

White solid; m.p.: 125 - 126 °C.

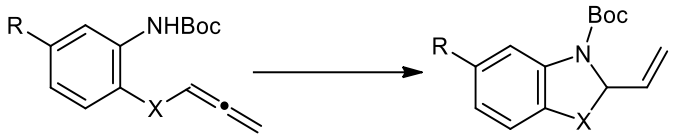
^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.17 (dd, *J* = 8.4, 1.3 Hz, 1 H), 7.60 (d, *J* = 8.4 Hz, 2 H), 7.22–7.32 (m, 3 H, 2 H after exchange with D_2O), 7.18 (br. s, 1 H), 7.10 (t, *J* = 6.2 Hz, 1 H), 6.75 (td, *J* = 7.9, 1.5 Hz, 1 H), 6.34 (dd, *J* = 7.9, 1.5 Hz, 1 H), 5.02 (d, *J* = 6.2 Hz, 2 H), 2.46 (s, 3 H), 1.52 (s, 9 H), ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.2 (s), 152.8 (s), 144.7 (s), 137.9 (s), 134.6 (s), 130.1 (d), 129.9 (d), 129.5 (d), 128.3 (d), 125.4 (s), 121.9 (d), 120.3 (d), 102.2 (d), 88.2 (t), 80.9 (s), 28.5 (q), 21.9 (q), ppm.

IR: ṽ = 3422, 2981, 1728, 1595, 1516, 1445, 1355 cm^{-1}.

MS (ESI): m/z = 423.1 $[M+Na]^+$. ($C_{21}H_{24}N_2O_4S$).

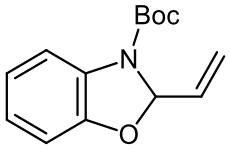
General procedure for hydroamination reactions on allenes



11a-e, 12 **13a-e, 14**

$Pd(PPh_3)_4$ (8 mol %) and PPh_3 (10 mol %) were added to a solution of the corresponding allene (1 equiv.) in toluene (15 mL/mmol) and the mixture was stirred at 80 °C for 8 h. The reaction mixture was concentrated in vacuo, brine was added and the mixture extracted with AcOEt (3 ×). The combined organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel.

***tert*-Butyl 2-vinylbenzo[*d*]oxazole-3(2*H*)-carboxylate (13a)**



Yield: 94%.

Colourless oil.

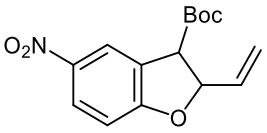
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (br. s, 1 H), 6.87–6.94 (m, 2 H), 6.80 (d, *J* = 7.7 Hz, 1 H), 6.40 (br. s, 1 H), 5.94–6.02 (m, 1 H), 5.55 (d, *J* = 16.8 Hz, 1 H), 5.38 (d, *J* = 10.2 Hz, 1 H), 1.58 (s, 9 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.1 (s), 146.8 (s), 132.8 (d), 130.1 (s), 123.3 (d), 121.3 (d), 119.3 (t), 114.0 (d), 108.7 (d), 93.4 (d), 82.2 (s), 28.3 (q) ppm.

IR: $\tilde{\nu}$ = 3409, 3060, 2978, 2932, 1875, 1712 cm^{-1}.

MS (ESI): m/z = 270.1 $[M+Na]^+$. ($C_{14}H_{17}NO_3$).

***tert*-Butyl 5-nitro-2-vinylbenzo[*d*]oxazole-3(2*H*)-carboxylate (13b)**



Yield: 51%.

Colourless oil.

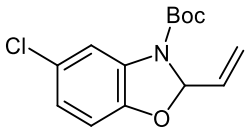
^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.30 (br. s, 1 H), 7.92 (dd, *J* = 8.7, 2.4 Hz, 1 H), 6.80 (d, *J* = 8.7 Hz, 1 H), 6.52 (d, *J* = 6.0 Hz, 1 H), 5.96 (ddd, *J* = 16.5, 10.2, 6.0 Hz, 1 H), 5.57 (d, *J* = 16.5 Hz, 1 H), 5.44 (d, *J* = 10.2 Hz, 1 H), 1.57 (s, 9 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.5 (s), 149.8 (s), 142.9 (s), 132.1 (d), 130.8 (s), 121.1 (d), 120.8 (t), 109.8 (d), 108.1 (d), 95.9 (d), 83.8 (s), 28.4 (q) ppm.

IR: $\tilde{\nu}$ = 3413, 3131, 2980, 2931, 2853, 2425, 2303, 1875, 1721 cm^{-1}.

MS (ESI): m/z = 315.1 $[M+Na]^+$. ($C_{14}H_{16}N_2O_5$)

tert-Butyl 5-chloro-2-vinylbenzo[_d_]oxazole-3(2_H_)-carboxylate (13c)



Yield: 72%.

Colourless oil.

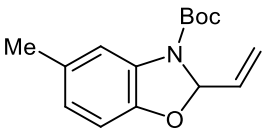
^{1}H NMR (200 MHz, CDCl3): δ = 7.50 (br. s, 1 H), 6.85 (dd, *J* = 8.4, 2.2 Hz, 1 H),), 6.66 (d, *J* = 8.4 Hz, 1 H), 6.38 (d, *J* = 6.4 Hz, 1 H), 5.94 (ddd, *J* = 17.0, 10.8, 6.4 Hz, 1 H), 5.52 (d, *J* = 17.0 Hz, 1 H), 5.38 (d, *J* = 10.8 Hz, 1 H), 1.55 (s, 9 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 150.1 (s), 149.2 (s), 132.7 (d), 130.7 (s), 126.4 (s), 122.9 (d), 119.9 (t), 114.7 (d), 109.3 (d), 94.6 (d), 83.0 (s), 28.5 (q) ppm.

IR: ṽ = 3491, 2979, 2932, 1716, 1599 cm^{-1}.

MS (ESI): m/z = 304.0 $[M+Na]^+$. ($C_{14}H_{16}ClNO_3$).

tert-Butyl 5-methyl-2-vinylbenzo[_d_]oxazole-3(2_H_)-carboxylate (13d)



Yield: 74%.

Colourless oil.

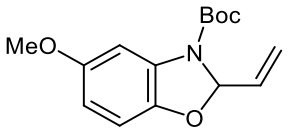
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (br. s, 1 H), 6.70 (d, *J* = 7.9 Hz, 1 H), 6.65 (d, *J* = 7.9 Hz, 1 H), 6.35 (br. s, 1 H), 5.90–5.98 (m, 1 H), 5.51 (d, *J* = 16.9 Hz, 1 H), 5.35 (d, *J* = 10.2 Hz, 1 H), 2.29 (s, 3 H), 1.55 (s, 9 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 150.5 (s), 148.3 (s), 133.1 (d), 131.1 (s), 129.4 (s), 123.5 (d), 119.4 (t), 115.1 (d), 108.4 (d), 93.8 (d), 82.3 (s), 28.5 (q), 21.3 (q) ppm.

IR: ṽ = 2977, 2930, 1713, 1645 cm^{-1}.

MS (ESI): m/z = 261.9 $[M+Na]^+$. ($C_{15}H_{19}NO_3$).

tert-Butyl 5-methoxy-2-vinylbenzo[_d_]oxazole-3(2_H_)-carboxylate (13e)



Yield: 75%.

Colourless oil.

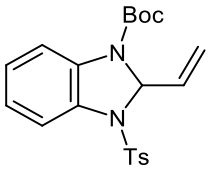
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (br. s, 1 H), 6.66 (d, *J* = 8.6 Hz, 1 H), 6.40 (dd, *J* = 8.6, 2.7 Hz, 1 H), 6.34 (br. s, 1 H), 5.90–5.99 (m, 1 H), 5.51 (d, *J* = 16.8 Hz, 1 H), 5.35 (d, *J* = 10.3 Hz, 1 H), 3.76 (s, 3 H), 1.55 (s, 9 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.7 (s), 150.1 (s), 144.3 (s), 132.8 (d), 129.9 (s), 119.2 (t), 108.3 (d), 107.6 (d), 101.3 (d), 93.9 (d), 82.3 (s), 55.9 (q), 28.3 (q) ppm.

IR: $\tilde{\nu}$ = 3409, 3090, 2977, 2933, 2834, 1711, 1622 cm^{-1}.

MS (ESI): m/z = 300.1 $[M+Na]^+$. ($C_{15}H_{19}NO_4$).

tert-Butyl 3-tosyl-2-vinyl-2,3-dihydro-1_H_-benzo[_d_]imidazole-1-carboxylate (14)



Yield: 60%.

Pale yellow oil.

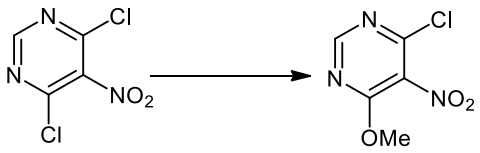
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 7.2 Hz, 1 H), 7.51–7.55 (m, 1 H), 7.42 (d, *J* = 8.1 Hz, 2 H), 7.03–7.30 (m, 4 H), 6.24 (br. s, 1 H), 5.83–5.91 (m, 1 H), 5.48 (d, *J* = 16.2 Hz, 1 H), 5.28 (d, *J* = 10.2 Hz, 1 H), 2.34 (s, 3 H), 1.44 (s, 9 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9 (s), 143.9 (s), 138.7 (s), 134.2 (s), 133.1 (s), 132.7 (d), 129.5 (d), 128.2 (d), 127.2 (d), 126.6 (d), 123.3 (d), 118.7 (d), 117.9 (t), 115.1 (d), 80.5 (s), 28.1 (q), 21.5 (q) ppm.

IR: $\tilde{\nu}$ = 3427, 2978, 2931, 1919, 1713 cm^{-1}.

MS (ESI): m/ z = 423.1 $[M+Na]^+$. ($C_{21}H_{24}N_2O_4S$).

Synthesis of 4-chloro-6-methoxy-5-nitropyrimidine (16)



To a solution of 4,6-dichloro-5-nitropyrimidine **15** (1 equiv.) in MeOH (5 mL/mmol) was added triethylamine (1 equiv.). The reaction mixture was stirred at rt for 24 h. The reaction mixture was concentrated in vacuo, brine was added and the mixture extracted with AcOEt (3 ×). The combined organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel.

Yield: 99%.

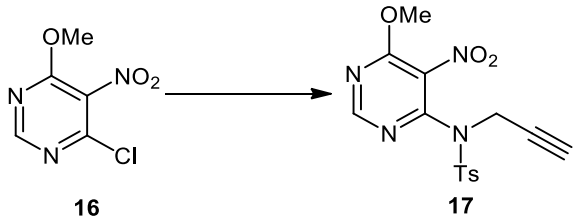
Pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.64 (s, 1 H), 4.15 (s, 3 H) ppm.

MS (ESI): m/ z = 190.5 $[M+H]^+$. ($C_5H_4ClN_3O_3$).

Synthesis of

***N*-(6-methoxy-5-nitropyrimidin-4-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (17)**



To a solution of compound **16** (1.2 equiv.) in DMF, was added, under nitrogen atmosphere, K_2CO_3 (5 equiv.), TBA-HSO_4 (10 mol %) and **16** (1 equiv.). The reaction mixture was stirred at 40 °C for 24 h. The reaction mixture was concentrated in vacuo, brine was added and the mixture extracted with AcOEt (3 ×). The combined organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel.

Yield: 62%

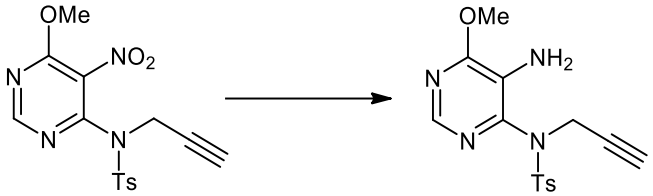
Pale yellow solid; m. p.: 118 - 122 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.66 (s, 1 H), 7.67 (d, *J* = 8.2 Hz, 2 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 4.36 (d, *J* = 2.6 Hz, 2 H), 4.16 (s, 3 H), 2.45 (s, 3 H), 2.15 (t, *J* = 2.6 Hz, 1 H) ppm.

MS (ESI): m/ z = 363.5 $[M+H]^+$. ($C_{15}H_{14}N_4O_5S$).

Synthesis of

***N*-(5-amino-6-methoxypyrimidin-4-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (18)**



Fe powder (6 equiv.) was added to a suspension of **17** (1 equiv.) in a mixture of AcOH (20 % in H_2O, 2.5 ml/mmol), EtOH (5 ml/mmol). The resulting suspension was heated at reflux for 3 h. The reaction mixture was filtered through a pad of Celite using AcOEt to remove the iron excess. The filtrate was washed with $NaHCO_3$ sat. (3 ×), dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the product.

Yield: 84%.

Pale yellow solid; m. p.: 159 - 161 °C.

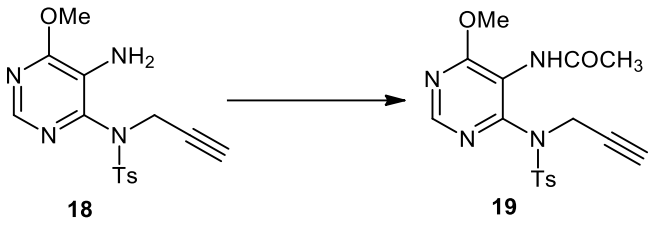
^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.94 (s, 1 H), 7.56 (d, *J* = 8.4 Hz, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 4.40 (bs, exchange with D_2O, 2 H), 4.29 (d, *J* = 2.6 Hz, 2 H), 4.04 (s, 3 H), 2.41 (s, 3 H), 2.10 (t, *J* = 2.6 Hz, 1 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 160.2 (s), 145.1 (d), 144.7 (s), 140.8 (s), 134.2 (s), 129.8 (2C, d), 129.4 (s), 128.6 (2C, d), 77.5 (s), 73.1 (d), 54.6 (q), 39.5 (t), 21.8 (q) ppm.

IR: $\tilde{\nu}$ = 3458, 3358, 3271, 2947, 2126, 1608 cm^{-1}.

MS (ESI): m/z = 333.1 $[M+H]^+$. ($C_{15}H_{16}N_4O_3S$).

Synthesis of
_N_-(4-methoxy-6-(4-methyl-_N_-(prop-2-yn-1-yl)phenylsulfonamido)pyrimidin-5-yl)acetamide (19)



Compound **18** (1 equiv.) was dissolved in THF (10 mL/mmol) and the solution cooled to 0 °C, then $(CH_3CO)_2O$ (2 equiv.) was added dropwise. The resulting mixture was stirred for 3 h. After completion of the reaction the mixture was concentrated under reduced pressure and extracted with AcOEt (3 ×). The organic phases were washed with a saturated solution of $NaHCO_3$ sat. (2 x) and water, dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel.

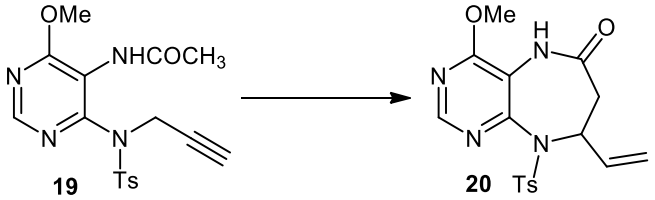
Yield: 65%.

Colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.56 (s, 1 H,), 7.56 (d, *J* = 8.4 Hz, 2 H), 7.28 (br. s, exchange with D_2O, 1 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 4.51 (q, *J* = 7.0 Hz, 2 H), 4.50 (d, *J* = 2.6 Hz, 2 H), 2.25 (t, *J* = 2.6 Hz, 1 H), 2.41 (s, 3 H), 2.10 (s, 3 H), 1.38 (t, *J* = 7.0 Hz, 3 H) ppm.

MS (ESI): m/z = 397.0 $[M+Na]^+$. ($C_{17}H_{18}N_4O_4S$).

Synthesis of
4-methoxy-9-tosyl-8-vinyl-8,9-dihydro-5*H*-pyrimido[4,5-*b*][1,4]diazepin-6(7*H*)-one (20)



The compound **19** (1 equiv.) was dissolved in THF (12 mL/mmol) at room temperature. *t*BuOK (2.5 equiv.) was added to the solution in one portion and the mixture was stirred for 1 h. Then, water was added and the mixture extracted with AcOEt (3 ×). The solvent was removed in vacuo and the crude was purified by flash chromatography on silica gel to afford the product.

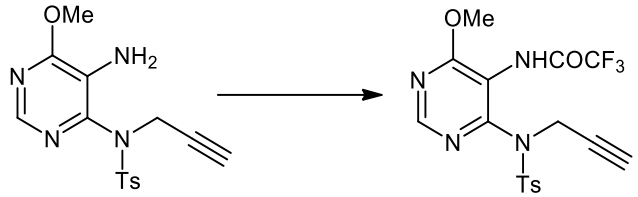
Yield: 40%.

Colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.56 (d, *J* = 8.4 Hz, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 5.90 (m, 1 H), 5.41 (m, 2 H, 1 H after exchange with D_2O), 5.25 (1H, d, *J* = 9.9 Hz), 4.47 (1H, m), 4.51 (2H, q, *J* = 7.0 Hz), 2.76 (2H, m), 2.41 (s, 3 H), 1.43 (9H, s), 1.38 (3H, t, *J* = 7.0 Hz) ppm.

MS (ESI): m/z = 397.1 $[M+Na]^+$. ($C_{17}H_{18}N_4O_4S$).

Synthesis of
2,2,2-trifluoro-*N*-(4-methoxy-6-(4-methyl-*N*-(prop-2-yn-1-yl) phenylsulfonamido)pyrimidin-5-yl)acetamide (21)



Compound **18** (1 equiv.) was dissolved in THF (10 mL/mmol) and the solution cooled to 0 °C, then $(CF_3CO)_2O$ (2 equiv.) was added dropwise. The resulting mixture was stirred for 3 h at 40 °C. After completion of the reaction the mixture was concentrated under reduced pressure and extracted with AcOEt. The organic phases were washed with $NaHCO_3$ sat. (2 x) and water, dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel.

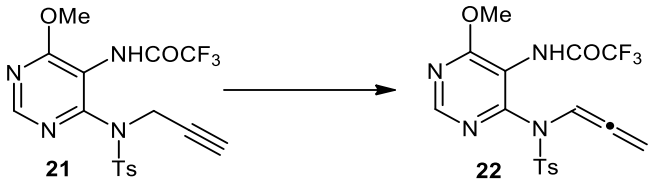
Yield: 86%.

Colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.51 (s, 1 H), 8.38 (br. s, 1 H, exchange with D_2O), 7.66 (d, *J* = 8.2 Hz, 2 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 6.60 (t, *J* = 6.2 Hz, 1 H), 5.16 (d, *J* = 6.2 Hz, 2 H), 4.09 (s, 3 H), 2.45 (s, 3 H) ppm.

MS (ESI): m/z = 429.3 $[M+H]^+$. ($C_{17}H_{15}F_3N_4O_4S$).

Synthesis of
2,2,2-trifluoro-*N*-(4-methoxy-6-(4-methyl-*N*-(propa-1,2-dien-1-yl)phenylsulfonamido) pyrimidin-5-yl)acetamide (22)



The compound **21** (1 equiv.) was dissolved in THF (12 mL/mmol) at room temperature. *t*BuOK (2.5 equiv.) was added to the solution in one portion and the mixture was stirred for 1 h. Then added water and the mixture extracted with AcOEt (3 ×). The solvent was removed in vacuo and the crude was purified by flash chromatography on silica gel to afford the product.

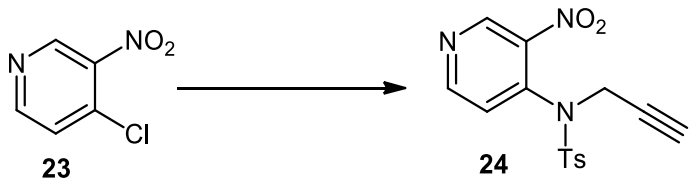
Yield: 64%.

Pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.51 (s, 1 H), 8.38 (br. s, exchange with D_2O, 1 H), 7.66 (d, *J* = 8.2 Hz, 2 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 6.60 (t, *J* = 6.2 Hz, 1 H), 5.16 (d, *J* = 6.2 Hz, 2 H), 4.09 (s, 3 H), 2.45 (s, 3 H) ppm.

MS (ESI): m/z = 429.3 $[M+H]^+$. ($C_{17}H_{15}F_3N_4O_4S$).

Synthesis of 4-methyl-*N*-(3-nitropyridin-4-yl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (24)



To a solution of 4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (1.2 equiv.) in DMF, was added, under nitrogen atmosphere, K_2CO_3 (5 equiv.), TBA-HSO_4 (10 mol %) and **23** (1 equiv.). The reaction mixture was stirred at 40 °C for 24 h. The reaction mixture was concentrated in vacuo, brine was added and the mixture extracted with AcOEt (3 ×). The combined organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel.

Yield: 47%.

Yellow solid; m.p.: 110 - 112 °C.

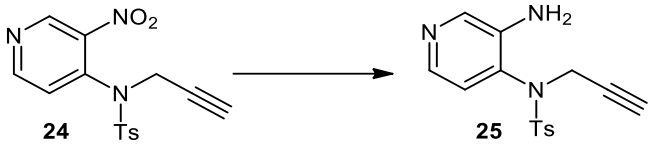
^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.13 (s, 1 H), 8.78 (d, *J* = 5.1 Hz, 1 H), 7.59 (d, *J* = 8.2 Hz, 2 H), 7.38 (d, *J* = 5.1 Hz, 1 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 4.55 (d, *J* = 2.6 Hz, 2 H), 2.44 (s, 3 H), 2.27 (t, *J* = 2.6 Hz, 1 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 154.4 (d), 146.9 (d), 154.2 (s), 140.1 (s), 135.4 (s), 130.1 (d), 128.1 (d), 126.4 (d), 117.6 (s), 77.1 (s), 75.5 (d), 40.7 (t), 21.8 (q) ppm.

IR: $\tilde{\nu}$ = 3436, 3277, 2122 cm^{-1}.

MS (ESI): m/z = 332.4 $[M+H]^+$. ($C_{15}H_{13}N_3O_4S$).

Synthesis of *N*-(3-aminopyridin-4-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (25)



Fe powder (6 equiv.) was added to a suspension of **24** (1 equiv.) in a mixture of AcOH (20 % in H_2O, 2.5 ml/mmol), EtOH (5 ml/mmol). The resulting suspension was heated at reflux for 8 h. The reaction mixture was filtered through a pad of Celite using AcOEt to remove the iron excess. The filtrate was washed with $NaHCO_3$ sat. (3 ×), dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the product.

Yield: 81%

White solid; m.p.: 118 - 119 °C.

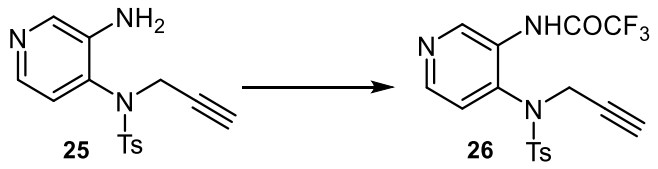
^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.24 (d, 1 H), 7.84 (br. d, *J* = 5.1 Hz, 1 H), 7.64 (d, *J* = 8.2 Hz, 2 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 6.54 (d, *J* = 5.1 Hz, 1 H), 4.36 (d, *J* = 2.6 Hz, 2 H), 4.28 (br. s, 2 H, exchange with D_2O), 2.45 (s, 3 H), 2.17 (t, *J* = 2.6 Hz, 1 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.8 (s), 142.8 (s), 140.2 (d), 139.7 (d), 135.1 (s), 131.1 (s), 129.8 (d), 128.5 (d), 123.1 (d), 77.6 (s), 74.3 (d), 40.6 (t), 21.8 (q) ppm.

IR: $\tilde{\nu}$ = 3295, 2925, 2121, 1615 cm^{-1}.

MS (ESI): m/z = 302.2 $[M+H]^+$. ($C_{15}H_{15}N_3O_2S$).

Synthesis of
2,2,2-trifluoro-*N*-(4-(4-methyl-*N*-(prop-2-yn-1-yl)phenylsulfonamido)pyridin-3-yl)acetamide (26)



Compound **25** (1 equiv.) was dissolved in THF (10 mL/mmol) and the solution cooled to 0 °C, then $(CF_3CO)_2O$ (2 equiv.) was added dropwise. The resulting mixture was stirred for 3 h at 40 °C. After completion of the reaction the mixture was concentrated under reduced pressure and extracted with AcOEt (3 ×). The organic phases were washed with a saturated solution of $NaHCO_3$ (2 x) and water, dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel.

Yield: 91%.

Colourless oil.

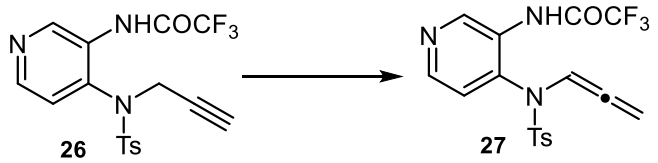
^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.01 (br. S, 1 H), 8.91 (br. s, 1 H, exchange with D_2O), 8.55 (d, *J* = 5.3 Hz, 1 H), 7.48 (d, *J* = 5.3 Hz, 1 H), 4.32 (d, *J* = 2.2 Hz, 2 H), 2.39 (t, *J* = 2.2 Hz, 1 H), 1.53 (s, 9 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.6 (q, *J* = 38.1 Hz), 153.6 (s), 149.0 (d), 147.7 (d), 142.9 (s), 127.5 (s), 119.7 (d), 116.0 (q, *J* = 288.4 Hz), 84.6 (s), 78.7 (s), 73.5 (d), 40.8 (t), 28.2 (q) ppm.

IR: ṽ = 3291, 2983, 2123, 1713 cm^{-1}.

MS (ESI): m/z = 398.0 $[M+H]^+$. ($C_{17}H_{14}F_3N_3O_3S$).

Synthesis of 2,2,2-trifluoro-*N*-(4-(4-methyl-*N*-(propa-1,2-dien-1-yl)
phenylsulfonamido)pyridin-3-yl)acetamide (27)



The compound **26** (1 equiv.) was dissolved in THF (12 mL/mmol) at room temperature. *t*BuOK (2.5 equiv.) was added to the solution in one portion and the mixture was stirred for 1 h. Then, water was added and the mixture extracted with AcOEt (3 ×). The solvent was removed in vacuo and the crude was purified by flash chromatography on silica gel to afford the product.

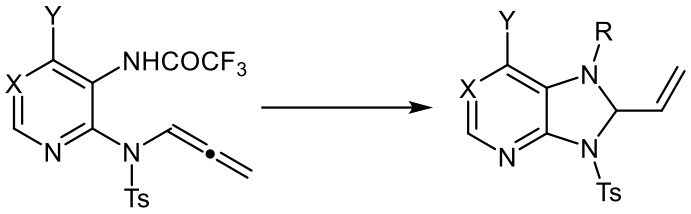
Yield: 40%.

