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**DOTTORATO DI RICERCA IN
SCIENZA DEL FARMACO XXIII CICLO**

EXPERIENCING MULTI-COMPONENT REACTIONS:

FROM POST-CONDENSATION MODIFICATIONS TO "CHEMICAL PLATFORM" AND "SUBSTRATE DESIGN" CONCEPTS.

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3. Search for novel Multi-Component Reactions

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LIST OF ACRONYMS AND ABBREVIATIONS

MCR: Multi-Component Reaction

U-4CR: Ugi 4 Components Reaction

P-3CR: Passerini 3 Components Reaction

IMCR: Isocyanide-based Multi-Component Reaction

HOMO: Highest Occupied Molecular Orbital

LUMO: Lowest Unoccupied Molecular Orbital

C-C: carbon-carbon

DMF: dimethylformamide

THF: tetrahydrofuran

RCM: Ring-Closing Metathesis

LiHMDS: lithium hexamethyldisilazide

DFT: Density Functional Theory

TMEDA: tetramethylethylenediamine

KHMDS: Potassium bis(trimethylsilyl)amide

DMSO: dimethyl sulfoxide

NMP: N-methyl-2-pyrrolidinone

CH$_3$CN: acetonitrile

TMSN$_3$: trimethylsilyl azide

DCM: dichloromethane

M: molar

EtOAc: Ethyl Acetate

IC$_{50}$: half maximal inhibitory concentration

SPA: Substance P Antagonist

NK$_1$: Neurokinin 1Receptor

CINV: Chemotherapy-Induced Nausea and Vomiting

FDA: Food and Drug Administration

TFE: trifluoroethanol

MS 4Å: Molecular Sieves 4Å

DoE: Design of Experiments

TsOH: p-Toluenesulfonic acid

n-BuLi: $normal$ Butillithium

t-BuLi: $tert$ Butillithium

DIC: diisopropylcarbodiimide

Boc: $tert$- butoxy carbonyl

DMG: Directed Metalation Group

DoM: Directed ortho Metallation

CIPE: Complex-Induced Proximity Effect

TMSCl: trimethylsilyl chloride

DBU : 1,8-Diazabicyclo[5.4.0]undec-7-ene

IMDA: Intra-Molecular Diels-Alder

o-DCB:*ortho*-dichlorobenzene

TMSOTf: Trimethylsilyl Trifluoromethane- sulfonate

"The human enterprise was once largely

limited to what Nature produced. We are

now limited only by what we can imagine." **[1]**

1. Introduction

1.1 Definition of Multi Component Reactions

The always increasing demand for large libraries of compounds readily available for High Throughput Screening assays in the discovery process of new drugs is allowing more and more the development of new and faster methodologies for the rapid construction of novel chemical entities.

Nowadays, the challenge in synthesis is how a molecule can be made in a practical fashion as close as possible to an "ideal" one. In this sense, Multi-Component Reactions (MCRs) are well known to be selective (minimizing the number of by-products), efficient (providing good yields), atom economic, time saving, easy to perform requiring readily available (commercial or easy to prepare) starting materials.[1]

MCRs are ordered pot reactions, where three or more starting materials react in a sequence of steps, until a final one, to give a final product which contain most of the portions of all the initial components.[2,3] A MCR is thus a domino process by definition.[4,5]

MCRs allow the formation of several bonds in one single operation, usually without isolating the intermediates, changing reaction conditions and/or adding further reagents. The advantages are evident since in multistep synthesis temporal and preparative complexity increases in proportion to the number of steps. The *bond forming efficiency*, that is, the number of bonds formed in one process, is indeed an important measure introduced by Tietze to determine the quality of a MCR.[6] Creating several bonds per reactions means to generate molecular complexity that means highly efficient processes.

A major characteristic of MCRs is their *high exploratory power*: the exploration of a very big chemical space with exceptional synthetic efficiency.

The structure of the reaction product can easily be diversified by systematic variation of each input. The MCRs can be classified according to the reaction mechanism, the components involved or their intrinsic variability. As Zhu states in *Multicomponent Reactions* (Zhu, J., Bienaymé, H., Eds.; Wiley: Weinheim, 2005), "The development of novel MCRs is an intellectually challenging task since one has to consider not only the reactivity match of the starting materials but also the reactivities of the intermediate molecules generated *in situ*, their compatibility and their compartmentalization." Finally it is important to point out that MCRs have already had an important role in drug development, from lead discovery to lead optimization to production, even before the advent of combinatorial technologies as demonstrated by the identification of nifedipine (Adalat®), a highly active calcium antagonist, by means of a Hantzsch reaction or by the synthesis of piperazine-2-carboxamide, the core structure of the HIV protease inhibitor Crixivan, by a Ugi-4CR.


Nifedipin
(Adalat)

Indinavir
(Crixivan)
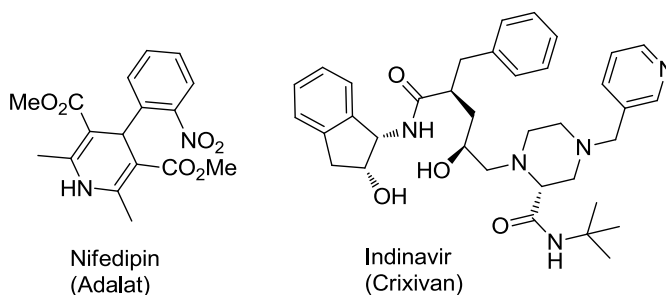
1.2 Some History of MCRs

The general ordering principle of MCRs is followed by the α-amino alkylation, in which an oxo compound and a primary or a secondary amine undergoes electrophilic addition to an electron-rich position of a molecule.[7] The Strecker synthesis of α-amino acids via α-amino cyanides was first published in 1850 and is generally considered to be the first MCR.[8] In this reaction an aldehyde is condensed with ammonium chloride in the presence of potassium cyanide to form an α-aminonitrile, which is subsequently hydrolyzed to give the desired amino acid (Table 1).

Many important heterocycle synthesis are MCRs. 1,4-dihydropyridines were first synthesized over one hundred years ago in a four component reaction by

Hantzsch (H-4CR) from ammonia, aldehyde and two equivalents of acetoacetic ester.[9] After half a century, at the Bayer AG company, a very successful dihydropyridine preparation for the therapy of cardiovascular disease named Nifedipin was developed, based on the Hantzsch synthesis.[10]
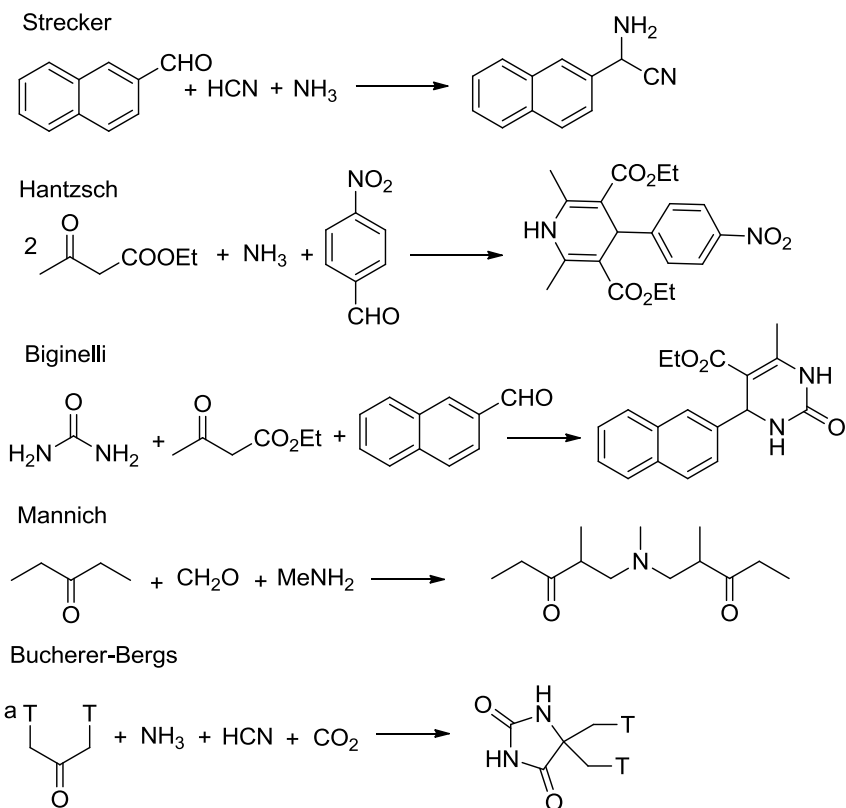
[a] T = Thymine

Table 1. *Examples of some historically significant MCRs. Many of them are based on the reactivity of carbonyl or imine groups.*

Other very famous and useful MCRs are the Biginelli and the Mannich reactions discovered in 1891 and 1912. The Biginelli reaction affords 3,4-dihydropyrimidin-2(1*H*)-ones starting from ethylacetoacetate, an aldehyde and urea. The Mannich reaction consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group with formaldehyde and

ammonia or any primary or secondary amine; the final product is a β-aminocarbonyl compound also known as a Mannich base.

In 1921, the first MCR involving an isocyanide, the Passerini reaction (P-3CR) was reported.

A further important MCR is the Bucherer-Bergs reaction (BB-4CR). [11] It can be understood as an extension of the S-3CR using an additional component (CO_2). Whereas the Strecker 3-CR is an equilibrium reaction and often delivers the product in unsatisfactory yields, the BB-4CR is practically irreversible upon addition of CO_2. It still is an important method for the synthesis of unnatural α-amino acids.

1.3 Isocyanides, Preparation and Chemistry

A large and important class of MCRs are the Isocyanide Multi-Component Reactions (IMCRs). Isocyanides are the only class of stable organic compounds with a formally divalent carbon. In exothermic reactions C^{II} is oxidized to C^{IV}.[12] Most of volatile isocyanides have a strange repulsive odor described from Gautier as "reminiscent of artichokes and phosphorus at the same time".[13] People who inhaled volatile isocyanides such as allyl, benzyl, methyl, or *tert*-butyl isocyanide over a long period of time reported the sensory perception of the smell of hay[3] and a prolonged inhalation is said to increase the intensity of dreams at night. Higher molecular weight isocyanides are often solid and odorless. This class of compounds showed however to have only a slight toxicity, apart from few exceptions. Isocyanides were first synthesized in 1859 by Lieke, who did not recognize them and believed them to be nitriles.[14] It was Gautier the first to understand the isomeric relationship between isocyanides and nitriles in 1869.[15] At the same time Hofmann[16] found a new approach to isocyanides with the reaction of primary amines with potash and chloroform (Scheme 1). Anyway, all methods known at that time were complicated, poorly generalizable and low yields affected, with difficult separation of isocyanides from their isomeric accompanying nitriles.
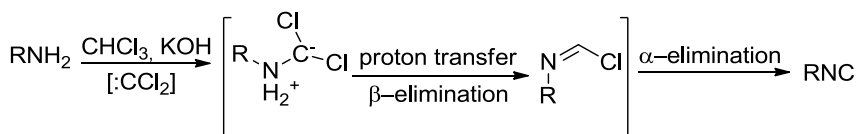
**Scheme 1.** *The Hofmann carbylamine reaction.*

Nowadays there are many convenient and effective methods to access to isocyanides that can be divided into seven different basic routes:

1) Alkylation and alkynylation of cyanides; 2) Reaction of primary amines with dichlorocarbene; 3) Dehydration of *N*-formamides; 4) Further elaboration of isocyanides; 5) Use of organometallic isocyanides; 6) Reduction of isocyanates, isothiocyanates, isoselenocyanates, and isocyanide dihalides; 7) Miscellaneous methods. [17]

The method of choice regarding cost, yield and execution remains however the dehydration of the corresponding *N*-formamides with inorganic dehydratants and organic matching bases, such as $POCl_3$ or Phosgene, and Triethylamine.[18]

Isocyanide chemistry is characterized by three properties: the *α*-acidity, the *α*-addition, an intrinsic high affinity toward metallorganic reagents and their subsequent reactions, and the easy formation of radicals. Especially phenyl-isocyanides are substrates for radical-induced cyclizations. The *α*-acidity is increased by the presence of electron-withdrawing substituents in the *α*-position. *α*-metalated isocyanides can be seen as easy-to-handle *α*-amino anion equivalents, very useful for the synthesis of *α, β*-unsaturated isocyanides, heterocycles and amino acids.[19] Isocyanides polymerize under Lewis acid catalysis to polyiminomethylenes.[20] Synthetically, the most important property of isocyanides is the reaction with nucleophiles and electrophiles at the isocyanide carbon atom: the "*α*-addition", leading to the "*α*-adduct". Most other functional groups in organic chemistry react with nucleophiles and electrophiles at different centers. Only carbene and carbon monoxide share this property with the isocyanides. The different reactivities of the isomeric nitriles and isocyanides are to be ascribed to the higher orbital coefficient of the isocyanides at the carbon atom in the π^* orbital, compared

to nitriles, which leads to nucleophlic attack of the carbon atom. Electrophiles react with the σ orbital of the HOMO-1 and therefore also with the carbon atom. Nitriles instead are attacked by nucleophiles at the carbon atom (higher π* orbital coefficient) and by electrophiles at the nitrogen atom (higher π orbital coefficient). The great potential of isocyanides for the development of MCRs lies in the diversity of bond forming processes available, their functional group tolerance, and the high level of chemo- and regio-selectivity often observed.
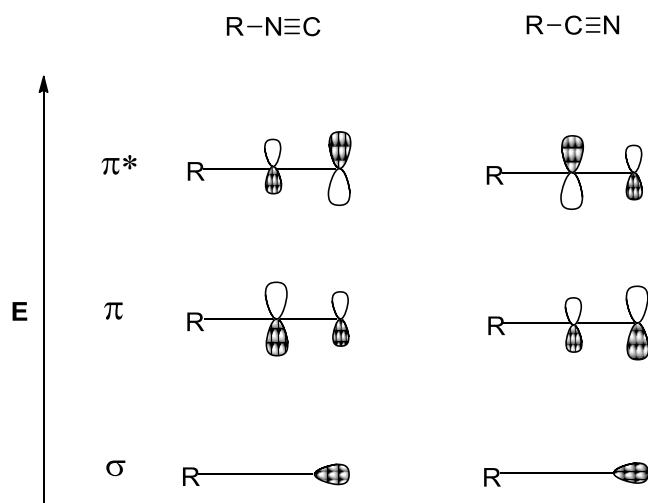

Figure1. *Qualitative comparison of the frontier orbitals of isocyanides and nitriles, showing the different reactivities of the two isomeric functional groups.*

1.4 Passerini 3-CR and Ugi 4-CR

Today most MCRs chemistry performed with isocyanides relates to the classical reactions of Passerini and Ugi, and most part of nowadays described IMCRs was born as their modifications or combinations with other types of reactions. Passerini reaction, described for the first time in 1921, involves an oxo-component (an aldehyde or a ketone), an isocyanide and a nucleophile (typically a carboxylic acid) to afford α-acyloxycarboxamides. Ugi reaction could be seen as the aza-version of the Passerini 3-CR, as it involves an amine

as additional fourth component: it is indeed the reaction of a Schiff base or an enamine with a nucleophile and an isocyanide affording α-acylaminoamides. The Ugi 4-CR is much more versatile than the Passerini in terms of library size and scaffold. The mechanisms of these reactions have often been discussed[21]; kinetic and preparative investigations have led to different mechanistic suggestions.[22] In contrast to the Ugi 4-CR, the Passerini 3-CR is accelerated by aprotic solvents, indicating a nonionic mechanism. Passerini himself postulated hemiacetals between the carboxylic acid and the oxo component as intermediates. From kinetic studies and the observation of a third-degree reaction order, bipolar intermediates were assumed. Other Authors have discussed *N*-protonated isocyanides as reactive intermediates. A plausible mechanism which agrees with experimental data is the formation of a loosely hydrogen-bonded adduct **4** from a carbonyl compound **1** and a carboxylic acid **2**, followed by the α-addition of the electrophilic carbonyl carbon and the nucleophilic oxygen atom of the carboxylic acid to the isocyanide carbon of **3** (Scheme 2) under formation of a cyclic transition state with all three parent compounds. The α-adduct **5**, which cannot be isolated[23], rearranges in an intramolecular transacylation to the stable α-acyloxycarboxyamide **6**.
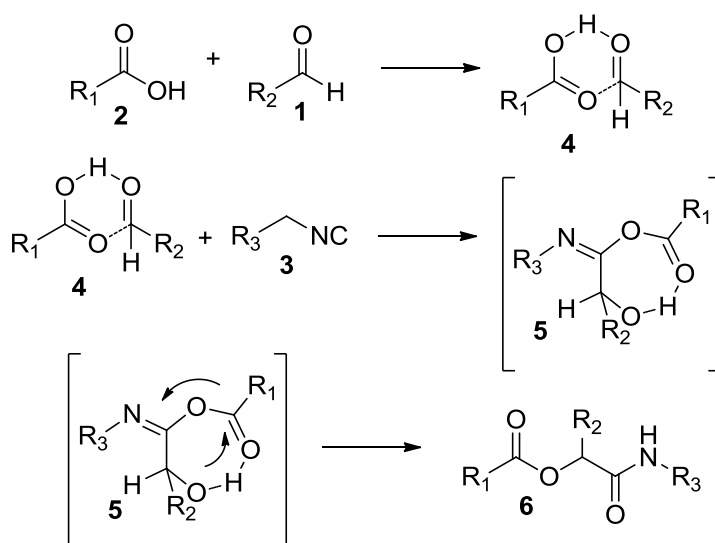
Scheme 2. *Suggested mechanism of P-3CR.*

The Passerini reaction is carried out at high concentrations of the starting materials and in inert solvents at or below room temperature. The P-3CR is particularly suitable for the synthesis of compounds containing the α-acyloxy carboxamide group. The easily performed reduction of Passerini products opens the way to a multitude of *N*-substituted β-hydroxyamines. The mechanistic scenario for the U-4CR may be different and more complex than that shown for the P-3CR. First of all the U-4CR is favored in a polar solvent (MeOH being the most common) in contrast the P-3CR. A strongly simplified reaction mechanism is showed in Scheme 3. In the first step the oxo component and the amine condense to the imine, the Schiff base, via a hydroxyl aminal. It is also possible that the hydroxyl aminal can be transformed directly in the course of the reaction without formation of a Schiff base under certain circumstances. Imines can be seen as carbonyl analogues. Like most imine reactions, the U-4CR runs better upon activation of the Schiff base. For this, the acid component protonates the nitrogen atom of the Schiff base, thus increasing the electrophilicity of the C=N bond. Another way to increase the electrophilicity of the imines is the addition of a Lewis acid such as $TiCl_4$ or $BF_3 \cdot OEt_2$, being especially the case for electron-rich, weakly electrophilic Schiff bases. Depending on the solvent, the ions can be present as a salt pair or separately. The electrophilic iminium ion and the nucleophilic acid anion add to the isocyanide carbon atom. The α-adduct thus formed can be seen as a hetero analogue of an acid anhydride in which an *exo*-oxygen atom has been substituted by an NR group. Acid anhydrides are strong acylating agents, as are their heteroanalogues formed here. The acylable atom is the nitrogen of the former amine. After an intramolecular acylation, the stable Ugi linear, peptide-like adduct is obtained. This type of intramolecular acylation was first described in 1910 by Mumm and was subsequently called the Mumm rearrangement.[24] All elementary steps of this reaction are equilibria; however, the last step, the rearrangement to the stable α-acylaminoamide, lied exclusively on the product side. The driving force of the total reaction sequence is the oxidation of the isocyanide C^{II} atom to the amide C^{IV} atom. It is interesting to follow the changes in nucleophilia and electrophilia of the components during the U-4CR. In the course of the individual steps the reactive centers of the acid component and the imines change the sign of their reactivity several times. At first the C=N bond of the imine behaves like a base towards the acid component. Then the protonated Schiff base functions as the electrophilic and the acid anion as the nucleophilic component of the α-addition. Due to the α-addition to the isocyanide, the amine nitrogen atom becomes the nucleophilic reaction

partner of the electrophilic *O*-acylcarboxylic acid amide system in the α-adduct. In the course of the cycloaddition and the elimination, the reactive centres change their philia signs once again. In the course of the U-4CR, one C-C bond and several heteroatom-C bonds are newly formed. The diversity of the basic structures of the U-4CR is primarily due to the variety of the acid components and their rearrangement opportunities, but also to the structures of the amines as well as the many intramolecular variations. McFarland was the first to examine the product distribution of the U-4CR depending on different reaction conditions systematically. Isocyanides reactivity is mainly influenced by inductive and mesomeric and to a lesser extent by steric effects. The reactants concentration is much more important than the properties of the solvent. Generally the reaction proceeds better if the reactants are present in high concentrations, that is 0.5 to 2 molar. Low-molecular-weight alcohols, such as methanol, ethanol or trifluoroethanol are used as solvents. Aprotic polar solvents like DMF, dichloromethane and THF, or also aprotic apolar solvents such as chloroform or dioxane have also been described as advantageous. In addition, the U-4CR can be performed in biphasic, aqueous solvent mixtures.
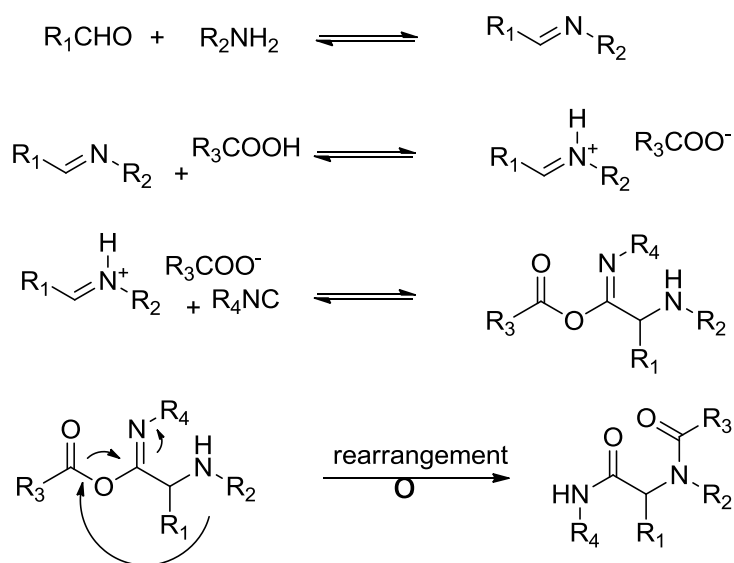
Scheme 3. *Simplified reaction mechanism of U-4CR.*

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2. Post-condensation modifications

2.1 Introduction to post-condensation modifications

Multicomponent reactions are an extremely powerful synthetic tool for medicinal chemistry and pharmaceutical industry not only for all the already mentioned advantages, but also because after a scaffold is synthesized, it can be used for other post-modifications depending on the functional groups introduced during the MCR. In this way it is really simple and fast to synthesize large libraries of structurally diverse complex molecules for biological screenings. Potentially, the number of post-condensation modificationsare countless relying on the chemistry offer: classic textbooks organic reactions such as Pictet- Spengler cyclization,[1] intramolecular Diels-Alder,[2] Mitsunobu reaction and acyl migration,[3] Knovenagel condensation,[4] amide reduction,[5] metathesis reaction,[6] just to cite few of them, or also sequential multi-component transformations as Ugi-Ugi[7] and Ugi-Petasis.[8] In this chapter, two projects related with post-modifications reaction after a classical MCR will be presented. The first one deals with an attempt to synthesize benzo-oxazepinediones, while the second deals with the synthesis of 1-Aryl-5-Aroyl Tetrazoles.[9] The following projects have been investigated under the supervision of Prof. Gian Cesare Tron.

2.2 Buchwald-Hartwig/Goldberg trans-amidation as modification of a 3-C Passerini reaction adduct.

This project aimed at the synthesis of benzo-oxazepinediones of general structure **1** through a sequence of a classical Passerini 3-CR and an intramolecular *N*-arylation reaction under Buchwald-Hartwig or Goldberg conditions. There are many examples in literature of Passerini 3-CR followed by post-condensation transformations as intramolecular Wittig-type reactions[10], *N*-deprotection/ *O-* to *N*-acyl migration[11], ring-closing metathesis[12] (RCM), and others.
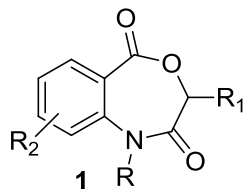
Figure 1. *Target benzo-oxazepine dione structure*

The Passerini product to use as test-substrate for cyclization reactions was obtained by reacting heptanal, *n*- pentylisocyanide and 2-iodobenzoic acid, in dichlorometane as solvent, to afford 1-(ethylamino)-1-oxobutan-2-yl-2-iodobenzoato **2**, in 59% yield. (For details on the mechanism see the Introduction). This adduct was then used as test substrate to screen a wide range of reaction conditions for the transition metal- catalyzed cross coupling amide *N*-arylation reaction.
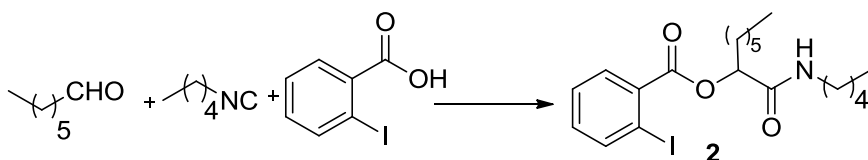
Scheme 1. *Passerini 3-CR for the synthesis of the test substrate for N-arylation cyclizations reaction.*

2.3 Buchwald-Hartwig N-arylation reaction: important features.

The Buchwald-Hartwig *N*-arylation reaction is an aryl halogen/ amide exchange in order to form a new C-N bond performed in the presence of a palladium source as catalyst, a phosphine as ligand and a non-nucleophilic organic or inorganic strong base. This type of reaction is mainly used for amination of aryl halides, formation of aryl ethers through reaction with alcohols, and formation of new C-C bonds in α-arylation of carbonyl, arylation of ketones, aldehydes, esters, γ-arylation of enones and others. The first example of a trans-amination reaction of an aryl halide palladium catalyzed was published in 1983 by Migita[13]; this reaction employed aryl bromides and aminotin compounds providing the corresponding aniline

derivatives in moderate to good yields, in the presence of tri-o-tolylphosphine palladium (0). The limitations associated with the use of toxic and quite unstable tin derivatives were overcome by Buchwald[14] and Hartwig[15] in 1995, who independently described a tin-free procedure. They generated the amide *in situ*, starting from an amine and a strong base, that was for Buchwald sodium *tert*-butoxide and for Hartwig the lithium hexamethyldisilazide (LiHMDS). Among all the efforts to increase the scope of substrates and the efficiency of the reaction, fine tuning of the ligands has shown the biggest impact. Subsequent research allowed to identify a large number of ligands, many of which are now commercially available.
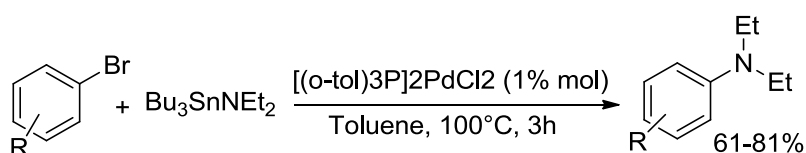
Scheme 2. *Migita trans amination reaction.*
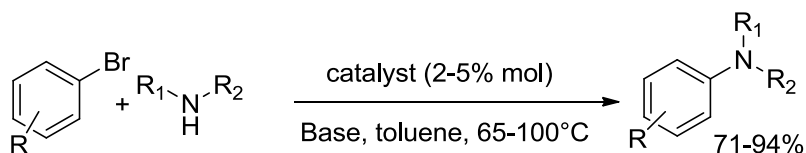
cat: Pd$_2$dba$_3$/(o-tolil)$_3$P, [(o-tolil)$_3$P]$_2$Pd, [(o-tolil)$_3$P]$_2$PdCl$_2$
base: *t*-BuONa, LiHMDS

Scheme 3. *Modifications by Buchwald and Hartwig of Migita trans-amination reaction conditions.*

They are bisphosphonane chelating ligands such as binap[16] (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) **a** (figure 2) and dppf[17] (1,1'-Bis(diphenylphosphino)ferrocene) **b** in an early stage and then derivatives such as XantPhos **c**, or monodentate phosphanes such as dialkyl-biarylphosphanes **d-g**. Best results were obtained with dialkylbiaryl phosphane ligands: they often allows, indeed, short reaction times, low catalyst loadings, and mild reactions conditions.
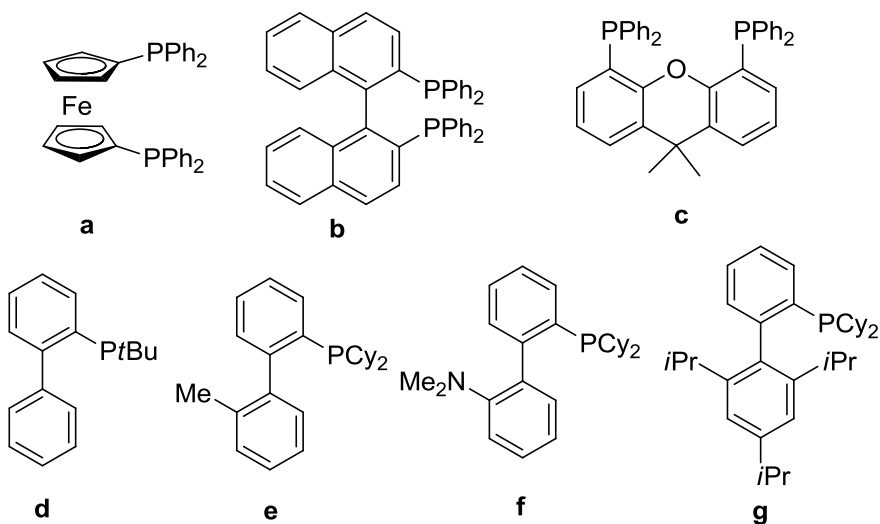
Figure 2. *Examples of chelating phosphanes (**a-c**), and biaryl phosphanes (**d-g**).*

To further optimize catalyst design, much attention has been directed towards a deep understanding of these effects and an intensive study of the mechanism of the palladium catalyzed amination with numerous ligand systems.

The Pd^{II} catalyst is reduced to the active Pd^0 species which is stabilized by the ligand L (**1**). In the case of the dialkylbiaryl phosphanes the catalytically active species is believed to be the mono-ligated, highly reactive $[LPd^0]$ complex, which exists in equilibrium with the $[L_2Pd^0]$ species.[18] The catalytic cycle starts with coordination of the aryl halide to palladium (0) followed by oxidative addition to intermediate **2**. In the next step a halide atom is replaced by the nitrogen atom of the amine to intermediate **3**. The enhanced acidity of the amine when coordinated to palladium allows these compound to be deprotonated with a strong base to give intermediate **4**. This latter give the reductive elimination to the desired aryl amine **5** liberating $[LPd^0]$ species ready to start a new cycle.

Pd⁰ or Pd^II Precatalyst/L

Pd^0 or Pd^{II} Precatalyst/L
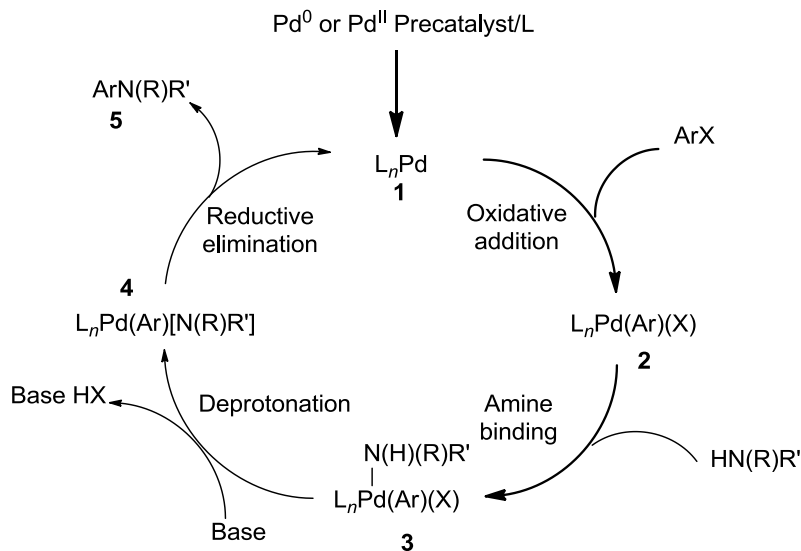
Figure 2. *Proposed catalytic cycle.*

substituents on the lower ring play a role in promoting the formation of the reactive $[LPd^0]$ species.   Other studies demonstrated, through deuterium labeling, that in case of 2'-monosubstituted dialkylbiaryl ligands, the Pd^{II} precatalysts have a tendency to form palladacycles [20] **3** (Figure 3). This effect would serve to reduce the rate of catalyst activation, as such palladacycle are only slowly converted into the active catalyst.[21] Another characteristic of the dialkyl phosphane ligands which is believed to promote catalyst stability and increase electron density at the metal center is the possibility of palladium-arene interactions between the metal atom and the lower ring of the ligands (**4**, Figure 3).
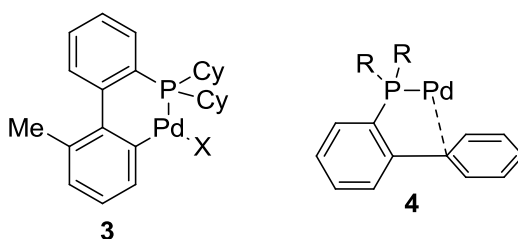
Figure 3. *Example of palladacycle 3, and interaction palladium-arene in 4.*

Such interactions have been observed in the X-ray crystal structures of a number of palladium-biaryl phosphane complexes,[22-28] and even in an oxidative addition complex with methyl triflate.[29] Anyway, obtaining experimental informations on the importance of these interactions in the catalytically active species has proven to be more difficult.[30] DFT calculations, however, have underlined the importance of the palladium-arene interactions in intermediates in the catalytic cycle.[31,32] Finally, these studies also indicated that the lower ring promotes the reductive elimination step. The palladium-arene interaction stabilizes the aminopalladium intermediate and reduces the energy of the transition state when the palladium center is proximal to the lower ring (Figure 4). In a recent review[33], Hartwig enlightened the electronic effects on reductive elimination from palladium (II) complexes. He stated that in many cases the scope of the cross coupling is controlled by the rate and scope of the reductive elimination process. For example, palladium-catalyzed couplings to form C-N and C-O bonds were challenging to develop because palladium amido and palladium alkoxo complexes were reluctant to undergo reductive elimination.[34] Until recently, it was unclear whether all classes of C-X bond-forming reductive elimination processes would depend equally on the overall electron density at the metal center or whether each process would be controlled by its own set of electronic effects. Dealing with steric effects, it is generally true that complexes with more hindered ancillary ligands undergo reductive elimination faster than complexes with less hindered ancillary ligands. This effect presumably arises from a relief in steric congestion upon generation of the free organic product and a resulting metal center with a reduced coordination number. For electronic effects, mainly two were observed. First reductive elimination is usually slower from more electron-rich complexes than from electron-poor ones. This effect can be explained by the observation that strongly donating ancillary ligands make the metal center more electron-rich, and electron-rich metal centers tend to undergo reductive processes more slowly than electron-poor metal centers. Second, theoretical and early experimental studies suggested that complexes with more strongly electron-donating reacting ligands undergo concerted reductive eliminations faster than do complexes with more weakly electron-donating reacting ligands. An explanation for this effect could be the consideration that electron-withdrawing groups on the reactive ligand lead to an increase in the strength of the M-C or M-X bond. These electron-withdrawing groups make the M-C or M-X bond more ionic, and this ionic character increases the thermodynamic bond strength. Thus, groups whose electronic properties

increase the strength of the M-C bonds tend to decrease the thermodynamic driving force for reductive elimination.

Experimental data on electronic effects on C-N bond-forming reductive elimination show that this process in arylamines is faster from complexes with more electron-rich amido ligands than from complexes with more electron-poor amido ligands.[35]


Substituent fixes conformation enhances rate of reductive elimination

Alkyl groups increase electron density at phosphorous, promote oxidative addition. Increased steric bulk at P promotes reductive elimination. Large substituents on P promote [L^1Pd^0].

Large substituents prevent cyclometalation, increase stability, promote [L^1Pd^0]

Lower aryl ring allows stabilizing Pd-arene interactions and promotes reductive elimination.

Figure 4. *Important structural features of dialkylbiaryl phosphanes.*

2.4 Goldberg reaction: an overview.

In the Goldberg reaction an amine or an amide is coupled with an aryl halide in the presence of a stoichiometric amount of copper as catalyst, and a base. (Scheme 4) It is a variation of the Ullmann condensation between a phenol and an aryl halide to afford a diaryl ether (Scheme 5).[36]
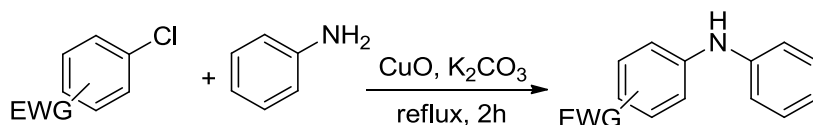
Scheme 4. *Goldberg condensation.*
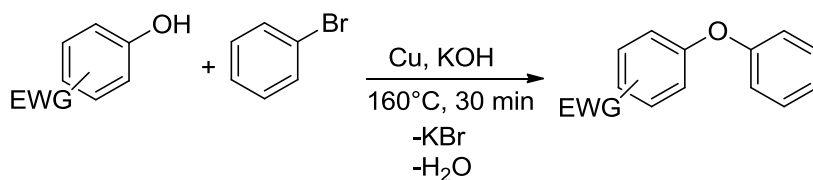
Scheme 5. *Ullmann condensation.*

Both the Ullmann and the Goldberg reactions predate the palladium-catalyzed amination methodology by many decades. Nevertheless, the methods have remained relatively undeveloped. The necessity to use temperatures as high as 210°C, highly polar solvents, and often large amounts of copper reagents, as well as the modest yields often realized, have undoubtedly prevented these reactions from being employed to their full potential. An important alternative has been reported where aryl boronic acids are used as arylating agents instead of aryl halides.[37] Unluckily, the method suffers from high costs and poor availability of functionalized boronic acids, as well as limited scope of the process. The traditional protocol for Goldberg amidation reaction prescribe simple copper salts or often copper metal as catalyst. Very few reports have focused on deliberate use of ligands to facilitate the copper catalyzed amidation reaction, until, in 2002, Buchwald reported an experimentally simple and inexpensive catalyst system for the amidation of aryl halides by using 0.2-10% mol of CuI, 5-20% mol of a 1,2-diamine ligand, and K_3PO_4, K_2CO_3 or Cs_2CO_3 as base (Scheme 6).[38] This system proved to be extremely efficient and general for *N*-amidation of aryl and heteroaryl iodides and bromides, and in some cases even unactivated aryl chlorides. The reaction scope was extended using *N,N'*-dimethylethylenediamine and *trans-N,N'*-dimethyl-1,2-cyclohexanediamine as ligand.
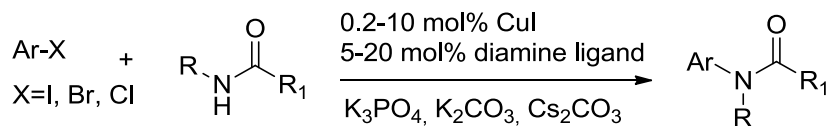
Scheme 6. *Buchwald modification of Goldberg amidation reaction conditions.*

In this study Buchwald reported a variety of effective 1,2-diamine ligands; their structure has a pronounced effect on their ability to facilitate the copper-catalyzed aryl amidation reactions. The degree of substitution and consequently the steric bulk of diamine ligands play the most important role. The N,N'-dimethyldiamine **L2** and **L5** have higher activity than the unsubstituted diamines **L1**, **L3** and **L4**. On the other end, bulky N-substituents on the ligand, e.g. isopropyl as in **L7** and ethyl as in **L6** decrease the rate of aryl amidation reaction. Further substitution at the nitrogen center leads to a completely inactive ligand (e.g. TMEDA). Ligands **L2** and **L5** are commercially available, and ligand **L5** showed to be slightly more active than **L2**; the difference becomes significant in more difficult reactions such as in the amidation of aryl chlorides. The role of the chelating amine could simply be to increase the stability constant of the catalycally active copper-amine complex. Anyway, further studies are required to ascertain this hypothesis. Different readily available copper sources were also tested, and Cu_2O, CuI and CuCl produced acceptable results, being the air-stable and inexpensive CuI the best one with more difficult substrates. It is interesting to note that copper compounds in various oxidation states are catalytically active and presumably are transformed to the same active catalyst under the reaction conditions.[39]
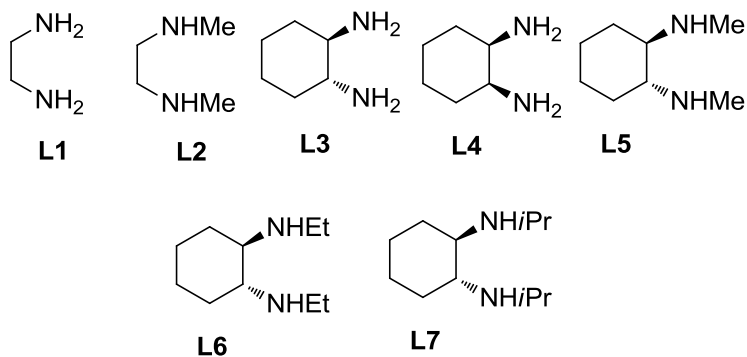
Figure 5. *Some diamine ligands in Buchwald version of Goldberg amidation.*

The choice of the base plays a more important role than the nature of the copper precatalyst. Amidation of aryl iodides proceeds best with K_3PO_4 as base; the reaction is much slower with K_2CO_3. In contrast many amidations of aryl bromides, which typically react more slowly than aryl iodides, fail in the presence of K_3PO_4. In those cases, complete conversion of the aryl bromide can nevertheless be achieved with a weaker base such as K_2CO_3. Further insight into this interesting phenomenon was provided by an experiment where a solution of a strong base, KHMDS, was slowly added to a reaction mixture including an aryl iodide and an amide: nearly complete conversion was achieved while less of 1% conversion was detected if the base was added in a single portion. These observations suggest that the rate of deprotonation of the amide has to match the rate of amidation reaction. If an excess of deprotonated amide is formed, it impedes the desired aryl amidation reaction presumably via formation of an unreactive cuprate complex (Scheme 7).

Experimental data with organic bases demonstrated that the pK_{HA} of the base employed in the arylation reaction should be below the pK_{HA} of the amide substrate unless the base is delivered gradually as the reaction proceeds. A similar rational can be applied to inorganic bases such as K_3PO_4 or K_2CO_3. Presumably these bases are thermodynamically very strong in aprotic solvents[40]; nevertheless, their extremely low solubility in nonpolar organic solvents ensures the rates of deprotonation that are optimal for the arylation of amides.
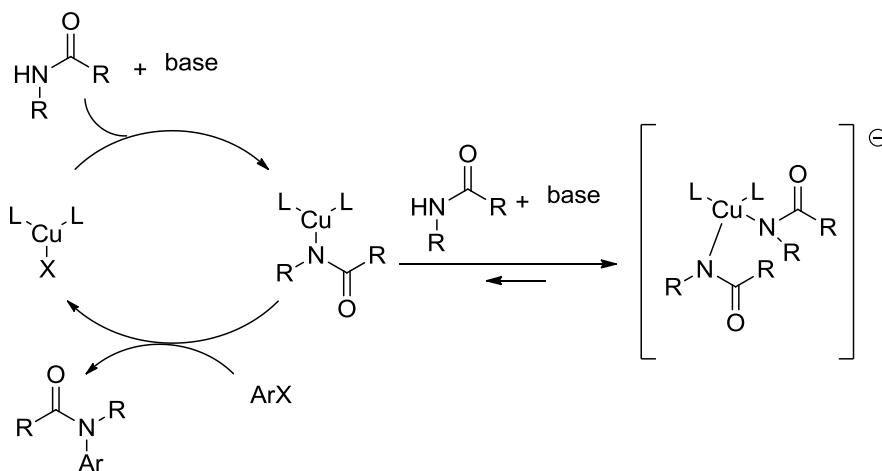
Scheme 7. *Catalytic cycle of Goldberg amidation, and formation of unreactive cuprate complexes.*

This catalytic system provides an excellent complement to the palladium-catalyzed methodology, particularly if aryl halides with strong electron-donating groups or free N-H groups have to be amidated. There are also some practical benefits of this copper-diamine-catalyzed amidation protocol. Although the reactions are moderately sensitive to oxygen and have to be performed under inert atmosphere, there is no need to use glove-box techniques nor to purify the commercially available reagents. Most of the reactions are extremely clean: no reduction or homocoupling of the aryl halide, which often takes place in the Pd-catalyzed cross-coupling reactions, is normally observed. Another notable feature of the process is the low molecular weight of diamine ligands: this is a definitive advantage if the cost per mole of the ligand is considered. A more recent paper by Buchwald[42] describes initial insight into the mechanism of aryl iodide activation, complementing the kinetic study of a Cu(I)-catalyzed Goldberg reaction with a direct *N*- arylation of a Cu(I) amidate. Anyway the precise mechanism of the Cu(I)-mediated activation has not been established precisely and warrants further studies.

2.5 Buchwald-Hartwig/ Goldberg experimented conditions on Passerini adduct **2**.

In the attempt to obtain our benzoxazepinic scaffold starting from the P-3CR adduct **2** we unsuccessfully experimented different copper catalyzed Goldberg amidation reactions, (Scheme 8) selecting from literature examples of linear secondary and cyclic amidic substrate.[42-47] We chose cooper iodide (CuI) as catalyst, and the 1,2-diamine ligands **L2** and **L5**. We also used thiophene-2-carboxylic acid **L8** as ligand (Figure 6) which has been reported by Zhu to successfully afford benzodiazepindiones derivatives in a Buchwald-Hartwig copper catalyzed amidation reaction.[43]

L8
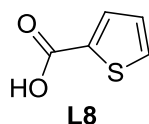
Figure 6. *Thiophene-2-carboxylic acid.*

Another tested procedure was by Lange[44] using *N*-methyl-2-pyrrolidinone (NMP) as solvent. The reaction is described to be very fast under Microwave irradiation, but it is possible to have a quite complete conversion of the substrate experimented even at room temperature. As reported in Table 1, solvents tested were toluene (the classical solvent described for this reaction) (entry **2**,**3**,**6**,**7**,**10**) , but also DMSO (entry **1**), dioxane (entry **9**), NMP (entry **5**), THF (entry **4**) and mix toluene/CH$_3$CN (entry **8**). The screened bases in our reaction conditions were K$_2$CO$_3$ (entry **1-3**,**5**,**6**,**8**) and Cs$_2$CO$_3$ (**4**,**7**,**9**,**10**).
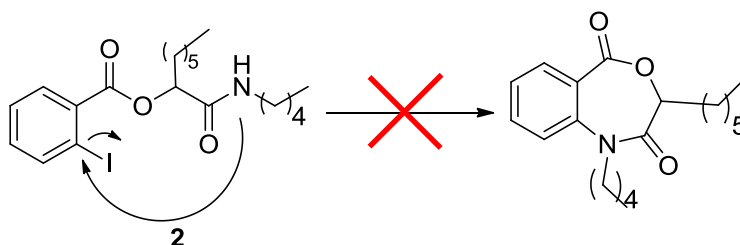
Scheme 8. *Attempted cyclizations of Passerini adduct **2**.*

Unfortunately, all the experimented conditions failed to afford the desired product. We were only able to recover the unreacted α-acyloxy-amide **2**. When higher temperatures were used (as in entry **5**) we only observed degradation of the starting substrate to an intractable mixture. When required, air-free conditions were used, with degassed solvents, and the reactions performed in a Schlenk tube under a positive pressure of nitrogen.