Colourless oil.

^{1}H-MNR (200 MHz, $CDCl_3$): δ = 9.18 (s, 1 H), 8.52 (d, *J* = 5.1 Hz, 1 H), 8.35 (br. s, 1 H, exchange with D_2O), 7.24 (d, *J* = 5.1 Hz, 1 H), 7.09 (t, *J* = 6.2 Hz, 1 H), 5.14 (d, *J* = 6.2 Hz, 2 H), 1.50 (s, 9 H) ppm.

MS (ESI): m/z = 398.0 $[M+H]^+$. ($C_{17}H_{14}F_3N_3O_3S$).

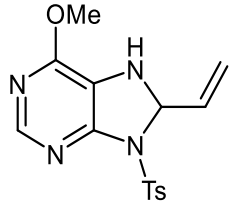
General procedure for hydroamination reactions on allenes



22, 27 **28, 29**

$Pd(PPh_3)_4$ (8 mol %) were added to a solution of the corresponding allene (1 equiv.) in toluene (15 mL/mmol) and the mixture was stirred at rt for 1-2 h. The reaction mixture was concentrated in vacuo, brine was added and the mixture extracted with AcOEt (3 ×). The combined organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel.

6-Methoxy-9-tosyl-8-vinyl-8,9-dihydro-7*H*-purine (28)



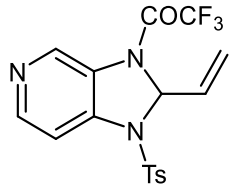
Yield: 73%.

Colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.49 (s, 1 H), 7.84 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 6.63 (d, *J* = 4.4 Hz, 1 H), 5.81 (m, 1 H), 5.55 (d, *J* = 16.9 Hz, 1 H), 5.38 (d, J = 10.6 Hz, 1 H), 4.05 (s, 3 H), 2.43 (br. s, 1 H, exchange with D_2O), 2.40 (s, 3 H) ppm.

MS (ESI): m/z = 333.3 $[M+H]^+$. ($C_{15}H_{16}N_4O_3S$).

2,2,2-Trifluoro-1-(1-tosyl-2-vinyl-1H-imidazo[4,5-*c*]pyridin-3(2*H*)-yl)ethanone (29)



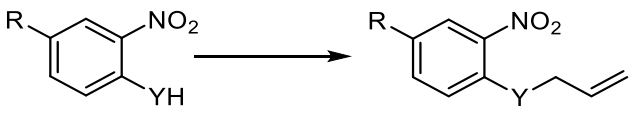
Yield: 64%.

Colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.10 (s, 1 H), 8.51 (d, *J* = 5.1 Hz, 1 H), 7.50 (d, *J* = 8.1 Hz, 2 H), 7.42 (d, J = 5.1 Hz, 1 H), 7.22 (d, *J* = 8.1 Hz, 2 H), 6.49 (d, *J* = 4.4 Hz, 1 H), 5.86 (ddd, *J* = 16.9, 10.3, 4.4 Hz, 1 H), 5.52 (d, *J* = 16.9 Hz, 1 H), 5.42 (d, *J* = 10.3 Hz, 1 H), 2.38 (s, 3 H) ppm.

MS (ESI): m/z = 398.4 $[M+H]^+$. ($C_{17}H_{14}F_3N_3O_3S$).

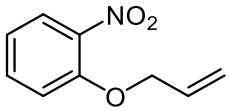
General procedure for the preparation of *O*-allyl ethers and *N*-allyl amide



30a-c, 6 **31a-d**

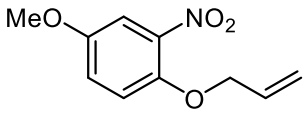
Under N_2, K_2CO_3 was added (1.2 equiv.) to a stirred solution of compound **30a-c** or **6** (1 equiv.) in THF/DMF (3 mL/1 mL/mmol) at room temperature. The mixture was cooled to 0 °C and a solution of allyl bromide (1.2 equiv.) was added dropwise. The resulting mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the mixture was extracted with AcOEt and then washed with brine (3 ×). The organic phases were dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by crystallization or flash chromatography on silica gel.

1-(Allyloxy)-2-nitrobenzene (31a)



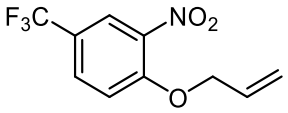
Yield: 95%. Data are consistent with literature.[106]

1-(Allyloxy)-4-methoxy-2-nitrobenzene (31b)



Yield: 95%. Data are consistent with literature.[107]

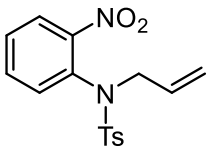
1-(Allyloxy)-2-nitro-4-(trifluoromethyl)benzene



^{1}H NMR (200 MHz; $CDCl_3$): δ = 8,12 (d, *J* = 1.8 Hz, 1 H), 7,76 (m, 1 H), 7,18 (d, *J* = 8.8 Hz, 1 H), 6,03 (m, 1 H), 5,43 (m, 2 H), 4,76 (m, 2 H) ppm.

MS (ESI): m/z = 248.0 $[M+H]^+$. ($C_{10}H_8F_3NO_3$).

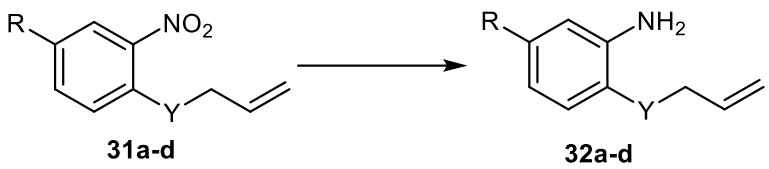
***N*-Allyl-4-methyl-*N*-(2-nitrophenyl)benzenesulfonamide**



^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.85 (s, 1 H), 7.50 (m, 5 H), 7.29 (s, 1 H), 7.11 (m, 1 H), 5.90 (m, 1 H), 5.05 (m, 2 H), 4.24 (d, *J* = 7.1 Hz, 2 H), 2.44 (s, 3 H) ppm.

MS (ESI): m/z = 333.0 [M+H]+. ($C_{16}H_{16}N_2O_4S$).

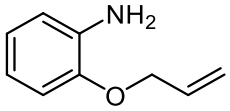
General procedure for reduction of nitro group



31a-d **32a-d**

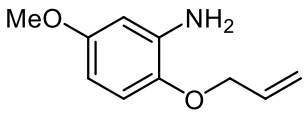
Fe powder (6 equiv.) was added to a suspension of **31** (1 equiv.) in a mixture of AcOH (20% in H_2O, 2.5 ml/mmol), EtOH (5 ml/mmol). The resulting suspension was heated at reflux for 8 h. The reaction mixture was filtered through a pad of Celite using AcOEt to remove the iron excess. The filtrate was washed with $NaHCO_3$ (3 ×), dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the product.

2-(Allyloxy)aniline (31a)



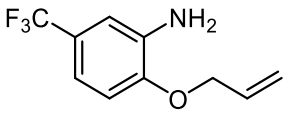
Yield: 95%. Data are consistent with literature.[108]

2-(Allyloxy)-5-methoxyaniline (31b)



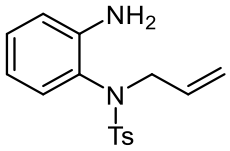
Yield: 95%. Data are consistent with literature.[107]

2-(Allyloxy)-5-(trifluoromethyl)aniline (31c)



Yield: 95%. Data are consistent with literature.[109]

_N_-Allyl-_N_-(2-aminophenyl)-4-methylbenzenesulfonamide (32d)



Yield: 82%.

Pale yellow oil.

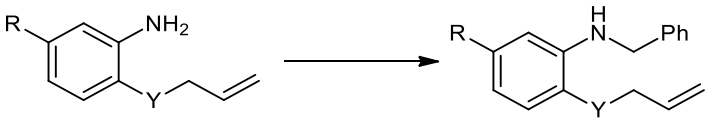
^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.59 (d, *J* = 8.1 Hz, 2 H), 7.28 (d, *J* = 9.5 Hz, 2 H), 7.06 (t, *J* = 7.1 Hz, 1 H), 6.75 (d, *J* = 8.1 Hz, 1 H), 6.51 (t, *J* = 8.1 Hz, 1 H), 6.31 (d, *J* = 6.6 Hz, 1 H), 5.77 (m, 1 H), 5.05 (m, 2 H), 4.44 (m, 1 H), 4.17 (br. s, 1 H), 4.10 (m, 2 H), 3.79 (m, 1 H), 2.45 (s, 3 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 146.9 (s), 143.9 (s), 135.7 (s), 132.7 (d), 129.7 (d), 129.5 (d), 128.8 (d), 128.3 (d), 124.9 (s), 119.4 (t), 118.0 (d), 116.9 (d), 56.4 (t), 21.8 (q) ppm.

IR: $\tilde{\nu}$ = 3479, 3383, 3204, 3067, 3032, 2982, 2923, 2863, cm^{-1}.

MS (ESI): m/z = 303.1 $[M+H]^+$. ($C_{16}H_{18}N_2O_2S$).

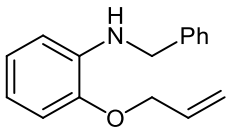
General procedure for preparation of benzyl derivatives



32a-d **33a-d**

To a solution of **32** (1 equiv.) in EtOH (5 ml/mmol) was added benzaldehyde at 0 °C. The reaction mixture was stirred at 40 °C for 24 h. Then $NaBH_4$ (1.1 equiv.) was added and the reaction was warmed at 70 °C for 4 h. The solvent was removed under reduced pressure and the mixture was extracted with AcOEt and then washed with brine (3 ×). The organic phases were dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by crystallization or flash chromatography on silica gel.

2-(Allyloxy)-_N_-benzylaniline (33a)



Yield: 60%.

Colourless oil.

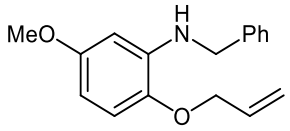
^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.32 (m, 5 H), 6.83 (m, 2 H), 6.64 (m, 2 H), 6.08 (m, 1 H), 5.34 (m, 2 H), 4.85 (br. s, 1 H, exchange with D_2O), 4.58 (m, 2 H) 4.37 (s, 2 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 146.1 (s), 139.9 (s), 138.7 (s), 133.9 (d), 128.8 (d), 127.6 (d), 127.3 (d), 121.9 (d), 117.7 (t), 116.8 (d), 111.5 (d), 110.7 (d), 69.6 (t), 48.3 (t) ppm.

IR: $\tilde{\nu}$ = 3428, 3063, 3029, 2917, 2850 cm^{-1}.

MS (ESI): m/z = 240.1 $[M+H]^+$. ($C_{16}H_{17}NO$).

2-(Allyloxy)-*N*-benzyl-5-methoxyaniline (33b)



Yield: 82%.

Colourless oil.

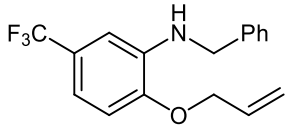
^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.39 (m, 4 H), 7.33 (m, 1 H), 6.76 (d, *J* = 8.6 Hz, 1 H), 6.29 (d, *J* = 2.8 Hz, 1 H), 6.20 (dd, *J* = 8.6 Hz; *J* = 2,8, 1 H), 6.12 (m, 1 H), 5.44 (m, 1 H), 5.32 (m, 1 H), 4.71 (br. s, 1 H, exchange with D_2O), 4.57 (m, 2 H), 4.40 (s, 2 H), 3.76 (s, 3 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 155.1 (s), 140.4 (s), 139.7 (s), 139.4 (s), 133.9 (d), 128.7 (d), 128.2 (d), 127.2 (d), 117.4 (t), 112.1 (d), 99.1 (d), 98.5 (d), 70.2 (t), 55.4 (q), 48.0 (t) ppm.

IR: $\tilde{\nu}$ = 3428, 3063, 3029, 2917, 2850 cm^{-1}.

MS (ESI): m/z = 270.1 $[M+H]^+$. ($C_{17}H_{19}NO_2$).

2-(Allyloxy)-*N*-benzyl-5-(trifluoromethyl)aniline (33c)



Yield: 91%.

Colourless oil.

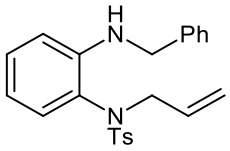
^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.32 (m, 5 H), 6.92 (m, 1 H), 6.79 (m, 2 H), 6.05 (m, 1 H), 5.35 (m, 2 H), 4.85 (br. s, 1 H, exchange with D_2O), 4.62 (m, 2 H), 4.37 (s, 2 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 148.5 (s), 138.4 (s), 137.8 (s), 133.0 (d), 128.9 (d), 127.96 (, d), 127.7 (d), 124.8 (q, J = 271.3 Hz), 123.9 (q, J = 37.0 Hz), 118.4 (t), 114.8 (d), 110.5 (d), 69.7 (t), 48.4 (t) ppm.

IR: $\tilde{\nu}$ = 3428, 3063, 3029, 2917, 2850 cm^{-1}.

MS (ESI): m/z = 308.1 $[M+H]^+$. ($C_{17}H_{16}F_3NO$).

_N_-Allyl-_N_-(2-(benzylamino)phenyl)-4-methylbenzenesulfonamide (33d)



Yield: 97%.

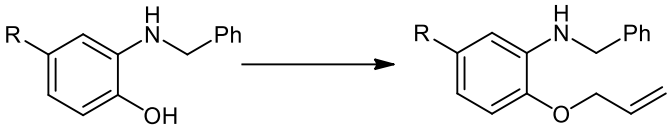
Colourless oil.

^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.61 (d, *J* = 8.4 Hz, 2 H), 7.31 (m, 7 H), 7.02 (m, 1 H), 6.61 (d, *J* = 1.1 Hz, 1 H), 6.44 (m, 2 H), 5.76 (m, 1 H), 5.16 (br. s, 1 H, exchange with D_2O), 5.04 (m, 2 H), 4.44 (m, 1 H), 4.37 (d, *J* = 5.5 Hz, 2 H), 3.79 (m, 1 H), 2.44 (s, 3 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 147.4 (s), 143.9 (s), 139.3 (s), 135.5 (s), 132.6 (d), 129.7 (d), 128.8 (d), 128.6 (d), 128.4 (d), 127.4 (d), 127.3 (d), 124.6 (s), 119.6 (t), 116.4 (d), 112.2 (d), 54.9 (t), 47.9 (t), 218 (q) ppm.

MS (ESI): m/z = 393.3 $[M+H]^+$. ($C_{23}H_{24}N_2O_2S$).

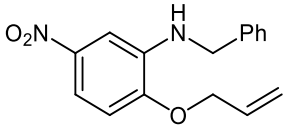
General procedure for allylation reactions



34a-c **35a-c**

To a solution of **34** (1 equiv.) in THF (5 ml/mmol) at 0 °C, was added Cs_2CO_3 (1.2 equiv.) and allyl bromide (1.1 equiv.). The reaction mixture was stirred at rt for 48 h. The solvent was removed under reduced pressure and the mixture was extracted with AcOEt and then washed with brine (3 ×). The organic phases were dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by crystallization or flash chromatography on silica gel.

2-(Allyloxy)-_N_-benzyl-5-nitroaniline (35a)



Yield: 40%.

Pale yellow oil.

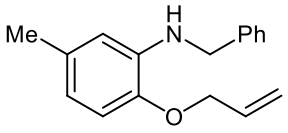
^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.61 (dd, *J* = 2.6 Hz; *J* = 8.8 Hz, 2 H), 7.34 (m, 5 H), 6.77 (d, *J* = 8.8 Hz, 1 H), 6.05 (m, 1 H), 5.38 (m, 2 H), 4.67 (m, 3 H, 2 H after exchange with D_2O), 4.42 (s, 2 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 150.7 (s), 142.8 (s), 138.6 (s), 138.4 (s), 132.3 (d), 129.3 (d), 128.8 (d), 127.8 (d), 127.7 (d), 119.0 (t), 113.5 (d), 109,5 (d), 69.9 (t), 47.9 (t) ppm.

IR: $\tilde{\nu}$ = 3428, 3063, 3029, 2917, 2850 cm^{-1}.

MS (ESI): m/z = 285.1 $[M+H]^+$. ($C_{16}H_{16}N_2O_3$).

2-(Allyloxy)-*N*-benzyl-5-methylaniline (35b)



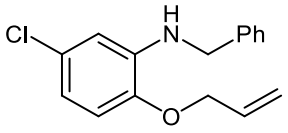
Yield: 20%.

Colourless oil.

^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.32 (m, 5 H), 6.68 (t, *J* = 4.0 Hz, 1 H), 6.45 (m, 2 H), 6.06 (m, 1 H), 5.32 (m, 2 H), 4,63 (br. s, 1 H, exchange with D_2O), 4.54 (m, 2 H), 4.35 (s, 2 H), 2.22 (s, 3 H) ppm.

MS (ESI): m/z = 254.3 $[M+H]^+$. ($C_{17}H_{19}NO$).

2-(Allyloxy)-*N*-benzyl-5-chloroaniline (35c)



Yield: 48%.

Colourless oil.

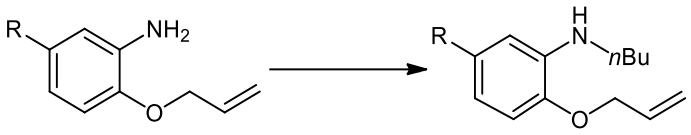
^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.33 (m, 5 H), 6.64 (m, 3 H), 6.06 (m, 1 H), 5.35 (m, 2 H), 4.75 (br. s, 1 H, exchange with D_2O), 4.56 (m, 2 H), 4.34 (s, 2 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 144.5 (s). 139.7 (s). 139.1 (s). 133.4 (d). 128.9 (d), 127.6 (d), 127.5 (d), 127.0 (s), 118.1 (t), 115.9 (d), 112.0 (d), 110.4 (d), 69.8 (t), 48.0 (t) ppm.

IR: $\tilde{\nu}$ = 3428, 3063, 3029, 2917, 2850 cm^{-1}.

MS (ESI): m/z = 274.5 $[M+H]^+$. ($C_{16}H_{16}ClNO$).

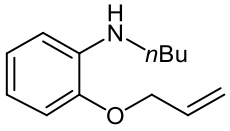
General procedure for *N*-alkylation of allyl derivatives



32a-b **36a-b**

To a solution of **32** (1 equiv.) in THF (5 ml/mmol) at 0 °C, was added *n*-BuLi (1.2 equiv.) and *n*-butyl bromide (1.1 equiv.). The reaction mixture was stirred at rt for 48 h. The solvent was removed under reduced pressure and the mixture was extracted with AcOEt and then washed with brine (3 ×). The organic phases were dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by crystallization or flash chromatography on silica gel.

2-(Allyloxy)-*N*-butylaniline (36a)



Yield: 40%.

Colourless oil.

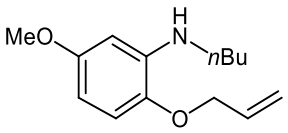
^{1}H NMR (200 MHz; $CDCl_3$): δ = 6.83 (m, 3 H), 6.61 (m, 1 H), 6.07 (m, 1 H), 5.34 (m, 2 H), 4.55 (m, 2 H), 4.21 (br. s, 1 H, exchange with D_2O), 3.13 (t, *J* = 6,9 Hz, 2 H), 1.53 (m, 4 H), 0.96 (t, *J* = 7.3 Hz, 3 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 145.9 (s), 139.1 (s), 133.9 (d), 121.9 (d), 117.5 (t), 116.2 (d), 111.3 (d), 110.2 (d), 69.5 (t), 43.6 (t), 31.9 (t), 20.6 (t), 14.7 (q) ppm.

IR: $\tilde{\nu}$ = 3428, 3063, 3029, 2917, 2850 cm^{-1}.

MS (ESI): m/z = 206.1 $[M+H]^+$. ($C_{13}H_{19}NO$)

2-(Allyloxy)-*N*-butyl-5-methoxyaniline (36b)



Yield: 53%.

Colourless oil.

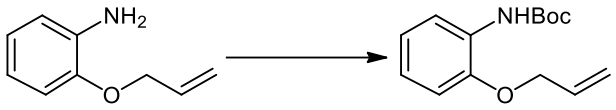
^{1}H NMR (200 MHz; $CDCl_3$): δ = 6.67 (d, *J* = 8.4 Hz, 1 H), 6.21 (d, *J* = 2.9, 1 H), 6.05 (m, 2 H), 5.32 (m, 2 H), 4.49 (m, 2 H), 4.24 (br. s, 1 H, exchange with D_2O), 3.76 (s, 3 H), 3.10 (t, *J* = 7.0 Hz, 2 H), 1.62 (m, 2 H), 1.43 (m, 2 H), 0.95 (t, *J* = 7.0 Hz, 3 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 155.4 (s), 140.6 (s), 140.3 (s), 134.2 (d), 117.4 (t), 112.3 (d), 98.6 (d), 98.2 (d), 70.4 (t), 55.7 (q), 43.5 (t), 31.8 (t), 20.6 (t), 14.1 (q) ppm.

IR: $\tilde{\nu}$ = 3428, 3063, 3029, 2917, 2850 cm^{-1}.

MS (ESI): m/z = 236.1 $[M+H]^+$. ($C_{14}H_{21}NO_2$).

Synthesis of *tert*-butyl (2-(allyloxy)phenyl)carbamate (37)



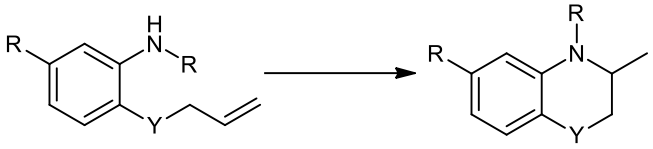
32a **37**

To a solution of **32a** (1 equiv.) in THF (5mL/mmol), Boc_2O (1.2 equiv.) was added at room temperature and the reaction mixture was stirred at room temperature for 24-48h. The solvent was then removed under reduce pressure, brine was added and the solution was extracted with AcOEt (3 x). The collected organic phases dried over Na_2SO_4, and the solvent removed under reduced pressure. The crude product was purified by silica gel flash column chromatography.

^{1}H NMR (300 MHz; $CDCl_3$): δ = 8.08 (br. s, 1 H), 7.09 (br. s, 1 H, exchange with D_2O), 6.93 (m, 2 H), 6.83 (m, 1 H), 6.06 (ddd, *J* = 17.3, 10.7, 4.2 Hz, 1 H), 5.40 (dd, *J* = 17.3, 1.4 Hz, 1 H), 5.32 (dd, *J* = 10.7, 1.4 Hz, 1 H) 4.59 (dd, *J* = 4.1, 1.4 Hz, 2 H), 1.53 (s, 9 H) ppm.

MS (ESI): m/z = 249.1 $[M+H]^+$. ($C_{14}H_{19}NO_3$).

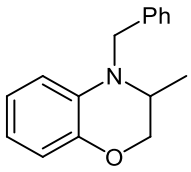
General procedure for hydroamination reaction



33a-d, 35a-c, 36a-b, 37 **38a-i**

$PtCl_2$ (5 mol %) and Xantophos (5 mol %) were added to a solution of the corresponding allyl derivative (1 equiv.) in toluene (15 mL/mmol) and the mixture was stirred at 110 °C for 5 h. The reaction mixture was concentrated in vacuo, brine was added and the mixture extracted with AcOEt (3 ×). The combined organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel.

4-Benzyl-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (38a)



Yield: 93%.

Colourless oil.

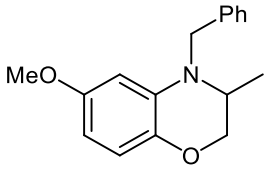
^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.30 (m, 5 H), 6.79 (m, 2 H), 6.59 (m, 2 H), 4.46 (q, *J* = 16.5 Hz, 2 H), 4.20 (m, 1 H), 4.06 (m, 1 H), 3.51 (m, 1 H), 1.23 (d, *J* = 6.6 Hz, 3 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 143.9 (s), 139.0 (s), 135.1 (s), 128.9 (d), 127.3 (d), 127.0 (d), 122.1 (d), 117.5 (d), 116.4 (d), 113.1 (d), 69.5 (t), 53.3 (t), 51.5 (d), 15.8 (q) ppm.

IR: $\tilde{\nu}$ = 3400, 3063, 3031, 2973, 2924, 2873 cm^{-1}.

MS (ESI): m/z = 240.1 $[M+H]^+$. ($C_{16}H_{17}NO$).

4-Benzyl-6-methoxy-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (38b)



Yield: 57%.

Colourless oil.

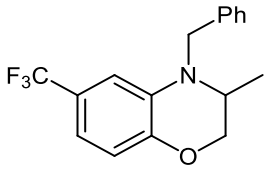
^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.28 (m, 5 H), 6.73 (m, 1 H), 6.15 (m, 2 H), 4.44 (q, *J* = 16.8 Hz, 2 H), 4.13 (m, 1 H), 4.01 (m, 1 H), 3.64 (s, 3 H), 3.49 (m, 1 H), 1.23 (d, *J* = 6.6 Hz, 3 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 155.2 (s), 138.8 (s), 138.2 (s), 135.8 (s), 128.9 (d), 127.3 (d), 126.9 (d), 116.2 (d), 101.1 (d), 99.9 (d), 69.4 (t), 55.7 (q), 53.2 (t), 51.6 (d), 15.9 (q) ppm.

IR: $\tilde{\nu}$ = 3400, 3063, 3031, 2973, 2924, 2873 cm^{-1}.

MS (ESI): m/z = 270.1 $[M+H]^+$. ($C_{17}H_{19}NO_2$).

4-Benzyl-3-methyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (38c)



Yield: 88%.

Colourless oil.

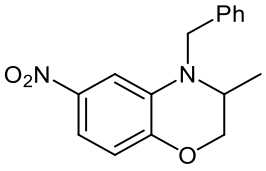
^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.31 (m, 5 H), 6.88 (s, 2 H), 6.87 (s, 1 H), 4.47 (q, *J* = 46.5 Hz; *J* = 16.5 Hz, 2 H), 4.14 (m, 2 H), 3.51 (m, 1 H), 1,22 (d, *J* = 6,6 Hz, 3 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 146.5 (s), 137.3 (s), 134.2 (s), 129.2 (d), 127.8 (d), 127.4 (d), 127.37 (s), 124.6 (q, J = 329.7 Hz), 124.2 (q, J = 32.0 Hz), 116.d (d), 115.3 (d), 110.2 (d), 69.2 (t), 53.4 (t), 50.8 (d), 15.4 (q) ppm.

IR: $\tilde{\nu}$ = 3400, 3063, 3031, 2973, 2924, 2873 cm^{-1}.

MS (ESI): m/z = 308.1 $[M+H]^+$. ($C_{17}H_{16}F_3NO$).

4-Benzyl-3-methyl-6-nitro-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (38d)



Yield: 70%.

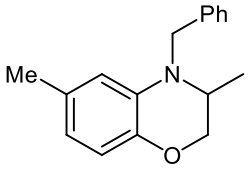
Colourless oil.