Entry	Catalyst	Ligand	Base	Solv./ Temp	Time
1	CuI 10% mol	**L8** 20%mol	K_2CO_3 2 eq	DMSO 110°C	20h
2	CuI 5% mol	**L2** 10%mol	K_2CO_3 2 eq	Toluene 100°C	20h
3	CuI 5% mol	**L5** 10%mol	K_2CO_3 2 eq	Toluene 110°C	20h
4	CuI 20% mol	**L2** 40%mol	Cs_2CO_3 2 eq	THF 60°C	20h
5	CuI 2.5% mol	-------	K_2CO_3 1 eq	NMP 180°C	17h
6	CuI 5% mol	**L2** 10%mol	K_2CO_3 2 eq	Toluene 180°C	20h
7	Pd(OAc)$_2$ 3.3% mol	**L9** 5%mol	Cs_2CO_3 1.4 eq	Toluene 100°C	24h
8	Pd(OAc)$_2$ 5% mol	**L9** 5%mol	K_2CO_3 2 eq	Tol/CH_3CN 100°C	24h
9	Pd(dba)$_3$ 2% mol	**L10** 6% mol	Cs_2CO_3 1.4 eq	Dioxane 110°C	24h

| 10 | Pd(OAc)$_2$ 3.3% mol | **L10** 5%mol | Cs$_2$CO$_3$ 1.4 eq | Toluene 100°C | 24h |

Table 1. *Buchwald-Goldberg experimented conditions.*

Table 1 also reports Buchwald-Hartwig palladium catalyzed amidation experimental reaction conditions. Use of palladium acetate (entry **7**,**8**,**10**) and tris(dibenzylideneacetone) dipalladium (entry **9**) is reported. Two different phosphines (**L9**, **L10**) were used as ligands (Figure 7).
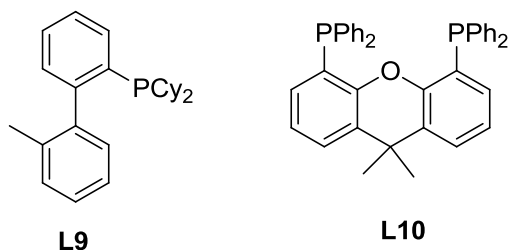
Figure 7. *Phosphine ligands used in test reactions.*

2.6 Synthesis of 1-Aryl-5-Aroyl Tetrazole derivatives using an Ugi-like 4-component reaction followed by a biomimetic transamination.

This project aimed to identify a novel and operationally simple strategy for the synthesis of elusive 1-aryl-5-aroyl tetrazoles by means of an Ugi-like four component reaction (4-CR), followed by a hydrogenolysis/transamination post-transformation. The superimposition between a potent anti-tubulinic chalcone and 1-aryl-5-aroyl tetrazoles revealed that, potentially, this scaffold could be a bioisostere[48] of chalcones and so could generate metabolically stable[49] chalcone-like analogues with anti-tubulinic activity (Figure 7).
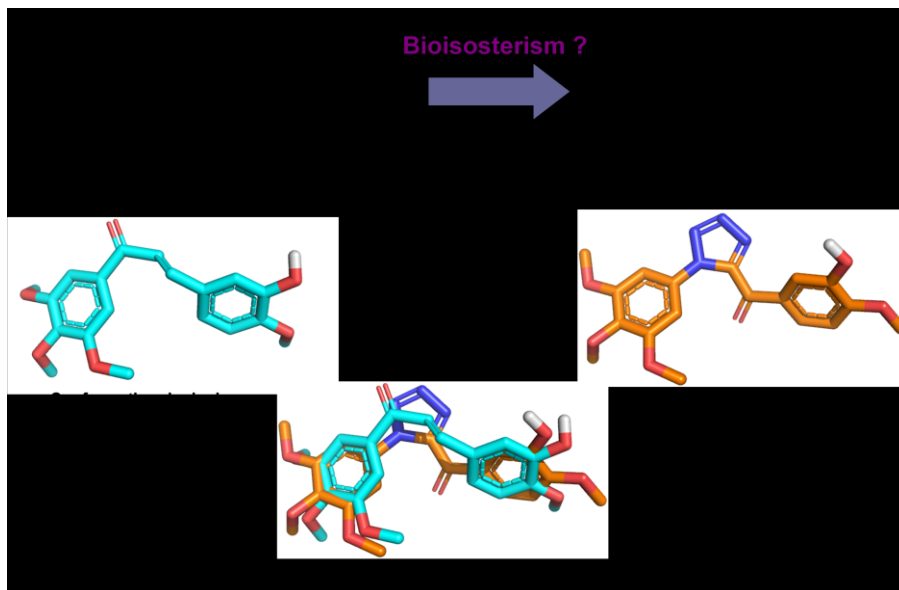
Figure 7. *Superimposition between a potent anti-tubulinic chalcone and 1-aryl-5-aroyl tetrazoles.*

Surprisingly, a Sci-Finder® and CrossFire® survey revealed that only four 1-aryl-5-aroyl tetrazoles (Figure 8) have been reported to date and only two synthetic strategies have been reported with poor chemo-selective and low yield synthetic routes developed (Figure 9).
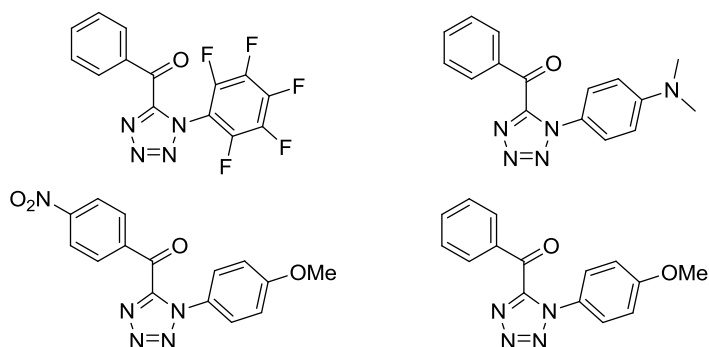
Figure 8. *1-aryl-5-aroyl tetrazoles reported in literature.*
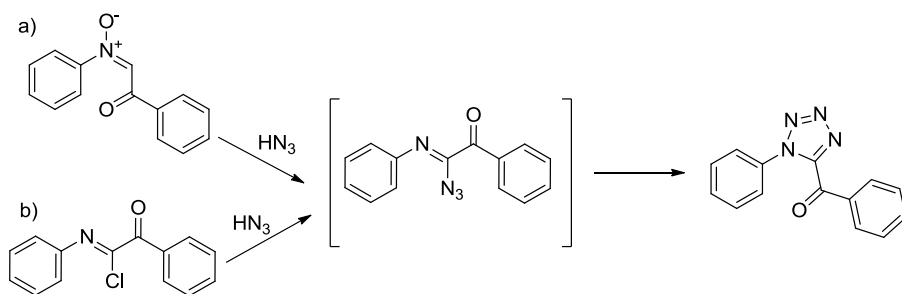
Figure 9. *Reported syntheses for the generation of 1-aryl-5-aroyl tetrazoles.*

In the first strategy, nitrones react with hydrazoic acid followed by an intramolecular [1,3]-cycloaddition[50], while the second synthetic strategy consists in the reaction between isocyanides and acyl chlorides to give α-ketoimidoyl chlorides which undergo nucleophilic substitution with an excess of hydrazoic acid, followed by an intramolecular [1,3]-cycloaddition.[51] Very recently, Sharpless' group has devised a synthesis of 5-acyltetrazoles from azides and acyl cyanides, but the reaction was incompatible with aryl azides in order to generate 1-aryl-5-aroyl tetrazoles.[52]

In a first attempt, we envisaged the possibility to synthesize this scaffold through a Passerini 3-CR using trimethylsilyl azide in the place of the acidic component, followed by an oxidation step (Scheme 9).
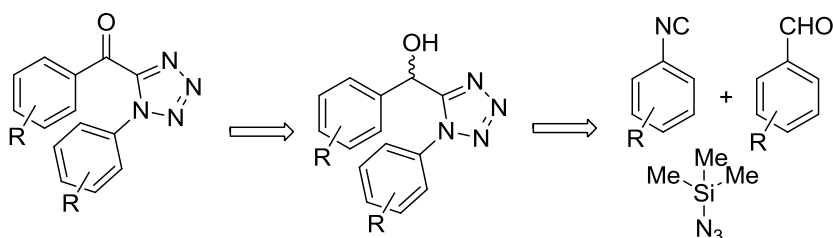
Scheme 9. *First retrosynthetic analysis.*

It is interesting to notice that, in a comprehensive review on Passerini reaction by Banfi *et al.*, there are no examples of tetrazole scaffolds generated by aromatic aldehydes and aromatic isocyanides.[53] When we reacted 3,4,5-trimethoxyphenylisocyanide (**1**), *p*-anisaldehyde (**2**) and trimethylsilyl azide (**3**) in dichloromethane at room temperature, we could only isolate the 3,4,5-trimethoxyphenyl-1*H*-tetrazole (**4**) in 90 % yield (Scheme 10). [54]
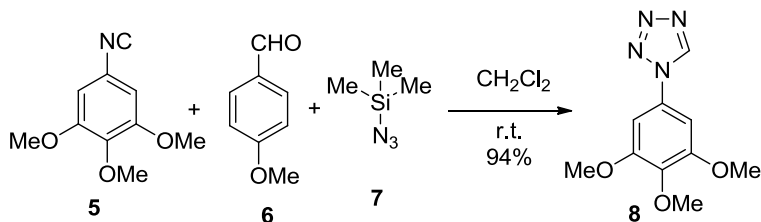
Scheme 10. *Formation of 3,4,5-trimethoxyphenyl-1H-tetrazole (4).*

We therefore screened different Lewis acids as catalysts (zinc triflate, lithium bromide, indium trichloride, zinc chloride, aluminium trichloride, cerium trichloride, ytterbium triflate, boron trifluoride and dysprosium acetate) in order to activate the aldehyde component. Our test reactions revealed that AlCl$_3$ was the only catalyst able to promote the multicomponent process, affording, after column chromatography, in 30 % yield an inseparable mixture formed by the desired tetrazole compound (**9**) and the α-hydroxy-amide product (**10**) in a 1:1 ratio. This latter derives from water addition to the intermediate nitrilium ion (Scheme 11). Attempts to avoid the formation of **10**, using anhydrous sodium sulphate, 4 Å molecular sieves or ultra dry AlCl$_3$ did not suppress the formation of the by-product **10**.
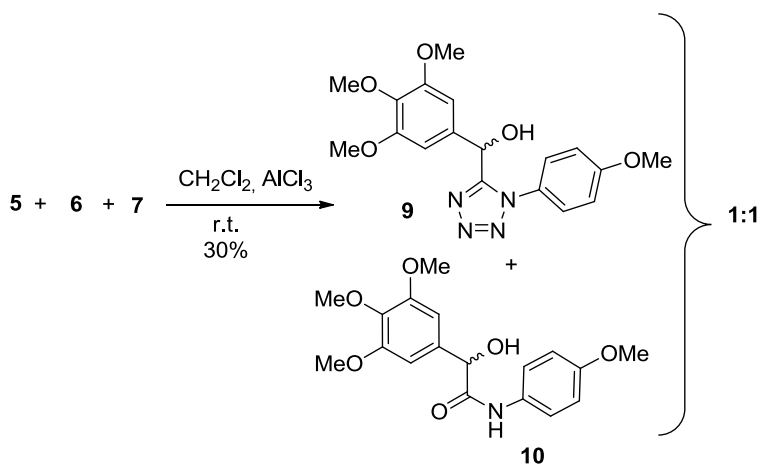
Scheme 11. *MCR between an aromatic isocyanide, an aromatic aldehyde and trimethylsilyl azide catalyzed by aluminum trichloride.*

Recently Zhu and co-workers demonstrated that the formation of the α-hydroxyamide derivatives depends on the catalyst and cannot be suppressed.[55] In this paper Zhu described the asymmetric synthesis of 5-(1-

Hydroxyalkyl)tetrazoles by a catalytic enantioselective Passerini-type reaction. Isobutyraldehyde **11**, 4-methoxyphenylisocyanide **12** and $TMSN_3$ **7** were used as test reaction components, at 0°C and in the presence of catalyst **13**. The test reaction afforded the desired tetrazole and a significant amount of 2-hydroxy-*N*-(4-methoxy-phenyl)-3-methylbutanamide **16**.
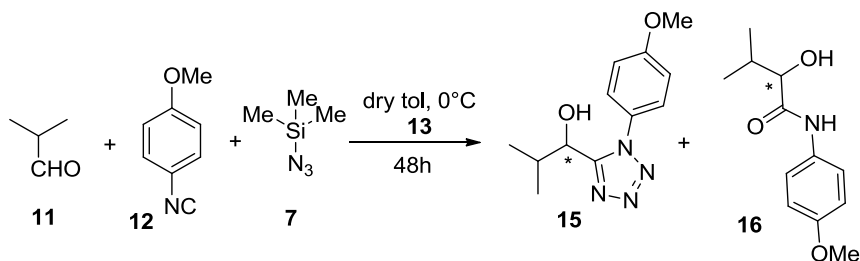
Scheme 12. *Passerini 3-CR test reaction reported by Zhu.*
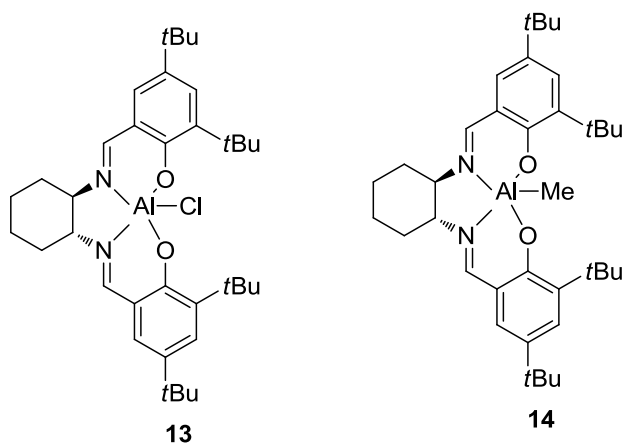
Figure 10. *Catalyst used in the asymmetric P-3CR by Zhu.*

Decreasing the reaction temperature, using additives (Na_2SO_4, 4 Å molecular sieves) or using HN_3 did not avoid the formation of **16**. Control experiments indicated that in the absence of Al catalyst under otherwise identical reaction conditions, formation of **16** did not occur and the yield of **15** was significantly reduced. These results indicated that the formation of both **15** and **16** was catalyzed by [(salen)$Al^{III}Cl$] complex **13**. Reasoning that reaction of $TMSN_3$

29

or HN_3 with **13** might produce TMSCl (or HCl), with concurrent generation of an Al-azide complex, a potential mechanism for the formation of **15** and **16** was proposed. Herein, nucleophilic addition of isocyanide to the aldehyde-Al complex (**A**) affords the nitrilium ion (**B**), which is trapped by hydrazoic acid to provide tetrazole **D**. Concurrently, reaction of **B** with TMSCl or HCl affords the chloroimidate **C**, which in the presence of adventitious water, is converted into the α-hydroxyamide **E**. Finally they succeded to synthesize the desired tetrazole **15** in almost quantitative yield and 83% ee with [(salen)Al^{III}Me] catalyst **14**.
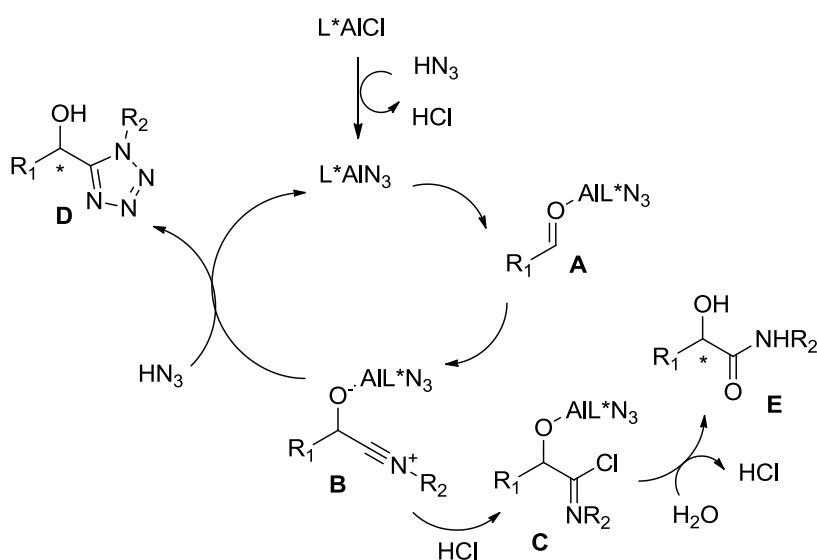
Scheme 13. *Proposed mechanism of α-hydroxyamide side product* **E** *formation.*

In light of that, our strategy based on P-3CR was therefore abandoned, as it suffered from low yields, formation of by-products and difficult purification, features incompatible with the generation of a library during the drug discovery process. We consequently devised another retrosynthetic analysis, always using a MCR as key step for the introduction of all the functionalities in one single operation. In practice, the carbonyl group of 1-aryl-5-aroyl

tetrazoles could be created through a transamination/oxidation reaction. The amine intermediate would derive from an Ugi-like 4CR using benzylamine, arylisocyanide, arylaldehyde and trimethylsilyl azide[56,57] followed by a hydrogenolytic cleavage of the *N*-benzyl group (Scheme 14).
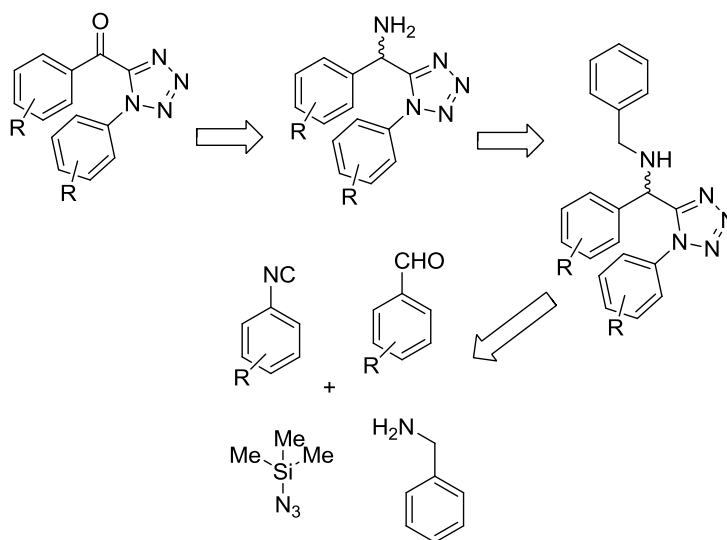
Scheme 14. *Second retrosynthetic analysis.*

Initial experiments were carried out using benzylamine (**17**), trimethylsilyl azide (**7**), 4-methoxyphenylisocyanide (**18**) and 3,4,5-trimethoxybenzaldehyde (**19**) as test substrates. The four compounds reacted in methanol at room temperature affording after 20 hours the desired adduct (**20**) which precipitated and could be collected by simple filtration in 59 % yield. Compound **20** was then hydrogenolyzed to cleave the benzyl group, using palladium on charcoal 10 % as catalyst, in methanol at 60°C providing, after filtration over a celite pad and evaporation of the solvent, the amino derivative (**21**) in 91 % yield. Finally, **21** was subjected to the transamination/oxidation reaction to afford the desired 1-aryl-5-aroyl tetrazoles. After an extensive screening, we identified the Rapoport procedure[58] as the transamination/oxidation reaction able to give the best yields, allowing us to isolate, after acidic work up and column chromatography, the 1-aryl-5-aroyl tetrazoles derivative (**22**) in 50 % yield. (Scheme 15).
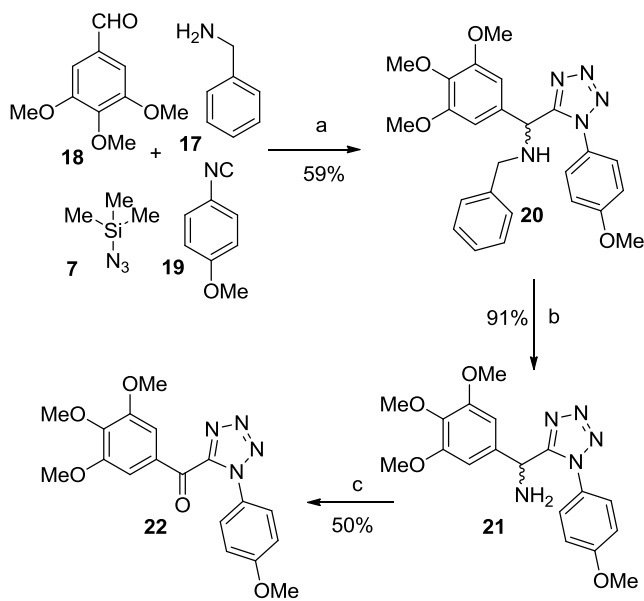
[**a)** : MeOH, rt, 48h; **b)** H2, Pd/C 10%, MeOH, 60°C, 24h; **c)** i) 4-formyl-1-methyl pyridinium benzene sulphonate, DCM/DMF 3:1, 8h; ii) TEA, 30 min; iii) oxalic acid aq. sln. 6h]

Scheme 15. *General procedure for the synthesis of 1-Aryl-5-Aroyl Tetrazoles.*

The Rapoport transamination/oxidation reaction represents a simple and mild biomimetic conversion of amines to carbonyls in the presence of 4-formyl-1-methylpyridinium benzenesulfonate as pyridoxal phosphate (vitamin B6) surrogate. The amine and the formyl derivative were stirred in DCM/DMF 3:1 for 8 hours at room temperature. Triethylamine was then added and deprotonation occured under mild conditions forming an azaenolate. After about 30 minutes, the resonance-stabilized anion was protonated and hydrolyzed with an aqueous solution of oxalic acid to give the 4-(aminomethy)-1-methyl pyridinium salt and the desired carbonyl compound (Scheme 16).
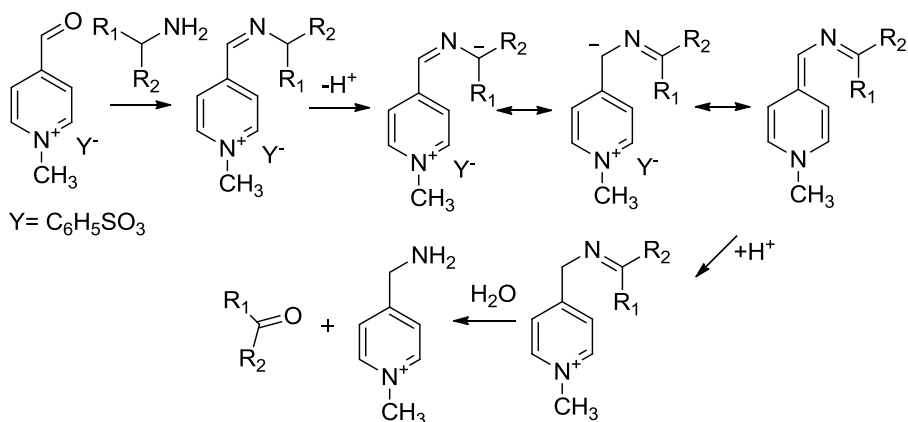
Scheme 16. *The Rapoport biomimetic transamination/oxidation.*

To demonstrate the scope and generality of this new synthetic strategy seven aldehydes (**6**, **18**, **23-27**), eight isocyanides (**5**, **19**, **28-33**) with different electron withdrawing and electron donor substituents were employed. The reaction was usually performed with unsubstituted benzylamine **17**, but it was also tested with substituted benzylamines **34**, **35** (Figure 10).

Ugi-like 4-CR reaction was performed mixing the aldehyde, isocyanide, benzylamine and trimethylsilyl azide in methanol (2M), stirring at room temperature for three days. All MCR products (**20**, **36-51**) were isolated in high yields (59-86 %) (Table 2). In case of isocyanide **28**, the Ugi is performed with the *O*-protected *tert*-butyl-dimethylsilyl derivative **28a**. The *tert*-butyl-dimethylsilyl was then cleaved under conditions reported in literature (for details see experimental section of the chapter).
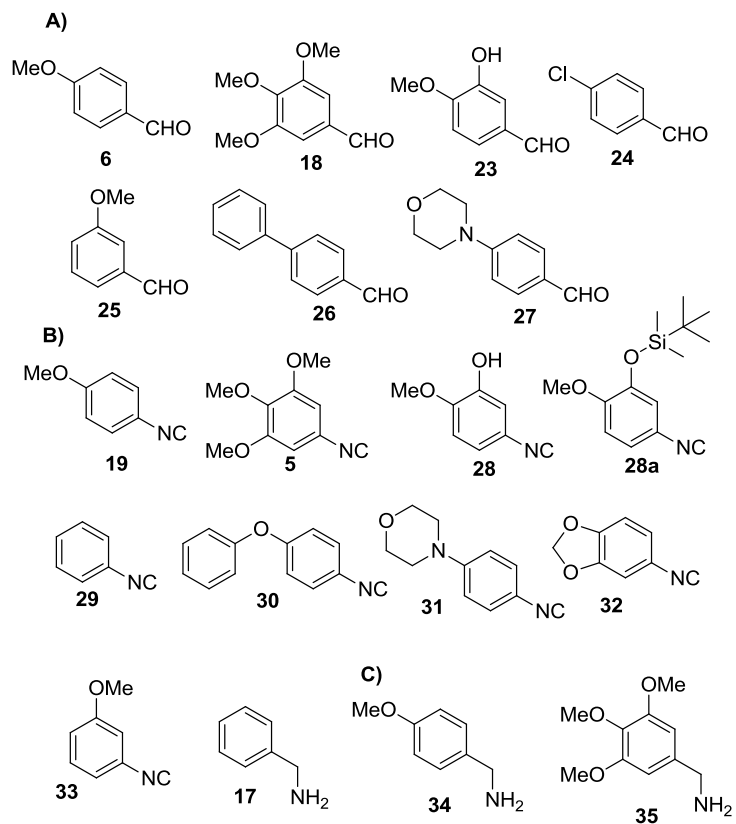
Figure 11. *Aldehydes (A), isocyanides (B) and benzylamines (C) building blocks.*
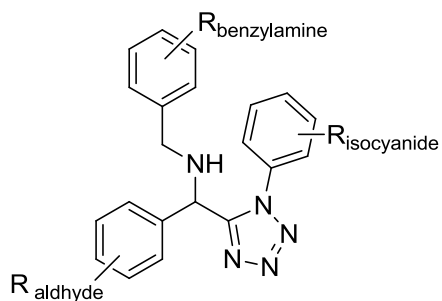
Product	Aldehyde	Isocyanide	Benzylamine	Yield
20	18	19	17	59%
36	6	5	17	70%
37	26	30	17	74%
38	18	32	17	78%
39	18	30	17	86%
40	23	32	17	53%
41	24	32	17	87%
42	24	29	17	65%
43	27	29	17	71%
44	25	5	17	63%
45	26	29	17	69%
46	24	31	17	82%
47	18	28a*	17	75%
48	18	33	17	81%
49	18	29	34	39%
50	18	28a*	35	67%
51	23	33	35	72%

Table 2. *Synthesized Ugi adducts.*

When the product was solid it was possible to obtain it just filtering the precipitate under vacuum, while, in the case of oily products, they were purified by chromatographic column using petroleum ether/EtOAc as eluent. Hydrogenolysis was carried out for 24 hours and the resulting primary amines (**21**, **52-64**) were isolated by simple filtration in excellent yields (60-95 %) (Table 3). Finally, the amine derivatives were subjected to the biomimetic

transformation giving the desired 1-aryl-5-aroyl tetrazoles (**22**, **65-77**) in moderate to good yields (38-61%) (Figure 6).
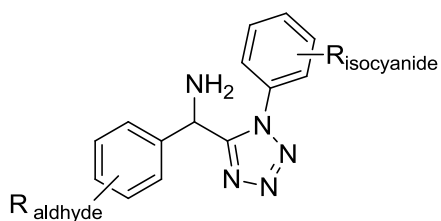
Product	Starting Ugi adduct	Yield
21	20	91%
52	36	72%
53	37	95%
54	38	93%
55	39	70%
56	40	68%
57	41	77%
58	42	77%
59	43	92%
60	44	71%
61	45	60%
62	46	92%
63	47	66%
64	48	92%

Table 3. *Synthesized primary amines from benzyl hydrogenolytic cleavage.*
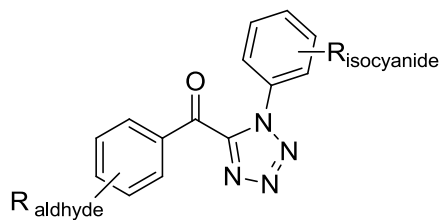
Product	Starting Ugi adduct	Yield
22	21	50%
65	52	50%
66	53	44%
67	54	63%
68	55	50%
69	56	46%
70	57	40%
71	58	38%
72	59	61%
73	60	41%
74	61	39%
75	62	46%
76	63	46%
77	64	38%

Table 4. *Trans-amination final 1-aroyl-5-aryl-tetrazole adducts.*

2.7 Medicinal chemistry interest of 1-Aryl-5-Aroyl Tetrazole derivatives as biomimetic of antitubulinic chalcones.

A growing solid tumor needs a new developing vasculature for oxygen, nutrients, depuration, etc.[59] If the developed vascular bed is disrupted or destroyed, the tumor stops its growing. The first proof of concept that this idea could be feasible was provided when a ricin-conjugated antibody directed against an endothelial protein was able to eradicate the tumoral mass in mice.[60] Therapeutically it is possible to adopt two different strategies: 1) arresting the development of the growing tumoral vasculature and 2) destroying the already established vasculature perfusing the tumoral mass. It is demonstrated that it is possible targeting selectively the tumoral neovasculature endothelial cells over the normal vasculature, as they both express unique proteins. If we consider a plasma membrane protein expressed uniquely on the tumoral vasculature, we could envisage the use of specific antibodies conjugated with toxins, vaccines, etc. Yet it is possible that the neovasculature is more sensitive over normal tissues to more traditional small-molecule drugs. Also this strategy has been exploited, and a number of compounds have entered or are entering clinical trials, referred as "low molecular weight vasculature-disrupting agents". For example, the growth of the neovasculature is dependent on activation of the vascular endothelial growth factor receptor, and therefore, a number receptor antagonists have been devised and are currently tested or employed.[61] Disruption of tubulin polymerization also disrupts the formation of tumoral vasculature, and it is therefore no surprise that a number of agents have been brought forward into drug pipeline that share this mechanism of action.

The interest in 1-aryl-5-aroyl-tetrazole scaffold arose from its structural similarity with some antitubulinic chalcones as already shown in paragraph 2.6. Chalcones are open-chain molecules consisting of two aromatic rings linked by a three-carbon enone fragment. It has been demonstrated that they can act as tubulin polymerization inhibitors by binding to the colchi-site of tubulin in a reversible manner (**78**, **79** Figure 12).[62] To date, despite the interesting pharmacological properties demonstrated by this class of compounds, there are no chalcones as antitubulinic agents in clinic or pre-clinic studies. This seems to be due to their metabolic instability *in vivo*. Indeed, the phenolic group can easily undergo phase II metabolism and the

enone system can undergo Michael additions with biological nucleophiles such as glutathione.

citotoxicity
78: IC_{50}= 4.3 nM
79: IC_{50}= 0.21 nM

antitubulinic activity
78: IC_{50}= 1.0 mM
79: IC_{50}= 1.8 mM
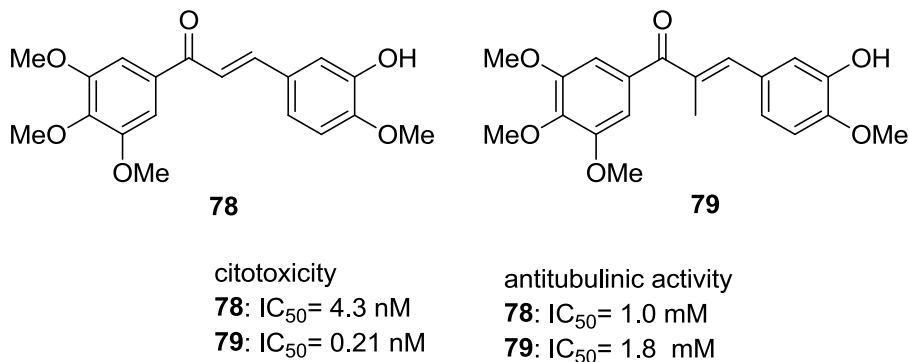
Figure 12. *Examples of chalcones 78 and 79 and their IC_{50}s.*

Other drawbacks can be: a) chalcones are promiscuous structures with a plethora of biological activities; and b) they can have patentability problems. For these reasons, over the last decades, chalcones have been used as starting points to design and synthesize novel stable analogues with the same antimitotic effect and a better efficacy/safety window.[63] In particular, modifications on the chalcone scaffold regarding the replacement of the double bond have been fulfilled maintaining cytotoxicity and antitubulin action, suggesting that the double bond is not strictly required for this biological activity (**80-84**) (Figure 13).[64] Taking advantage of the possibility to replace the olefinic bond to set up rapid synthetic approaches that might be used to generate libraries based on the chalcone scaffold, we thought to substitute the double bond of chalcones with a tetrazole moiety, a metabolically stable and chemically inert heterocyclic ring (Figure 7).
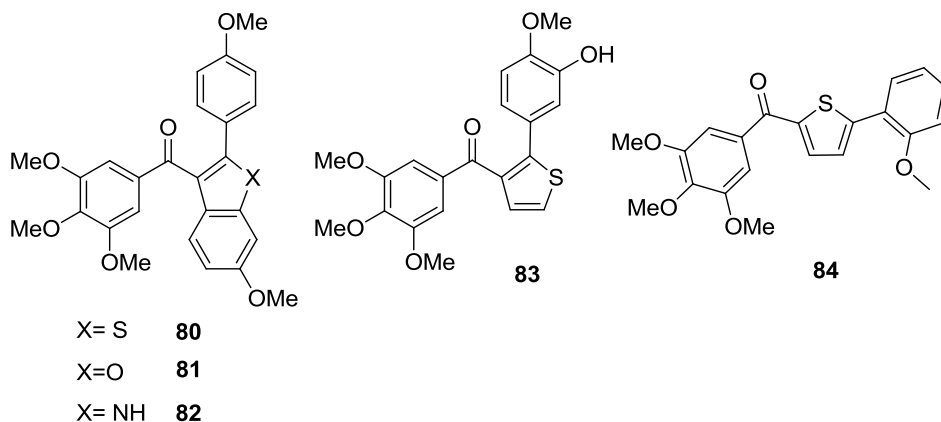
Figure 13. *Some literature reported modifications of chalcone scaffold.*

Preliminary molecular modelling studies were performed, superimposing chalcone structure **78** with scaffold **76** (Figure 14). Conformation of **78**, docked into the colchi-site of tubulin, was used as reference and superimpositions were made by using the VegaZZ[65] software. Visual inspection allowed us to see that tetrazole analogues can replace the double bond of chalcone, maintaining the correct alignment of the pharmacophoric groups (Figure 7). To investigate the biological activity of the synthesized compounds, we opted for SH-SY5Y cells, a neuroblastoma cell line which we have previously shown to be sensitive to antitubulin agents (*e.g.* combretastatin, taxol).[66] In brief, cells were treated for 48 hours with the selected compounds and viability was determined by the MTT method. In this cell line, chalcone **1** displayed an IC_{50} for cell death of 50 ± 3 nM, confirming the choice of cellular model. All compounds were first screened at a concentration of 10 μM.. The tetrazole derivatives were also inactive except for compound **76** (Figure 14 and 15). We therefore proceeded with a concentration response curve of the active compounds under the same conditions (Figure 16). **76** displayed an IC_{50} for cell viability of $4.1 + 0.3$ μM. To confirm the mechanism of action of these compounds, we performed a cell cycle analysis. It would be expected that antitubulin agents, by disrupting the mitotic spindle, induce a G2/M block. For these experiments, cells were treated for 16 hours at a concentration twice the determined IC_{50}. As expected, chalcone induced a strong G2/M block, and this effect was reproduced when using compound **76**.
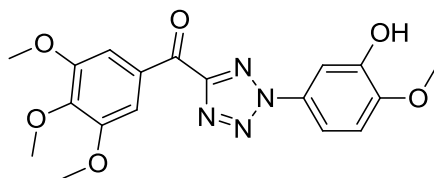
Figure 14. *Compound 76.*
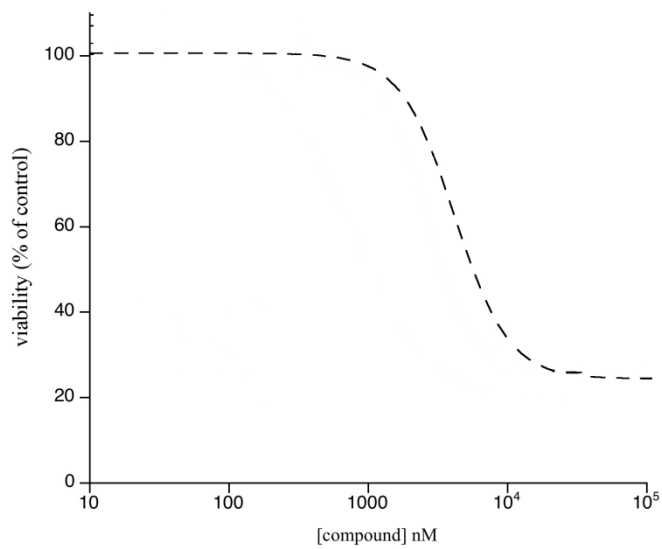
Figure 15. *MTT essay for compound 76.*
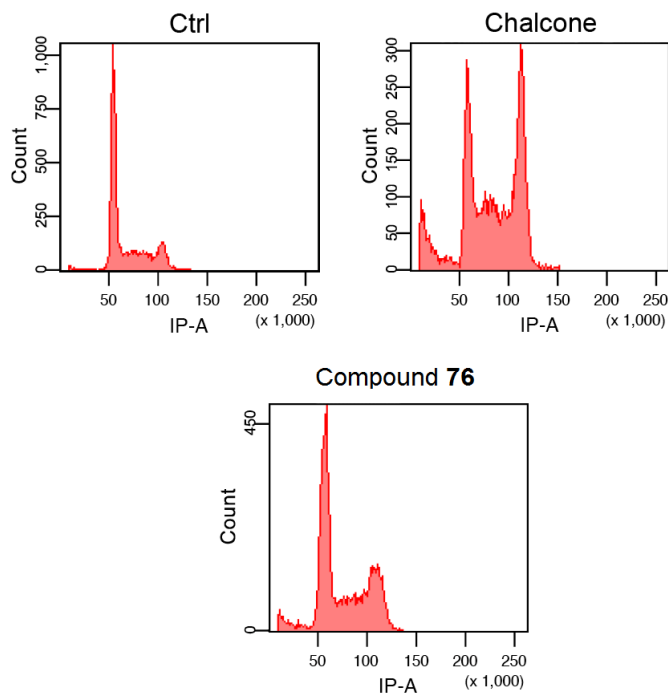
Figure 16. *Cell-cycle inhibition essays.*

In conclusion, replacement of the double bond with tetrazole has been considered for antitubulinic chalcones.[67] Only one compound (**76**) retained activity, albeit displaying a very low potency compared to chalcone **78**. This new scaffold has the advantage of being amenable to rapid synthesis via a multicomponent reaction and could therefore be envisaged to generate a large array of analogues. Yet, it should be noticed that the potency reported here for **76** is in the same order of magnitude as other analogues previously reported which attempted to replace the olefinic bond, raising the question on whether, unlike combretastatin, the olefinic bridge on chalcones is not merely a structural linker.

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3. Search for novel Multi-Component Reactions

3.1 About the identification of novel MCRs

While the use of a MCR followed by post-condensation modifications is a successful strategy for the easy and fast access to usually elusive and challenging molecules, the identification of new Multi-Component Reactions is, however, a more difficult and interesting task. In this chapter will be presented the study of an interrupted Ugi reaction in order to obtain the morpholin-2-one scaffold that unlucky failed to reach good yields and remained undeveloped, and some small paragraphs on "substrate design" based projects. This concept is based on a multi-functionalized starting material which, when introduced in a known MCR, could undergo new and different transformations, deviating the reaction mechanism toward a new pathway.

3.2 Morpholin-2-ones through an interrupted Ugi reaction

Morpholin-2-ones are essentially δ-lactones and have been studied as amino acid analogues[1] and as building blocks for pharmaceutically interesting compounds.[2] They have been employed as conformationally more stable cyclic analogues of acyclic α-amino acids esters for asymmetric induction in the formation of amide bonds through aminolysis.[3] The morpholinone skeleton has also been fully investigated as an effective template for asymmetric reactions[4] and identified as calpain and thrombin inhibitor.[5] Anyway, in the last ten years, the great interest for this scaffold is to be ascribed to the development of Aprepitant, an antiemetic drug acting as substance P antagonist (SPA). It mediates its effect by blocking the neurokinin 1 (NK_1) receptor. Aprepitant is manufactured by Merck & Co. under the brand name Emend[®] for prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) and for prevention of postoperative nausea and vomiting. It was approved by the FDA in 2003.[6] The morpholine core plays a pivotal role in the aprepitant maintaining the correct allignement of the pharmacophoric groups (Figure 1). Over the last

decades there has been a scientific effort to get an easy access to morpholinones intermediates allowing a more practical and less costly synthesis of Aprepitant.
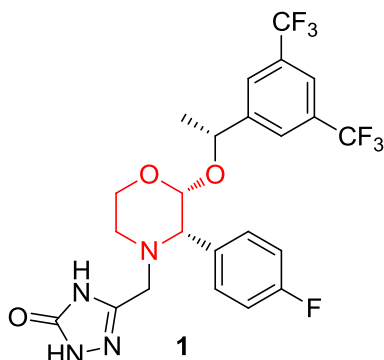
Figure 1. *Aprepitant structure showing its morpholinone core*.

Basically, the morpholi-2-one scaffold is synthesized starting from *N*-benzyl-2-amino alcohols and bromo esters[7], or substituted phenylglycines and benzaldehyde, followed by *N*-alkylation with bromo ethane and a thermal cyclizations of the resulting *N*-benzyl-bromoethyl derivatives.[8] Other methods reported in literature started with amide derivative of substituted *N*-benzyl-glycine and bromo ethanol,[9] or *N*-substituted amino ethanols and divinyl fumarate[10] or, still, with ethentricarboxylic acid diesters (Figure 2).[11]

All these methods are affected by problems of low yields, limitation in starting material availability, scope and/or scaling up processes.
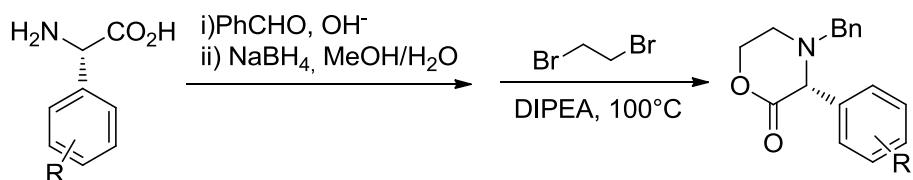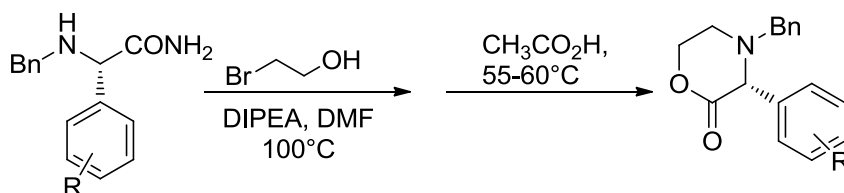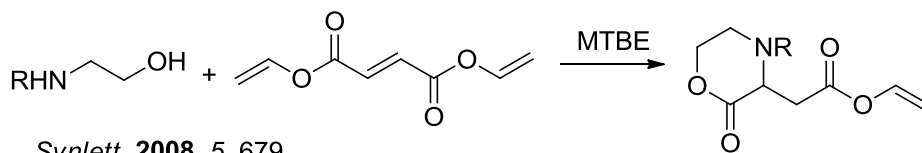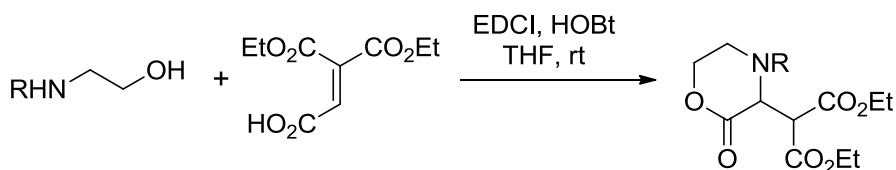
Figure 2. *Some literature reported procedures for the synthesis of morpholin-2-ones.*

We therefore decided to find a novel synthetic method for the construction of morpholin-2-one using a multicomponent transformation. Disconnection of morpholin-2-one scaffold (**1**) shows us that it might be synthesized by an interrupted Ugi reaction (Figure 3), where the nitrilium ion intermediate (**2**) is trapped intramolecularly by the hydroxyl group of *N*-benzylethanolamine (Scheme 1). (For general mechanism of Ugi 4-CR see Introduction). The mechanism is shown in Scheme 2. A Schiff base (**5**) , formed by an aldehyde (**3**) and N-benzylethanolamine (**4**) undergoes a nucleophilic addition mediated

50

by the isocyanide (**6**), to afford a nitrilium ion intermediate (**2**). This latter undergoes an intramolecular nucleophilic addition to the hydroxyl group of the *N*-benzylethanolamine, affording an imino ether derivative (**7**), which after hydrolisys of the imino function and elimination of an amine molecule bearing the isocyanide radical affords the desired morpholin-2-ones (**1**).
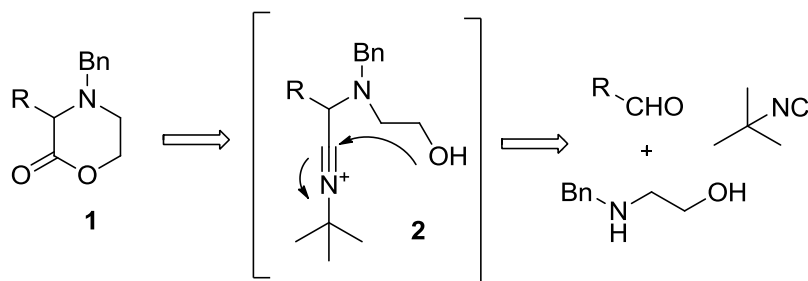
Figure 3. *Disconnection of morpholin-2-ones.*
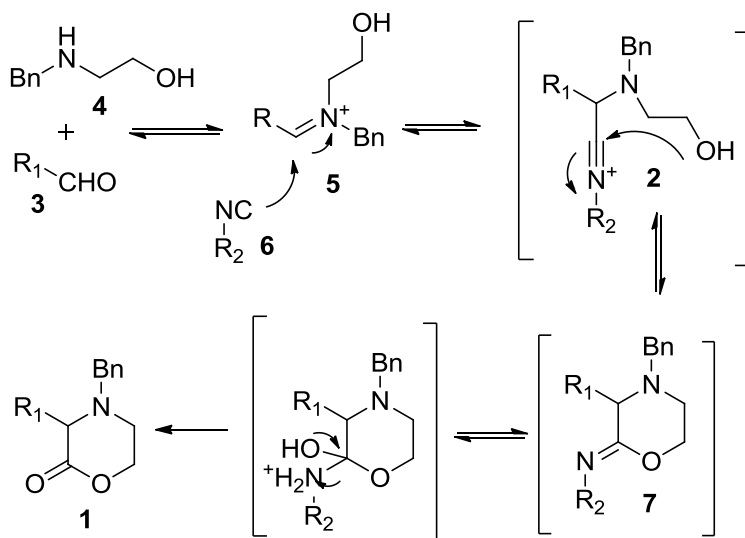
Scheme 1. *Mechanism of the exploited interrupted Ugi.*

For the test reactions biphenyl-4-carboxaldehyde (**8**), *N*-benzylethanolamine (**2**) and *tert*-butyl-isocyanide (**9**) were chosen (Figure 5).
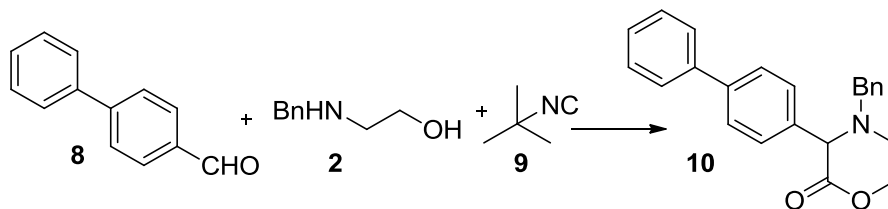
Scheme 2. *Test reaction for experimental conditions screening.*

The solvents were trifluoroethanol (TFE) (entry **1**, **5-12**), methanol (entry **2**), water (entry **3**) and toluene (entry **4**), with TFE being the best one (entry **1**). In some cases a weak acid (entry **4**), Lewis acids (entry **5-11**) or molecular sieves (entry **12**) to facilitate the Schiff base formation were added, but no improvement in yields were observed. In addition, an *in situ* reduction of the imino ether derivative (**7**, Figure 4) with sodium cyanoborohydride was attempted, but it still failed to increase the yield of morpholin-2-one. All the experimented conditions failed to afford the desired morpholin-2-one in more than 48% yield (entry **1**).