^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.52 (m, 2 H), 7.32 (m, 5 H), 6.84 (m, 1 H), 4.45 (m, 2 H), 4.19 (m, 2 H), 3.56 (m, 1 H), 1.23 (d, *J* = 6.2 Hz, 3 H) ppm.

IR: ṽ = 3400, 3063, 3031, 2973, 2924, 2873 cm^{-1}.

MS (ESI): m/z = 285.1 $[M+H]^+$. ($C_{16}H_{16}N_2O_3$).

4-Benzyl-3,6-dimethyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (38e)



Yield: 87%.

Colourless oil.

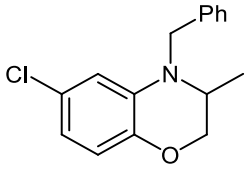
^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.31 (m, 5 H), 6.75 (d, *J* = 7.7 Hz, 1 H), 6.45 (m, 2 H), 4.47 (q, *J* = 16.5 Hz, 2 H), 4.10 (m, 2 H), 3.48 (m, 1 H), 2.19 (s, 3 H), 1.22 (d, *J* = 6.6 Hz, 3 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 141.7 (s), 139.1 (s), 134.8 (s), 131.4 (s), 128.8 (d), 127.2 (d), 127.0 (d), 118.0 (d), 116.1 (d), 113.6 (d), 69.4 (t), 53.2 (t), 51.3 (d), 21.4 (q), 15.7 (q) ppm.

IR: ṽ = 3400, 3063, 3031, 2973, 2924, 2873 cm^{-1}.

MS (ESI): m/z = 254.1 $[M+H]^+$. ($C_{17}H_{19}NO$).

4-Benzyl-6-chloro-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (38f)



Yield: 97%.

Colourless oil.

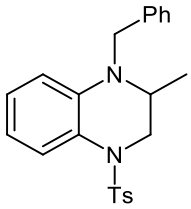
^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.31 (m, 5 H), 6.75 (d, *J* = 8.4 Hz, 1 H), 6.56 (m, 2 H), 4.44 (q, *J* = 16.5 Hz, 2 H), 4.09 (m, 2 H), 3.50 (m, 1 H), 1.23 (d, *J* = 6.6 Hz, 3 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 42.4 (s), 138.0 (s), 135.9 (s), 129.0 (d), 127.5 (d), 127.0 (d), 126.9 (s), 117.1 (d), 116.9 (d), 112.4 (d), 69.3 (t), 52.9 (t), 51.1 (d), 15.7 (q) ppm.

IR: $\tilde{\nu}$ = 3400, 3063, 3031, 2973, 2924, 2873 cm^{-1}.

MS (ESI): m/z = 274.5 $[M+H]^+$. ($C_{16}H_{16}ClNO$).

1-Benzyl-2-methyl-4-tosyl-1,2,3,4-tetrahydroquinoxaline (38g)



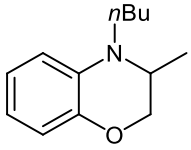
Yield: 30%.

Colourless oil.

^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.54 (d, *J* = 8.5 Hz, 2 H), 7.28 (m, 5 H), 7.06 (d, *J* = 2.6 Hz, 2 H), 6.93 (t, *J* = 6.6 Hz, 1 H). 6.66 (t, *J* = 6.9 Hz, 1 H), 6.47 (d, *J* = 1.2 Hz, 1 H), 4.23 (s, 2 H), 4.05 (dd, *J* = 13.9, 4.0 Hz, 1 H), 3.59 (m, 1 H), 3.24 (m, 1 H), 2.42 (s, 3 H), 1.06 (d, *J* = 6.2 Hz, 3 H) ppm.

MS (ESI): m/z = 415.2 $[M+H]^+$. ($C_{23}H_{24}N_2O_2S$).

4-Butyl-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (38h)



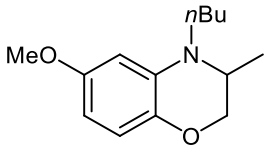
Yield: 10%.

Colourless oil.

^{1}H NMR (200 MHz; $CDCl_3$): δ = 6.77 (m, 2 H), 6.57 (m, 2 H), 4.01 (d, *J* = 1.8 Hz, 2 H), 3.44 (m, 1 H), 3.21 (m, 2 H), 1.56 (m, 2 H), 1.28 (m, 5 H), 0.95 (t, *J* = 7.3 Hz, 3 H) ppm.

MS (ESI): m/z = 206.1 $[M+H]^+$. ($C_{13}H_{19}NO$).

4-Butyl-6-methoxy-3-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (38i)



Yield: 35%.

^{1}H NMR (200 MHz; $CDCl_3$): δ = 6.70 (d, *J* = 8.4 Hz, 1H), 6.20 (m, 1 H), 6.11 (dd, *J* = 8.4, 2.6 Hz, 1 H), 3.94 (m, 2 H), 3.75 (s, 3 H), 3.40 (m, 1 H), 3.17 (m, 2 H), 1.58 (m, 2 H), 1.35 (m, 2 H), 1.20 (d, *J* = 6.6 Hz, 3 H), 0.95 (t, *J* = 7.3 Hz, 3 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 155.2 (s), 138.1 (s), 135.4 (s), 116.0 (d), 99.7 (d), 91.1 (d), 69.2 (t), 55.8 (q), 51.3 (d), 48.9 (t), 29.6 (t), 20.6 (t), 16.2 (q), 14.2 (q) ppm.

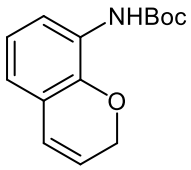
MS (ESI): m/z = 236.1 $[M+H]^+$. ($C_{14}H_{21}NO_2$).

General procedure for hydroarilation reaction

3a-f, 8 **39a-e**

To a solution of propargyl derivative **3** or **8** (1 equiv.) in toluene (5 ml/mmol) was added $PtCl_2$ (5 mol %) and was stirred at 80 °C for 3 h. The reaction mixture was concentrated in vacuo, brine was added and the mixture extracted with AcOEt (3 ×). The combined organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel.

***tert*-Butyl 2*H*-chromen-8-ylcarbamate (39a)**



Yield: 40%.

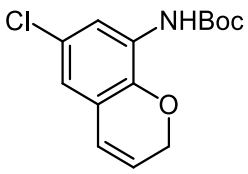
Colourless oil.

^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.91 (d, *J* = 8.2 Hz, 1 H), 6.93 (br. s, 1 H, exchange with D_2O), 6.84 (t, *J* = 7.9 Hz, 1 H), 6.64 (dd, *J* = 7.5, 1.4 Hz, 1 H), 6.41 (dt, *J* = 9.9, 1.8 Hz, 1 H), 5.76 (dt, *J* = 9.9, 3.5 Hz, 1 H), 4.83 (dd, *J* = 3.5, 1.9 Hz, 2 H), 1.54 (s, 9 H) ppm.

IR: ṽ = 3425, 2970, 1920, 1720 cm^{-1}.

MS (ESI): m/z = 270.0 $[M+Na]^+$. ($C_{14}H_{17}NO_3$).

***tert*-Butyl (6-chloro-2*H*-chromen-8-yl)carbamate (39b)**



Yield: 20%.

Colourless oil.

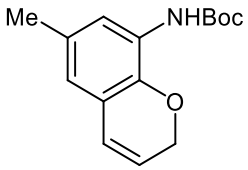
^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.99 (s, 1 H), 6.94 (br. s, 1 H, exchange with D_2O), 6.63 (d, *J* = 2.5 Hz, 1 H), 6.34 (dt, *J* = 9.9, 1.9 Hz, 1 H), 5.81 (dt, *J* = 9.9, 3.5 Hz, 1 H), 4.84 (dd, *J* = 3.5, 1.9 Hz, 2 H), 1.54 (s, 9 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 152.6 (s), 140.1 (s), 128.1 (s), 126.6 (s), 124.1 (d), 122.8 (d), 122.6 (s), 119.7 (d), 118.2 (d), 81.0 (s), 66.1 (t), 28.5 (q) ppm.

IR: ṽ = 3432, 2979, 2930, 1728 cm^{-1}.

MS (ESI): m/z = 304.0 $[M+Na]^+$. ($C_{14}H_{16}ClNO_3$).

tert-Butyl (6-methyl-2_H_-chromen-8-yl)carbamate (39c)



Yield: 65%.

Colourless oil.

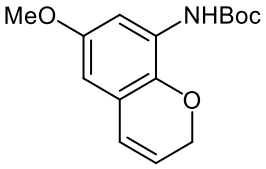
Massa: (m/z)

^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.72 (d, *J* = 16.2 Hz, 1 H), 6.88 (m, 1 H), 6.46 (br. s, 1 H, exchange with D_2O), 6.37 (dt, *J* = 9.8, 1.7 Hz, 1 H), 5.75 (dt, *J* = 9.8, 3.5 Hz, 1 H), 4.79 (dd, *J* = 3.5, 1.8 Hz, 2 H) 2.24 (s, 3 H), 1.53 (s, 9 H) ppm.

IR: ṽ = 3436, 2977, 2920, 1728 cm^{-1}.

MS (ESI): m/z = 284.0 $[M+Na]^+$. ($C_{15}H_{19}NO_3$).

tert-Butyl (6-methoxy-2_H_-chromen-8-yl)carbamate (39d)



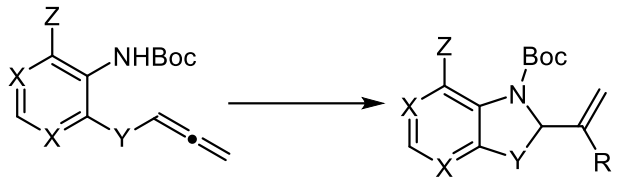
Yield: 65%.

^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.61 (d, *J* = 2.6 Hz, 1 H), 6.94 (s, 1 H), 6.37 (m, 1 H), 6.23 (d, *J* = 2.6 Hz, 1 H), 5.81 (m, 1 H), 4.75 (m, 2 H), 3.76 (s, 3 H), 1,52 (s, 9 H) ppm.

IR: ṽ = 3435, 2911, 2934, 2844, 1727 cm^{-1}.

MS (ESI): m/z = 300.1 $[M+Na]^+$. ($C_{15}H_{19}NO_4$).

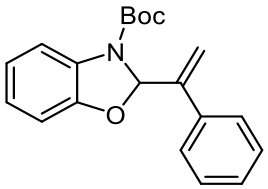
General procedure for the carboamination reactions



11a-d, 12, 22, 27 → **43a-p, 44a-b**

K_2CO_3 (1.4 equiv.), $Pd(PPh_3)_4$ (5 mol %) and the corresponding aryl iodide or bromide (1.4 equiv.) was added to a solution of the corresponding allene (1 equiv.) in MeCN (20 mL/mmol) and the mixture was heated at 80 °C for 8 h. The reaction mixture was concentrated in vacuo, then brine was added and the mixture extracted with AcOEt (3 ×). The organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel.

***tert*-Butyl 2-(1-Phenylvinyl)benzo[*d*]oxazole-3(2*H*)-carboxylate (43a)**



Yield: 76%.

White solid; m.p.: 76 - 78 °C.

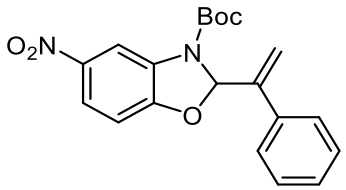
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (br. s, 1 H), 7.44–7.46 (m, 2 H), 7.29–7.36 (m, 3 H), 6.87–6.94 (m, 2 H), 6.79 (d, *J* = 8.5 Hz, 2 H), 5.55 (s, 1 H), 5.52 (s, 1 H), 1.53 (s, 9 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.3 (s), 149.9 (s), 144.9 (s), 137.5 (s), 130.2 (s), 128.3 (d), 128.0 (d), 127.2 (d), 123.3 (d), 121.2 (d), 117.0 (t), 113.8 (d), 108.8 (d), 94.5 (d), 82.3 (s), 28.2 (q) ppm.

IR: $\tilde{\nu}$ = 3411, 2970, 2930, 1722, 1600 cm^{-1}.

MS (ESI): m/z = 346.0 $[M+Na]^+$. ($C_{20}H_{21}NO_3$).

tert-Butyl 5-nitro-2-(1-phenylvinyl)benzo[_d_]oxazole-3(2_H_)-carboxylate (43b)



Yield: 62%.

Colourless oil.

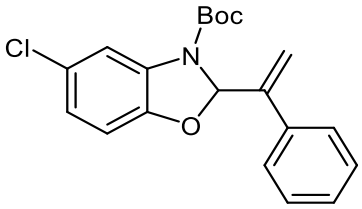
^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.28 (br. s, 1 H), 7.90 (dd, *J* = 8.7, 2.4 Hz, 1 H), 7.26–7.39 (m, 5 H), 6.87 (br. s, 1 H), 6.77 (d, *J* = 8.7 Hz, 1 H), 5.57 (s, 1 H), 5.53 (s, 1 H), 1.53 (s, 9 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.5 (s), 149.8 (s), 144.2 (s), 142.9 (s), 136.9 (s), 132.4 (d), 131.4 (s), 128.6 (d), 127.5 (d), 121.2 (d), 109.5 (d), 118.7 (t), 108.1 (d), 97.2 (d), 83.9 (s), 28.3 (q), ppm.

IR: $\tilde{\nu}$ = 3423, 2978, 2933, 1721 cm^{-1}.

MS (ESI): m/z = 391.0 $[M+Na]^+$. ($C_{20}H_{20}N_2O_5$).

tert-Butyl 5-chloro-2-(1-phenylvinyl)benzo[_d_]oxazole-3(2_H_)-carboxylate (43c)



Yield: 54%.

Colourless oil.

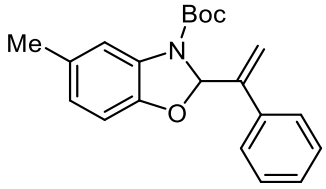
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.49 (s, 9 H), 5.48 (s, 1 H), 5.53 (s, 1 H), 6.65 (d, *J* = 8.4 Hz, 1 H), 6.75 (s, 1 H), 6.85 (dd, *J* = 8.4, 2.2 Hz, 1 H), 7.26–7.65 (m, 6 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.4 (q), 83.1 (s), 95.8 (d), 109.3 (d), 114.4 (d), 117.7 (t), 123.0 (d), 126.4 (s), 127.5 (d), 128.4 (d), 128.6 (d), 131.6 (s), 137.4 (s), 144.7 (s), 149.0 (s), 150.1 (s) ppm.

IR: $\tilde{\nu}$ = 3415, 2980, 2930, 1721 cm^{-1}.

MS (ESI): m/z = 380.0 $[M+Na]^+$. ($C_{20}H_{20}ClNO_3$).

tert-Butyl 5-methyl-2-(1-phenylvinyl)benzo[_d_]oxazole-3(2_H_)-carboxylate (43d)



Yield: 48%.

Colourless oil.

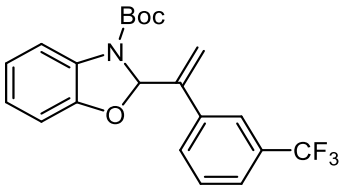
^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.37–7.46 (m, 3 H), 7.27–7.36 (m, 3 H), 6.63–6.73 (m, 3 H), 5.52 (s, 1 H), 5.48 (s, 1 H), 2.30 (s, 3 H), 1.50 (s, 9 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 150.5 (s), 148.1 (s), 145.0 (s), 137.8 (s), 131.1 (s), 130.3 (s), 128.6 (d), 128.2 (d), 127.4 (d), 123.6 (d), 117.1 (t), 114.9 (d), 108.4 (d), 94.9 (d), 82.4 (s), 28.4 (q), 21.4 (q) ppm.

IR: $\tilde{\nu}$ = 3436, 2976, 2920, 1708 cm^{-1}.

MS (ESI): m/z = 360.0 $[M+Na]^+$. ($C_{21}H_{23}NO_3$).

tert-Butyl 2-(1-(3-(trifluoromethyl)phenyl)vinyl)benzo[_d_]oxazole-3(2_H_)-carboxylate (43e)



Yield: 57%.

White solid; m.p.: 58 - 60 °C.

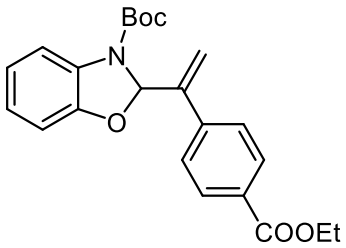
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (br. s, 1 H), 7.55– 7.60 (m, 2 H), 7.22–7.44 (m, 2 H), 6.86–6.94 (m, 2 H), 6.79 (d, J = 7.5 Hz, 1 H), 6.76 (br. s, 1 H), 5.62 (s, 1 H), 5.58 (s, 1 H), 1.54 (s, 9 H), ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9 (s), 149.8 (s), 138.2 (s), 130.9 (s), 130.6 (d), 130.2 (s), 128.7 (d), 124.7 (d), 124.3 (d), 124.0 (s), 123.4 (d), 123.1 (s), 121.4 (d), 118.7 (t), 113.8 (d), 108.8 (d), 94.4 (d), 82.5 (s), 28.2 (q), ppm.

IR: $\tilde{\nu}$ = 3420, 2985, 2973, 1717 cm^{-1}.

MS (ESI): m/ z = 414.0 $[M+Na]^+$. ($C_{21}H_{20}F_3NO_3$).

tert-Butyl 2-(1-(4-(ethoxycarbonyl)phenyl)vinyl)benzo[_d_]oxazole-3(2_H_)-carboxylate (43f)



Yield: 78%.

Colourless oil.

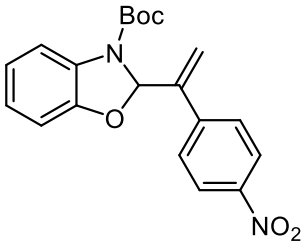
^{1}H NMR (200 MHz, CDCl3): δ = 7.94–8.00 (m, 2 H), 7.44–7.50 (m, 3 H), 6.85–6.91 (m, 2 H), 6.73–6.78 (m, 2 H), 5.59 (s, 1 H), 5.58 (s, 1 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 1.50 (s, 9 H), 1.38 (t, *J* = 7.1 Hz, 3 H), ppm.

^{13}C NMR (50 MHz, CDCl3): δ = 166.5 (s), 150.5 (s), 150.1 (s), 144.3 (s), 142.2 (s), 130.2 (s), 130.1 (s), 129.8 (d), 127.5 (d), 123.6 (d), 121.6 (d), 118.9 (t), 114.1 (d), 109.0 (d), 94.7 (d), 82.7 (s), 61.2 (t), 28.4 (q), 14.5 (q) ppm.

IR: $\tilde{\nu}$ = 3415, 3059, 2979, 1712, 1609 cm^{-1}.

MS (ESI): m/z = 418.0 [M+Na]$^{+}$. ($C_{23}H_{25}NO_5$).

tert-Butyl 2-(1-(4-nitrophenyl)vinyl)benzo[_d_]oxazole-3(2_H_)-carboxylate (43g)



Yield: 71%.

Colourless oil.

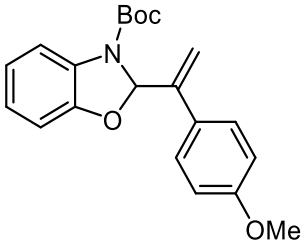
^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 6.6, 1.8 Hz, 2 H), 7.56 (dd, *J* = 6.6, 1.8 Hz, 2 H), 7.29–7.49 (br. s, 1 H), 6.86–6.95 (m, 2 H), 6.74–6.79 (m, 2 H), 5.67 (s, 1 H), 5.63 (s, 1 H), 1.51 (s, 9 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 150.5 (s), 149.9 (s), 147.8 (s), 144.3 (s), 143.5 (s), 129.9 (s), 128.5 (d), 123.8 (d), 123.7 (d), 121.8 (d), 120.4 (t), 114.2 (d), 109.1 (d), 94.5 (d), 83.0 (s), 28.4 (q) ppm.

IR: $\tilde{\nu}$ = 3412, 3073, 2978, 2933, 1712 cm^{-1}.

MS (ESI): m/z = 391.0 [M+Na]$^{+}$. ($C_{20}H_{20}N_2O_5$).

tert-Butyl 2-(1-(4-methoxyphenyl)vinyl)benzo[_d_]oxazole-3(2_H_)-carboxylate (43h)



Yield: 65%.

Colourless oil.

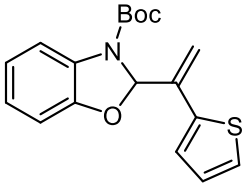
^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.55 (br. s, 1 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 6.75–6.95 (m, 6 H), 5.48 (s, 1 H), 5.42 (s, 1 H), 3.79 (s, 3 H), 1.52 (s, 9 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.8 (s), 150.6 (s), 150.3 (s), 144.3 (s), 130.4 (s), 130.2 (s), 128.6 (d), 123.5 (d), 121.5 (d), 116.0 (t), 114.1 (d), 114.0 (d), 109.0 (d), 95.0 (d), 82.4 (s), 55.4 (q), 28.5 (q) ppm.

IR: $\tilde{\nu}$ = 3414, 2978, 2934, 1713, 1609 cm^{-1}.

MS (ESI): m/z = 376.0 $[M+Na]^+$. ($C_{21}H_{23}NO_4$).

tert-Butyl 2-(1-(thiophen-2-yl)vinyl)benzo[_d_]oxazole-3(2_H_)-carboxylate (43i)



Yield: 64%.

Colourless oil.

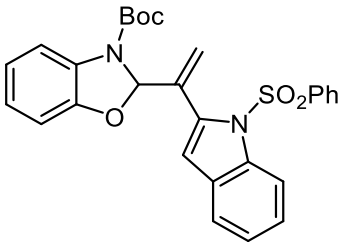
^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.37–7.66 (br. s, 1 H), 7.20 (dd, *J* = 5.1, 1.1 Hz, 1 H), 7.10 (d, *J* = 3.2 Hz, 1 H), 6.85–6.98 (m, 3 H), 6.76–6.80 (m, 1 H), 6.72 (br. s, 1 H), 5.65 (s, 1 H), 5.41 (s, 1 H), 1.50 (s, 9 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 150.5 (s), 150.3 (s), 139.5 (s), 138.3 (s), 130.3 (s), 127.6 (d), 125.5 (d), 125.4 (d), 123.6 (d), 121.6 (d), 116.3 (t), 114.1 (d), 109.1 (d), 94.8 (d), 82.7 (s), 28.4 (q) ppm.

IR: $\tilde{\nu}$ = 3410, 3072, 2977, 2931, 1713 cm^{-1}.

MS (ESI): m/z = 352.0 $[M+Na]^+$. ($C_{18}H_{19}NO_3S$).

tert-Butyl 2-(1-(1-(phenylsulfonyl)-1_H_-indol-3-yl)vinyl)-benzo[_d_]oxazole-3(2_H_)-carboxylate (43j)



Yield: 67%.

Colourless oil.

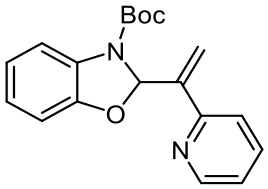
^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.91 (dd, *J* = 6.6, 1.5 Hz, 1 H), 7.66 (dd, *J* = 7.0, 2.5 Hz, 1 H), 7.44–7.62 (m, 4 H), 7.19–7.42 (m, 5 H), 6.80–7.00 (m, 3 H), 6.67 (br. s, 1 H), 5.78 (s, 1 H), 5.70 (s, 1 H), 1.47 (s, 9 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 150.5 (s), 138.1 (s), 136.3 (s), 136.2 (s), 134.9 (d), 133.9 (d), 130.3 (s), 129.5 (d), 127.4 (s), 127.0 (d), 125.0 (d), 124.3 (d), 123.7 (d), 123.6 (d), 121.6 (d), 120.6 (s), 120.3 (t), 117.9 (s), 113.9 (d), 113.7 (d), 108.7 (d), 96.3 (d), 82.7 (s), 28.4 (q) ppm.

IR: $\tilde{\nu}$ = 3415, 2977, 2931, 1711 cm^{-1}.

MS (ESI): m/ z = 525.0 $[M+Na]^+$. ($C_{28}H_{26}N_2O_5S$).

tert-Butyl 2-(1-(pyridin-2-yl)vinyl)benzo[_d_]oxazole-3(2_H_)-carboxylate (43k)



Yield: 86%.

White solid; m.p.: 86 - 88 °C.

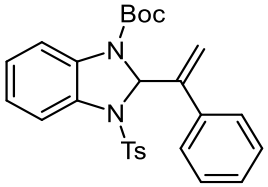
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.66 (d, *J* = 4.1 Hz, 1 H), 7.69 (t, *J* = 7.4 Hz, 1 H), 7.58 (d, *J* = 7.8 Hz, 1 H), 7.48 (br. s, 1 H), 7.31 (br. s, 1 H), 7.21–7.24 (m, 1 H), 6.87–6.97 (m, 2 H), 6.77–6.79 (m, 1 H), 6.04 (s, 1 H), 5.65 (s, 1 H), 1.50 (s, 9 H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1 (s), 150.4 (s), 150.0 (s), 149.0 (d), 136.6 (d), 130.1 (s), 130.0 (s), 123.4 (d), 122.7 (d), 121.2 (d), 120.8 (d), 117.6 (t), 113.9 (d), 109.1 (d), 91.9 (d), 82.2 (s), 28.2 (q) ppm.

IR: $\tilde{\nu}$ = 3434, 3058, 2978, 2292, 1871, 1716 cm^{-1}.

MS (ESI): m/z = 347.1 $[M+Na]^+$. ($C_{19}H_{20}N_2O_3$).

***tert*-Butyl 2-(1-phenylvinyl)-3-tosyl-2,3-dihydro-1*H*-benzo[*d*]-imidazole-1-carboxylate (43l)**



Yield: 86%.

Pale yellow solid; m.p.: 99 - 101 °C.

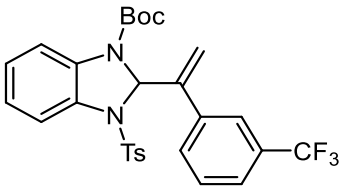
^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.53 (dd, *J* = 7.3, 1.8 Hz, 1 H), 7.38 (d, *J* = 8.1 Hz, 2 H), 7.23–7.32 (m, 5 H), 7.10 (d, *J* = 8.1 Hz, 2 H), 6.95–7.03 (m, 3 H), 6.52 (br. s, 1 H), 5.38 (s, 1 H), 5.24 (s, 1 H), 2.31 (s, 3 H), 1.36 (s, 9 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 150.1 (s), 145.4 (s), 144.8 (s), 138.0 (s), 135.3 (s), 133.3 (s), 131.9 (s), 129.7 (d), 128.4 (d), 128.2 (d), 128.1 (d), 127.6 (d), 127.0 (d), 123.5 (d), 119.6 (d), 117.3 (t), 115.2 (d), 82.3 (s), 78.6 (d), 28.2 (q), 21.7 (q) ppm.

IR: $\tilde{\nu}$ = 3402, 2973, 2928, 1709 cm^{-1}.

MS (ESI): m/z = 499.0 $[M+Na]^+$. ($C_{27}H_{28}N_2O_4S$).

***tert*-Butyl**
3-Tosyl-2-(1-(3-(trifluoromethyl)phenyl)vinyl)-2,3-dihydro-1*H*-benzo[*d*]imidazole-1carboxylate (43m)



Yield: 70%.

White solid; m.p.: 114 - 116 °C.

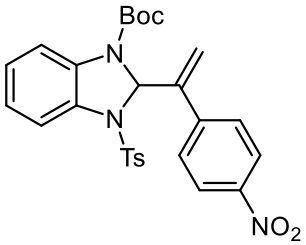
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.62 (m, 8 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 7.06–7.12 (m, 1 H), 7.03 (d, *J* = 7.6 Hz, 1 H), 6.58 (br. s, 1 H), 5.51 (br. s, 1 H), 5.32 (s, 1 H), 2.34 (s, 3 H), 1.38 (s, 9 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 149.9 (s), 144.8 (s), 144.4 (s), 138.7 (s), 134.9 (s), 133.1 (s), 131.8 (d), 130.8 (s), 129.7 (d), 128.6 (d), 127.5 (d), 126.9 (d), 125.3 (d), 125.2 (d), 124.7 (d), 123.9 (s), 123.6 (d), 121.4 (s), 118.6 (t), 115.2 (d), 82.5 (s), 78.6 (d), 28.2 (q), 21.6 (q) ppm.

IR: $\tilde{\nu}$ = 3435, 2980, 2932, 1716 cm^{-1}.

MS (ESI): m/z = 567.0 $[M+Na]^+$. ($C_{28}H_{27}F_3N_2O_4S$).

***tert*-Butyl 2-(1-(4-nitrophenyl)vinyl)-3-tosyl-2,3-dihydro-1*H*benzo[*d*]imidazole-1-carboxylate (43n)**



Yield: 65%.

Pale-yellow solid; m.p.: 145 - 147 °C.

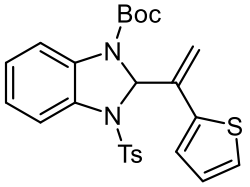
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.5 Hz, 2 H), 7.45–7.53 (m, 3 H), 7.39 (d, *J* = 7.9 Hz, 2 H), 7.02–7.20 (m, 5 H), 6.61 (br. s, 1 H), 5.51 (s, 1 H), 5.36 (s, 1 H), 2.34 (s, 3 H), 1.41 (s, 9 H) ppm.

^{13}C NMR (50 MHz, CDCl3): δ = 147.7 (s), 145.0 (s), 144.7 (s), 143.8 (s), 134.9 (s), 132.9 (s), 131.8 (s), 129.8 (d), 129.4 (d), 127.5 (d), 127.2 (d), 125.3 (s), 123.8 (d), 123.4 (d), 119.3 (t), 115.3 (d), 82.8 (s), 28.3 (q), 21.7 (q), ppm.

IR: $\tilde{\nu}$ = 3413, 3071, 2980, 2932, 2258, 1925, 1713 cm^{-1}.

MS (ESI): m/z = 544.2 $[M+Na]^+$. ($C_{27}H_{27}N_3O_6S$).

***tert*-Butyl 2-(1-(thiophen-2-yl)vinyl)-3-tosyl-2,3-dihydro-1*H*benzo[*d*]imidazole-1-carboxylate (43o)**



Yield: 46%.

Yellow solid; m.p.: 141 - 142 °C

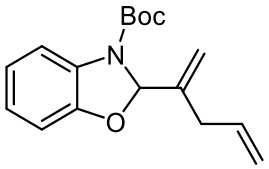
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.39 (s, 9 H), 2.33 (s, 3 H), 5.23 (s, 1 H), 5.47 (s, 1 H), 6.52 (br. s, 1 H), 6.94 (dd, *J* = 5.13, 3.6 Hz, 2 H), 7.01– 7.33 (m, 6 H), 7.41 (d, *J* = 8.4 Hz, 2 H), 7.55 (d, *J* = 8.1 Hz, 1 H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.8 (q), 28.3 (q), 78.5 (d), 82.6 (s), 114.9 (d), 116.8 (t), 119.6 (d), 123.5 (d), 125.4 (d), 126.3 (d), 127.0 (d), 127.6 (d), 127.7 (d), 129.7 (d), 132.0 (s), 133.2 (s), 135.5 (s), 138.6 (s), 139.4 (s), 144.9 (s), 150.0 (s) ppm.

IR: $\tilde{\nu}$ = 3429, 2971, 2921, 1709 cm^{-1}.

MS (ESI): m/z = 505.1 $[M+Na]^+$. ($C_{25}H_{26}N_2O_4S_2$).

tert-Butyl 2-(penta-1,4-dien-2-yl)benzo[_d_]oxazole-3(2_H_)-carboxylate



Yield: 65%.

Colourless oil.

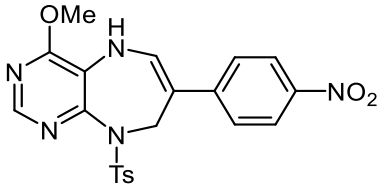
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (br. s, 1 H), 6.86–6.94 (m, 2 H), 6.78 (d, *J* = 7.1 Hz, 1 H), 6.41 (br. s, 1 H), 5.81 (m, 1 H), 5.32 (s, 1 H), 5.13 (s, 1 H), 5.00–5.06 (m, 2 H), 2.82 (s, 2 H), 1.56 (s, 9 H), ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6 (s), 150.3 (s), 143.1 (s), 134.9 (d), 130.1 (s), 123.2 (d), 121.1 (d), 116.9 (t), 116.2 (t), 113.8 (d), 108.3 (d), 95.8 (d), 82.2 (s), 33.7 (t), 28.3 (q), ppm.

IR: ṽ = 3401, 3079, 2978, 2931, 1713 cm^{-1}.

MS (ESI): m/z = 309.9 $[M+Na]^+$. ($C_{17}H_{21}NO_3$).

4-Methoxy-7-(4-nitrophenyl)-9-tosyl-8,9-dihydro-5_H_-pyrimido[4,5-_b_][1,4]diazepine (44a)



Yield: 35%.

Orange solid; m.p.: 235 - 238 °C

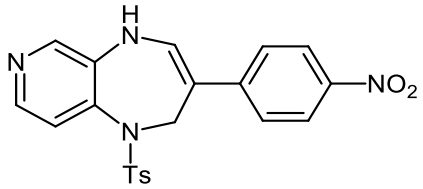
^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.22 (s, 1 H), 8.16 (d, *J* = 9.1 Hz, 2 H), 7.98 (d, *J* = 8.1 Hz, 2 H), 7.41 (d, *J* = 9.1 Hz, 2 H), 7.30 (d, *J* = 8.1 Hz, 2 H), 6.67 (d, *J* = 7.0 Hz, 1 H), 6.51 (br. d, *J* = 7.0 Hz, 1 H, exchange with D_2O), 4.55 (s, 2 H), 4.07 (s, 3 H), 2.43 (s, 3 H) ppm.

^{13}C NMR (50 MHz, DMSO): δ = 160.5 (s), 147.6 (s), 147.4 (d), 146.2 (s), 144.8 (s), 144.2 (s), 138.3 (s), 132.6 (d), 130.1 (d), 128.4 (d), 124.8 (d), 124.6 (d), 119.5 (s), 112.2 (s), 55.4 (q), 50.0 (t), 21.7 (q) ppm.

IR: ṽ = 3368, 2921, 1712, 1645 cm^{-1}.

MS (ESI): m/z = 452.2 $[M]^-$. ($C_{21}H_{19}N_5O_5S$).

3-(4-Nitrophenyl)-1-tosyl-2,5-dihydro-1*H*-pyrido[3,4-*b*][1,4]diazepine (44b)



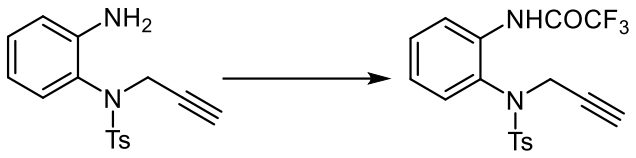
Yield: 42%.

Orange oil.

^{1}H MNR (200 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.0 Hz, 2 H); 8.16 (d, *J* = 9.1 Hz, 2 H); 8.00 (d, *J* = 5.1 Hz, 1 H); 7.86 (s, 1 H); 7.53 (d, *J* = 5.1 Hz, 1 H); 7.52 (d, *J* = 8.0 Hz, 2 H); 7.41 (d, *J* = 9.1 Hz, 2 H); 6.36 (s, 1 H); 5.51 (s, 2 H); 4.39 (br. s, 1 H, exchange with D_2O) ppm.

MS (ESI): m/z = 421.2 $[M]^-$. ($C_{21}H_{18}N_4O_4S$).

Synthesis of
2,2,2-trifluoro-*N*-(2-(4-methyl-*N*-(prop-2-yn-1-yl)phenylsulfonamido)phenyl)acetamide (45)



7 **45**

The compound **7** (1 equiv.) was dissolved in THF (3.5 mL/mmol) and the solution cooled to 0 °C, then $(CF_3CO)_2O$ (3.5 equiv.) was added dropwise. The resulting mixture was stirred for 1 h. After completion of the reaction the mixture was concentrated under reduced pressure and extracted with AcOEt (3 ×). The organic phases were washed with a saturated solution of $NaHCO_3$ (2 x) and water, dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel.

Yield: 75%.

Pale-yellow solid; m.p.: 133 -135 °C.

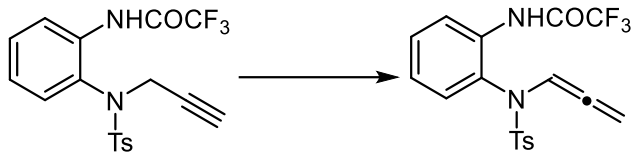
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.15 (br. s, 1 H, exchange with D_2O), 8.24 (dd, *J* = 8.3, 1.4 Hz, 1 H), 7.54 (d, *J* = 8.4 Hz, 2 H), 7.41 (td, *J* = 8.4, 1.4 Hz, 1 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.09 (td, *J* = 8.0, 1.4 Hz, 1 H), 6.80 (dd, *J* = 8.3, 1.4 Hz, 1 H), 4.48 (br. s, 1 H), 4.30 (br. s, 1 H), 2.45 (s, 3 H), 2.21 (t, *J* = 2.6 Hz, 1 H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.3 (q, *J* = 38.0 Hz), 145.2 (s), 135.4 (s), 133.9 (s), 130.4 (d), 130.0 (s), 129.9 (d), 128.9 (d), 128.5 (d), 126.5 (d), 123.0 (d), 115.9 (q, *J* = 288.6 Hz), 77.2 (s), 74.6 (d), 42.2 (t), 21.9 (q) ppm.

IR: $\tilde{\nu}$ = 3393, 3206, 3069, 2923, 2126, 1738, 1597, 1548 cm^{-1}.

MS (ESI): m/z = 419.0 $[M+Na]^+$. ($C_{18}H_{15}F_3N_2O_3S$).

Synthesis of
2,2,2-trifluoro-*N*-(2-(4-methyl-*N*-(propa-1,2-dien-1-yl)phenylsulfonxamido)phenyl)acetamide (46)



45 **46**

The compound **45** (1 equiv.) was dissolved in THF (15 mL/mmol). The solution was cooled to 0 °C and *t*BuOK (2 equiv) was added in one portion. The reaction was stirred for 5 min, then water was added and the mixture was extracted with AcOEt (3 × 50 mL). The solvent was removed in vacuo and the crude was purified by flash chromatography on silica gel to afford the product.

Yield: 35%.

Pale-yellow solid; m.p.: 111 - 114 °C.

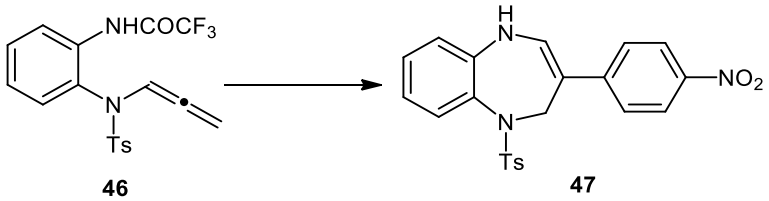
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.80 (br. s, 1 H, exchange with D_2O), 8.23 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.56 (d, *J* = 8.3 Hz, 2 H), 7.39 (td, *J* = 8.0, 1.4 Hz, 1 H), 7.30 (d, *J* = 8.3 Hz, 2 H), 7.10 (t, *J* = 6.2 Hz, 1 H), 7.03 (td, *J* = 8.0, 1.4 Hz, 1 H), 6.55 (dd, *J* = 8.0, 1.4 Hz, 1 H), 5.05 (d, *J* = 6.2 Hz, 2 H), 2.46 (s, 3 H), ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.7 (s), 155.1 (q, *J* = 37.5 Hz), 145.4 (s), 134.6 (s), 133.8 (s), 130.4 (d), 130.3 (d), 130.1 (d), 128.2 (d), 127.8 (s), 125.9 (d), 122.8 (d), 115.8 (q, *J* = 289.6 Hz), 101.9 (d), 88.7 (t), 21.8 (q), ppm.

IR: $\tilde{\nu}$ = 3403, 3057, 2922, 1966, 1931, 1744, 1733, 1598, 1543 cm^{-1}.

MS (ESI): m/z = 419.0 $[M+Na]^+$. ($C_{18}H_{15}F_3N_2O_3S$).

Synthesis of
3-(4-nitrophenyl)-5-tosyl-2,5-dihydro-1*H*-benzo[*b*][1,4]diazepine (47)



46 **47**

K_2CO_3 (1.4 equiv.), $Pd(PPh_3)_4$ (5 mol %) and 1-iodo-4-nitrobenzene (1.4 equiv.) was added to a solution of the compound **46** (1 equiv.) in MeCN (20 mL/mmol) and the mixture was heated at 80 °C for 8 h. The reaction mixture was concentrated in vacuo, then brine was added and the mixture extracted with AcOEt (3 ×). The organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel.

Yield: 78%.

Red solid; m.p.: 215 - 217 °C.

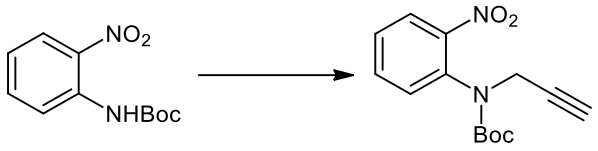
^{1}H NMR (500 MHz, DMSO): δ = 8.78 (d, *J* = 7.1 Hz, 1 H, exchange with D_2O), 8.15 (d, *J* = 9.0 Hz, 2 H), 7.33 (d, *J* = 9.0 Hz, 2 H), 7.13– 7.28 (m, 6 H), 6.90–6.96 (m, 2 H), 6.28 (d, *J* = 7.2 Hz, 1 H), 4.70 (br. s, 2 H), 2.38 (s, 3 H), ppm.

^{13}C NMR (125 MHz, DMSO): δ = 148.8 (s), 144.4 (s), 144.1 (s), 141.4 (s), 137.6 (s), 132.5 (d), 132.3 (d), 129.9 (d), 128.9 (s), 128.8 (d), 128.0 (d), 124.7 (d), 124.6 (d), 121.9 (d), 120.4 (s), 107.9 (s), 52.1 (t), 21.9 (q) ppm.

IR: $\tilde{\nu}$ = 3372, 3064, 2921, 2431, 1736, 1644, 1584 cm^{-1}.

MS (ESI): *m*/*z* = 444.2 $[M+Na]^+$. ($C_{22}H_{19}N_3O_4S$).

Synthesis of *tert*-butyl *N*-(2-Nitrophenyl)-*N*-(prop-2-yn-1-yl)carbamate (49)



48 **49**

A solution of compound **48** (1 equiv.) in THF/DMF (5 mL/1 mL) was cooled to 0 °C and NaH (1.5 equiv.) was added. The mixture was stirred for 15 min at 0 °C and propargyl bromide (1.5 equiv.) was added. The resulting mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was extracted with AcOEt (3 ×) and then washed with brine. The organic phases were dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel.

Yield: 85%.

Pale-yellow solid; m.p.: 52 - 55 °C.

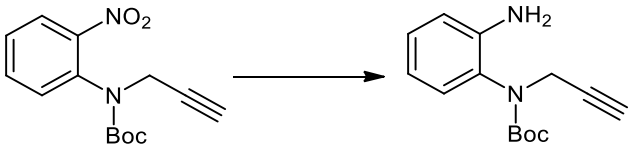
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.0 Hz, 1 H), 7.57–7.66 (m, 2 H), 7.41–7.46 (m, 1 H), 4.81 (dd, *J* = 17.8, 2.0 Hz, 1 H), 4.12 (dd, *J* = 17.8, 2.0 Hz, 1 H), 2.27 (t, *J* = 2.4 Hz, 1 H), 1.51 (s, 3 H), 1.30 (s, 6 H) ppm.

^{13}C NMR (75 MHz, CDCl3): δ = 152.9 (s), 146.8 (s), 135.4 (s), 133.8 (d), 130.3 (d), 128.2 (d), 125.1 (d), 82.4 (s), 79.5 (s), 73.1 (d), 39.3 (t), 28.0 (q) ppm.

R: ṽ = 3393, 3254, 2980, 2118, 1703, 1606, 1580, 1525 cm^{-1}.

MS (ESI): m/z = 298.9 $[M+Na]^+$. ($C_{14}H_{16}N_2O_4$).

Synthesis of *tert*-butyl *N*-(2-aminophenyl)-*N*-(prop-2-yn-1-yl)carbamate (50)



49 **50**

Fe powder (6 equiv.) was added to a suspension of compound **49** (1 equiv.) in a mixture of AcOH (20 % in H_2O, 2.5 ml/mmol), EtOH (5 ml/mmol). The resulting suspension was heated at reflux for 3 h. The reaction mixture was filtered through a pad of Celite using AcOEt as eluent to remove the excess iron. The filtrate was washed with water (3 ×), dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the product.

Yield: 98%.

Colourless oil.

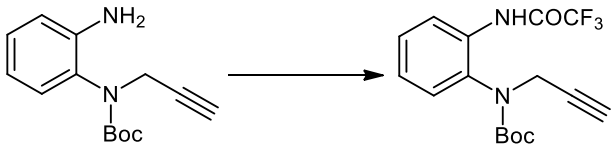
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06–7.12 (m, 2 H), 6.77 (d, *J* = 8.0 Hz, 2 H), 4.32 (br. s, 1 H), 4.23 (br. s, 1 H), 3.72 (br. s, 2 H, exchange with D_2O), 2.24 (s, 1 H), 1.42 (s, 9 H), ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.9 (s), 143.2 (s), 128.7 (d), 128.6 (d), 128.3 (s), 118.9 (d), 116.4 (d), 80.3 (s), 77.5 (s), 72.0 (d), 38.8 (t), 28.5 (q), ppm.

IR: ṽ = 3467, 3367, 3290, 2979, 2932, 2119, 1694, 1621, 1503 cm^{-1}.

MS (ESI): m/z = 268.9 $[M+Na]^+$. ($C_{14}H_{18}N_2O_2$).

Synthesis of *tert*-butyl *N*-Prop-2-yn-1-yl-*N*-(2-(2,2,2-trifluoroacetamido)-phenyl)carbamate (51)



50 **51**

The compound **50** (1 equiv.) was dissolved in THF (5 mL) and the solution cooled to 0 °C, then $(CF_3CO)_2O$ (1.5 equiv.) was added dropwise. The resulting mixture was stirred for 1h. After completion of the reaction the mixture was concentrated under reduced pressure and extracted with AcOEt (3 ×). The organic phases were washed with a saturated solution of $NaHCO_3$ (2 x) and water, dried with Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel.

Yield: 75%.

White solid; m.p.: 55 - 58 °C.

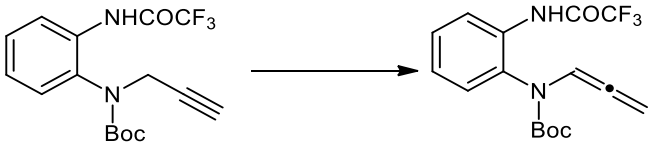
1H NMR (300 MHz, CD_3CN): δ = 8.84 (br. s, 1 H, exchange with D_2O), 7.80 (d, *J* = 7.6 Hz, 1 H), 7.52 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.35–7.47 (m, 2 H), 4.33 (s, 2 H), 2.60 (t, *J* = 2.5 Hz, 1 H), 1.43 (s, 9 H), ppm.

^{13}C NMR (75 MHz, CD_3CN): δ = 155.3 (q, *J* = 37.0 Hz), 153.8 (s), 135.5 (s), 132.3 (s), 128.4 (d), 128.0 (d), 127.8 (d), 124.9 (d), 114.7 (q, *J* = 288.0 Hz), 81.8 (s), 80.0 (s), 72.9 (d), 39.9 (t), 27.5 (q), ppm.

IR: $\tilde{\nu}$ = 3314, 3262, 2985, 2936, 1732, 1686, 1674, 1601, 1589 cm^{-1}.

MS (ESI): m/ z = 364.9 $[M+Na]^+$. ($C_{16}H_{17}F_3N_2O_3$).

Syntesis of *tert*-butyl *N*-(propa-1,2-dien-1-yl)-*N*-(2-(2,2,2-trifluoroacetamido) phenyl)carbamate (52)



51 **52**

The compound **51** (1 equiv.) was dissolved in THF (15 ml/mmol). The solution was cooled to 0 °C and *t*BuOK (2 equiv) was added in one portion. The reaction was stirred for 5 min, then water was added and the mixture was extracted with AcOEt (3 × 50 mL). The solvent was removed in vacuo and the crude was purified by flash chromatography on silica gel to afford the product.

Yield: 85%.

Colourless oil.

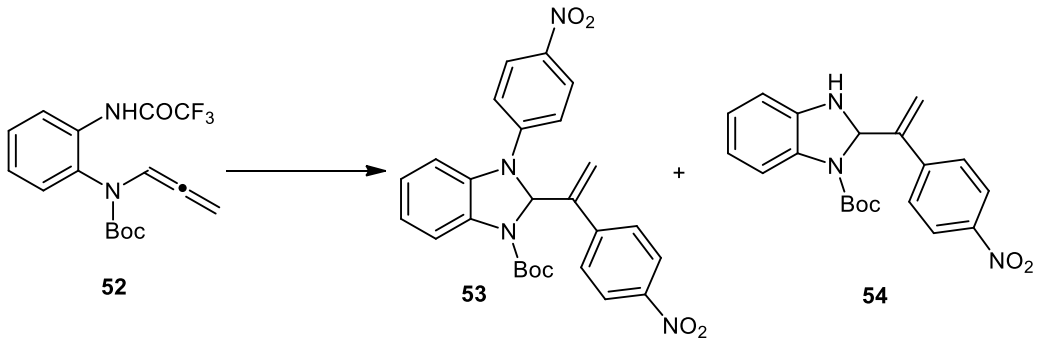
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (br. s, 1 H, exchange with D_2O), 8.05 (d, *J* = 8.2 Hz, 1 H), 7.32–7.39 (m, 2 H), 7.20–7.28 (m, 2 H), 5.05 (d, *J* = 6.3 Hz, 2 H), 1.45 (s, 9 H), ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.7 (s), 155.0 (q, *J* = 37.5 Hz), 152.2 (s), 132.1 (s), 130.7 (s), 129.3 (d), 129.2 (d), 129.1 (d), 126.3 (d), 116.0 (q, *J* = 288.6 Hz), 101.1 (d), 87.7 (t), 83.3 (s), 28.2 (q), ppm.

IR: $\tilde{\nu}$ = 3414, 3292, 2982, 1715, 1600, 1540 cm^{-1}.

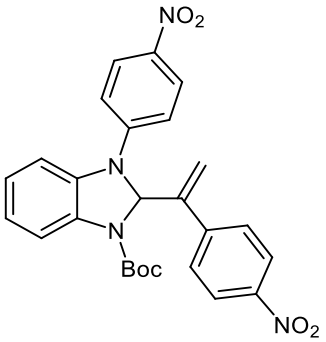
MS (ESI): m/z = 364.9 $[M+Na]^+$. ($C_{16}H_{17}F_3N_2O_3$).

Synthesis of
***tert*-Butyl 3-(4-nitrophenyl)- 2-(1-(4-nitrophenyl)vinyl)-2,3-dihydro-1*H*-benzo[*d*]imidazole-1-carboxylate (53)**
and
***tert*-Butyl 2-(1-(4-nitrophenyl)vinyl]-2,3-dihydro-1*H*-benzo[*d*]- imidazole-1-carboxylate (54)**



K_2CO_3 (3 equiv.), $Pd(PPh_3)_4$ (5 mol %) and 1-iodo-4-nitrobenzene (2.5 equiv.) were added to a solution of compound **52** (1 equiv.) in MeCN (20 ml/mmol) and the mixture was heated at 80 °C for 48 h. It was then concentrated in vacuo, brine was added and the mixture extracted with AcOEt (3 ×). The combined organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The mixture was purified by flash chromatography on silica gel to obtain pure compound 53 and a mixture of compounds 53 and 54 (20%).

***tert*-Butyl 3-(4-nitrophenyl)-2-[1-(4-nitrophenyl)vinyl]-2,3-dihydro-1*H*-benzo[d]imidazole-1-carboxylate (53)**



Yield: 50%.

Orange solid; m.p.: 180 - 182 °C.

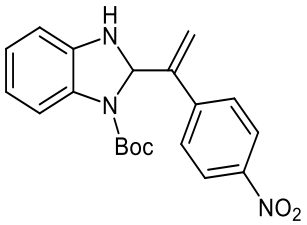
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 9.2 Hz, 2 H), 7.99 (d, *J* = 8.6 Hz, 2 H), 7.32 (d, *J* = 9.2 Hz, 2 H), 7.27 (m, 3 H), 7.02 (m, 1 H), 6.82–6.90 (m, 2 H), 6.66 (br. s, 1 H), 5.78 (s, 1 H), 5.48 (s, 1 H), 1.57 (s, 9 H), ppm.

^{13}C NMR (75 MHz, CDCl3): δ = 150.5 (s), 147.7 (s), 147.4 (s), 144.4 (s), 143.8 (s), 141.9 (s), 129.4 (d), 125.9 (d), 123.5 (d), 123.4 (d), 123.0 (d), 122.2 (t), 116.9 (d), 115.5 (d), 111.4 (d), 83.4 (s), 82.5 (d), 28.5 (q), ppm.

IR: $\tilde{\nu}$ = 3435, 2969, 2919, 2850, 1705, 1586 cm^{-1}.