Entry	Solvent	Additive	Yield
1	TFE	None	48%
2	MeOH	None	5%
3	H$_2$O	None	NP
4	Toluene	NH$_4$Cl	NP
5	TFE	Phenylacetic acid	38%
6	TFE	Benzoic acid	NP

7	TFE	PTSA	NP
8	TFE	MgSO$_4$ (2 eq RNC)	40%
9	TFE	MgSO$_4$	40%
10	TFE	MgSO$_4$, then NaBH$_3$CN	41%
11	TFE	Na$_2$SO$_4$, then NaBH$_3$CN	NP
12	TFE	MS 4Å then NaBH$_3$CN	36%

NP = not purified

Table1. *Experimental conditions.* (Reaction time 24h ; room temperature)

The idea of the *in situ* reduction arose from the observation of an open-chain by-product formed by hydrolysis of the imino ether derivative (**7**, Scheme 1). This intermediate, indeed, can undergo the desired elimination of *tert*-butyl amine (path A), but the tetrahedric intermediate can also follow a different fate (path B) to give an open chain amide **11** (Scheme 3). It is important to highlight that the ring-opening process is likely to be thermodynamically favorable due to formation of the stable amide bond.

Very recently, Motherwell and Sheppard described the ring-expansion of oxazolidines **12** to morpholin-2-ones via reaction with an isocyanide followed by hydrolysis.[12] The reaction conditions were improved using a design of experiments approach (DoE), being the factors investigated the acid catalyst (mol%), the isocyanide (equivalents) and solvent type. Anyway DoE investigation failed to yield the desired morpholin-2-ones in more than 51% yield (DMSO 0.5M as solvent, TsOH 1.1 eq. as acid catalyst, isocyanide 1 eq. heating to 75°C under an atmosphere of nitrogen for 24h) (Figure 4).
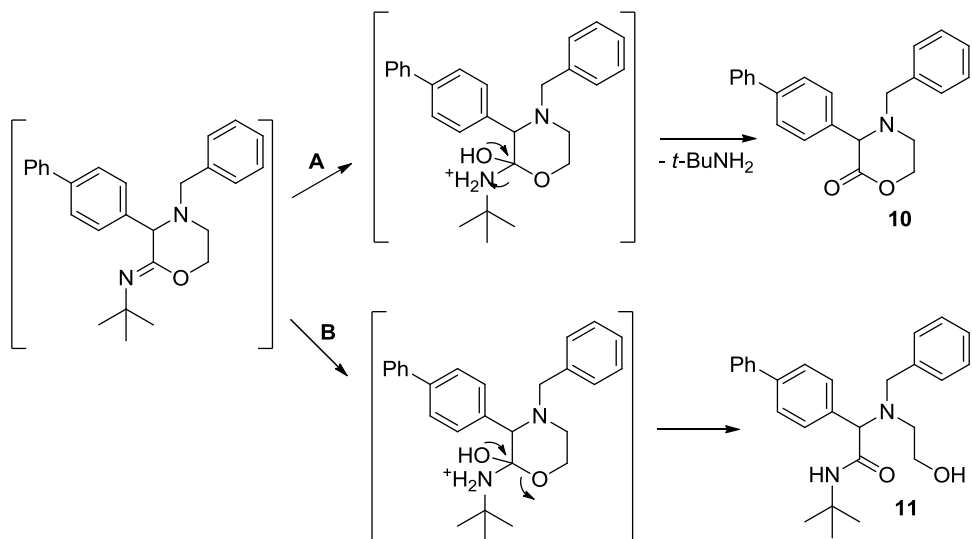
Scheme 3. *Alternative pathways affording the desired morpholin-2-one and the amide side product **12**.*
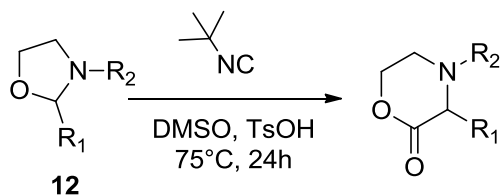
Figure 4. *Oxazolidine ring-expansion investigated by Motherwell and Sheppard.*

Sorensen et al reported recently the synthesis of indoxyls and aminoindoles through an interrupted Ugi 3-CR.[13] Other examples of morpholin-2-ones synthesized through MCRs were reported by Kim et al. in 2001 and by Motherwell and et al. in 2006. [14,15]

3.3 Substrate design approach in search for novel MCRs

In Jieping Zhu laboratories I worked on the "substrate design approach" for the search of novel MCRs. The rationale of this approach is as follows: it consists of designing new poly-functionalized substrates for known MCRs that, when mixed with the other components, would react in a highly ordered manner and productive fashion to afford in high yield an interesting scaffold. The new function introduced on one of the MCR- substrates would be able, indeed, to deviate the course of the reaction toward new pathways : in this way a novel MCR can be uncovered.[16] In this context, Zhu et al. demonstrated that simply switching the ester function of α-isocyano acetate **13** to amide, the resulting isocyanoacetamide **14** displayed completely different reactivity profile as compared to **13** (Figure 5).[17]
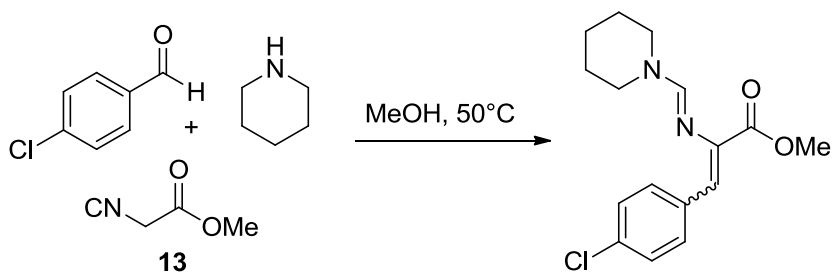
Matsumoto K. et al. *J. Org. Chem.* **1978**, *43*, 4933
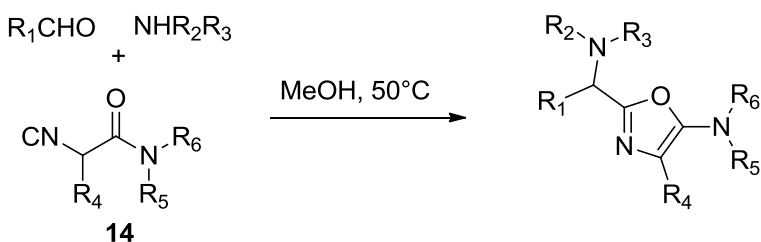
Zhu J. et al. *J. Am. Chem. Soc.* **2002**, *124*, 2560

Figure 5. *Isocyano acetate and isocyano acetamide based MCRs.*

By taking advantage of the chemical reactivities of 5-amino oxazole and based on the three- component synthesis of 5-amino oxazoles starting from isocyano acetamides, dozens of MCRs were developed by judicious selection

of reaction partners.[18] Some representative heterocycles synthesized are showed in Figure 6. Zhu et al. subsequently developed isocyanides **15** and **16** (Figure 7) and MCRs thereof. [19, 20]
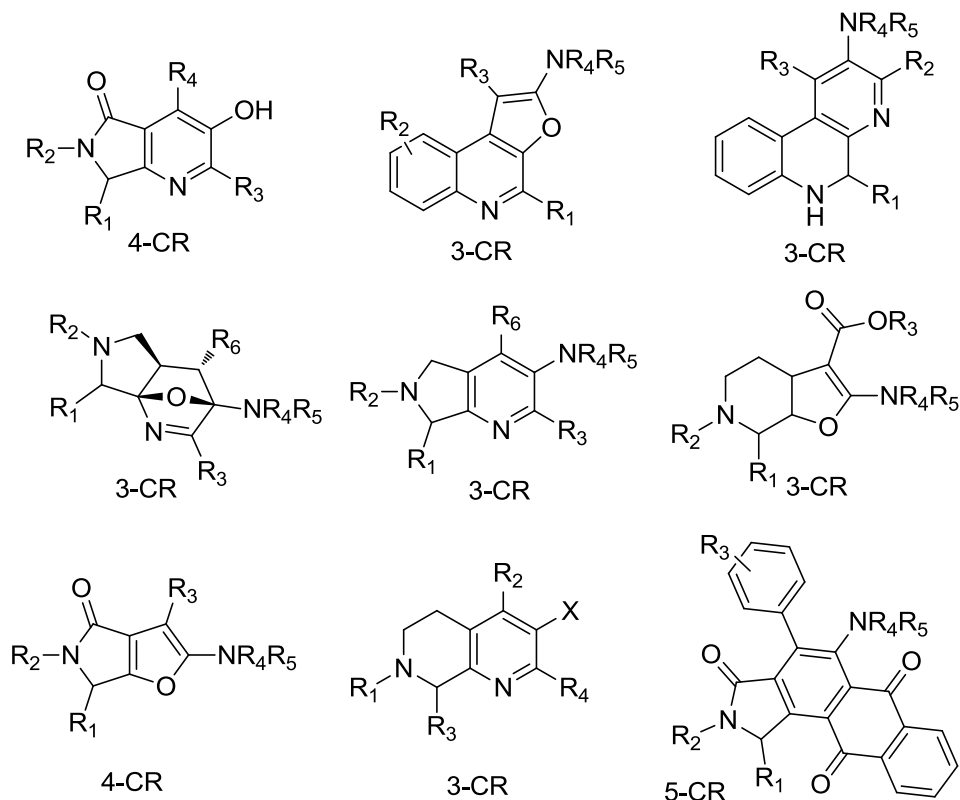
Figure 6. *Some representative examples synthesized starting from isocyano acetamides **14***.
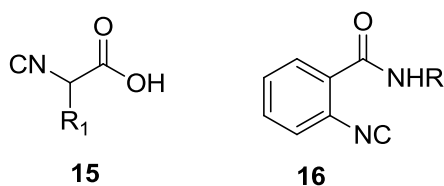
Figure 7. *Other examples of synthesized isocyanides for the development of new "substrate design approach" based MCRs.*

Investigation and synthesis of *N*-isocyanobenzamide **17** (Figure 8) is thus a logical extension of the "substrate design approach" herein presented. To better understand the design of this isocyanide you have to compare it with compound **18**, which presents the same framework of isocyano acetamide **14** with the methylene group replaced by a nitrogen to give a *N*-isocyano-*N,N'*-disubstituted urea. Zhu's group already tried to synthesize **18**, but it lacked in stability to be easy handled and isolated. If we observe structure **18** not as an urea but as an isocyano acetamide **14** with a NH function instead of a CH$_2$, we could think that changing the CONHR$_1$ of **18** into a COR framework could enhance the stability of such a molecule.
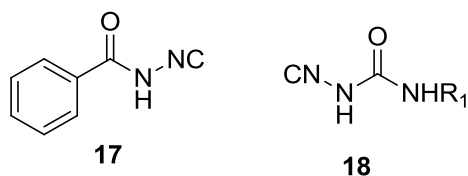
Figure 8. *New functionalized isocyanide investigated by Zhu.*

The disconnection of **17** shows that it could be synthesize in three steps starting from benzoic acid coupling with hydrazine, formylation of this derivative and dehydration of *N*-formyl function to isocyanide (Figure 9).
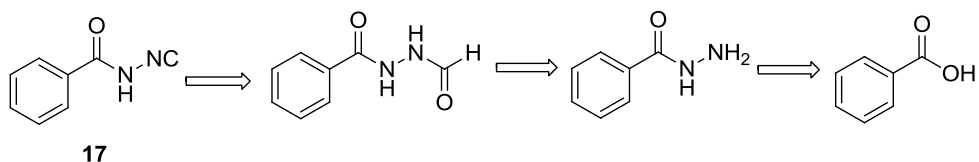
Figure 9. *Disconnection of 17.*

Monoacylation of hydrazine was achieved in 92% yield starting from ethyl benzoate **19** as reported in literature,[21] affording benzohydrazide **20** that, after

purification by flash chromatography was refluxed in formic acid for 30 minutes[22] to give N-formyl benzohydrazide **21** (100% conversion) (Scheme 4).
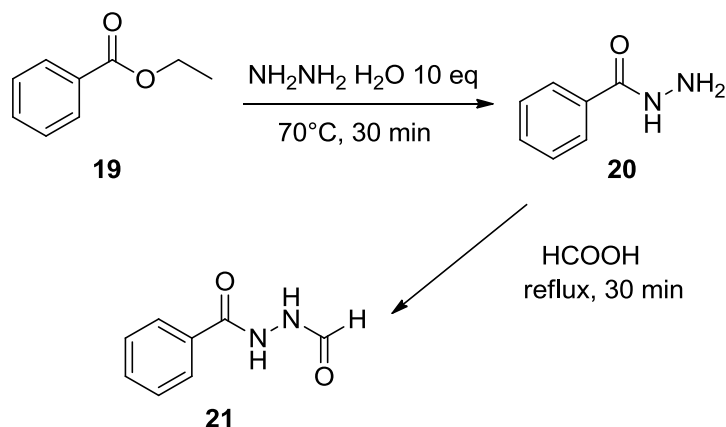
Scheme 4. *Synthesis of N-formyl benzohydrazide 21.*

Different dehydration conditions were then tested on compound **21** in order to obtain the desired   isocyanide **17**, ranging from the classical POCl$_3$/TEA or COCl$_2$/TEA systems[23] at different temperatures (-78°C, -5°C) to less conventional and milder method as the one employing Burgess reagent (-78°C, -50°C, -18°C, rt and 50°C).[24] Burgess reagent or methyl *N*-(triethylammoniumsulfonyl) carbamate **22** (Scheme 5) is an inner salt used as mild and selective dehydrating reagent to convert secondary and tertiary alcohols with an adjacent proton into alkenes, primary amides into nitriles, formamides into isocyanides and it is also employed in the synthesis of some heterocycles.[25] One of its great advantage is to be orthogonal with other functional groups which are often problematic in the presence of the common dehydrating agents. Its mechanism of action involves as first step the formation of a sulfamate ester **23**, where the part then acting as leaving group has been incorporated. This part has multiple H$^+$ acceptor sites, lowering the free energy of the process owing to an increased positive entropy contribution. Second step is therefore a hydrogen transfer followed by elimination of methoxycarbonyl sulfo-amide **24**. Anyway, all the dehydrating experimented conditions only afforded the cyclizations adduct 2-phenyl-1,3,4-oxadiazole **25** plus starting material depending on the reaction conditions (Scheme 6). In

order to compare chromatographic and spectroscopic data of compound yielded by different dehydration test reactions, compound **25** was synthesized as reported in literature (P$_2$O$_5$, toluene, reflux, 2.5h).[26] All the compared data perfectly matched.
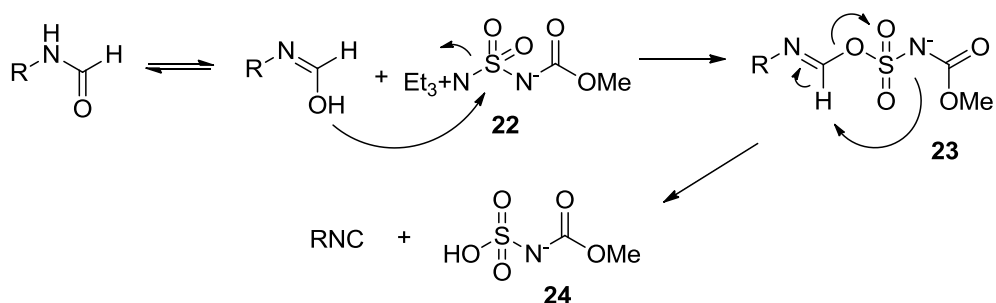
Scheme 5. *Mechanism of action of Burgess reagent.*
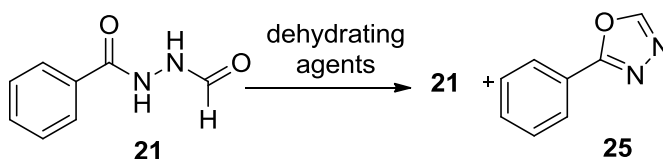
Scheme 6. *Dehydration of **21** only afforded 2-phenyl-1,3,4-oxadiazole **25**.*

Hypothesizing that, under dehydrating conditions , as soon as the isocyanide was formed, or not even formed, it cyclized to the more stable 1,3,4-oxadiazole derivative **25**, we tried to get the desired compound through a ring-opening strategy hoping that at very low temperatures the open-chain isocyanide form would be enough stable to exist. Even if oxazoles ring-opening is something already reported in literature, ring-opening strategy for the synthesis of functionalized isocyanides starting from oxazoles was described for the first time by Pirrung et al. in 2006.[27] Oxazoles **26** are readily metalated by treatment at -78°C in THF with *n*-BuLi at the 2-position

(Scheme 7). The resulting anion **27** equilibrates (by α-elimination/ring-opening) with α-isocyano enolate **28**. With oxazoles and benzoxazoles the latter form predominates and has been observed by NMR.[28] Trapping of **28** by *O*-Acylation with an acyl chloride gives product such as **29** (Scheme 4).
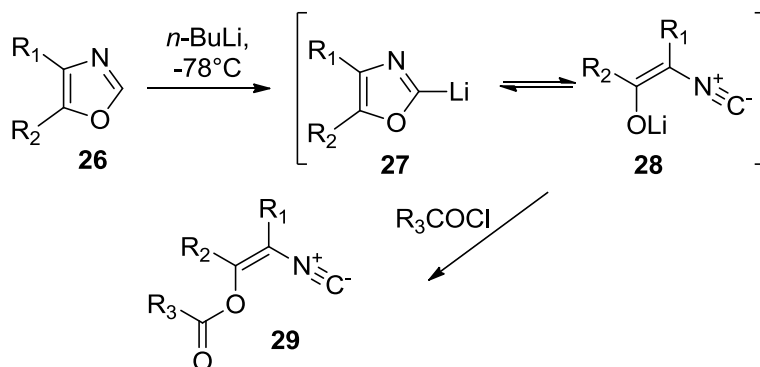
Scheme 7. *Oxazole ring-opening strategy described by Pirrung et al.*

Despite different test reactions performed, this strategy, when applied to oxadiazoles (Scheme 8), failed to afford the *O*-Acylated isocyanide **30**, giving back starting material and traces of an unidentified product. When the reaction was performed at -18°C, with 1.05 equivalents of *n*-BuLi, a dimer with the proposed structure **31** was isolated (Figure 10).[29] A possible scenario accounting for the formation of **31** is shown in Scheme 9. Herein **25** is readily metalated at 4 position, giving the lithiated derivative **32**, which is then reacting with acetyl chloride added *in situ* to give **33**. A second molecule of **32** could then undergo a nucleophilic addition into **33** to give dimer **31**. If **30** could be isolated, then an *O*-acyl cleavage could be attempted in order to get **17**. We are not able to state if the α-isocyano enolate was formed or not or also if it was formed and the equilibrium is biased toward the ring-closed metalated oxadiazole. Structural investigation of the equilibrium between 2-Lithium oxazole, thiazole and imidazole derivatives and their acyclic isomers showed that the tendency of these compounds to undergo ring-opening parallels the leaving group properties of the various subunits [ROLi>RSLi>R₂NLi].[30] To date, there is no metalated oxadiazole ring-opening described. The project was therefore abandoned.
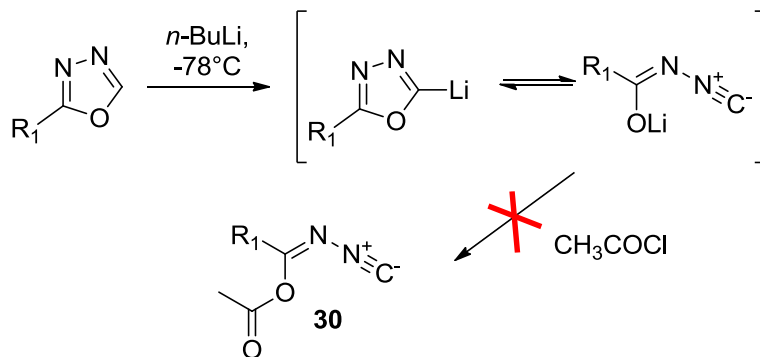
Scheme 8. *Oxadiazole ring-opening strategy tested in order to get compound 17.*
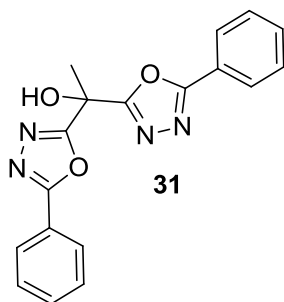
Figure 10. *Proposed dimer structure for a side product obtained during one of ring-opening test reactions.*
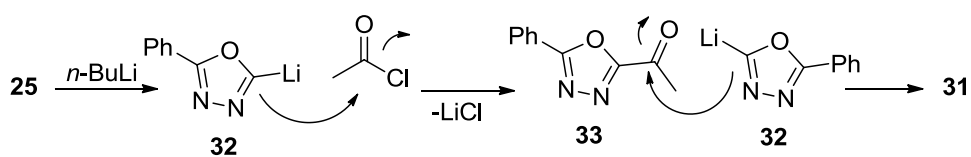
Scheme 9. *Proposed mechanism for the formation of 31.*