MS (ESI): m/z = 511.0 $[M+Na]^+$. ($C_{26}H_{24}N_4O_6$).

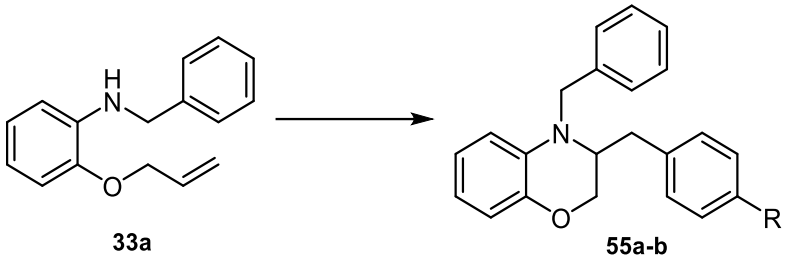
tert-Butyl 2-(1-(4-nitrophenyl)vinyl)-2,3-dihydro-1_H_-benzo[_d_]-imidazole-1-carboxylate (54)



^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 9.1 Hz, 2 H), 7.55 (d, *J* = 9.1 Hz, 2 H), 7.28 (m, 1 H), 6.72–6.85 (m, 2 H), 6.60 (dd, *J* = 1.4, 7.7 Hz, 1 H), 6.32 (br. s, 1 H), 5.51 (s, 1 H), 5.48 (s, 1 H), ppm.[a]

[a] only distinguishing signals found in the mixture are reported.

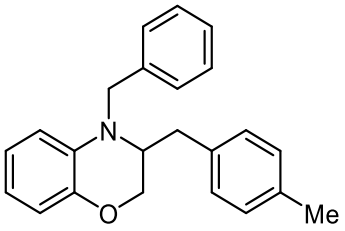
General procedure for carboamination reaction



33a **55a-b**

The compound **33a** (1 equiv.) in toluene (10 ml/mmol) were added to a solution of $Pd_2(dba)_3$ (2 mol %) and Xantphos (8 mol %) in toluene (2 ml). Then were added the corresponding aryl bromide (1.4 equiv.) and *t*BuONa (1.4 equiv.) and the mixture was heated at 110 °C for 4 h. The reaction mixture was concentrated in vacuo, then brine was added and the mixture extracted with AcOEt (3 ×). The organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel.

4-Benzyl-3-(4-methylbenzyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (55a)



Yield: 70%.

White solid; m.p.: 76 – 78 °C.

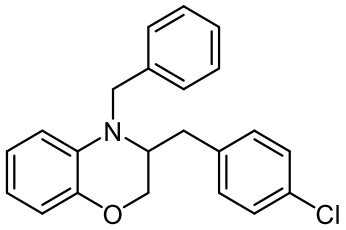
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (m, 5 H), 7.13 (m, 3 H), 6.80 (m, 3 H), 6.69 (m, 2 H), 4.43 (d, *J* = 13.8 Hz, 1 H), 4.38 (d, *J* = 13.8 Hz, 1 H), 4.31 (m, 1 H), 3.26 (m, 3 H), 2.86 (m, 1 H), 2.36 (s, 3 H) ppm.

^{13}C NMR (75 MHz, CDCl3): δ = 143.8 (s), 238.3 (s), 136.4 (s), 135.3 (s), 134.4 (s), 129.5 (d), 129.5 (d), 128.9 (d), 127.3 (d), 127.2 (d), 121.7 (d), 118.2 (d), 116.8 (d), 112.7 (d), 74.5 (d), 55.3 (t), 51.3 (t), 39.2 (t), 21.3 (q) ppm.

IR: $\tilde{\nu}$ = 3435, 3023, 2913, 1601, 1577, 1502 cm^{-1}.

MS (ESI): m/z = 330.3 $[M+H]^+$. ($C_{23}H_{23}NO$).

4-Benzyl-3-(4-chlorobenzyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (55b)



Yield: 80%.

White solid; m.p.: 101 – 103 °C.

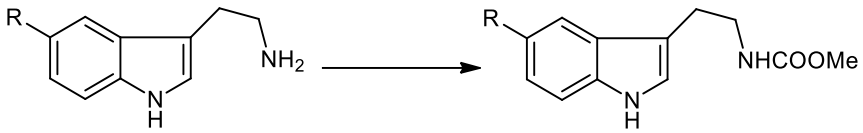
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (m, 7 H), 7.14 (m, 2 H), 6.74 (m, 2 H), 6.34 (m, 2 H), 4.45 (d, *J* = 15.4 Hz, 1 H), 4.40 (d, *J* = 15.4 Hz, 1 H), 4.35 (m, 1 H), 3.25 (m, 1 H), 3.03-3.17 (m, 2 H), 2.84 (m, 1 H) ppm.

^{13}C NMR (75 MHz, CDCl3): δ = 143.5 (s), 138.2 (s), 136.0 (s), 135.2 (s), 132.7 (s), 131.0 (d), 128.9 (d), 128.8 (d), 127.4 (d), 127.3 (d), 121.8 (d), 118.3 (d), 116.8 (d), 112.7 (d), 74.0 (d), 55.2 (t), 51.1 (t), 38.8 (t) ppm.

IR: $\tilde{\nu}$ = 3440, 2900, 1601, 1575, 1516 cm^{-1}.

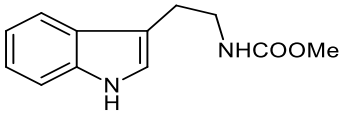
MS (ESI): m/z = 350.6 $[M+H]^+$. ($C_{22}H_{20}ClNO$).

Synthesis of methyl (2-(indol-3-yl)ethyl)carbamates (57a-b)



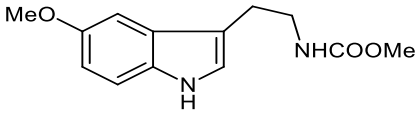
The products were synthesized following the procedure reported in literature.[110]

Methyl (2-(1*H*-indol-3-yl)ethyl)carbamate (57a)



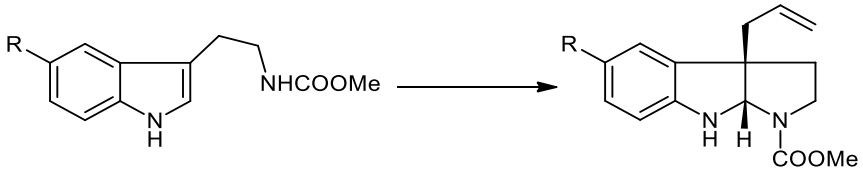
Data are consistent with literature.[111]

Methyl (2-(5-methoxy-1*H*-indol-3-yl)ethyl)carbamate



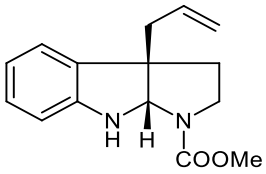
Data are consistent with literature.[112]

Synthesis of tetrahydropyrrolindoles (58a-b)



To a solution of $Pd(PPh_3)_4$ (0.5 mol %) in THF (5 ml/mmol), cooled at 0 °C, was added the appropriate methyl (2-(indolin-3-yl)ethyl) carbamate **2** (1 equiv.), allyl alcohol (1.2 equiv), and Et_3B (1 M in THF, 1.2 equiv). The reaction mixturewas stirred at rt for 24 h. Then the reaction mixture was poured into sat. $NaHCO_3$, concentrated under vacuum and extracted with AcOEt (3 x). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The product was purified trough silica gel chromatography.

Methyl 3a-allyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole- 1(2*H*)-carboxylate (58a)



Yield: 77%.

White solid; m.p.: 94 - 96 °C.

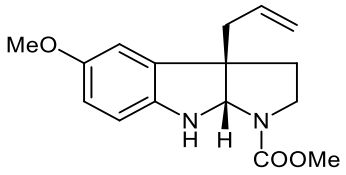
^{1}H NMR (300 MHz; C_6D_6): δ = 6.99 (m, 1 H), 6.83 (m, 1 H), 6.73 (m, 1 H), 6.33 (m, 1 H), 5.59 (m, 1 H), 5.22 (s, 0.6 H, exchange with D_2O), 5.14 (s, 1 H), 4.89 (m, 2 H), 4.41 (s, 0.4 H, exchange with D_2O), 3.70 (t, *J* = 9.2 Hz, 0.3 H), 3.49 (s, 1 H), 3.45 (s, 2 H), 3.32 (t, *J* = 9.2 Hz, 0.7 H), 2.92 (m, 1 H), 2.16 (d, *J* = 6.9 Hz, 2 H), 1.68 (m, 1 H), 1.55 (m, 1 H) ppm.

^{13}C NMR (75 MHz; C_6D_6): δ = 154.3 (s), 154.2 (s), 149.8 (s), 149.5 (s), 134.1 (s), 131.6 (s), 128.6 (d), 132.3 (d), 118.9 (d), 118.6 (d), 117.9 (t), 117.8 (t), 109.5 (d), 109.2 (d), 80.6 (d), 79.7 (d), 57.5 (s), 56.2 (t), 51.9 (q), 51.8 (q), 45.9 (t), 45.5 (t), 42.6 (t), 42.2 (t), 34.9 (t) ppm.

IR: $\tilde{\nu}$ = 3352, 2949, 2890, 1686, 1608 cm^{-1}.

MS (ESI): m/z = 259.2 $[M+H]^+$, 258.1 $[M+Na]^+$. ($C_{15}H_{18}N_2O_2$).

Methyl 3a-allyl-5-methoxy-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1(2*H*)-carboxylate (58b)



Yield: 91%.

White solid; m.p.: 65 - 67 °C.

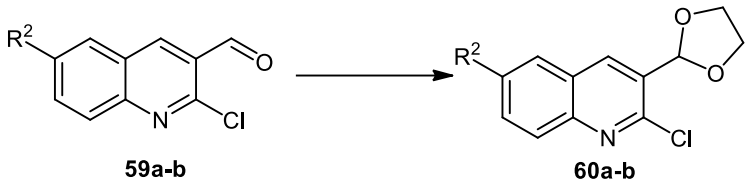
^{1}H NMR (200 MHz; $CDCl_3$): δ = 6.58 (m, 3 H), 5.73 (m, 1 H), 5.09 (m, 3 H), 4.87 (br. s, 1 H, exchange with D_2O), 3.74 (s, 3 H), 3.67 (s, 3 H), 3.58 (m, 1 H), 3.05 (m, 1 H), 2.43 (d, *J* = 7.5 Hz, 2 H), 2.13 (m, 2 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 155.7 (s), 154.9 (s), 153.9 (s), 153.7 (s), 143.4 (s), 143.1 (s), 133.8 (d), 133.5 (s), 133.4 (s), 118.7 (t), 113.3 (d), 113.2 (d), 110.6 (d), 110.5 (d), 110.2 (d), 110.1 (d), 81.8 (d), 80.5 (d), 58.1 (s), 57.0 (s), 56.2 (q), 52.7 (q), 52.4 (q), 46.0 (t), 45.7 (t), 42.5 (t), 42.2 (t), 35.1 (t) ppm.

IR: $\tilde{\nu}$ = 3350, 2949, 1693 cm^{-1}.

MS (ESI): m/z = 289.1 $[M+H]^+$. ($C_{16}H_20N_2O_3$).

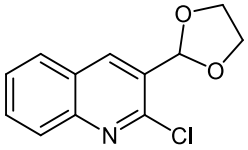
Synthesis of preparation of 2-chloroquinoline-3-dioxolanes (60a-b)



59a-b **60a-b**

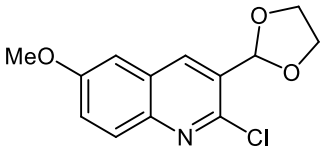
The products were synthesized following the procedure reported in literature. [113]

2-Chloro-3-(1,3-dioxolan-2-yl)quinolone (60a)



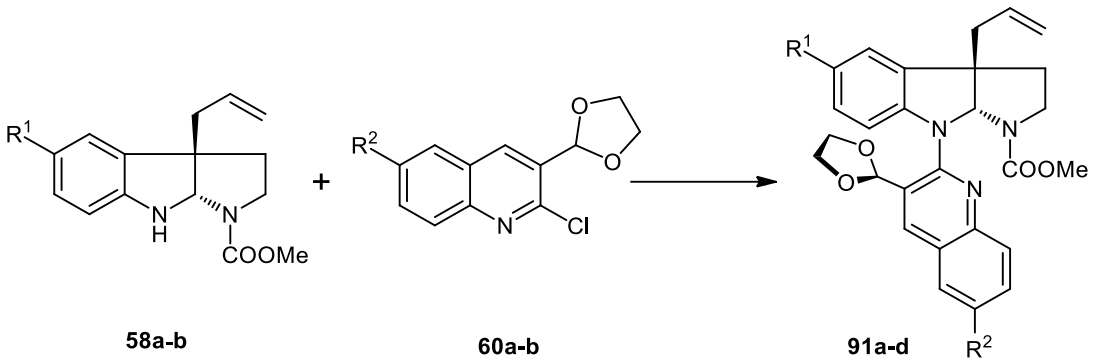
Data are consistent with literature. [114]

2-Chloro-3-(1,3-dioxolan-2-yl)-6-methoxyquinoline (60b)



Data are consistent with literature. [113]

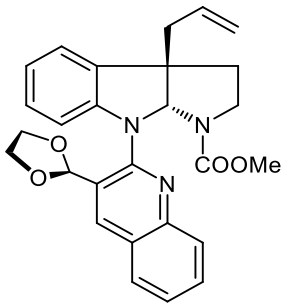
General procedure for *N*-arylation of tetrahydropyrrolindoles (31a-d)



58a-b **60a-b** **91a-d**

To a solution of $Pd_2(dba)_3$ (2 mol %) and triisobutylphosphatrane (8 mol %) in toluene (25 ml/mmol) were added the compound **58** (1 equiv.), the appropriate 2-chloroquinoline **60** (1 equiv.) and *t*BuONa (1.4 equiv.). The reaction mixture was warmed at 110 °C for 5 h. After completion the reaction mixture was filtered through a Celite pad, washed with brine (3 x) and extracted with AcOEt. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude was purified trough silica gel chromatography.

Methyl 8-(3-(1,3-dioxolan-2-yl)quinolin-2-yl)-3a-allyl- 3,3a,8,8a-tetrahydropyrrolo [2,3-*b*]indole-1(2*H*)-carboxylate (61a)



Yield: 87%.

White solid. m.p.: 127 - 130 °C.

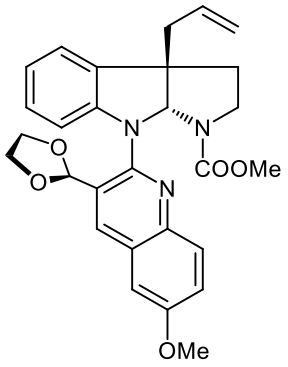
^{1}H NMR (200 MHz; $CDCl_3$): δ = 8.52 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.68 (m, 1H), 7.51 (m, 1H), 7.11 (m, 2H), 6.84 (m, 1H), 6.66 (m, 1H), 6.14 (s, 1H), 6.11 (s, 1H), 5.94 (m, 1H), 5.15 (m, 2H), 4.22 (m, 2H), 3.97 (m, 2H), 3.33 (m, 2H), 2.85 (s, 3H), 2.70 (m, 2H), 2.22 (m, 2H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 55.1 (s), 154.5 (s), 149.2 (s), 148.3 (s), 136.8 (d), 134.2 (d), 133.5 (s), 130.2 (d), 129.7 (s), 128.9 (d), 128.6 (d), 128.0 (d), 127.2 (s), 126.5 (d), 123.4 (d), 120.2 (d), 118.9 (t), 110.0 (d), 100.4 (d), 84.8 (d), 65.8 (t), 65.6 (t), 57.6 (s), 51.9 (q), 45.8 (t), 43.4 (t), 36.1 (t) ppm.

IR: $\tilde{\nu}$ = 3423 (br.), 2950, 2855, 1706 cm^{-1}.

MS (ESI): m/z = 480.3 $[M+Na]^+$. ($C_{27}H_{27}N_3O_4$).

Methyl 8-(3-(1,3-dioxolan-2-yl)-6-methoxyquinolin-2-yl)-3a-allyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1(2*H*)-carboxylate (61b)



Yield: 92%.

White solid: m.p.: 152-155 °C.

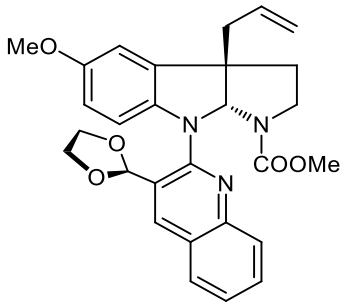
^{1}H NMR (200 MHz; $CDCl_3$): δ = 8.41 (s, 1 H), 7.89 (d, *J* = 9.5 Hz, 1 H), 7.33 (m, 1 H), 7.14 (m, 1 H), 7.05 (m, 2 H), 6.81 (m, 1 H), 6.55 (m, 1 H), 6.16 (s, 1 H), 6.07 (s, 1 H), 5.93 (m, 1 H), 5.17 (m, 2 H), 4.17 (m, 2 H), 4.03 (m, 2 H), 3.92 (s, 3 H), 3.31 (m, 2 H), 2.90 (s, 3 H), 2.69 (m, 2 H), 2.18 (m, 2 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 158.0 (s), 155.2 (s), 152.6 (s), 149.6 (s), 144.4 (s), 135.4 (d), 135.3 (d), 133.4 (s), 130.4 (d), 130.0 (s), 128.6 (d), 128.2 (s), 123.3 (d), 122.9 (d), 120.0 (d), 118.8 (t), 109.7 (d), 105.5 (d), 100.5 (d), 85.0 (d), 65.8 (t), 65.6 (t), 57.6 (s), 55.8 (q), 51.9 (q), 45.8 (t), 43.5 (t), 36.3 (t) ppm.

IR: $\tilde{\nu}$ = 3402 (br.), 2951 (br.), 1705 cm^{-1}.

MS (ESI): m/z = 488.5 $[M+H]^+$, 510.3 $[M+Na]^+$. ($C_{28}H_{29}N_3O_5$).

Methyl 8-(3-(1,3-dioxolan-2-yl)quinolin-2-yl)-3a-allyl-5-methoxy-3,3a,8,8a-tetrahydropyrrolo [2,3-*b*]indole-1(2*H*)-carboxylate (61c)



Yield: 92%.

White solid; m.p.: 154 - 159 °C

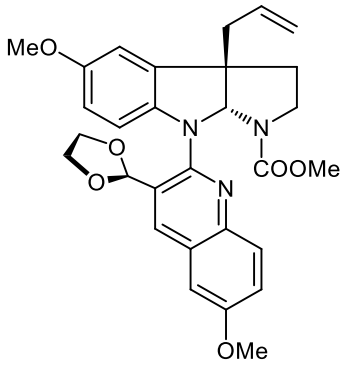
^{1}H NMR (200 MHz; $CDCl_3$): δ = 8.49 (s, 1 H), 7.97 (d, *J* = 8.0 Hz, 1 H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.66 (m, 1 H), 7.48 (m, 1 H), 6.69 (m, 3 H), 6.20 (s, 1 H), 6.13 (s, 1 H), 5.95 (m, 1 H), 5.16 (m, 2 H), 4.24 (m, 2 H), 4.07 (m, 2 H), 3.75 (s, 3 H), 3.31 (m, 2 H), 2.93 (s, 3 H), 2.70 (m, 2 H), 2.18 (m, 2 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 155.2 (s), 154.5 (s), 148.2 (s), 143.3 (s), 136.8 (d), 135.2 (s), 134.9 (s), 134.2 (d), 130.2 (d), 129.5 (s), 128.8 (t), 128.0 (d), 127.0 (s), 126.3 (d), 118.9 (s), 113.2 (d), 110.9 (d), 110.4 (d), 100.5 (d), 85.3 (d), 65.8 (t), 65.6 (t), 57.8 (s), 56.2 (q), 51.9 (q), 45.9 (t), 43.1 (t), 35.8 (t) ppm.

IR: $\tilde{\nu}$ = 3416 (br.), 2950 (br.), 1705 cm^{-1}.

MS (ESI): m/z = 488.4 $[M+H]^+$, 510.3 $[M+Na]^+$. ($C_{28}H_{29}N_3O_5$).

Methyl 8-(3-(1,3-dioxolan-2-yl)-6-methoxyquinolin-2-yl)-3a-allyl-5-methoxy-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1(2*H*)-carboxylate (61d)



Yield: 88%.

White solid; m.p.: 142 - 145 °C.

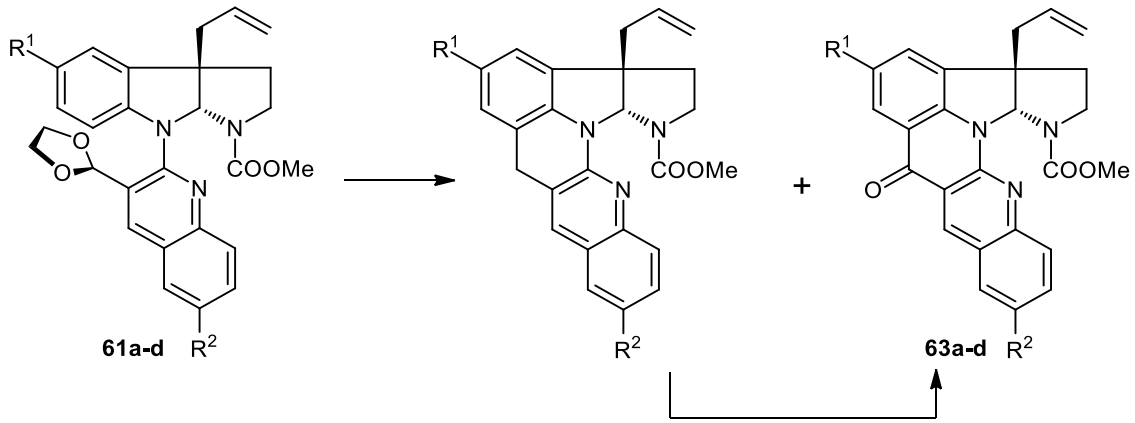
^{1}H NMR (300 MHz; CDCl3): δ = 8.36 (s, 1 H), 7.87 (d, *J* = 9.3 Hz, 1 H), 7.32 (d, *J* = 9.3 Hz, 1 H), 7.12 (d, *J* = 2.6 Hz, 1 H), 6.74 (d, *J* = 1.8 Hz, 1 H), 6.60 (m, 2 H), 6.10 (s, 1 H), 6.01 (s, 1 H), 5.95 (m, 1 H), 5.18 (m, 2 H), 4.20 (m, 2 H), 4.04 (m, 2 H), 3.91 (s, 3 H), 3.74 (s, 3 H), 3.30 (m, 2 H), 2.95 (s, 3 H), 2.70 (m, 2 H), 2.12 (m, 2 H) ppm.

^{13}C NMR (75 MHz; CDCl3): δ = 158.0 (s), 155.4 (s), 154.6 (s), 144.5 (s), 144.0 (s), 135.6 (d), 135.3 (s), 134.4 (d), 130.5 (d), 130.0 (s), 128.2 (s), 123.0 (d), 119.0 (t), 118.8 (s), 113.4 (d), 110.8 (d), 110.5 (d), 105.7 (d), 100.7 (d), 85.6 (d), 66.0 (t), 65.8 (t), 57.9 (s), 56.4 (q), 56.0 (q), 52.1 (q), 46.0 (t), 43.4 (t), 36.1 (t) ppm.

IR: $\tilde{\nu}$ = 3393 (br.), 2951 (br.), 1705 cm^{-1}.

MS (ESI): m/z = 518.2 $[M+H]^+$, 540.2 $[M+Na]^+$. ($C_{29}H_{31}N_3O_6$).

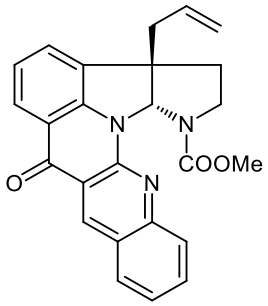
General procedure for the intramolecular Friedel-Crafts and oxidation reactions



a) To a solution of compound **61** (1 equiv.) in CH_2Cl_2 (10 ml/mmol), cooled at 0 °C, was added BF_3-Et_2O (3 - 5 equiv.). The reaction mixture was stirred at rt for 48 h. After completion the mixture was poured into a $NaHCO_3$ sat. at 0 °C, and stirred for 30 min. Then was extracted with CH_2Cl_2 (3 x) and the organic layer was dried under vacuum.

b) The crude was dissolved in THF (20 ml/mmol) and water (5 ml/mmol), and MnO_2 (3 equiv.) and *m*-CPBA (5 mmol %) were added. The reaction mixture was warmed at 60 °C for 12 h. After the complete oxidation of the intermediate, the reaction mixture was filtered through a Celite pad and concentrated under vacuum. Then was extracted with AcOEt and washed with water (3 x). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude was purified trough silica gel chromatography.

Methyl 3a-allyl-7-oxo-3,3a,7,14a-tetrahydrobenzo[*g*]pyrrolo [20,3':2,3]indolo[1,7-*ab*][1,8]naphthyridine-1(2*H*)-carboxylate (63a)



Yield: 50%.

Yellow solid; m.p.: 133 - 135 °C.

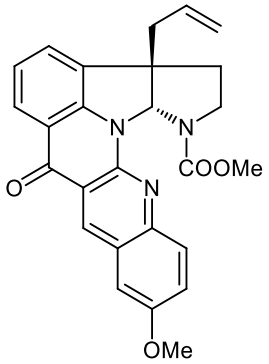
^{1}H NMR (200 MHz; $CDCl_3$): δ = 9.28 (d, 1 H), 8.12 (d, *J* = 8.1 Hz, 1 H), 7.96 (m, 2 H), 7.72 (td, *J* = 6.8, 1.4 Hz, 1 H), 7.55 (dd, *J* = 7.1, 0.9 Hz, 1 H), 7.44 (td, *J* = 7.1, 0.9 Hz, 1 H), 7.25 (m, 1 H), 7.02 (s, 1 H), 5.68 (m, 1 H), 5.27 (m, 2 H), 4.12 (m, 1 H), 3.97 (s, 3 H), 2.84 (m, 3 H), 2.12 (m, 2 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ =179.7 (s), 155.4 (s), 150.0 (s), 147.9 (s), 145.8 (s), 139.5 (d), 135.5 (s), 132.8 (d), 132.7 (d), 129.9 (d), 128.6 (d), 128.0 (d), 125.0 (d), 124.9 (d), 124.7 (s), 122.7 (d), 120.2 (t), 119.2 (s), 117.7 (s), 81.9 (d), 58.2 (s), 53.2 (q), 46.1 (t), 43.1 (t), 39.7 (t) ppm.

IR: $\tilde{\nu}$ = 3436 (br.), 1698, 1655 cm^{-1}.