Following the same "substrate design approach" synthesis of isocyanides **34**, **35** and **36** was investigated (Figure 11).
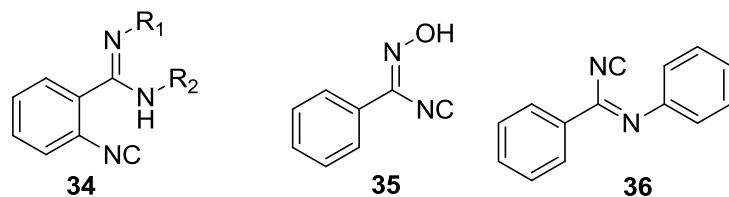
Figure 11. *Designed isocyanides 34, 35 and 36.*

As disconnection of **34** we thought to devise a three steps sequence starting from aniline (with or without a halogen group in the ortho position), formylating it, dehydrating the formyl derivative and then metalating the aromatic ring in the *ortho* position so that trapping with an electrophile could be possible (Figure 12).
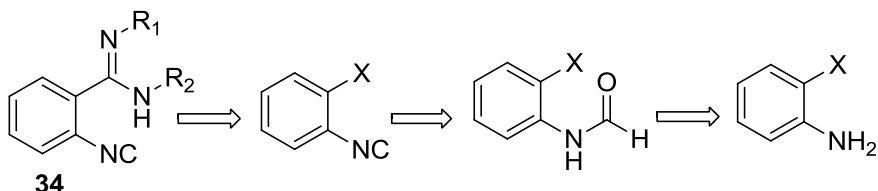
Figure 12. *Retro-synthetic pathway of 34.*

The iodo derivative **37** is described to undergo fast trans-metallation reactions when treated with *n*-BuLi or *t*-BuLi at very low temperatures (-78°C and -100°C). Trapping of the resulting ortho-lithiophenyl isocyanide **38** with different electrophiles (iodine, methyl chloroformiate, diphenyl sulfide, methyl formiate amd others) has been described allowing the synthesis of 2-substituted isocyanides **39**; when the electrophile is an isocyanates or an isothiocyanate 3*H*-quinazolin-4-ones and 3*H*-quinazolin-4-thiones **40** were formed in high yields (Scheme 10).[31] α-metallated isocyanides **41** are known since Schöllkopf and Gerhart[32] first exploited in 1968 how the electron-withdrawing effect of the isocyano group enhances the acidity of the α-C-H bonds (Figure 13). Since then, α-metallated isocyanides have been shown to participate in various types of co-cyclizations leading to different nitrogen containing heterocycles.[33] In 1977 Ito, Saegusa[34] *et al.* described γ-metallated

43 isocyanide: *ortho*-methylphenyl isocyanide metalated at the benzilic positions has been reported to underwent cyclizations to indoles. β-metallated isocyanides **42** have been reported for the first time in 1978 by Walborsky. [35] First reaction investigated was a halogen-metal exchange of *o*-iodo-phenyl isocyanide **37** synthesized starting from the aniline derivative as reported in literature[31] in order to trap the deriving *ortho*-lithio isocyanide **38** with a carbodiimide (for test reaction we used commercially available diisopropyl carbodiimide, DIC **44**). Two different cyclizations adducts were isolated **45** and **46**, being the former *N*-(3-isopropylquinazolin-4(3*H*)-ylidene)propan-2-amine and the latter the alkylated 2-butyl derivative in a 3/1 ratio (Scheme 11). The formation of the cyclization adduct probably is to be ascribed to the reaction mechanism, where, after the attack of the metalated isocyanide **38** β-carbon into the carbodiimide **44** electrophilic carbon atom, a negatively charged nitrogen containing intermediate **47** was formed. This latter could be then able to attack the isocyanide carbon atom here acting as electrophile to give intermediate **48**. This can then be quenched by moisture or aqueous work-up to afford the quinazoline **45**. A working hypothesis for the formation of the 2-alkylated derivative **46** is quenching of **45** by the *in situ* generated butyl iodide after the halogen-lithium exchange (Scheme 12). Reaction with the more bulky and less nucleophile *tert*-Butyllithium, which cannot generate *tert*-butyl iodide, and quenching (of the presumable intermediate **47**) with both NH$_4$Cl and acetic anhydride failed as well to give the desired compound **34**.
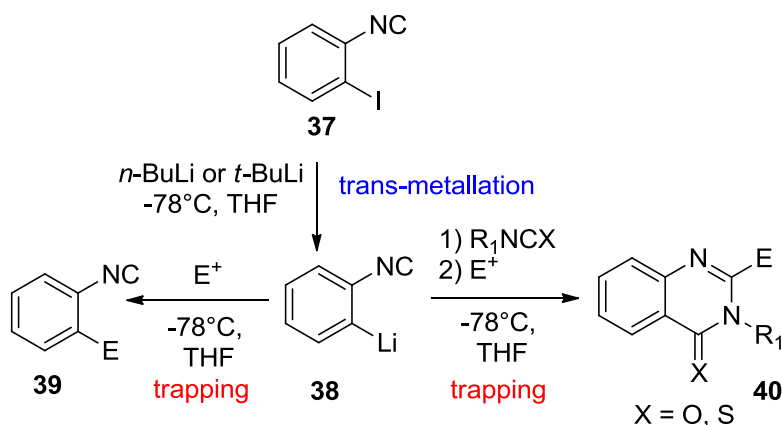
Scheme 10. *Reaction of ortho-lithiophenyl isocyanide with electrophiles described by de Mejere.*
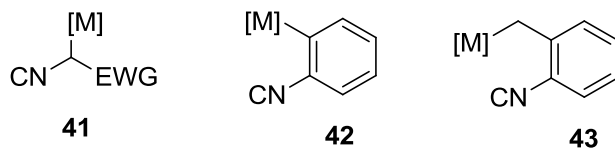
Figure 13.*α,β and γ-metallated isocyanides.*
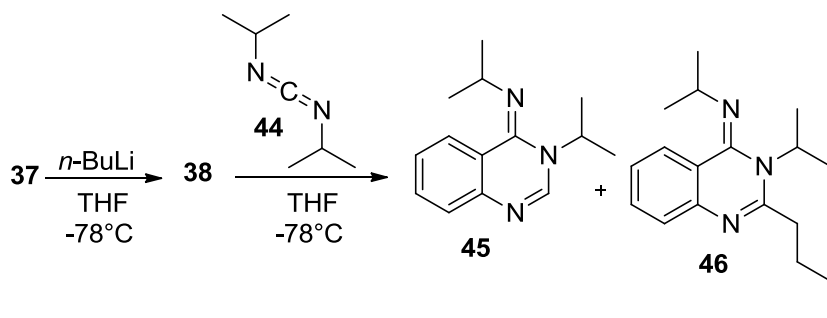
Scheme 11. *Reaction of 38 with DIC affording 53 and 46.*
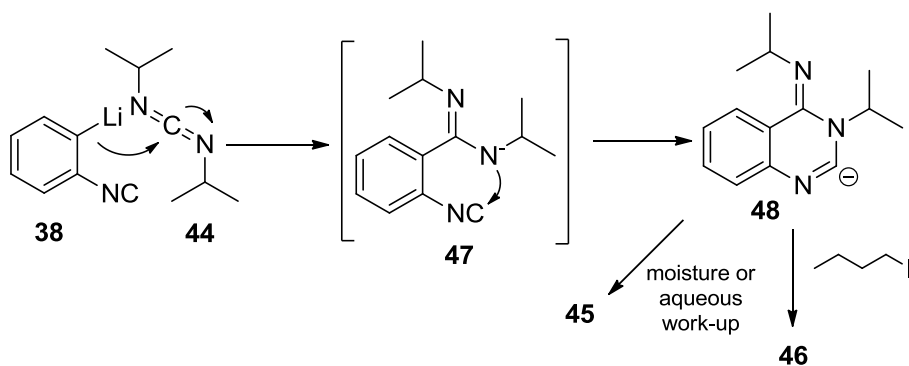
Scheme 12. *Possible scenario for the formation of 45 and 46.*

In order to avoid the formation of the cyclized adduct **48**, we tried an alternative approach and we started from *N*-phenyl formamide **50** (in order to try after dehydration of **49**) and *N*-Boc protected aniline **51** (tert-butyl phenyl

carbamate) (in order to de-protect **52** to **51**, and transform then the amine function in isocyanide through the conventional formylation/dehydration sequence)(figure 14).
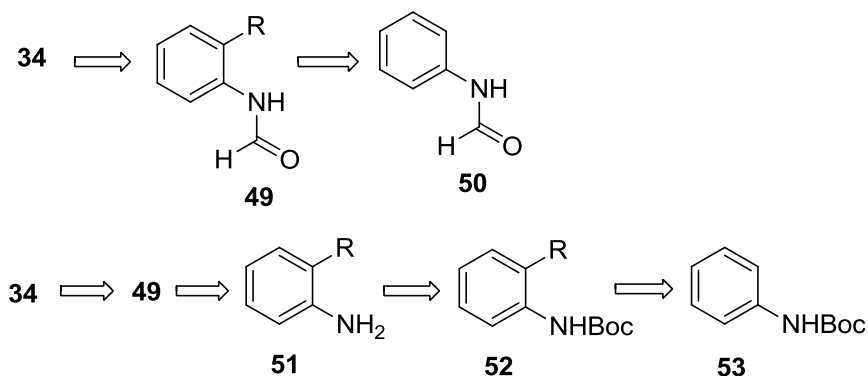
Figure 14. *Additional disconnection approaches for the synthesis of 34.*

Reaction of **50** with different equivalents (2.2 and 2.4) of *t*-BuLi and *n*-BuLi, in THF at -78°C, followed by *in situ* addition of carbodiimide **44** failed to afford the desired isocyanide **34**, but degradation, formation of unidentified dimers and recovering of the starting materials were observed. Direct *ortho* functionalization was however possible when **44** was reacted with lithiated **54** to afford **55** (Scheme 13).[36] This reaction requires 2.4 equivalents of alkyllithium reagent as a dianion **54** is formed. In this reaction the NH-Boc group acts as Directed Metallation Group (DMG) for Directed ortho Metallation (DoM).[37] NH-Boc group belongs to the class of Heteroatom-based DMGs and was described for the first time as that by Muchoswki in 1980.[36] There is no unifying mechanism for the DoM reaction that can explain all the subtleties observed experimentally. The most widely accepted one can be summarized in three steps (Scheme 14). A rapid equilibrium between alkyllithium aggregates and a prelithiation complex of the alkyllithium coordinated to the DMG **56**. In this complex the base is in close proximity to the *ortho* proton which allows the slow but irreversible proton abstraction forming the coordinated *ortho*-lithiated species **57**. Addition of an electrophile provides in the simplest cases the regioselective formation of a 1,2-

disubstituted arene **58**. The initial hypothesis for this mechanism was dubbed by Klumpp as the Complex-Induced Proximity Effect (CIPE).[38]
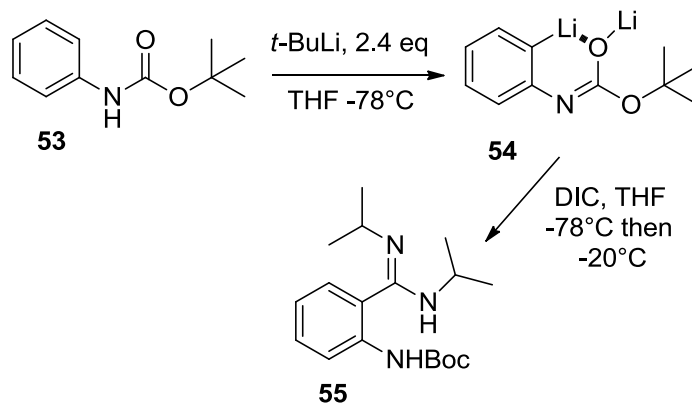
Scheme 13. *Formation of 55.*
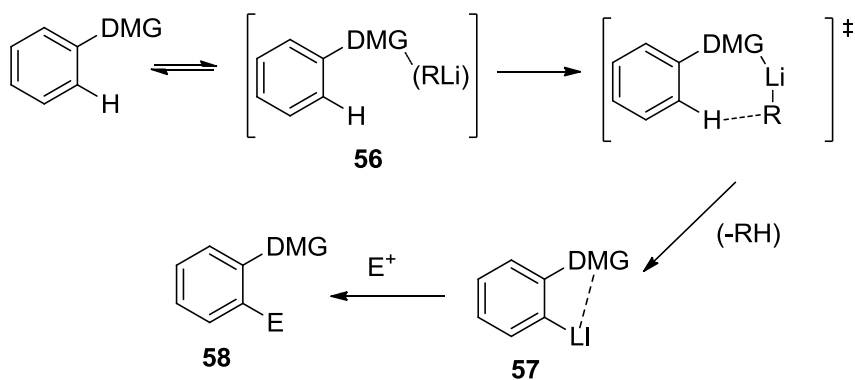
Scheme 14. *CIPE mechanism for DoM.*

Test reactions with **50** failed to afford the desired adduct **49** probably because the formyl group is not a good DMG. To date it has never been described as DMG, and as Snieckus stated a good DMG "must exhibit the somewhat schizophrenic properties of being a good coordinating site for alkyllithium

and a poor electrophilic site for attack by this strong base".[37] It is possible to imagine that the formyl group could be attacked by the alkyllithium and start different side reactions giving an intractable mixture.

Last test reaction was the ring-opening of **45** with *n*-BuLi in THF at -78°C followed by addition of TMSCl to trap the open-chain lithium isopropyl amide **60** in equilibrium with the ring-closed metalated derivative **59**. Only the ring-closed silyl derivative **61** was observed (98% conversion) (Scheme 15).[39] The project was so abandoned.
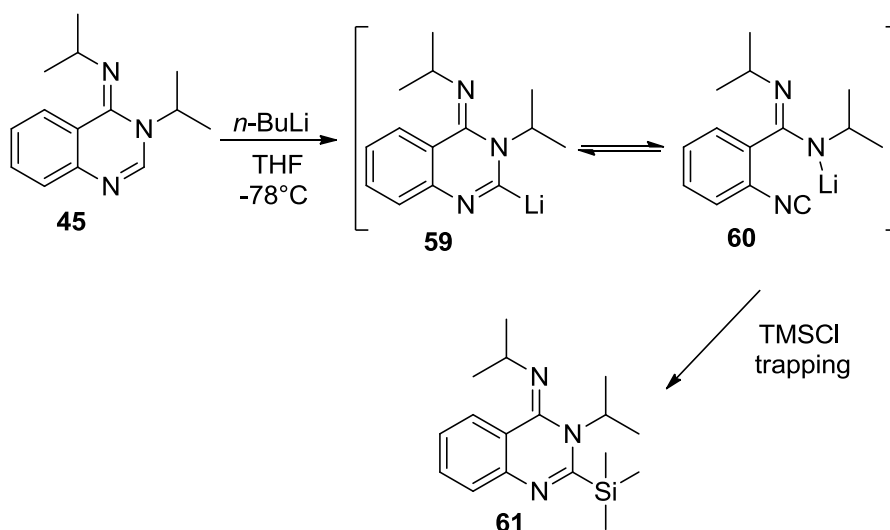
Scheme 15. *Ring-opening test reaction of 45.*

Synthesis of **35** could be possible in two steps starting from *N*-hydroxy benzimide acid **63**, through conversion of this latter in *N*-hydroxy benzimidoyl chloride **62** and then substitution with silver cyanide (AgCN) (Figure 15).
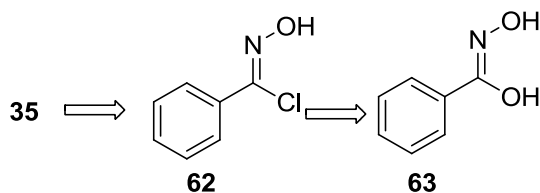
Figure 15. *Disconnection of 35.*

Chlorooxime **62** was synthesized as reported by Dubrovskiy and Larock.[40] Its synthesis is very fast and simple: in practice benzaldehyde, hydroxylamine hydrochloride and Na_2CO_3 were refluxed in water for two hours. After basic work-up, the residue was dissolved in chloroform and a drop of pyridine was added. After 5 minutes N-chlorosuccinimide was added portion-wise and the mixture was stirred overnight. **62** is enough stable to be purified by flash chromatography. Chloride substitution was attempted in dry DCM at room temperature and at 40°C (entry 1 and 2, table 2) with commercially available silver cyanide, but only starting material was recovered. Reaction with freshly prepared silver cyanide in dry DCM at room temperature (entry 3) was unsuccessful as well. Other test reaction conditions (entry 4-6) were experimented using ammonium salts **64** and **65** as phase-transfer catalysts (Figure 16).[41]
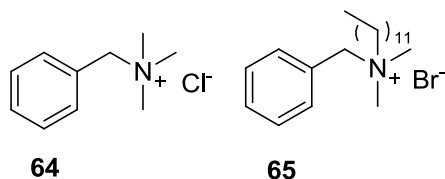
Figure 16. *Phase-transfer catalysts tested for the synthesis of 35.*

Entry	Salt	Temperature	Catalyst
1	AgCN (C)	rt	no
2	AgCN (C)	40°C	no
3	AgCN (FP)	rt	no

4	AgCN (FP) plus KCN	40°C	**64**
5	AgCN (FP) plus KCN	40°C	**65**
6	AgCN (FP) plus TMSCN	40°C	**64**

C= commercial; FP= freshly prepared.

Table 2. *Test reactions for the synthesis of 35.*

None of the tested reactions was able to give the desired isocyanide **35**. Before abandoning the project, 1,3,5-oxadiazole **66** ring-opening reaction with n-BuLi and *in situ* trapping with TMSCl was unsuccessfully attempted (Scheme 15).[42] As previously observed for compound **45,** only ring-closed trimethyl silylated derivative **67** was detected by 1H-NMR of the crude.[43] In conclusion all test reactions failed to yield the desired isocyanide **35**.
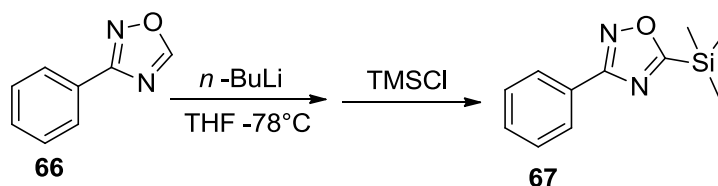
Scheme 15. *1,3,5-phenyloxadiazole 66 ring-opening test reaction.*

Disconnection of **36** suggest that it could be synthesized in two steps starting from N-phenyl benzamide **69**, passing through N-phenyl benzimidoyl chloride or bromide **68**, and trying a substitution with silver cyanide (Figure 17).
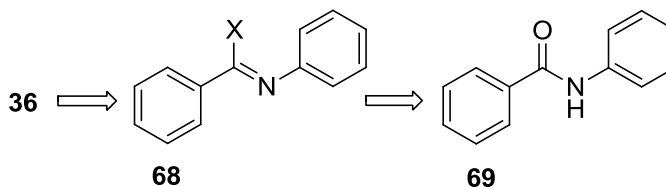
Figure 17. *Disconnection of 36.*

Synthesis of **36** is reported by Höfle and Lange[44] in 1977 and synthesis of **68** by a Bayer Patent of 1973.[45] Anyway, first attempts to get the imidoyl bromide **68** (X= Br) revealed to be difficult, with reaction showing a degration pattern on TLC. A deepened search in literature revealed that Ta-Shma and Rappoport[46] in 1977 wrote about them: " imidoyl bromides were stable when kept at 0°C in the dark and argon atmosphere. On dissolution in polar solvents (e.g. "dry" acetonitrile) a very rapid hydrolysis to the benzanilides took place." As the first requirement for an isocyanide starting material is a ready accessibility, and this was not the case, the project was abandoned.

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4. Between old and new: project in progress and future perspectives

4.1 The project in progress: an introduction.

While I am writing this thesis, the last project of my PhD research program is on-going in Zhu laboratories. This project involves a new MCR sequence, namely an Ugi/Aza-Wittig using the *N*-isocyanoiminotriphenylphosphorane **1** as key reagent (Figure 1) to afford the 1,3,4-oxadiazoles of general structure **2**.
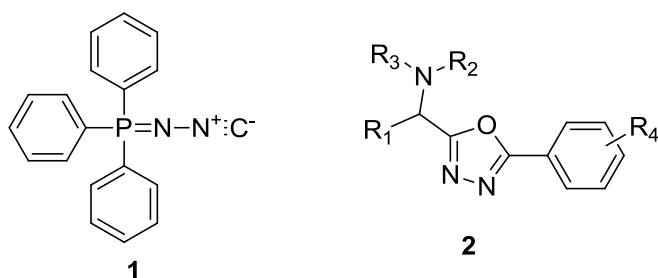
Figure 1. *N-isocyanoiminotriphenylphosphorane **1***.

Compound **1** is commercially available and also easily accessible synthetically in good yields, as described by Bio *et al.*, as a thermally stable off-white crystalline solid.[1] As shown in Scheme 1, **1** was obtained from reaction of commercially available formic hydrazide **3** with PPh$_3$ and CCl$_4$ using DBU as base.
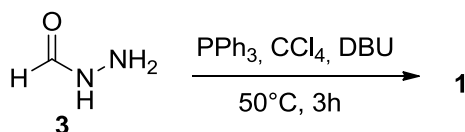
Scheme 1. *Synthesis of **1** as reported by Bio et al.*

1 has already been described for the synthesis of α-diazoketones and different *N*-containing heterocycles (Figure 2) as 2-aryl-1,3,4-oxadiazoles, 2-aryl-5-hydroxyalkyl-1,3,4-oxadiazoles, oxadiazepine derivatives, triazolo[4,3-*c*]quinazolines derivatives.[2-6] In the course of our investigation into the Ugi/Aza-Wittig sequence to give 2-aryl-5-aminoalkyl-1,3,4-oxadiazoles, the reaction was described by Iranian chemists.[7]
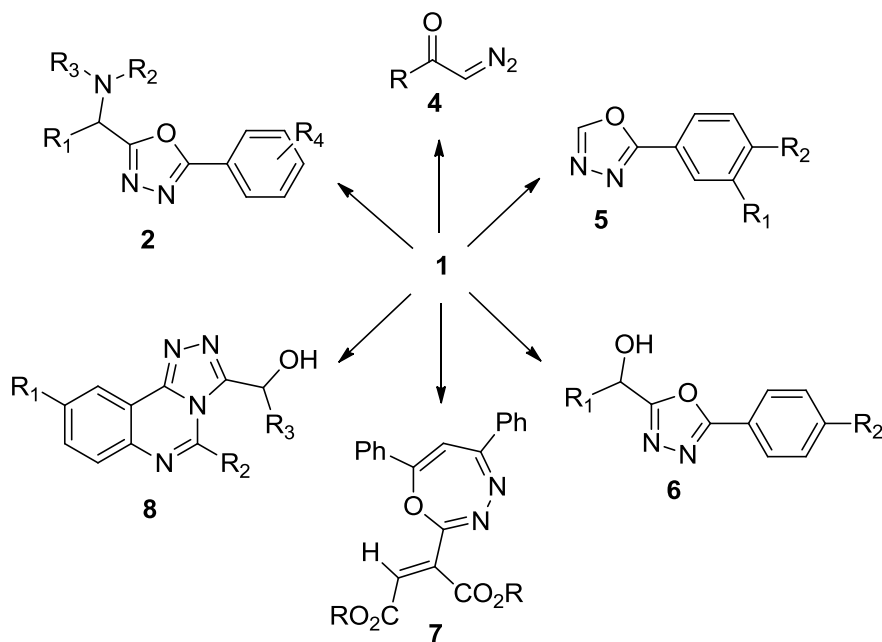
Figure 2. *Literature reported compounds synthesized starting from **1**.*

In all the reported examples **1** reacts first with its isocyanide moiety to give a nitrilium ion that underwent a further attack by a nucleophile (as for compounds **2,6-8**), followed by an intramolecular aza-Wittig reaction (except for compound **4**).

The intramolecular Aza-Wittig reaction has been recently reviewed with several carbonyl or analogous compounds.[8] In those reactions both phosphazene moiety and carbonyl-oxygen double bond (C=O) (aldehydes, ketones, esters, amides, anhydrides...) are present in the same molecule **a** (Figure 3). This strategy allows for a simple and effective method for the

preparation from five- to different size *N*-containing heterocyclic compounds **b** in very mild reaction conditions (apolar solvents, absence of catalysts, mild reflux or room temperature). Substitution on the phosphorus atom in phosphazene moiety with different alkyl groups could increase its reactivity decreasing the positive charge on the phosphorous atom and increasing the negative charge on nitrogen. According to Scheme 4 the reaction takes place via a tandem [2+2] cycloaddition-cycloreversion through a thermally allowed supra-supra mechanism, with **9** as a quite stable intermediate and transition states **TS1** and **TS2**.
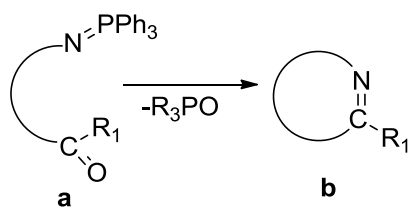
Figure 3. *General scheme of intramolecular Aza-Wittig reaction.*
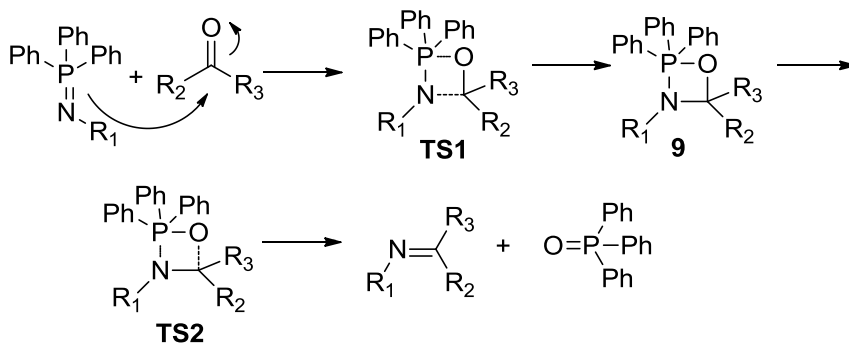
Scheme 4. *Mechanism of Aza-Wittig reaction.*

Our interest in oxadiazoles arose from the possibility to perform, once an alkyne moiety will be introduced on this scaffold, an intramolecular Diels-Alder reaction. In this scenario, the oxadiazole ring acts as diene, to afford different condensed bicylo-furans **14**, **15**, **20** (Scheme 5). Two different strategies for the introduction of the alkyne functional group were therefore approached: one using the amines **10** and **11** with a methyl or ethyl linker, so

that the Ugi adduct will already have incorporated the dienophile (A, Figure 4 and Scheme 5) and the second performing an *in-situ* amidation with a propargyl acid derivative (such as chloride **17** or activated ester **18**), after an Ugi reaction with a primary amine (B, Figure 4 and Scheme 5).
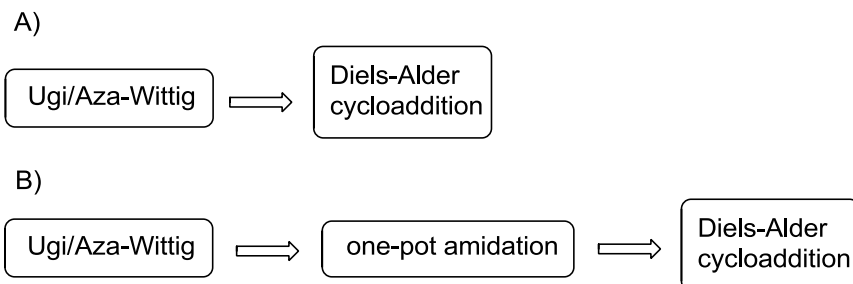
Figure 4. *Approaches for the project in progress.*
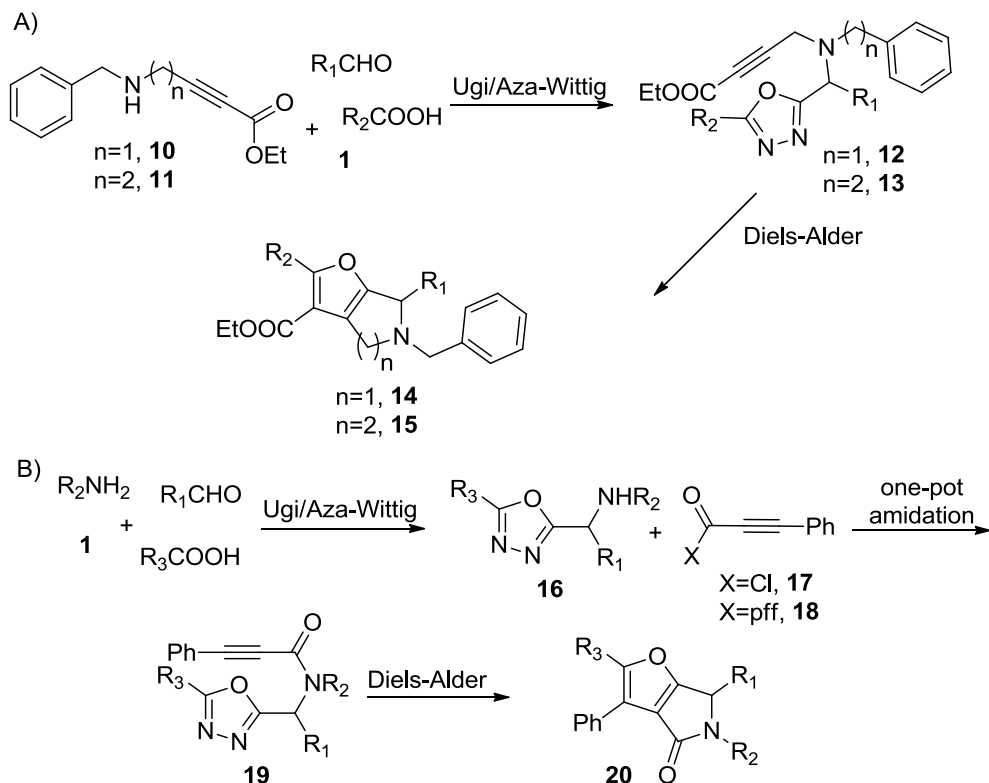
Scheme 5. *Approaches for the project in progress.*

4.2 Background of the project: Zhu's oxazoles chemistry.

The project is following a typical strategy performed in Zhu's laboratories. In 2001 he first published a three component synthesis of 5-amino-oxazoles **21** and their subsequent reaction with α,β-unsaturated acyl chlorides leading to polysubstituted pyrrolopyiridines **22**.[9] When the reaction was performed in toluene in the presence of ammonium chloride, it was possible to get the desired compound **22** in a one-pot fashion.[10] A triple domino process, acylation/IMDA/retro-Michael cycloreversion, was involved in the described synthesis.
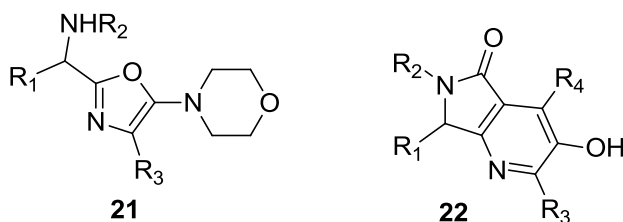
Figure 5. *5-Amino-oxazoles **21** and pyrrolopyridine **22** described by Zhu.*

In the individuation of this strategy Zhu was inspired by the possibility to expand the potential of MCR chemistry with its proper union with other sequential or domino processes for the complexity-generation/ diversity-oriented synthesis of drug-like compounds libraries. Compound **21** was obtained via a 3-CR starting from an aldehyde **23**, an amine **24** and an isocyano acetamide **25** in very mild reaction conditions and high yields. Heating then a solution of **21** and acid chloride **26** in toluene at reflux temperature led to formation of **22** in good yields (Scheme 6).
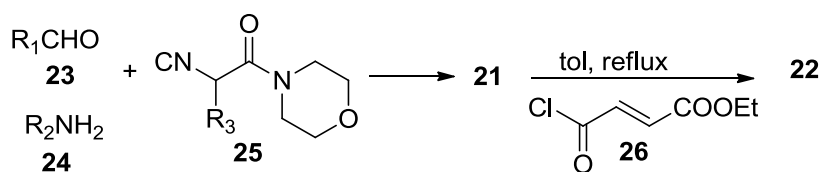
Scheme 6. *Domino process for the synthesis of **22**.*

The proposed scenario for the reaction is the formation of amide **27** which undergoes intramolecular Diels-Alder reaction affording the bridged tricyclic intermediate **28**. Base-catalyzed retro-Michael cycloreversion then furnished **22** (Scheme 7). The coupling constants between H_a and H_b (J_{Ha-Hb}= 4.1 Hz) indicated a gauche relationship (dihedral angle around 40°) between these two protons. For the inherent ring strain imposed by the connecting bridge, only the lactam-*exo*-ester-*endo* mode of cycloaddition was possible, leading to the observed compound **28**. In this intermediate, the proton H_b is properly aligned with C_c-O bond, which facilitates the difficult 5-*endo-trig* reversal leading to **22** and morpholine **29**.
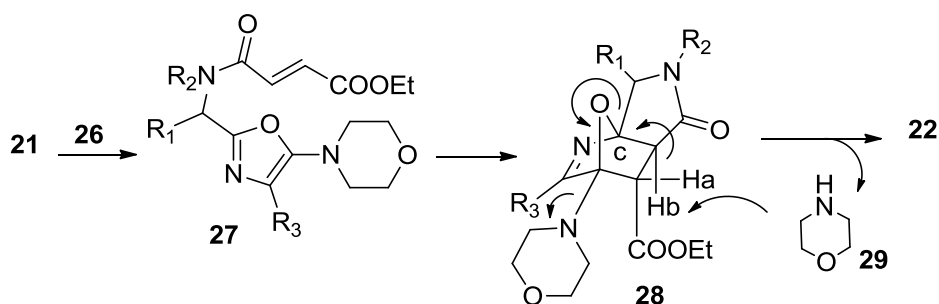
Scheme 7. *Proposed mechanism for acylation/IMDA/retro-Michael cycloreversion.*

Another example of how a 5-aminooxazole can be a chemical platform to get polysubstituted *N*-containing heterocycles is the one-pot 3-CR of an ortho-amino cinnamate **30**, α-isocyano acetamide **31** and an aldehyde **32**, giving **33**, that underwent an intramolecular Diels-Alder cycloaddition to give oxa-bridged tetracyclic tetrahydroquinolines **34** (Scheme 8).[11]
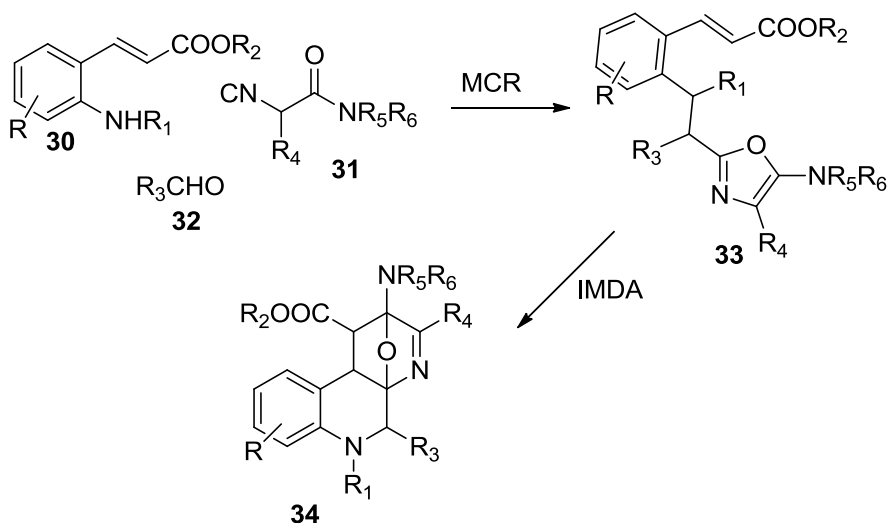
Scheme 8. *Synthesis of oxa-bridged tetracyclic tetrahydroquinolines.*

Again, changing the aniline from **30** to **35** affords furo[2,3-c]quinolines **39** always in a multicomponent domino fashion.[12] Reaction sequence is based on an intramolecular cycloaddition between the aza-diene oxazole **36** with a properly disposed triple bond to give an oxa-bridged heterocycle **37**. This latter, after extrusion of the nitrile unit by a retro Diels-Alder reaction, would provide the furan **38**, which undergoes oxidation by atmospheric oxygen to furnish furoquinolines **39**.
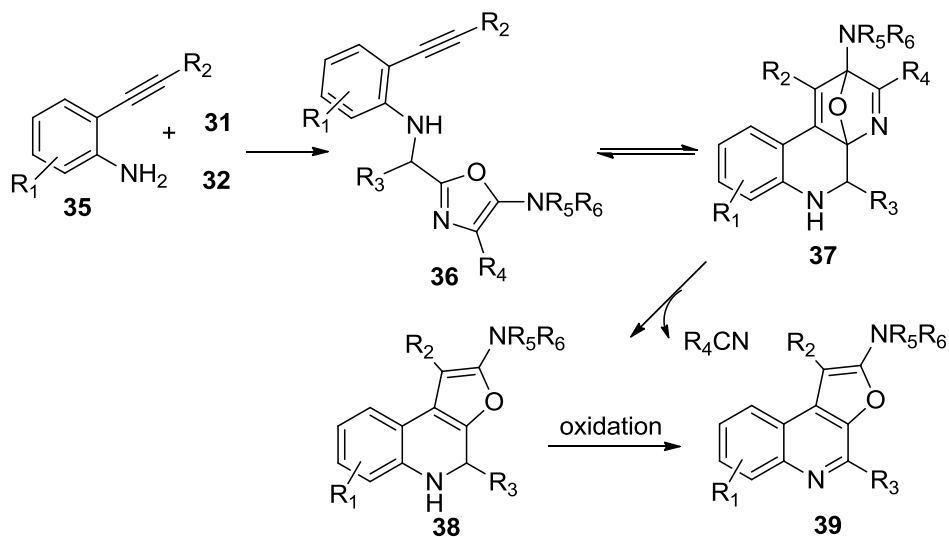
Scheme 9. *Reaction mechanism for the synthesis of 39.*

Continuing to exploit the potential of 5-aminooxazoles **21** Zhu described as well the synthesis of hexasubstituted benzenes **40** combining three component synthesis of oxazoles with two subsequent cycloaddition-based domino processes, which means in total a five component reaction.[13] Also in this case the sequence allows for a rapid and efficient construction of structurally complex molecules from readily available starting materials. Reaction of **21** and acyl chloride **41** provide the amide **42** that undergoes in a domino fashion a first intramolecular Diels-Alder cycloaddition, through intermediate **43**, to 5,6-dihydro-furo[2,3-c]pyrrol-4-one **44** and, after addition of one more dienophile **45** a retro Diels-Alder cycloaddition to yield , through **46**, hexasubstituted benzene **40** as shown in Scheme 10.
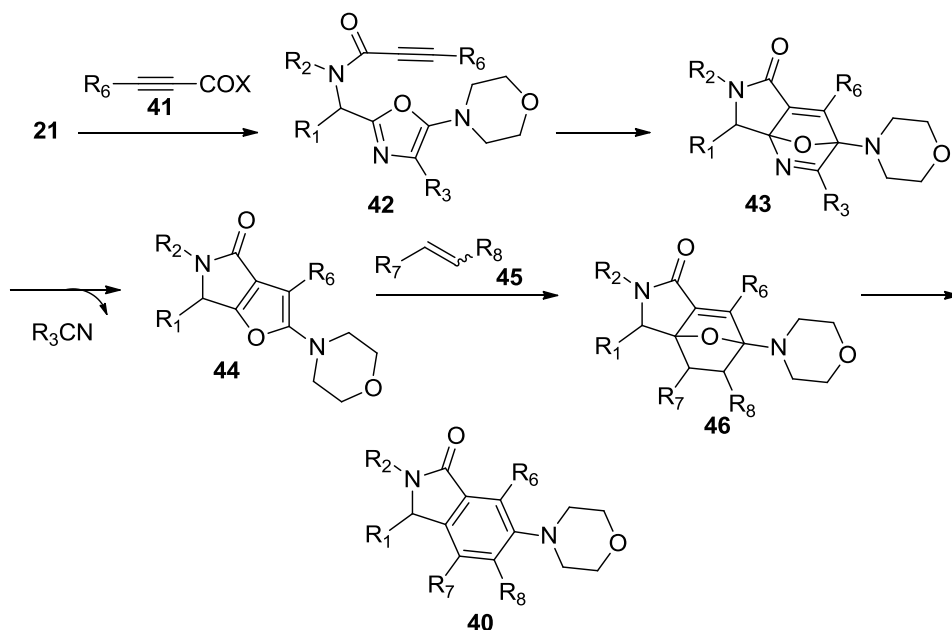
Scheme 10. *One-pot five component synthesis of hexasubstituted benzenes 40.*

When the dienophile was introduced in the 5-amino-oxazole as the starting amine **47**, then a fast and easy access to polysubstituted 4,5,6,7-tetrahydrofuro[2,3-c]pyridines **50** had been provided (Scheme 11).[14] **47**, **31** and **32** reacted to give first the 5-aminooxazole **48** and subsequentely an intramolecular Diels-Alder gave oxa-bridged intermediate **49**, which underwent fragmentation by a retro Diels-Alder to final compounds **50**. So, simply heating a solution of the three components in toluene, in the presence of ammonium chloride afforded the desired **50** in a one-pot domino fashion in high yields.
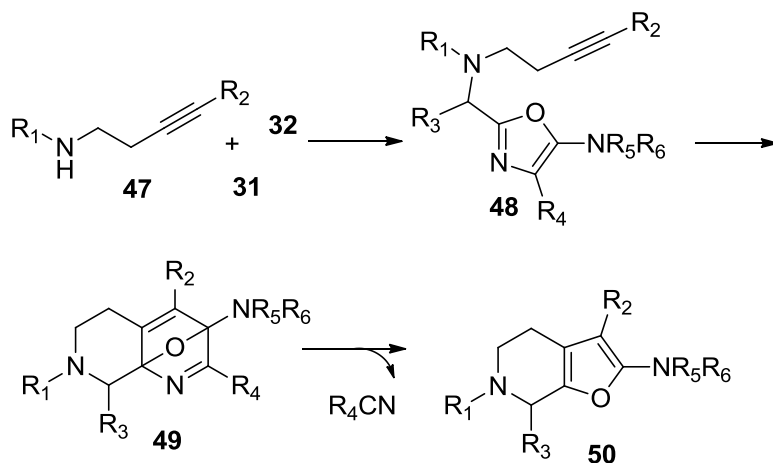
Scheme 11. *One-pot three component synthesis of* **50** *described by Zhu et al.*

A more recent application of the chemistry of 5-aminooxazoles as chemical platform describes the employment of methyl α-(p-nitrophenyl)-α-isocyano acetate **51** (Scheme 12).[15] As previously, **52** is yielded by a 3-CR between **51**, **23** and **24**. The resulting secondary amine **52** is then acylated to **53** through addition of an opportune chloride. The introduced dienophile allowed an intramolecular Diels-Alder to get the oxa-bridged intermediate **54**. A retro Diels-Alder reaction of **54** finally afforded the furopyrrolones **55**.
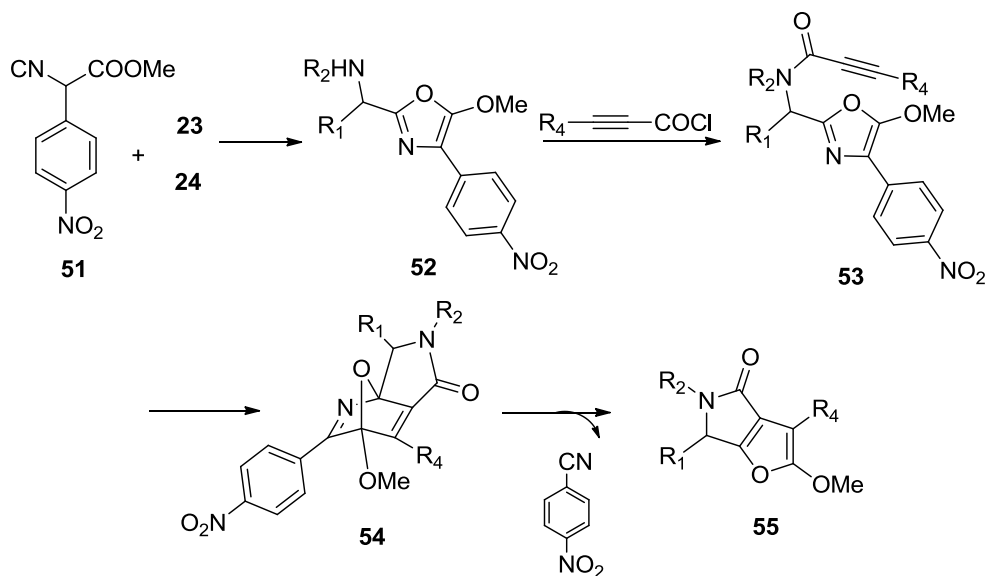
Scheme 12. *One-pot four component synthesis of* **55**.

4.3 The project in progress: results and discussion.

For the synthesis of compounds **14** and **15**, amines **10** and **11** were synthesized in order to obtain **12** and **13**. Before optimizing the one-pot procedure, a multi-step synthesis was performed in order to figure out the best reaction conditions. Amine **11** was synthesized as reported by Momose *et al.* (Scheme 13).[16]

Amine **11** was synthesized in four steps starting from but-3-yn-1-yl-methylbenezenesulfonate **56** and benzylamine **57** to get compound **58**.[17] The secondary amine **58** is then protected with a *tert*-butoxycarbonyl group in order to derivatize the terminal alkyne function of **59** with an alkyl lithium reagent and ethyl chloroformate. Finally **60** Boc protecting group was cleaved with a classical procedure to afford **11**. More problematic was the synthesis of amine **10** (Scheme 14). To our knowledge **10** is not described in literature, while a possible undesired adduct during the synthesis of **10** has been identified in Zhu's laboratories.[18]
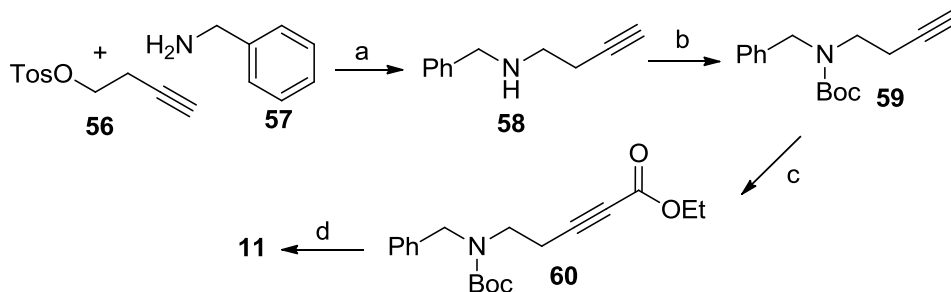
a) DMSO, NaI, 35h, rt; b) BocO2, Pyridine, 4h, 0°C; c) i: *n*-BuLi, THF, **-**78°C, 0.5h:
ii) ClCOOEt, THF, **-**78°C, 0.5h then rt, 2h; d) TFA, DCM, 0°C, overnight.