MS (ESI): m/z = 434.2 $[M+Na]^+$. ($C_{25}H_{21}N_3O_3$)

Methyl 3a-allyl-10-methoxy-7-oxo-3,3a,7,14a-tetrahydrobenzo[*g*]pyrrolo[20,3':2,3]indolo [1,7-*ab*][1,8]naphthyridine-1(2*H*)-carboxylate (63b)



Yield: 62%.

Yellow solid; m.p.: 157 - 160 °C.

^{1}H NMR (200 MHz; $CDCl_3$): δ = 9.22 (s, 1 H), 8.15 (dd, *J* = 8.1; 1.1 Hz, 1 H), 7.90 (d, *J* = 9.5 Hz, 1H), 7.54 (m, 2 H), 7.24 (m, 2 H), 7.01 (s, 1 H), 5.70 (m, 1 H), 5.09 (m, 2 H), 4.14 (m, 1 H), 3.97 (s, 3 H), 3.96 (s, 3 H), 2.94 (m, 3 H), 2.18 (m, 2 H) ppm.

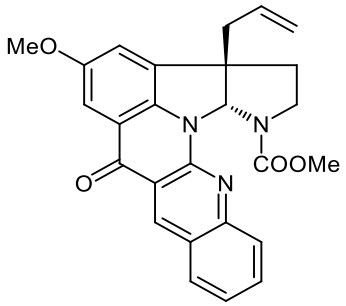
^{13}C NMR (50 MHz; $CDCl_3$): δ = 179.7 (s), 156.7 (s), 155.4 (s), 146.5 (s), 146.4 (s), 145.8 (s), 137.6 (d), 135.2 (s), 132.8 (d), 129.5 (d), 128.3 (d), 126.4 (d), 125.4 (s), 125.0 (d), 122.4 (d), 120.1 (t), 119.2 (s), 117.6 (s), 106.1 (d), 81.9 (d), 58.2 (s), 55.8 (q), 53.1 (q), 46.1 (t), 43.1 (t), 39.7 (t) ppm.

IR: $\tilde{\nu}$ = 3467 (br.), 1702, 1647 cm^{-1}.

MS (ESI): m/z = 440.3 $[M]^{-}$. ($C_{26}H_{23}N_3O_4$).

Methyl 3a-allyl-5-methoxy-7-oxo-3,3a,7,14a-tetrahydrobenzo[*g*]pyrrolo

[20,3':2,3]indolo[1,7-*ab*][1,8]naphthyridine-1(2*H*)-carboxylate (63c)



Yield: 70%.

Orange solid; m.p.: 165 - 167 °C.

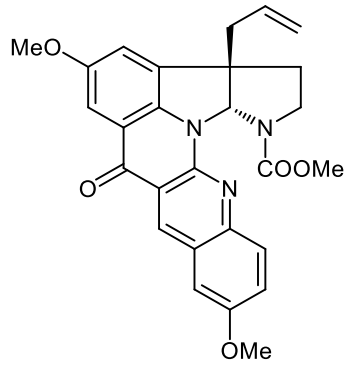
^{1}H NMR (200 MHz; $CDCl_3$): δ = 9.31 (s, 1 H), 7.97 (m, 2 H), 7.77 (m, 1 H), 7.50 (d, *J* = 2.5 Hz, 1 H), 7.44 (m, 1 H), 7.23 (d, *J* = 2.5 Hz, 1 H), 7.02 (s, 1 H), 5.71 (m, 1 H), 5.18 (m, 2 H), 4.12 (m, 1 H), 3.97 (s, 3 H), 3.91 (s, 3 H), 2.84 (m, 3 H), 2.16 (m, 2 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 179.3 (s), 156.5 (s), 155.3 (s), 150.0 (s), 147.4 (s), 140.9 (s), 139.5 (d), 137.1 (s), 132.6 (d), 132.6 (d), 129.9 (d), 128.0 (d), 124.7 (d), 124.6 (s), 120.3 (t), 120.2 (d), 118.7 (s), 117.5 (s), 103.8 (d), 82.1 (d), 58.1 (s), 56.3 (q), 53.2 (q), 46.0 (t), 43.0 (t), 39.6 (t) ppm.

IR: $\tilde{\nu}$ = 3467 (br.), 1701, 1647 cm^{-1}.

MS (ESI): m/z = 464.3 $[M+Na]^+$. ($C_{26}H_{23}N_3O_4$).

Methyl 3a-allyl-5,10-dimethoxy-7-oxo-3,3a,7,14a-tetrahydrobenzo[*g*]pyrrolo [20,3':2,3]indolo[1,7-*ab*][1,8]naphthyridine-1(2*H*)-carboxylate (63d)



Yield: 80%.

Orange solid; m.p.: 157 - 160 °C.

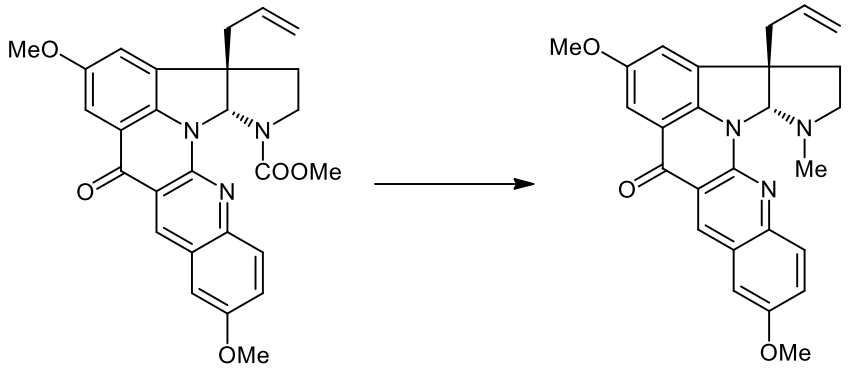
^{1}H NMR (200 MHz; $CDCl_3$): δ = 9.22 (s, 1 H), 7.87 (d, *J* = 9.2 Hz, 1 H), 7.48 (m, 2 H), 7.24 (m, 2 H), 7.00 (m, 1 H), 5.71 (m, 1 H), 5.16 (m, 2 H), 4.14 (m, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H), 3.92 (s, 3 H), 2.83 (m, 3 H), 2.36 (m, 2 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 179.3 (s), 156.6 (s), 156.3 (s), 155.4 (s), 146.5 (s), 146.1 (s), 140.9 (s), 137.5 (d), 137.2 (s), 132.7 (d), 129.5 (d), 126.5 (d), 125.3 (s), 120.3 (t), 120.1 (d), 118.7 (s), 117.3 (s), 106.0 (d), 103.6 (d), 82.1 (d), 58.1 (s), 56.3 (q), 56.8 (q), 53.2 (q), 46.0 (t), 43.0 (t), 39.6 (t) ppm.

IR: $\tilde{\nu}$ = 3437 (br.), 2959 (br.), 1713, 1645 cm^{-1}.

MS (ESI): m/z = 472.3 $[M+H]^+$, 494.3 $[M+Na]^+$. ($C_{27}H_{25}N_3O_5$).

Synthesis of 3a-allyl-5,10-dimethoxy-1-methyl-1,3,3a,14atetrahydrobenzo[*g*]pyrrolo[20,3':2,3]indolo[1,7-*ab*][1,8]naphthyridin-7(2*H*)-one (64)



63d **64**

To a solution of compound **63d** (1 equiv.) in toluene (10 ml/mmol), cooled at 0 °C, Red-Al® (65% in toluene, 10 mmol) was added dropwise. After 10 min at rt, the reaction mixture was warmed at 110 °C for 5 h. After completion the reaction mixture was poured into water at 0 °C, stirred at rt for 30 min. Then the mixture was filtered through a Celite pad with AcOEt and washed with water (3 x). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The product was purified trough silica gel chromatography.

Yield: 50%.

Orange solid; m.p.: 173 - 175 °C.

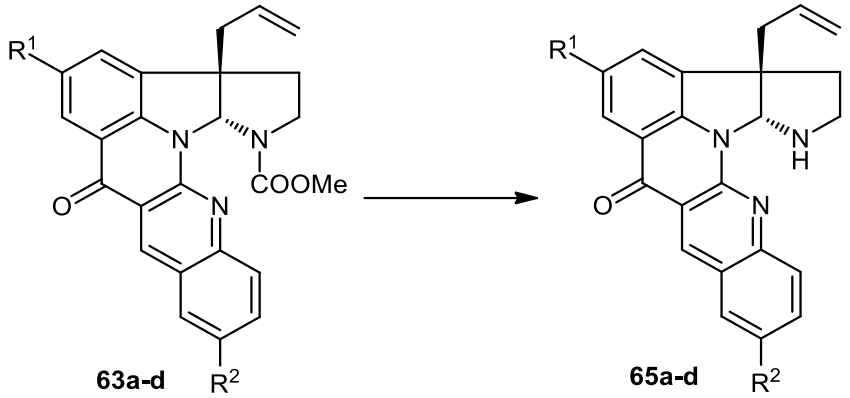
^{1}H NMR (200 MHz; $CDCl_3$): δ = 9.23 (s, 1 H), 7.91 (d, *J* = 9.1 Hz, 1 H), 7.50 (m, 2 H), 7.24 (m, 1 H), 7.18 (d, *J* = 2.4 Hz, 1 H), 5.99 (s, 1 H), 5.68 (m, 1 H), 5.11 (m, 2 H), 3.95 (s, 3 H), 3.91 (s, 3 H), 2.91 (s, 3 H), 2.82 (m, 2 H), 2.66 (m, 2 H), 2.34 (m, 1 H), 2.18 (m, 1H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 179.4 (s), 156.4 (s), 156.2 (s), 147.2 (s), 146.3 (s), 141.2 (s), 139.1 (s), 137.5 (d), 133.3 (d), 129.1 (d), 126.4 (d), 125.2 (s), 119.9 (d), 119.6 (t), 118.7 (s), 117.5 (s), 106.0 (d), 103.1 (d), 89.5 (d), 58.6 (s), 56.3 (q), 55.8 (q), 54.7 (t), 43.5 (t), 40.9 (q), 37.7 (t) ppm.

IR: $\tilde{\nu}$ = 3401 (br.), 2785 (br.), 1640 cm^{-1}.

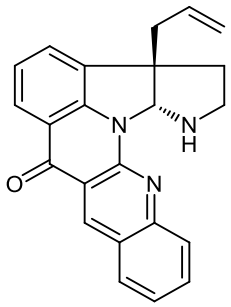
MS (ESI): m/z = 429.3 $[M+Na]^+$. ($C_{26}H_{25}N_3O_3$).

General procedure for hydrolysis of methylcarbamate derivatives



To a solution of compound **63a-d** (1 equiv.) in EtOH (30 ml/mmol) was added NaOH (15 equiv.) in H_2O (5 ml/mmol). The reaction mixture was warmed at 80 °C until the consumption of the starting material (monitored by TLC). After completion the reaction mixture was concentrated under vacuum, extracted with AcOEt and washed with water (3 x). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The product was purified trough silica gel chromatography.

3a-Allyl-1,3,3a,14a-tetrahydrobenzo[*g*]pyrrolo[20,3':2,3]indolo[1,7-*ab*][1,8]naphthyridin-7(2*H*)-one (65a)



Yield: 66%.

Yellow solid; m.p.: 125 - 128 °C.

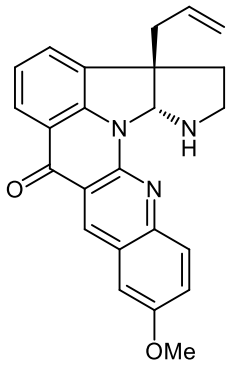
^{1}H NMR (200 MHz; $CDCl_3$): δ = 9.36 (s, 1 H), 8.08 (dd, *J* = 8.1; 0.8 Hz, 1 H), 7.98 (d, *J* = 9.1 Hz, 2 H), 7.77 (td, *J* = 7.0; 1.4 Hz, 1 H), 7.57 (dd, *J* = 7.0; 0.8 Hz, 1 H), 7.44 (td, *J* = 8.1; 0.8 Hz, 1 H), 7.21 (m, 1 H), 6.20 (s, 1 H), 5.80 (m, 1 H), 5.17 (m, 2 H), 3.42 (br. s, 1H, exchange with D_2O), 3.16 (m, 1 H), 2.80 (m, 3 H), 2.20 (m, 2 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 179.7 (s), 150.0 (s), 148.1 (s), 146.1 (s), 139.9 (d), 137.0 (s), 133.8 (d), 138.8 (d), 130.8 (d), 128.6 (d), 127.6 (d), 124.6 (d), 124.5 (s), 124.4 (d), 122.6 (d), 119.4 (t), 119.3 (s), 117.2 (s), 84.7 (d), 56.9 (s), 44.9 (t), 43.5 (t), 40.6 (t) ppm.

IR: $\tilde{\nu}$ = 3351 (br.), 2930 (br.), 1651 cm^{-1}.

MS (ESI): m/z = 354.2 $[M+H]^+$, 376.1 $[M+Na]^+$. ($C_{23}H_{19}N_3O$).

3a-Allyl-10-methoxy-1,3,3a,14a-tetrahydrobenzo[*g*]pyrrolo[20,3':2,3]indolo[1,7-*ab*][1,8]naphthyridin-7(2*H*)-one (65b)



Yield: 85%.

Yellow solid; m.p.: 94 - 96 °C.

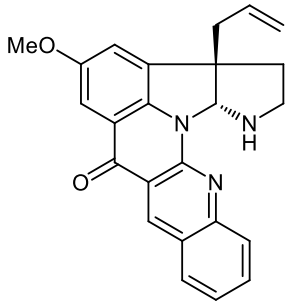
^{1}H NMR (200 MHz; $CDCl_3$): δ = 9.16 (s, 1 H), 8.07 (dd, *J* = 8.1; 1.1 Hz, 1 H), 7.88 (d, *J* = 9.2 Hz, 1 H), 7.53 (dd, *J* = 7.0; 1.1 Hz, 1 H), 7.43 (dd, *J* = 9.2; 2.6 Hz, 1 H), 7.20 (m, 2 H), 6.18 (s, 1 H), 5.76 (m, 1 H), 5.13 (m, 2 H), 3.92 (s, 3 H), 3.27 (br. s, 1H, exchange with D_2O), 3.14 (m, 1 H), 2.75 (m, 3 H), 2.17 (m, 2 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 179.6 (s), 156.4 (s), 146.8 (s), 146.4 (s), 146.1 (s), 137.9 (d), 137.0 (s), 133.9 (d), 129.0 (d), 128.4 (d), 126.4 (d), 125.2 (s), 124.3 (d), 122.3 (d), 119.3 (t), 119.0 (s), 117.0 (s), 106.2 (d), 84.7 (d), 56.9 (s), 55.8 (q), 44.9 (t), 43.5 (t), 40.6 (t) ppm.

IR: $\tilde{\nu}$ = 3435 (br.), 2932 (br.), 1647 cm^{-1}.

MS (ESI): m/z = 384.3 $[M+H]^+$. ($C_{24}H_{21}N_3O_2$).

3a-Allyl-5-methoxy-1,3,3a,14a-tetrahydrobenzo[*g*]pyrrolo[20,3':2,3]indolo[1,7-*ab*][1,8]naphthyridin-7(2*H*)-one (63c)



Yield: 68%.

Orange solid; m.p.: 165 - 168 °C.

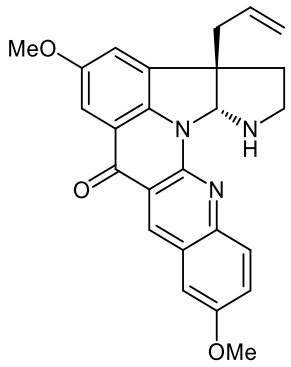
^{1}H NMR (200 MHz; $CDCl_3$): δ = 9.30 (s, 1 H), 7.97 (d, *J* = 8.8 Hz, 2 H), 7.76 (td, *J* = 7.7; 0.7 Hz, 1 H), 7.42 (m, 2 H), 7.23 (d, *J* = 2.3 Hz, 1 H), 6.21 (s, 1 H), 5.77 (m, 1 H), 5.15 (m, 2 H), 3.90 (s, 3 H), 3.43 (br. s, 1 H, exchange with D_2O), 3.15 (m, 1 H), 2.78 (m, 3 H), 2.25 (m, 1 H), 2.10 (m, 1 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 179.2 (s), 156.5 (s), 150.0 (s), 147.6 (s), 141.3 (s), 139.8 (d), 139.0 (s), 133.7 (d), 132.7 (d), 130.1 (d), 127.6 (d), 124.4 (d), 124.3 (s), 120.4 (d), 119.5 (t), 118.7 (s), 116.8 (s), 103.1 (d), 84.9 (d), 56.9 (s), 56.3 (q), 44.9 (t), 43.3 (t), 40.5 (t) ppm.

IR: $\tilde{\nu}$ = 3435 (br.), 1932 (br.), 1645 cm^{-1}.

MS (ESI): m/z = 384.3 $[M+H]^+$. ($C_{24}H_{21}N_3O_2$).

3a-Allyl-5,10-dimethoxy-1,3,3a,14a-tetrahydrobenzo[*g*]pyrrolo[20,3':2,3]indolo [1,7-*ab*][1,8]naphthyridin-7(2*H*)-one (63d)



Yield: 65%.

Orange solid; m.p.: 165 - 168 °C.

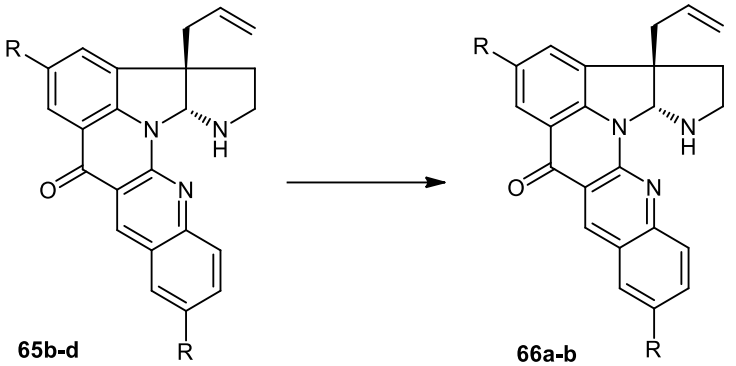
^{1}H NMR (200 MHz; $CDCl_3$): δ = 9.24 (s, 1 H), 7.92 (d, *J* = 9.1 Hz, 1 H), 7.43 (m, 2 H), 7.22 (m, 2 H), 6.21 (s, 1 H), 5.75 (m, 1 H), 5.16 (m, 2 H), 3.96 (s, 3 H), 3.92 (s, 3 H), 3.43 (br. s, 1 H, exchange with D_2O), 3.16 (m, 1H), 2.78 (m, 3 H), 2.24 (m, 1 H), 2.10 (m, 1 H) ppm.

^{13}C NMR (50 MHz; $CDCl_3$): δ = 179.0 (s), 156.3 (s), 146.5 (s), 146.3 (s), 141.3 (s), 139.0 (s), 137.8 (d), 133.7 (d), 129.0 (d), 126.4 (d), 125.1 (s), 120.2 (d), 119.4 (t), 118.7 (s), 116.6 (s), 106.1 (d), 102.9 (d), 84.9 (d), 56.9 (s), 56.2 (q), 55.8 (q), 44.9 (t), 43.3 (t), 40.5 (t) ppm.

IR: $\tilde{\nu}$ = 3435 (br.), 2933 (br.), 1640 cm^{-1}.

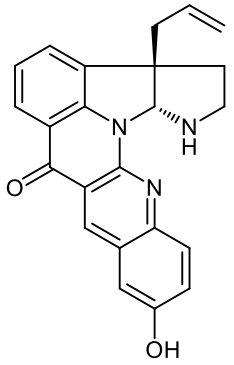
MS (ESI): m/z = 414.3 $[M+H]^+$. ($C_{25}H_{23}N_3O_3$).

General procedure for hydrolysis of methylether derivatives



To a solution of compound **65b-d** (1 equiv.) in CH_2Cl_2 (10 ml/mmol), cooled at -78 °C, was added dropwise BBr_3 (1 M in Hexane, 2.5-5 wquiv.). After 1 h at rt the mixture was warmed at 40 °C until the consumption of the starting material (monitored by TLC). Then, the mixture, cooled at 0 °C, was poured into a $NaHCO_3$ sat. and was extracted with CH_2Cl_2 (3 x). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The product was purified by crystallization (AcOEt/Hexane).

3a-Allyl-10-hydroxy-1,3,3a,14a-tetrahydrobenzo[*g*]pyrrolo[20,3':2,3]indolo [1,7-*ab*][1,8]naphthyridin-7(2*H*)-one (66a)



Yield: 70%.

Red solid; m.p.: 296 - 299 °C.

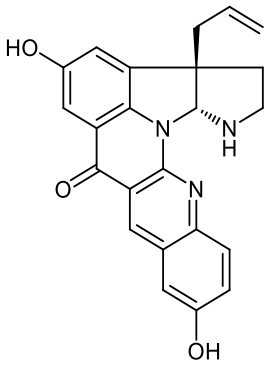
^{1}H NMR (200 MHz; DMSO): δ = 10.04 (s, 1 H, exchange with D_2O), 9.12 (s, 1 H), 7.88 (m, 2 H), 7.70 (d, *J* = 6.2 Hz, 1 H), 7.45 (m, 2 H), 7.22 (m, 1 H), 6.08 (s, 1 H), 5.70 (m, 1 H), 5.12 (d, *J* = 17.1 Hz, 1 H), 5.00 (dd, *J* = 10.1; 2.2 Hz, 1 H), 4.20 (br. s, 1 H, exchange with D_2O), 2.95 (m, 1 H), 2.65 (m, 3 H), 2.10 (m, 2 H) ppm.

^{13}C NMR (50 MHz; DMSO): δ = 179.0 (s), 154.6 (s), 146.4 (s), 146.1 (s), 145.3 (s), 137.7 (s), 137.4 (d), 135.0 (d), 129.4 (d), 129.0 (d), 126.9 (d), 125.8 (s), 123.8 (d), 122.7 (d), 119.4 (s), 119.2 (t), 116.5 (s), 110.2 (d), 84.5 (d), 57.4 (s), 57.4 (t), 45.3 (t), 43.1 (t) ppm.

IR: $\tilde{\nu}$ = 3419 (br.), 2961 (br.), 1643 cm^{-1}.

MS (ESI): m/z = 370.3 $[M+H]^+$. ($C_{23}H_{19}N_3O_2$).

3a-Allyl-5,10-dihydroxy-1,3,3a,14a-tetrahydrobenzo[*g*]pyrrolo[20,3':2,3]indolo [1,7-*ab*][1,8]naphthyridin-7(2*H*)-one (66b)



Yield: 80%.

Red solid; m.p.: 342 - 345 °C.

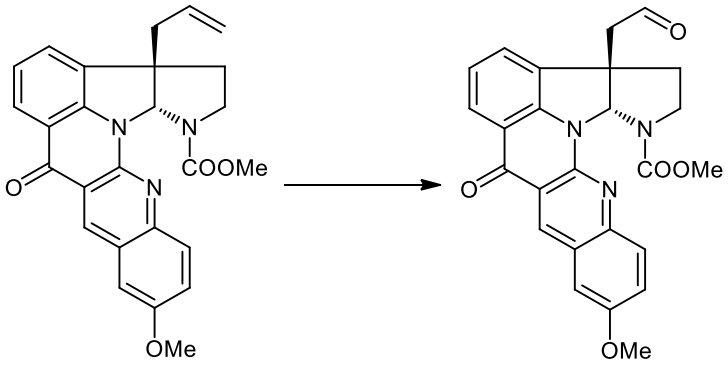
^{1}H NMR (200 MHz; DMSO): δ = 10.02 (br. s, 1 H, exchange with D_2O), 9.70 (br. s, 1 H, exchange with D_2O), 9.10 (s, 1 H), 7.85 (d, *J* = 9.2 Hz, 1 H), 7,51-7.23 (m, 4 H), 6.16 (s, 1 H), 6.57 (br. s, 1 H, exchange with D_2O), 5.66 (m, 1 H), 5.08 (m, 2 H), 3.14 (m, 1 H), 2.73 (m, 3 H), 2.17 (m, 2 H) ppm.

^{13}C NMR (50 MHz; DMSO): δ = 178.4 (s), 154.4 (s), 154.3 (s), 145.7 (s), 145.2 (s), 139.7 (s), 138.4 (s), 137.3 (d), 134.6 (d), 128.9 (d), 127.0 (d), 125.7 (s), 120.4 (d), 119.7 (s), 118.5 (t), 117.0 (s), 110.2 (d), 106.4 (d), 83.3 (d), 57.7 (s), 57.7 (t), 45.5 (t), 42.7 (t) ppm.

IR: $\tilde{\nu}$ = 3323 (br.), 1623 cm^{-1}.

MS (ESI): m/z = 386.3 $[M+H]^+$. ($C_{23}H_{19}N_3O_3$).

Synthesis of
10-methoxy-7-oxo-3a-(2-oxoethyl)-3,3a,7,14a-tetrahydrobenzo[*g*]pyrrolo[20,3':2,3]indolo [1,7-*ab*][1,8] naphthyridine-1(2*H*)-carboxylate (67)



To a solution of compound **65b** (1 equiv.) in THF (15 ml/mmol) and H_2O (3 ml/mmol) was added $NaIO_4$ (3 equiv.), lutidine (2 equiv.) and OsO4 (4% in H_2O, 5 mol %). The reaction mixture was stirred at rt. After 24 h the reaction mixture was concentrated under vacuum and was extracted with AcOEt. The organic layer was washed with water (3 x), dried Na_2SO_4 and concentrated under vacuum. The product was purified trough silica gel chromatography.

Yield: 75%.

Orange solid; m.p.: 241 - 243 °C.

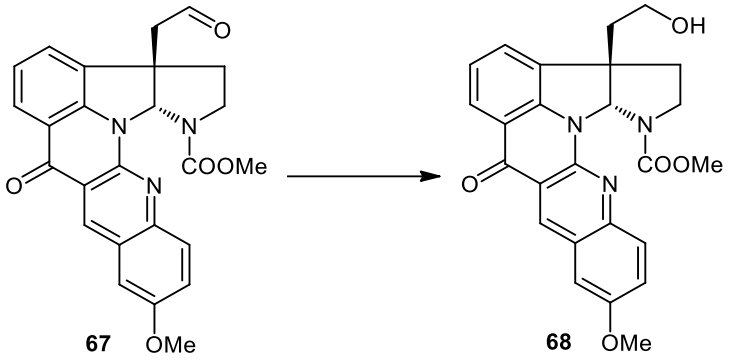
^{1}H NMR (300 MHz; $CDCl_3$): δ = 9.77 (s, 1 H), 9.16 (s, 1 H), 8.12 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.86 (d, *J* = 9.3 Hz, 1 H), 7.60 (dd, *J* = 7.1, 1.1 Hz, 1 H), 7.46 (dd, *J* = 9.3, 2.8 Hz, 1 H), 7.22 (m, 2 H), 7.12 (s, 1 H), 4.16 (m, 1 H), 3.96 (s, 3 H), 3.94 (s, 3 H), 3.27 (ddd, *J* = 22.5,18.1, 0.8 Hz, 2 H), 2.95 (dt, *J* = 12.1, 5.5 Hz, 1 H), 2.38 (m, 1 H), 2.22 (m, 1 H) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ = 198.8 (d), 179.5 (s), 156.7 (s), 155.4 (s), 146.3 (s), 145.6 (s), 137.7 (d), 134.2 (s), 129.4 (d), 128.7 (d), 126.5 (d), 125.5 (s), 125.4 (d), 122.6 (d), 119.1 (s), 117.6 (s), 106.1 (d), 82.5 (d), 55.9 (q), 54.9 (s), 53.3 (q), 52.2 (t), 45.7 (t), 40.2 (t) ppm.

IR: $\tilde{\nu}$ = 3437 (br.), 2945, 1718, 1701 cm^{-1}.

MS (ESI): m/z = 444.1 $[M+H]^+$. ($C_{25}H_{21}N_3O_5$).

Synthesis of
methyl 3a-(2-hydroxyethyl)-10-methoxy-7-oxo-3,3a,7,14atetrahydrobenzo[*g*]pyrrolo[20,3':2,3]indolo [1,7-*ab*][1,8]naphthyridine-1(2*H*)-carboxylate (68)



To a solution of compound **67** (1 equiv.) in MeOH (10 ml/mmol), cooled at 0 °C, was added $NaBH_4$ (1.2 equiv.) and the reaction mixture was stirred at rt. After 3 h the reaction mixture was poured into water and concentrated under vacuum. Then the mixture was extracted with AcOEt and washed with brine (3 x). The organic layer was dried Na_2SO_4 and concentrated under vacuum. The product was purified trough silica gel chromatography.

Yield: 65%.

Yellow solid; M.p.: 121 - 123 °C.

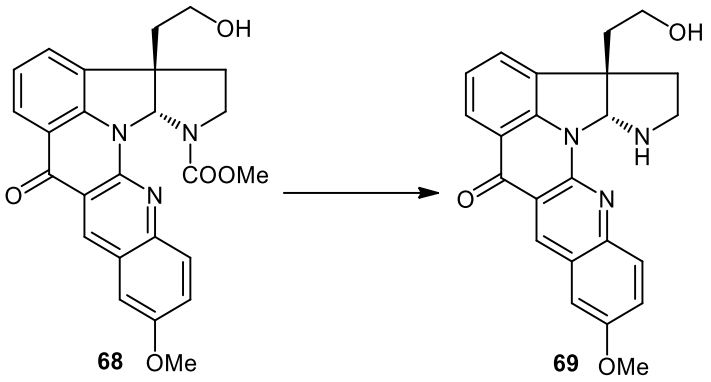
^{1}H NMR (300 MHz; $CDCl_3$): δ = 8.95 (s, 1 H), 7.91 (d, *J* = 8.1 Hz, 1 H), 7.73 (d, *J* = 9.3 Hz, 1 H), 7.48 (d, *J* = 7.1 Hz, 1 H), 7.35 (dd, *J* = 9.3; 2.6 Hz, 1 H), 7.21 (s, 1 H), 7.17 (m, 1 H), 7.10 (d, *J* = 2.6 Hz, 1 H), 4.05 (m, 1 H), 3.94 (s, 3 H), 3.91 (s, 3 H), 3.72 (m, 2 H), 2.83 (m, 1 H), 2.58 (br. s, 1 H, exchange with D_2O), 2.34 (m, 2 H). 2.17 (m, 2 H) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ = 179.4 (s), 156.5 (s), 155.5 (s), 146.2 (s), 145.8 (s), 137.4 (d), 134.6 (s), 129.1 (d), 128.3 (d), 126.4 (d), 125.2 (s), 124.9 (d), 122.2 (d), 118.8 (s), 117.3 (s), 106.1 (d), 82.2 (d), 59.7 (t), 57.0 (s), 55.8 (q), 53.1 (q), 45.5 (t), 41.0 (t), 40.7 (t) ppm.

IR: $\tilde{\nu}$ = 3451, 2956, 1673, 1650, 1626, 1606, 1598 cm^{-1}.

MS (ESI): m/z = 446.1 $[M+H]^+$. ($C_{25}H_{23}N_3O_5$).

Synthesis of
3a-(2-hydroxyethyl)-10-methoxy-1,3,3a,14atetrahydrobenzo[*g*]pyrrolo[20,3':2,3]indolo[1,7-*ab*][1,8] naphthyridin-7(2*H*)-one (69)



To a solution of compound **68** (1 equiv.) in EtOH (30 ml/ mmol) was added NaOH (15 equiv.) in H_2O (5 ml/mmol). The reaction mixture was warmed at 80 °C. After 6 h the reaction mixture was concentrated under vacuum, extracted with AcOEt and washed with water (3 x). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The product was purified trough silica gel chromatography.

Yield: 61%.

Yellow solid; m.p.: 211 – 213 °C

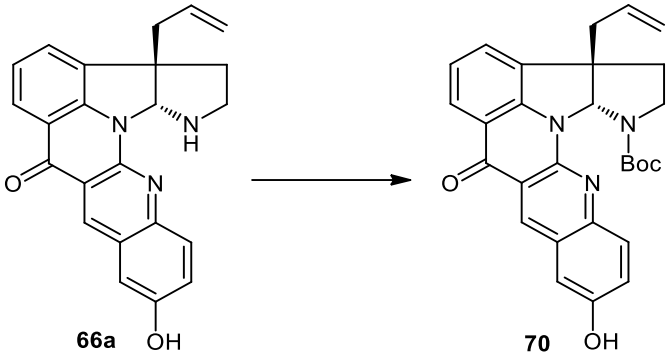
^{1}H NMR (300 MHz; DMSO): δ = 9.21 (s, 1 H), 7.90 (m, 2 H), 7.69 (d, *J* = 7.1 Hz, 1 H), 7.64 (d, *J* = 2.8 Hz, 1 H), 7.54 (dd, *J* = 9.2; 2.8 Hz, 1 H), 7.23 (m, 1 H), 6.30 (s, 1 H), 4.15 (t, *J* = 4.8 Hz, 1 H, exchange with D_2O), 3.90 (s, 3 H), 3.69 8 (br. s, 1 H, exchange with D_2O), 3.38 (m, 2 H), 2.95 (m, 1 H), 2.44 (m, 1 H), 2.27-1.97 (m, 4 H) ppm.

^{13}C NMR (75 MHz; DMSO): δ = 178.9 (s), 156.3 (s), 146.9 (s), 146.3 (s), 146.2 (s), 137.9 (d), 137.8 (s), 129.4 (d), 129.1 (d), 126.8 (d), 125.4 (s), 123.5 (d), 122.8 (d), 119.3 (s), 116.6 (s), 107.6 (d), 85.3 (d), 58.6 (s), 56.4 (t), 56.3 (q), 44.8 (t), 41.7 (t), 41.4 (t) ppm.

IR: $\tilde{\nu}$ = 3434 (br.), 2915, 2876, 1651 cm^{-1}.

MS (ESI): m/z = 388.1 $[M+H]^+$, 410.0 $[M+Na]^+$. ($C_{23}H_{21}N_3O_3$).

Synthesis of
***tert*-butyl 3a-allyl-10-hydroxy-7-oxo-3,3a,7,14a-tetrahydrobenzo[*g*]pyrrolo[2',3':2,3]indolo [1,7-*ab*][1,8]naphthyridine-1(2*H*)-carboxylate (70)**



To a solution of compound **66a** (1 equiv.) in EtOH (10 ml/mmol) was added TEA (3 equiv.) and $(Boc)_2O$ (3 equiv.). The reaction mixture was stirred at rt for 48 h. After consumption of starting material (monitored by TLC) the mixture was concentrated under vacuum and extracted with AcOEt. The organic layer was washed with water (3 x), dried over Na_2SO_4 and concentrated under vacuum. The crude, consisting of a mixture of mono- and di-protected product, was diluted in EtOH (10 ml) and piperidine (3 mmol) was added, in order to remove the Boc on the OH in position 10. The reaction mixture was stirred at 80 °C until the consumption of the di-protected intermediate (monitored by TLC). Then the mixture was poured in water and was extracted with CH_2Cl_2 (3 x). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The product was purified trough silica gel chromatography.

Yield: 60%.

Orange solid; m.p.: 147 - 149 °C.

^{1}H NMR (300 MHz; DMSO): δ =10.15 (s, 1 H, exchange with D_2O), 9.06 (s, 1 H), 7.91 (d. *J* = 8.1 Hz, 1 H), 7.76 (m, 2 H), 7.50 (dd, *J* = 9.1; 2.6 Hz, 1 H), 7.39 (d, *J* = 2.6 Hz, 1 H), 7.25 (m, 1 H), 6.88 (s, 1 H), 5.67 (m, 1 H), 5.18 (d, *J* = 17.1 Hz, 1 H), 5.07 (d, *J* = 9.9 Hz, 1 H), 3.89 (m, 1 H), 2.72 (m, 3 H), 2.09 (m, 2 H), 1.53 (s, 9 H) ppm.

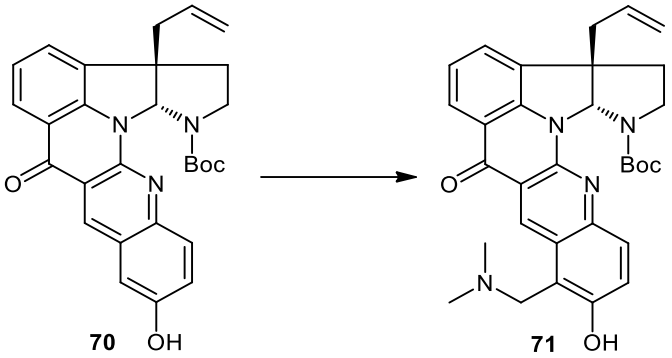
^{13}C NMR (75 MHz; DMSO): δ = 179.1 (s), 157.7 (s), 153.7 (s), 146.1 (s), 145.9 (s), 145.2 (s), 137.1 (d), 135.5 (s), 134.3 (d), 129.3 (d), 128.9 (d), 126.9 (d), 125.9 (t), 124.2 (d), 122.9 (d), 120.1 (s), 119.2 (s), 117.0 (s), 110.2 (d), 82.0 (d), 80.2 (s), 57.8 (s), 46.1 (t), 42.4 (t), 40.0 (t), 28.9 (q) ppm.

IR: $\tilde{\nu}$ = 3403, 2976, 2930, 1700, 1623, 1606, 1587 cm^{-1}.

MS (ESI): m/z = 470.0 $[M+H]^+$, 492.0 $[M+Na]^+$. ($C_{28}H_{27}N_3O_4$).

Synthesis of

tert-Butyl 3a-allyl-9-((dimethylamino)methyl)-10-hydroxy- 7-oxo-3,3a,7,14atetrahydrobenzo[_g_]pyrrolo[20,3':2,3]indolo[1,7-_ab_][1,8]naphthyridine-1(2_H_)-carboxylate (71)



To a solution of compound **70** (1 equiv.) in EtOH (25 ml/mmol) was added CH_2O (37% in H_2O, 4 equiv.) and Me_2NH (40% in H_2O, 3 equiv.). The reaction mixture was stirred at rt for 24-48 h. After consumption of starting material (monitored by TLC) the mixture was concentrated under vacuum and water was added. The mixture was extracted with CH_2Cl_2 (3 x). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The product was purified trough silica gel chromatography.

Yield: 56%.

Orange solid; m.p.: 125 - 127 °C dec.

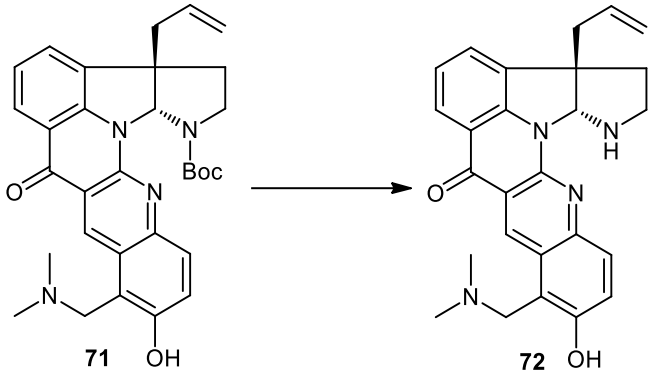
^{1}H NMR (300 MHz; $CDCl_3$): δ = 9.34 (s, 1 H), 8.16 (dd, *J* = 8.1; 1.0 Hz, 1 H), 7.97 (d, *J* = 9.1 Hz, 1 H), 7.57 (dd, *J* = 7.1; 1.0 Hz, 1 H), 7.47 (d, *J* = 9.1 Hz, 1 H), 7.26 (dd, *J* = 8.1; 7.1 Hz, 1 H), 7.08 (s, 1 H), 5.78 (m, 1H), 5.23 (dd, *J* = 8.5; 1.4 Hz, 1 H), 5.15 (d, *J* = 10.5 Hz, 1 H), 4.28 (s, 2 H), 4.10 (m, 1 H), 2.88 (m, 2 H), 2.73 (m, 2 H), 2.50 (s, 6 H), 2.18 (m, 2 H), 1.64 (s, 9 H) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ = 179.8 (s), 155.5 (s), 153.6 (s), 146.0 (s), 145.7 (s), 145.4 (s), 135.4 (s), 132.8 (d), 131.7 (d), 129.1 (d), 128.1 (d), 126.7 (d), 124.6 (d), 123.8 (s), 122.0 (d), 119.9 (t), 118.3 (s), 117.1 (s), 111.9 (s), 81.9 (d), 80.5 (s), 57.5 (t), 57.5 (s), 45.8 (t), 45.6 (q), 42.9 (t), 39.9 (t), 28.5 (q) ppm.

IR: $\tilde{\nu}$ = 3436, 3061, 2976, 2784, 1704, 1644, 1618, 1606, 1586 cm^{-1}.

MS (ESI): m/z = 527.0 $[M+H]^+$, 550.0 $[M+Na]^þ$. ($C_{31}H_{34}N_4O_4$).

Synthesis of
3a-allyl-9-((dimethylamino)methyl)-10- hydroxy-1,3,3a,14a
tetrahydrobenzo[*g*]pyrrolo[20,3':2,3]indolo[1,7-*ab*][1,8]naphthyridin-7(2*H*)-one (72)



To a solution of compund **71** (1 equiv.) in MeOH (20 ml/mmol) was added TMSCl (5 equiv.). The reaction mixture was stirred at rt for 6 h. After completion the mixture was poured into $NaHCO_3$ sat. and was extracted with CH_2Cl_2 (3 x). The organic layer was dried over Na_2SO_4 and was concentrated under vacuum. The product was purified trough silica gel chromatography.

Yield: 78%.

Orange solid; m.p.: 285 - 287 °C dec.

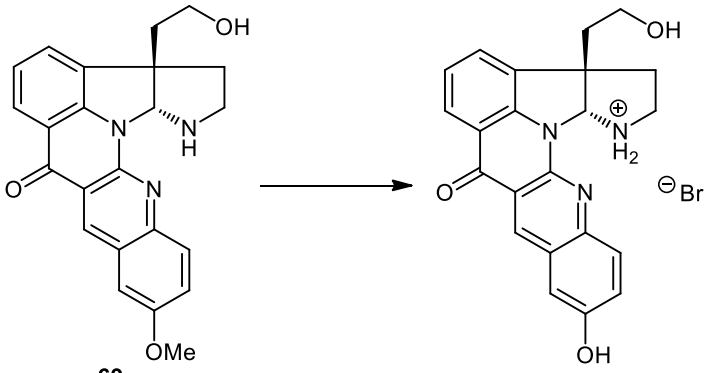
^{1}H NMR (300 MHz; DMSO): δ = 9.30 (s, 1 H), 7.88 (d, *J* = 7.1 Hz, 1 H), 7.79 (d, *J* = 9.1 Hz, 1 H), 7.70 (d, *J* = 7.1 Hz, 1 H), 7.47 (d, *J* = 9.1 Hz, 1 H), 7.20 (m, 1 H), 6.07 (s, 1 H), 5.70 (ddd, *J* = 17.0, 10.1, 2.0 Hz, 1 H), 5.12 (d, *J* = 17.0, 1 H), 5.00 (dd, *J* = 10.1, 2.0 Hz. 1 H), 4.04 (s, 2 H), 2.97 (m, 1 H), 2.80 (m, 1 H), 2.65 (m, 1 H), 2.50 (m, 1 H), 2.29 (s, 6 H), 2.05 (m, 2 H) ppm.

^{13}C NMR (75 MHz; DMSO): δ = 178.9 (s), 154.1 (s), 146.1 (s), 145.9 (s), 145.6 (s), 173.8 (s), 135.0 (d), 134.0 (d), 129.3 (d), 128.4 (d), 126.6 (d), 124.6 (s), 123.8 (d), 122.7 (d), 119.3 (t), 118.5 (s), 116.5 (s), 115.4 (s), 84.6 (d), 58.5 (s), 57.3 (t), 55.4 (t), 45.3 (t), 45.1 (q), 43.1 (t) ppm.

IR: $\tilde{\nu}$ = 3435, 3067, 2919, 2850, 1648, 1618, 1605, 1586 cm^{-1}.

MS (ESI): m/z = 427.0 $[M+H]^+$. ($C_{26}H_{26}N_4O_2$).

Synthesis of 10-hydroxy-3a-(2-hydroxyethyl)-7-oxo-1,2,3,3a,7,14a-tetrahydrobenzo[*g*]pyrrolo[20,3':2,3]indolo[1,7-*ab*][1,8]naphthyridin-1-ium bromide (73)



69 **73**

To a solution of compound **69** (1 equiv.) in CH_2Cl_2 (10 ml/mmol), cooled at 78 °C, was added dropwise BBr_3 (1 M in Hexane, 2.5 equiv.). After 1 h at rt the mixture was warmed at 40 °C for 12 h. Then the reaction mixture was poured over ice and the organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum. The crude product was used directly for the subsequent reaction without purification.

Yield: 50%.

Red solid; m.p.: 255 - 256 °C.

^{1}H NMR (300 MHz; DMSO): δ = 10.47 (br. s, 1 H, exchange with D_2O), 9.57 (br. s, 1 H, exchange with D_2O), 9.16 (s, 1 H), 8.00-7.83 (m, 3 H), 7.60 (m, 1 H), 7.48 (d, *J* = 2.7 Hz, 1 H), 7.36 (m, 1 H), 6.68 (s, 1 H), 4.70 (br. s, 2 H, exchange with D_2O), 3.46 (m, 2 H), 3.11 (m, 1 H), 2.88 (m, 1 H), 2.47 (m, 2 H), 2.24 (m, 2H) ppm.

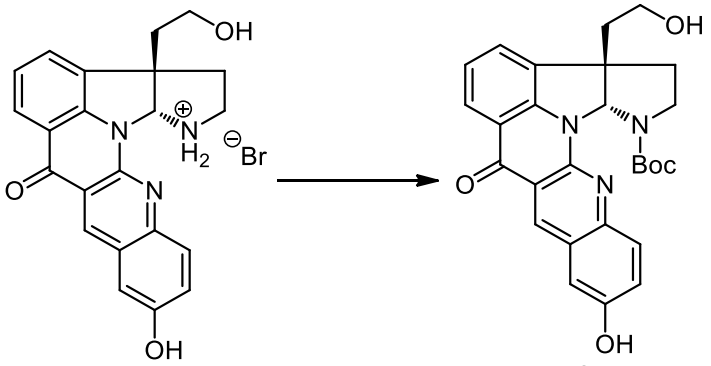
^{13}C NMR (75 MHz; DMSO): δ = 170.1 (s), 155.1 (s), 145.7 (s), 144.7 (s), 137.8 (d), 134.6 (s), 130.0 (d), 129.0 (d), 127.3 (d), 126.5 (s), 126.2 (s), 124.8 (d), 123.8 (d), 119.2 (s), 117.7 (s), 110.6 (d), 80.2 (d), 57.9 (t), 57.7 (s), 57.6 (t), 45.0 (t), 37.9 (t) ppm.

IR: $\tilde{\nu}$ = 3435, 2929, 2709, 1670, 1641, 1640 cm^{-1}.

MS (ESI): m/z = 374.3 $[M]^+$, 372.3 $[M]^-$. ($C_{22}H_{20}N_3O_3$).

Synthesis of

***tert*-butyl 10-hydroxy-3a-(2-hydroxyethyl)-7-oxo-3,3a,7,14a-tetrahydrobenzo[*g*]pyrrolo[20,3':2,3]indolo[1,7-*ab*][1,8]naphthyridine-1(2*H*)-carboxylate (74)**



73 **74**

To a solution of compound **73** (1 equiv.) in EtOH (10 ml/mmol) was added TEA (3 equiv.) and $(Boc)_2O$ (3 equiv.). The reaction mixture was stirred at rt for 48 h. After consumption of starting material (monitored by TLC) the mixture was concentrated under vacuum and extracted with AcOEt. The organic layer was washed with water (3 x), dried over Na_2SO_4 and concentrated under vacuum. The crude, consisting of a mixture of mono- and di-protected product, was diluted in EtOH (10 ml) and piperidine (3 mmol) was added, in order to remove the Boc on the OH in position 10. The reaction mixture was stirred at 80 °C until the consumption of the di protected intermediate (monitored by TLC). Then the mixture was poured in water and was extracted with CH_2Cl_2 (3 x). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The product was purified trough silica gel chromatography.

Yield: 80%.

Orange solid; m.p.: 207 - 209 °C dec.

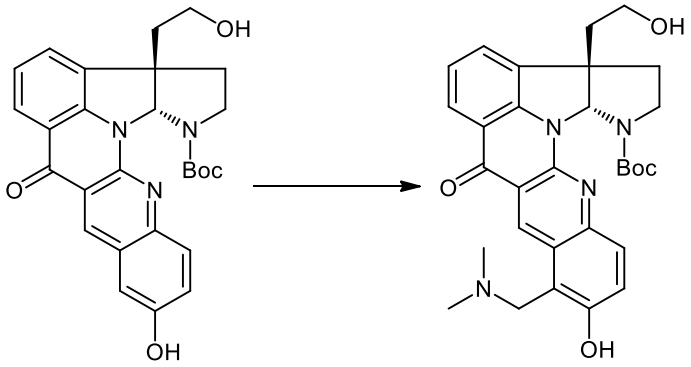
^{1}H NMR (300 MHz; C_3D_6O): δ = 9.06 (s, 1 H), 8.96 (s, 1 H, exchange with D_2O), 8.00 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1 H), 7.72 (dd, *J* = 7.1, 1.1 Hz, 1 H), 7.56 (dd, *J* = 9.2, 2.7 Hz, 1 H), 7.44 (d, *J* = 2.7 Hz, 1 H), 7.32 (s, 1 H), 7.27 (dd, *J* = 8.1, 7.1 Hz, 1 H), 4.06 (m, 1 H), 3.71-3.53 (m, 3 H, 2 H after exchange with D_2O), 2.80 (m, 1 H), 2.42-2.14 (m, 4 H), 1.62 (s, 9 H) ppm.

^{13}C NMR (75 MHz; C_3D_6O): δ = 178.8 (s), 154.3 (s), 154.2 (s), 146.4 (s), 146.3 (s), 145.6 (s), 136.4 (d), 135.8 (s), 129.3 (d), 128.7 (d), 125.8 (d), 125.7 (s), 123.9 (d), 122.1 (d), 119.3 (s), 117.2 (s), 109.6 (d), 82.7 (d), 79.6 (s), 58.7 (t), 58.6 (s), 45.2 (t), 41.4 (t), 40.1 (t), 28.1 (q) ppm.

IR: $\tilde{\nu}$ = 3414, 2959, 2927, 1702, 1638, 1622, 1608, 1586 cm^{-1}.

MS (ESI): m/z = 474.2 $[M+H]^+$. ($C_{27}H_{27}N_3O_5$).

Synthesis of *tert*-butyl 9-((dimethylamino)methyl)-10-hydroxy-3a-(2- hydroxyethyl)-7-oxo 3,3a,7,14a-tetrahydrobenzo[*g*]pyrrolo[20,3':2,3] indolo[1,7-*ab*][1,8]naphthyridine-1(2*H*)-carboxylate (75)



74 **75**

To a solution of compound **74** (1 equiv.) in EtOH (25 ml/mmol) was added CH_2O (37% in H_2O, 4 equiv.) and Me_2NH (40% in H_2O, 3 equiv.). The reaction mixture was stirred at rt for 24-48 h. After consumption of starting material (monitored by TLC) the mixture was concentrated under vacuum and H_2O was added. The mixture was extracted with CH_2Cl_2 (3 x). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The product was purified trough silica gel chromatography.

Yield: 60%.

Orange solid; m.p.: 157 - 159 °C dec.

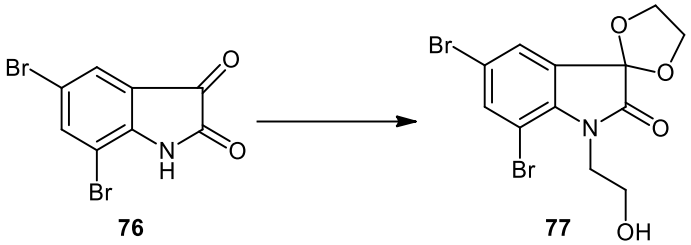
^{1}H NMR (300 MHz; $CDCl_3$): δ = 9.11 (s, 1 H), 7.86 (d, *J* = 7.7 Hz, 1 H), 7.63 (d, *J* = 9.1 Hz, 1 H), 7.41 (d, *J* = 6.9 Hz, 1 H), 7.22 (d, *J* = 9.1 Hz, 1 H), 7.16 (s, 1 H), 7.10 (m, 1 H), 6.50 (br. s, 1 H, exchange with D_2O), 4.40 (d, *J* = 14.7 Hz, 1 H), 4.22 (d, *J* = 14.7 Hz, 1 H), 3.90 (m, 1 H), 3.75 (br. s, 2 H), 2.68 (m, 1 H), 2.48 (s, 6 H), 2.38 (m, 3 H, 2 H after exchange with D_2O), 2.09 (m, 2 H), 1.51 (s, 9 H) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ = 179.5 (s), 155.5 (s), 153.9 (s), 145.8 (s), 145.6 (s), 144.9 (s), 134.9 (s), 131.8 (d), 128.6 (d), 128.0 (d), 126.7 (d), 124.5 (d), 123.7 (s), 121.9 (d), 118.0 (s), 116.8 (s), 112.3 (s), 82.0 (d), 80.8 (s), 59.7 (t), 57.9 (s), 56.4 (t), 45.6 (t), 44.9 (q), 41.4 (t), 40.6 (t), 28.7 (q) ppm.

IR: $\tilde{\nu}$ = 3435, 2974, 2954, 2928, 2882, 1698, 1645, 1619, 1606, 1584 cm^{-1}.

MS (ESI): m/z = 531.8 $[M+H]^+$. ($C_{30}H_{34}N_4O_5$).

Synthesis of 5',7'-dibromo-1'-(2-hydroxyethyl)spiro([1,3]dioxolane-2,3'-indolin)-2'-one (77)



76 **77**

To a solution on NaH (2 equiv.) in DMF (5 ml/mmol) at 0 °C, was added dropwise a solution of **76** in DMF (1 ml/mmol). After 10 minutes was added 2-bromoethanol (2 equiv.). The reaction mixture was stirred at 70 °C for 24 h. Then, the reaction mixture was concentrated in vacuo, extracted with AcOEt and washed with brine (5 x). The organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel.

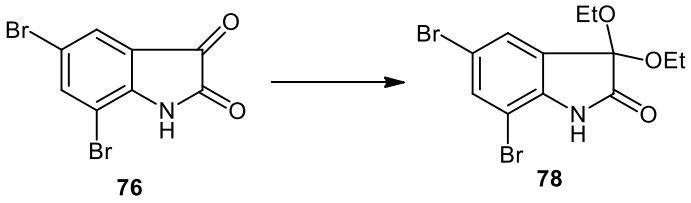
Yield: 75%.

White solid; m.p.: 107 – 110 °C.

^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.64 (d, *J* = 1.8 Hz, 1 H), 7.42 (d, *J* = 1.8 Hz, 1 H), 4.54 (m, 2 H), 4.28 (m, 4 H), 3.91 (t, *J* = 5.8 Hz, 2 H), 1.68 (br. s, 1 H, exchange with D_2O) ppm.

MS (ESI): m/z = 394.0 $[M+H]^+$. ($C_{12}H_{11}Br_2NO_4$).

Synthesis of 5,7-dibromo-3,3-diethoxyindolin-2-one (78)



76 **78**

5,7-dibromoisatin (**76**) was added to a solution of triethyl ortoformate (15 equiv.) in EtOH (5 ml/mmol). The reaction mixture was stirred at 70 °C for 48 h. Then, the reaction mixture was concentrated in vacuo, extracted with AcOEt and washed with water (3 x). The organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel.

Yield:

White solid; m.p.: 167 – 170 °C.

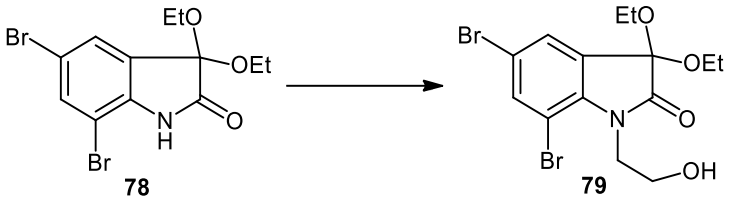
^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.98 (br. s, 1 H, exchange with D_2O), 7.59 (d, *J* = 1.8 Hz, 1 H), 7.45 (d, *J* = 1.8 Hz, 1 H), 3.86 (m, 4 H); 1.24 (t, *J* = 7.0 Hz, 6 H) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ = 171.42 (s), 139.01 (s), 135.40 (d), 129.18 (s), 127.33 (d), 115.87 (s), 104.55 (s), 97.85 (s), 59.39 (t), 15.41 (q) ppm.

IR: $\tilde{\nu}$ = 3430, 3204, 2974, 1728 cm^{-1}.

MS (ESI): m/z = 401.9 $[M+Na]^+$. ($C_{12}H_{13}Br_2NO_3$).

Synthesis of 5,7-dibromo-3,3-diethoxy-1-(2-hydroxyethyl)indolin-2-one (79)



The compound **78** (1 equiv.) in DMF (10 ml/mmol) was added dropwise to a solution of NaH (1.5 equiv.) in DMF (2 ml/mmol) at 0 °C. After 10 minutes was added 2-bromoethanol. The reaction mixture was stirred at 70 °C for 48 h. Then, the reaction mixture was concentrated in vacuo, extracted with AcOEt and washed with water (3 x). The organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel.

Yield: 85%.

White solid; m.p.: 90 – 92 °C.

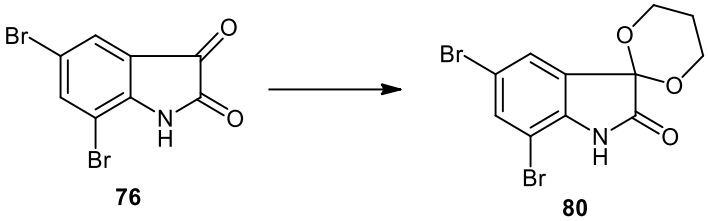
^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.63 (d, *J* = 1.8 Hz, 1 H), 7.46 (d, *J* = 1.8 Hz, 1 H), 4.31 (t, *J* = 5.9 Hz, 2 H), 3.91 (t, *J* = 5.9 Hz, 2 H), 3.78 (m, 4 H), 1.84 (s, 1 H, exchange with D_2O), 1.22 (t, *J* = 7.3 Hz, 6 H) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ = 172.7 (s), 139.4 (s), 138.3 (d), 131.1 (s), 127.3 (d), 116.2 (s), 103.5 (s), 95.9 (s), 61.6 (t), 59.5 (t), 43.5 (t), 15.4 (q).

IR: ν̃ = 3571; 3517; 3077; 2973; 2933; 2885; 1737 cm-1.

MS (ESI): m/z = 446.0 $[M+Na]^+$. ($C_{14}H_{17}Br_2NO_4$).

Synthesis of 5',7'-dibromospiro([1,3]dioxane-2,3'-indolin)-2'-one (80)



To a solution of **76** (1 equiv.) in toluene (10 ml/mmol) was added propylene glycol (10 equiv.) and *p*-TSA (5 mol %). The reaction mixture was refluxed with Marcusson apparatus for 24 h. Then, the reaction mixture was concentrated in vacuo, extracted with AcOEt and washed with $NaHCO_3$ sat. (1 x) and water (2 x). The organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel.

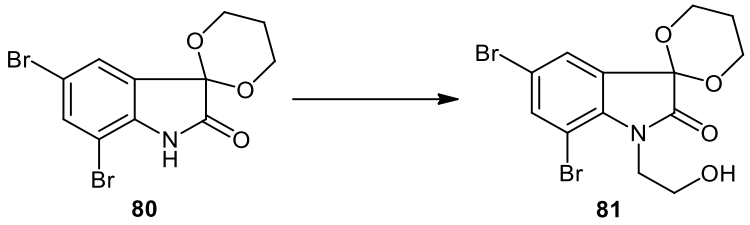
Yield: 60%.

White solid; m.p.: 193 -195 °C.

^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.57 (d, *J* = 1.9 Hz, 1 H), 7.49 (d, *J* = 1.9 Hz, 1 H), 7.44 (br. s, 1 H, exchange with D_2O), 4.93 (m, 2 H), 3.97 (m, 2 H), 2.38 (m, 1 H), 1.65 (m, 1 H) ppm.

MS (ESI): m/z = 385.8 $[M+Na]^+$. ($C_{11}H_9Br_2NO_3$).

Synthesis of 5',7'-dibromo-1'-(2-hydroxyethyl)spiro([1,3]dioxane-2,3'-indolin)-2'-one (81)



The compound **80** (1 equiv.) in DMF (10 ml/mmol) was added dropwise to a solution of NaH (1.5 equiv.) in DMF (2 ml/mmol) at 0 °C. After 10 minutes was added 2-bromoethanol. The reaction mixture was stirred at 70 °C for 48 h. Then, the reaction mixture was concentrated in vacuo, extracted with AcOEt and washed with water (3 x). The organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel.

Yield: 70%.

White solid; m.p.: 116 – 118 °C.

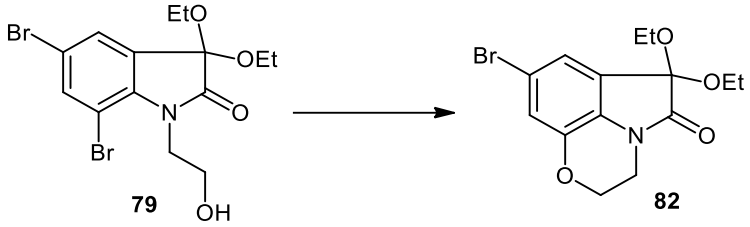
^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.60 (d, *J* = 1.9 Hz, 1 H), 7.50 (d, *J* = 1.9 Hz, 1 H), 4.93 (m, 2 H), 4.26 (t, *J* = 5.8 Hz, 2 H), 3.94 (m, 4 H), 2.39 (m, 1 H), 1.80 (br. s, 1 H, exchange with D_2O), 1.63 (M, 1 H) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ = 172.9 (s), 139.1 (s), 138.6 (d), 132.2 (s), 127.2 (d), 116.6 (s), 102.9 (s), 92.5 (s), 61.8 (t), 61.7 (t), 43.1 (t), 25.4 (t) ppm.

IR: $\tilde{\nu}$ = 3457, 2960, 1708, 1608, 1574 cm^{-1}.

MS (ESI): m/z = 429.5 $[M+Na]^+$. ($C_{13}H_{13}Br_2NO_4$).

Synthesis of 8-bromo-6,6-diethoxy-2,3-dihydro-[1,4]oxazino[2,3,4-*hi*]indol-5(6*H*)-one (82)



The compound **79** (1 equiv.) in toluene (10 ml/mmol) was added dropwise to a solution of NaH (2 equiv.) in toluene (5 ml/mmol) at 0 °C. After 10 minutes was added $Cu(OAc)_2$ (10 mol %). The reaction mixture was stirred at 110 °C for 2 h. Then, the reaction mixture was fitered through a celite pad and was concentrated in vacuo, extracted with AcOEt and washed with brine (3 x). The organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel.

Yield: 80%.

White solid; m.p.: 108 - 110 °C.

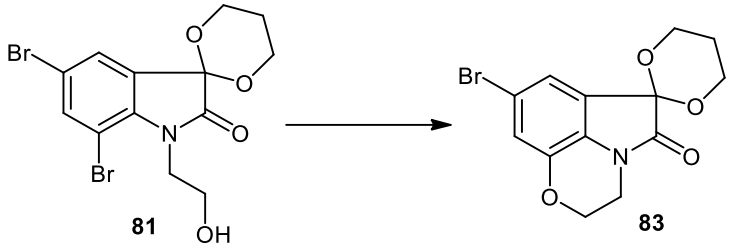
^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.13 (s, 1 H), 7.05 (s, 1 H), 4.25 (t, *J* = 4.4 Hz, 2 H), 3.96 (m, 2 H), 3.80 (m, 5 H), 1.24 (t, *J* = 6.6 Hz, 6 H) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ = 168.5 (s), 142.3 (s), 127.3 (s), 126.6 (s), 121.3 (d), 120.7 (d), 115.4 (s), 98.8 (s), 65.1 (t), 59.3 (t), 38.65 (t), 15.4 (q) ppm.

IR: $\tilde{\nu}$ = 3457, 2974, 2925, 1738 cm^{-1}.

MS (ESI): m/z = 365.9 $[M+Na]^+$. ($C_{14}H_{17}BrNO_4$).

Synthesis of 8-bromo-2*H*-spiroC[1,4]oxazino[2,3,4-*hi*]indole-6,2'-[1,3]dioxin)-5(3*H*)-one (83)



The compound **81** (1 equiv.) in toluene (10 ml/mmol) was added dropwise to a solution of NaH (2 equiv.) in toluene (5 ml/mmol) at 0 °C. After 10 minutes was added CuI (10 mol %) and 8-hydroxyquinoline (10 mol %). The reaction mixture was stirred at 110 °C for 2 h. Then, the reaction mixture was fitered through a celite pad and was concentrated in vacuo, extracted with AcOEt and washed with brine (3 x). The organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel.

Yield: 60%.

White solid; m.p.: 126 – 129 °C.

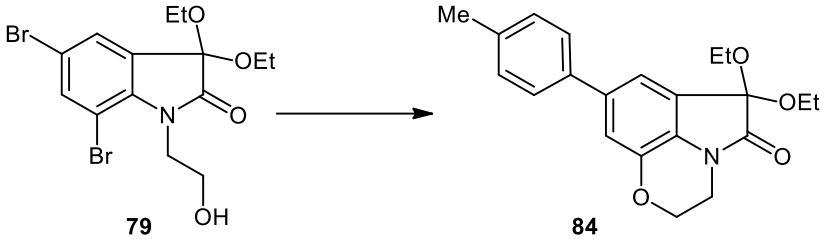
^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.20 (d, *J* = 1.3 Hz, 1 H), 7.06 (d, *J* = 1.3 Hz, 1 H), 4.91 (m, 2 H), 4.26 (m, 2 H), 4.07 (m, 1 H), 4.03 (m, 1 H), 3.78 (m, 2 H), 2.25-2.41 (m, 1 H), 1.72 (m, 1 H) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ = 169.2 (s), 142.0 (s), 127.6 (s), 127.1 (s), 121.1 (d), 120.7 (d), 115.8 (s), 95.9 (s), 65.1 (t), 61.5 (t), 38.5 (t), 25.4 (t) ppm.

IR: $\tilde{\nu}$ = 3425, 2965, 1714, 1638, 1497 cm^{-1}.

MS (ESI): m/z = 349.9 $[M+Na]^+$. ($C_{13}H_{12}BrNO_4$).

Synthesis of 6,6-diethoxy-8-(*p*-tolyl)-2,3-dihydro-[1,4]oxazino[2,3,4-*hi*]indol-5(6*H*)-one (84)



The compound **79** (1 equiv.) in toluene (10 ml/mmol) was added dropwise to a solution of NaH (2 equiv.) in toluene (5 ml/mmol) at 0 °C. After 10 minutes was added $Cu(OAc)_2$ (10 mol %). The reaction mixture was stirred at 110 °C for 2 h. Then, was added $Pd(OAc)_2$ (5 mol %), PPh_3 (5 mol %) and *p*-tolylboronic acid (1 equiv.) and the reaction mixture was stirred at 110 °C for additional 4 h. Then, the reaction mixture was fitered through a celite pad and was concentrated in vacuo, extracted with AcOEt and washed with brine (3 x). The organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel.

Yield: 50%.

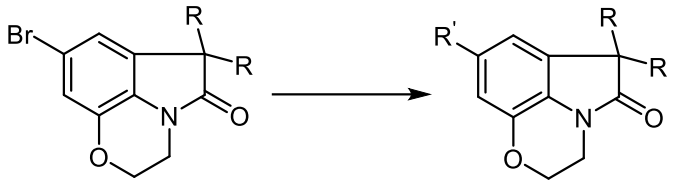
^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.42 (d, *J* = 8.0 Hz, 2 H), 7.23 (m, 3 H), 7.10 (d, *J* = 1.5 Hz, 1 H), 4.29 (dd, *J* = 7.7 Hz, *J* = 4.4 Hz, 2 H), 4.02 (m, 2 H), 3.82 (m, 4 H), 2.38 (m, 3 H), 1.26 (m, 6 H) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ = 169.1 (s), 141.9 (s), 138.3 (s), 137.4 (s), 137.3 (s), 129.7 (d), 127.2 (s), 127.1 (d), 127.1 (s), 125.6 (s), 171.2 (d), 116.2 (d), 99.4 (s), 65.0 (t), 59.2 (t), 38.9 (t), 21.3 (q), 15.5 (q).

IR: $\tilde{\nu}$ = 3429, 2978, 2933, 2898, 1727 cm^{-1}.

MS (ESI): m/z =376.1 $[M+Na]^+$.($C_{21}H_{23}NO_4$).

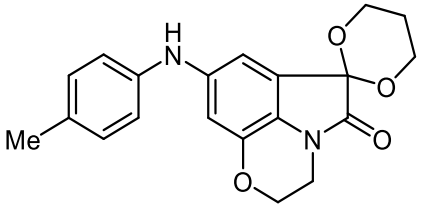
General procedure for the copper catalyzed amination or alkoxylation reaction



83,82 **85a-d**

To a solution of **82** or **83** (1 equiv.) in the appropriate solvent (1-2 ml/mmol) was added Cs_2CO_3 (1.5 equiv.), the appropriate aniline or pyrazole or phenol (1.5 equiv.) and the catalyst (10-15 mol %). The reaction mixture was stirred at 110 °C for 8-24 h. Then, the reaction mixture was fitered through a celite pad and was concentrated in vacuo, extracted with AcOEt and washed with brine (3 x). The organic phases were dried with Na_2SO_4, filtered and the solvent removed in vacuo. The product was purified by flash chromatography on silica gel.

8-(*p*-Tolylamino)-2*H*-spiro([1,4]oxazino[2,3,4-*hi*]indole-6,2'-[1,3]dioxan)-5(3*H*)-one (85a)



Yield: 40%.

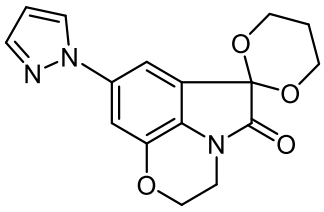
Colourless oil.

^{1}H NMR (300 MHz; CD_3CN): δ = 7.08 (d, *J* = 8.0 Hz, 2 H), 6.92 (d, *J* = 8.0, 1.9 Hz, 2 H), 6.75 (d, *J* = 1.9 Hz, 1 H), 6.63 (d, *J* = 1.9 Hz, 1 H), 6.40 (br. s, 1 H, exchange with D_2O), 4.75 (m, 2 H), 4.26 (m, 2 H), 3.99 (m, 2 H), 3.73 (m, 2 H), 1.78 (m, 2 H) ppm.

^{13}C NMR (75 MHz; CD_3CN): δ = 190.6 (s), 168.9 (s), 142.1 (s), 142.0 (s), 140.9 (s), 130.0 (d), 129.9 (d), 127.2 (s), 121.7 (s), 108.1 (d), 107.1 (d), 96.5 (s), 65.4 (t), 61.1 (t), 38.4 (t), 25.3 (t), 19.9 (q) ppm.

MS (ESI): m/z = 375.1 $[M+H]^+$. ($C_{20}H_{20}N_2O_4$).

8-(1*H*-pyrazol-1-yl)-2H-spiro[[1,4]oxazino[2,3,4-hi]indole-6,2'-[1,3]dioxan]-5(3H)-one (85b)



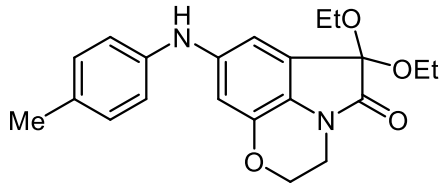
Yield: 20%.

Colourless oil.

^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.57 (d, *J* = 2.2 Hz, 1 H), 7.48 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.05 (d, *J* = 2.2, 1 H), 6.91 (dd, *J* = 8.0, 1.6 Hz, 1 H), 6.53 (td, *J* = 8.0, 1.6 Hz, 1 H), 4.43 (m, 2 H), 4.22 (m, 2 H), 3.76 (m, 2 H), 3.54 (m, 2 H), 2.17 (s, 3 H), 1.98 (m, 2 H) ppm.

MS (ESI): m/z = 336.1 $[M+Na]^+$. ($C_{16}H_{15}N_3O_4$).

6,6-Diethoxy-8-(p-tolylamino)-2,3-dihydro-[1,4]oxazino[2,3,4-*hi*]indol-5(6*H*)-one (85c)



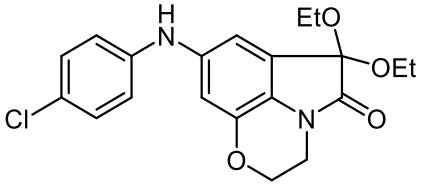
Yield: 50%.

Colourless oil.

^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.06 (d, *J* = 8.3 Hz, 2 H), 6.89 (d, *J* = 8.3 Hz, 2 H), 6.75 (d, *J* = 1.9 Hz, 1 H), 6.64 (d, *J* = 1.9 Hz, 1 H), 5.48 (br. s, 1 H, exchange with D_2O), 4.26 (m, 2 H), 3.96 (m, 2 H), 3.81 (m, 4 H), 2.29 (s, 3 H), 1.25 (t, *J* = 7.1 Hz, 6 H) ppm.

MS (ESI): m/z = 391.3 $[M+H]^+$. ($C_{21}H_{24}N_2O_4$).

8-((4-Chlorophenyl)amino)-6,6-diethoxy-2,3-dihydro-[1,4]oxazino[2,3,4-*hi*]indol-5(6*H*)-one (85d)



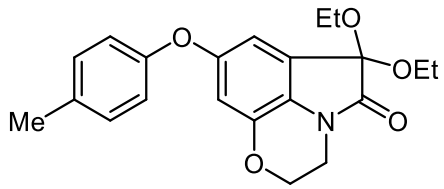
Yield: 40%.

Colourless oil.

^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.18 (d, *J* = 8.9 Hz, 2 H), 6.87 (d, *J* = 8.9 Hz, 2 H), 6.77 (d, *J* = 1.6 Hz, 1 H), 6.67 (d, *J* = 1.6 Hz, 1 H), 4.29 (br. s, 1 H, exchange with D_2O), 4.27 (m, 2 H), 3.89 (m, 2 H), 3.75 (m, 4 H), 1.25 (t, *J* = 7.1 Hz, 6 H) ppm.

MS (ESI): m/z = 413.6 $[M+H]^+$. ($C_{20}H_{21}ClN_2O_4$).

6,6-Diethoxy-8-(p-tolyloxy)-2,3-dihydro-[1,4]oxazino[2,3,4-*hi*]indol-5(6*H*)-one (86)



Yield: 10%.

Colourless oil.

^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.12 (d, *J* = 8.5 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 6.75 (d, *J* = 2.0 Hz, 1 H), 6.57 (d, *J* = 2.0, 1 H), 4.27 (m, 2 H), 3.94 (m, 2 H), 3.80 (m, 4 H), 2.32 (s, 3 H), 1.24 (t, *J* = 7.1 Hz, 6 H) ppm.

MS (ESI): m/z = 392.1 [M+H]+. ($C_{21}H_{23}NO_5$).

2. Biological evaluation

Inhibition growth assay

HeLa (human cervix adenocarcinoma cells) were grown in Nutrient Mixture F-12 [HAM] (Sigma Chemical Co.); H-460 (large cell lung carcinoma) and MSTO-211H (human biphasic mesothelioma cells) were grown in RPMI 1640 (Sigma Chemical Co.) supplemented with 2.38 g/l Hepes, 0.11 g/l pyruvate sodium and 2.5 g/l glucose. 1.5 g/L $NaHCO_3$, 10% heat-inactivated fetal calf serum (Invitrogen), 100 U/mL penicillin, 100 mg/mL streptomycin, and 0.25 mg/ml amphotericin B (Sigma Chemical Co.) were added to the media. The cells were cultured at 37 °C in a moist atmosphere of 5% carbon dioxide in air. Cells (3e4 x 104) were seeded into each well of a 24-well cell culture plate. After incubation for 24 h, various concentrations of the test agents were added to the complete medium and incubated for a further 72 h. A Trypan blue assay was performed to determine cell viability. Cytotoxicity data were expressed as GI_{50} values, i.e., the concentration of the test agent inducing 50% reduction in cell number compared with control cultures.

Linear flow dichroism

Linear dichroism (LD) measurements were performed on a Jasco J500A circular dichroism spectropolarimeter, converted for LD and equipped with an IBM PC and a Jasco J interface. Linear dichroism was defined as:

$LD_{(\lambda)} = A_{//} - A_{(\lambda)}$

where $A_{//}$ and $A_{\perp}$ correspond to the absorbances of the sample when polarized light was oriented parallel or perpendicular to the flow direction, respectively. The orientation was produced by a device designed by Wada and Kozawa[86] at a shear gradient of 500e700 rpm, and each spectrum was accumulated twice. Aqueous solutions of DNA (1.9×10^{-3} M) in 10 mM TRIS, 1 mM EDTA (pH 7.0) and 0.01 M NaCl were used (ETN buffer). Spectra were recorded at 25 °C at [drug]/[DNA] = 0 and 0.08.

Topoisomerase I-mediated DNA relaxation

Supercoiled pBR322 plasmid DNA (0.25 mg, Fermentas Life Sciences) was incubated with 2U topoisomerase I (human recombinant topoisomerase I, TopoGen) and the test compounds as indicated, for 60 min at 37 °C in 20 ml reaction buffer. Reactions were stopped by adding 4 ml stop buffer (5% sodium dodecyl sulfate (SDS), 0.125% bromophenol blue, and 25% glycerol), 50 mg/ml proteinase K (Sigma) and incubating for a further 30 min at 37 °C. The samples were separated by electrophoresis on a 1% agarose gel at room temperature. The gels were stained with ethidium bromide 1 mg/ml in TAE buffer (0.04 M Tris-acetate and 0.001 M EDTA), transilluminated by UV light, and fluorescence emission was visualized by a CCD camera coupled to a Bio-Rad Gel Doc XR apparatus.

Topoisomerase I-mediated DNA cleavage

Reaction mixtures (20 ml) containing 35mMTris-HCl (pH = 8.0), 72 mM KCl, 5 mM $MgCl_2$, 5 mM DTT, 5 mM spermidine, 0.01% bovine serum albumin, 20 ng pBR322 plasmid DNA (Fer- mentas Life Sciences), 5 U topoisomerase I (human recombinant topoisomerase I, TopoGen) and test compounds at indicated concentrations were incubated for 60 min at 37 °C. Reactions were stopped by adding 4 ml of stop buffer (5% SDS, 0.125% bromophenol blue and 25% glycerol), 50 mg/ml proteinase K (Sigma) and incubating for a further 30 min at 37 °C. The samples were separated by electrophoresis on a 1% agarose gel containing ethidium bromide 0.5 mg/ml (Sigma) at room temperature in TBE buffer (0.09 M Tris-borate and 0.002 M EDTA), transilluminated by UV light, and fluorescence emission was visualized by a CCD camera coupled to a Bio-Rad GelDoc XR apparatus.

3. Computational

The structure of the receptor was obtained from the crystal structure of the topoisomeraseI-DNA-topotecan ternary complex (PDB code: 1K4T) and prepared as previously described.[115] Docking calculations were performed with the software PLANTS.[116] The search space was defined by using the crystallographic ligand center of mass coordinates as the binding site center (x = 49.3764, y = 46.9081 and z = 48.2818) and the binding site radius was set to 14 Å, corresponding to the ligand radius of gyration augmented by 6 Å. Maximum accuracy was requested by setting the search_speed parameters to “speed1”. All the other parameterswere used as default. Ligands were prepared using MOE 2015,[117] and processed by SPORES in order to assign the correct atom types required for docking calculations with PLANTS.[118] By using this setup, the overlay between the lowest energy docked conformation of topotecan (binding energy = -129.4 kcal/mol, computed with the CHEMPLP scoring function)[119] and its crystallographic structure was excellent, with a RMSD of 1.52 Å, computed with VMD 1.9.1.[120]

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