Scheme 13. *Synthesis of amine 11.*
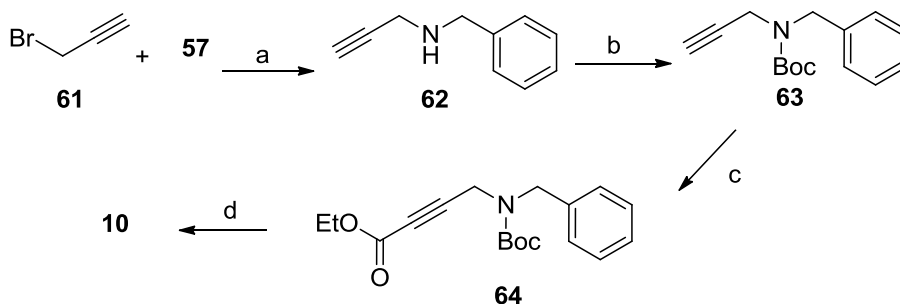
a) CH$_3$CN, K$_2$CO$_3$; b) Boc$_2$O, Pyr; c) i) BuLi, THF, -78°C,30'; ii) ClCO$_2$Et, THF,-78°C,30'
then rt, 2h; d) TFA, 0°C, 20'

Scheme 14. *Synthesis of amine 10.*

Analogously to amine **11**, amine **10** is synthesized in four steps starting from 3-bromo-prop-1-yne **61** and benzylamine **57** to get in a nucleophilic substitution **62**. The secondary amine **62** is then protected with a *tert*-butoxycarbonyl group in order to derivatize the terminal alkyne function of **63** with an alkyl lithium reagent and ethyl chloroformate. Finally **64** Boc protecting group is cleaved with a classical procedure to afford **10**. For the first three steps the yield are quite good, while the cleavage of Boc group was low yielding (52%) because of side reactions and low stability of product.

Synthesis of amine **65** (Figure 6) has previously been attempted in Zhu's laboratories, following an analogous procedure. During the cleavage of the Boc group of **66**, however, only 2-oxazolidinone **67** was recovered (Scheme 15), with yields ranging from 68% to 98% depending on deprotection reaction conditions. From classical procedures at different temperatures (TFA/DCM, HCl/AcOEt) to less conventional ones, employing TMSOTf , 2,6-lutidine and DCM have been screened. The cyclization of *N*-Boc-protected alkynlamines into the corresponding alkylidene 2-oxazolidinones has been reported in literature by Carretero et al.[19] as a gold catalyzed reaction(AuPPh$_3$Cl, 5 mol%; AgSbF$_6$ 5 mol%, DCM, rt). The gold catalysis allows for very short reaction times (5 minutes for yields up to 95%). The mechanism is shown in Scheme 16: it involves the nucleophilic attack of the carbamate carbonyl group on the activated Au(I)-alkyne complex **68** to afford the cationic vinyl-gold intermediate **69**. Subsequent tert-butyl fragmentation, likely by releasing isobutene and a proton, would give rise the oxazolidinone-Au complex **70**, which after protonation would provide the observed oxazolidinone **71**. An analogous mechanism could be envisaged to account for the formation of **67**, without the gold-mediated activation of the alkyne function (Scheme 17). In this case, **66** alkyne function would be already enough electrophilic to be attacked by the carbamate oxygen atom to give intermediate **72** bearing a negative charge. This latter would further undergo *t*-butyl cleavage and protonation to **67**.
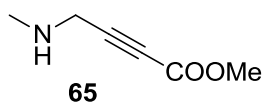
Figure 6. *Amine 65.*
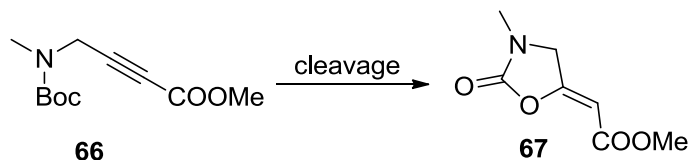
Scheme 15. *Obtainment of 67 from 66 cleavage.*
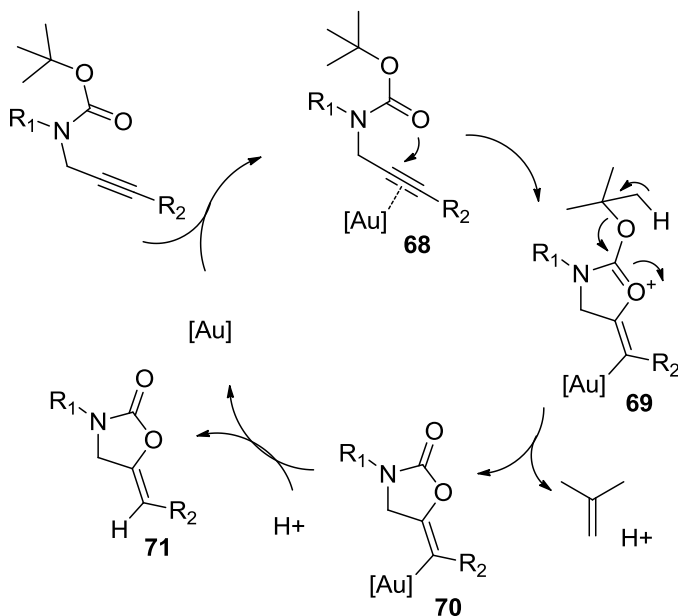
Scheme 16. *Carretero gold catalyzed 2-oxazolidinones formation mechanism.*
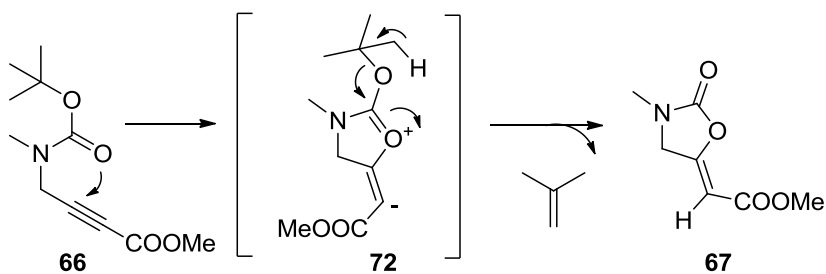
Scheme 17. *Proposed mechanism for the formation of 67.*

Ugi reaction performed with amines **10** and **11**, isovaleraldehyde **73**, isocyanide **1** and *para*-toluic acid **74** afforded the desired Ugi adducts **75** and **76** in 28% and 39% yields, respectively (A and B, Scheme 18). Low yields could be ascribed to a low reactivity of the amine, that is, a low availability of

the Schiff-base in the reaction mixture in DCM. Between 30% and 40% of Passerini/Aza-Wittig adduct **77** was indeed isolated in both Ugi-reactions, meaning that the isocyanide, the aldehyde and the acid prefer reacting in a Passerini/ Aza-Wittig fashion (Figure 7). Anyway different test reactions to increase the yield of the Ugi adduct are still in progress.
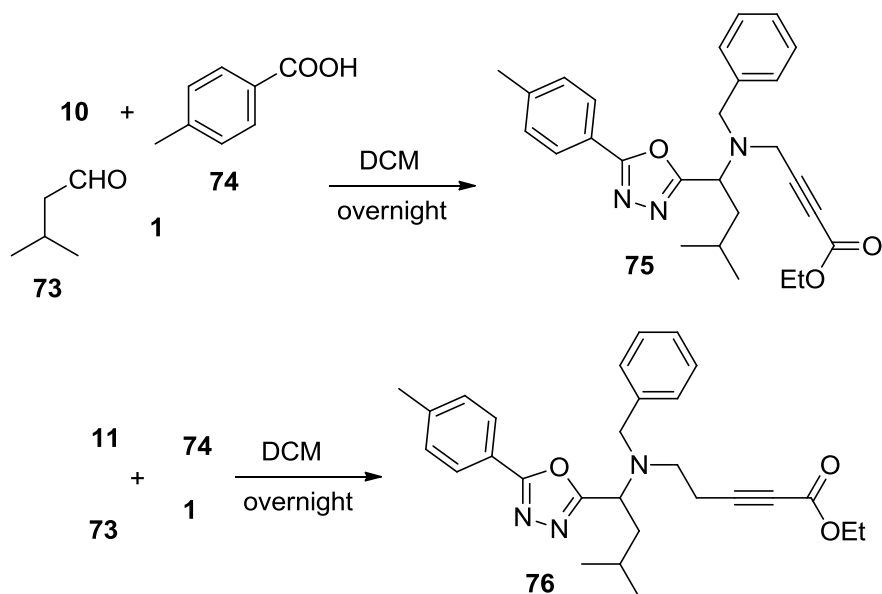
Scheme 18. *Test Ugi/Aza-Wittig reactions with amines **10** and **11**.*
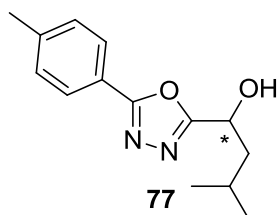
Figure 7. *Passerini/ Aza-Wittig adduct **77** isolated from Ugi/Aza-Wittig test reactions with amine **10** and **11**.*

Intra-molecular Diels Alder cyclizations of **75** and **76** to **78** and **79** (Scheme 19) are actually under investigations, screening different solvents and temperatures. After heating **76** under microwave conditions at 210 °C for 28 h compound **79** has been detected in quite low yields, encouraging anyway further optimization of reaction conditions. Probably higher temperatures are requested to allow the cyclization to be faster and minimize formation of side-products. Compound **75** was instead heated at 180 °C until disappearance of the starting material (4 d). In this case, the reaction profile seems to be much more complex, as a new unpredicted major product (not showed) was obtained. A full characterization of this latter, and studies about its reproducibility are in progress.
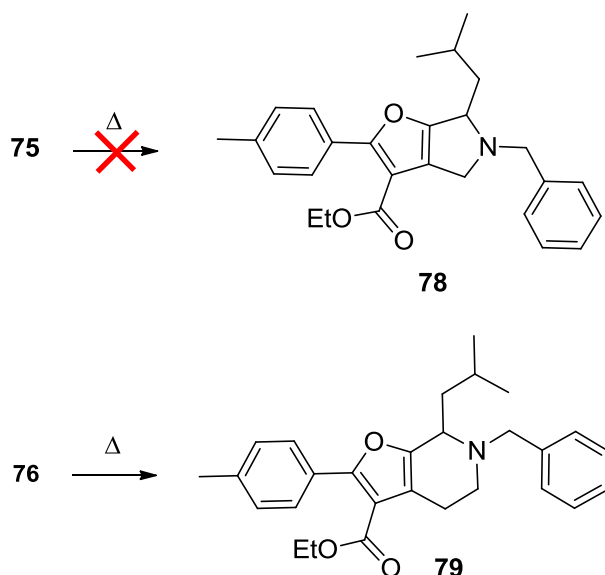
Scheme 19. *Attempted Intra-Molecular Diels-Alder cyclizations on substrate 75 and 76.*

Dealing with the synthesis of furo-pyrrolones **20**, in order to identify best conditions for the one-pot procedure, optimization of single-step reaction conditions was attempted. It is important to highlight that the central step of the one-pot procedure, that is, the amidation of the secondary nitrogen of the Ugi/Aza-Wittig adduct **16** (Scheme 5), is allowed by the use of a primary

amine in the former multi-component reaction (Figure 4). Focusing on the Ugi/Aza-Wittig sequence, a deep analysis of the reaction mechanism shows that with primary amines, in theory, two pathways are likely. Once the imine **80** is formed *in situ*, and the isocyanide **1** has been added to it, the carboxylate undergoes a nucleophilic addition into the nitrilium ion **81**, to give intermediate **82**. This latter could stand two different transformations. The first one follows the classical Ugi reaction mechanism with Mumm rearrangement of intermediate **82** followed by the Aza-Wittig reaction of intermediate **83** affording triazinone derivatives **84** (path A, Scheme 20). The second one (path B, Scheme 20) does not involve the Mumm rearrangement, to give directly the intramolecular Aza-Wittig reaction on **82** affording oxadiazoles derivatives **85**. It is important to remember that the Mumm rearrangement in the Ugi reaction is the key irreversible step of the reaction allowing the obtainment of the Ugi adduct in high yields (For details on Ugi reaction mechanism see Introduction). In the paper concerning the Ugi/Aza-Wittig sequence by Ramazani and Rezaei[7], only secondary amines have been described. In our test reaction (DCM, rt, 20h) with 2-phenethyl amine **86**, aldehyde **73**, isocyanide **1** and acid **74**, we were pleased to find that the four components Ugi/Aza-Wittig reaction with primary amines allowed the obtainment of the desired oxadiazol **87** in 70% yield (Scheme 21) suggesting that the Aza-Wittig reaction is kinetically favored over the Mumm rearrangement.
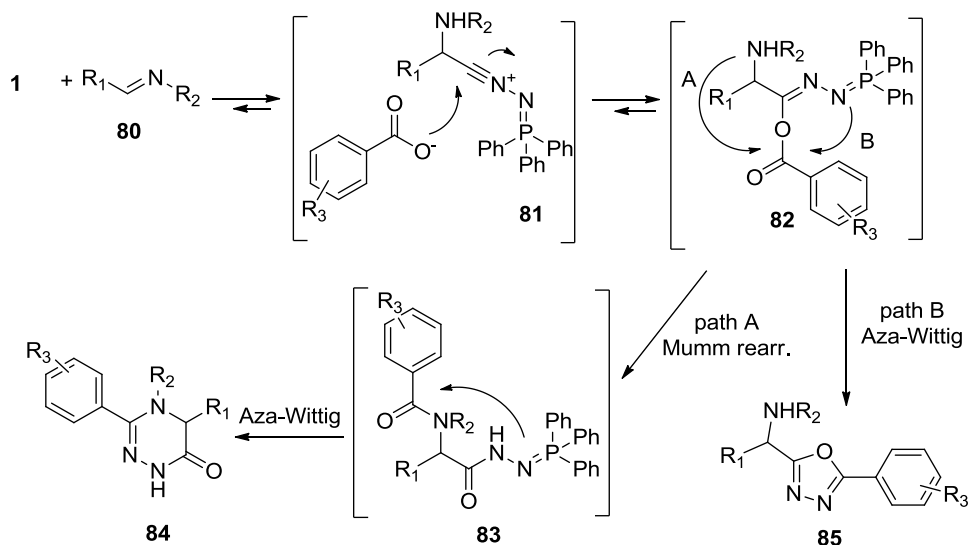
Scheme 20. *Reaction mechanism of Ugi/Aza-Wittig sequence with primary amines: in theory two different pathways are likely.*
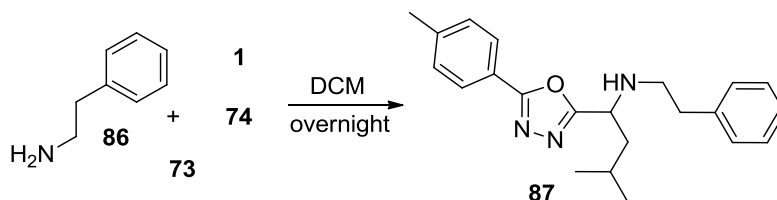
Scheme 21. *Test reaction with primary amine 86 giving the desired oxadiazole 87.*

Taking a closer look at compound **77**, an analogous reasoning could explain its formation. We can consider it, indeed, as a product deriving from the combination of **73**, **1** and **74** in a Passerini-like reaction. According to the classical mechanism of Passerini reaction intermediate **89**, given by the α-addition of the carboxylate **74** into the nitrilium ion **88**, should undergo an *O*-acyl transfer to give **90** (path A, Scheme 22), followed by the intramolecular Aza-Wittig reaction yielding oxadiazinone derivatives **91**. Anyway no traces of **91** were detected, but only **77** was obtained demonstrating again that the

intramolecular Aza-Wittig reaction is faster, that is kinetically favored over the *O*-acyl transfer (path B, Scheme 22). These reaction pathways could also be ascribed to the higher stability of five-membered fully conjugated oxadiazoles **77** and **85** over triazinone **84** and oxadiazinone **91** suggesting a likely concomitantly thermodynamic control influencing the reaction.
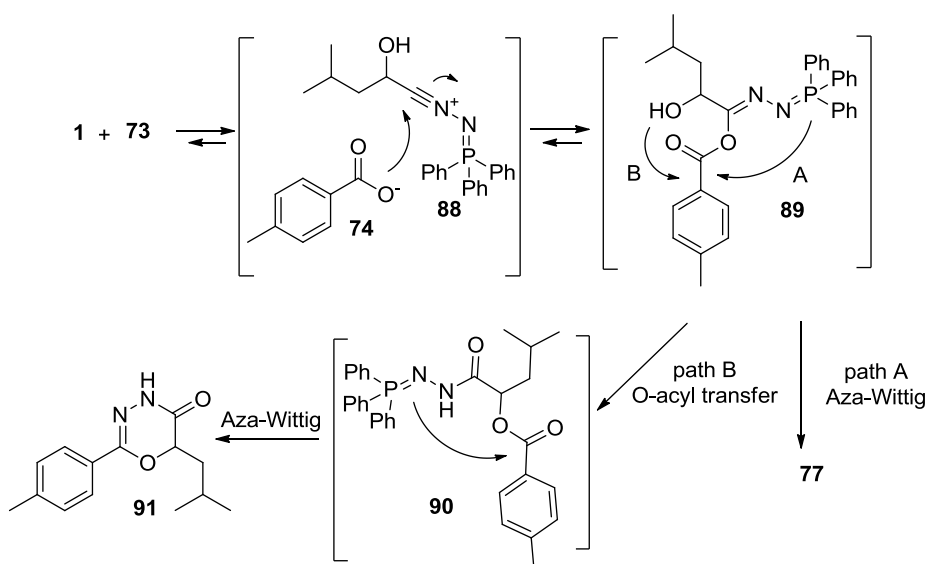
Scheme 22. *Reaction mechanism for the synthesis of **6**: two different pathways are likely in theory.*

Once the Ugi/Aza-Wittig adduct with primary amines **87** was established, we investigated the amidation reaction. Addition of triethylamine and 3-phenylpropriolyl chloride **17** (Scheme 5) to purified **87** afforded amide **92** in 67% yield (Scheme 23). Formation of a double-acylation unknown side product was observed and minimized by performing the reaction at 0°C for two hours.
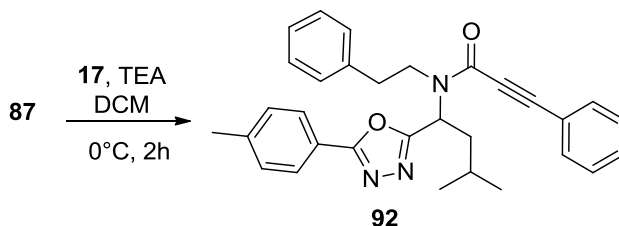
Scheme 23. *Amidation reaction of 87.*

Finally, stirring purified **92** overnight in a high-boiling solvent such as *ortho*-dichlorobenzene, afforded, by means of an intra-molecular diaza-Diels-Alder cyclization (IMDDA)/ retro-Diels-Alder sequence, furopyrrolone **93** in 87% yield (Scheme 24).
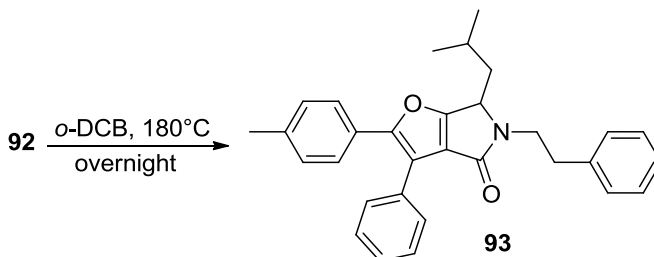
Scheme 24. *Intra-molecular Diels-Alder cyclization of 92.*

A possible scenario accounting for its formation is depicted in Scheme 25. The dienophile, the triple bond introduced in the amidation reaction, reacts with the 3,4-diaza diene moiety of the oxadiazole in a [4+2] cycloaddition to afford the oxa-bridged intermediate **94**. This latter undergoes a retro-Diels-Alder process favored by loss of nitrogen to give **93**. A test reaction with substrate **95** (Scheme 26), in the identical reaction conditions of **93**, failed to afford the Diels-Alder adduct **96** suggesting that the presence of electron-withdrawing substituents on the dienophile moiety could be important. This could be in agreement with a normal Diels-Alder reaction where the overlap between the highest occupied molecular orbital of the diene (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the dienophile is thermally allowed. In this case electron-withdrawing groups can decrease the energy of the LUMO, and the diene component should be as electron-rich as possible so

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that the provided molecular orbitals would be of similar energy. Anyway a more detailed study of our IMDA is requested to understand its nature. The Diels-Alder reaction of oxadiazoles is indeed usually described as an inverse electron demand Diels-Alder, where the diene acts as the LUMO and the dienophile provides the HOMO.[20] Vasilev,[21] Sauer,[22] Seitz[23] and Warrener[24] described examples of the participation of electron-deficient and typically symmetrical 1,3,4-oxadiazoles **97** in an intermolecular reaction cascade with electron-rich or strained olefins providing 2:1 cycloadducts (Scheme 27). The reaction with such alkenes proceed by an initial inverse demande Diels-Alder reaction to provide a cycloadduct **98** that loses N_2 to generate a carbonyl ylide **99** that in turn further reacts with the alkene in a 1,3-dipolar cycloaddition to give **100**. Boger et al. in 2002 reported for the first time intramolecular Diels-Alder and tandem intramolecular Diels-Alder cycloaddition reactions of 1,3,4-oxadiazoles.[25]
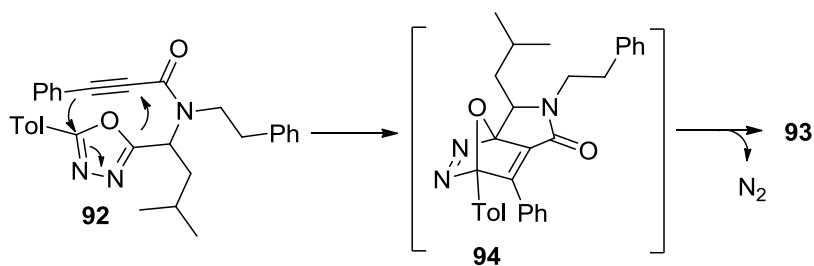
Scheme 25. *Proposed mechanism for the Intra-Molecular Diels-Alder of **92**.*
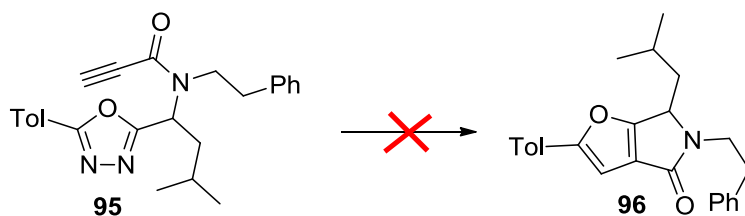
Scheme 26. *Test reaction of **95** failed to afford Diels-Alder adduct **96**.*
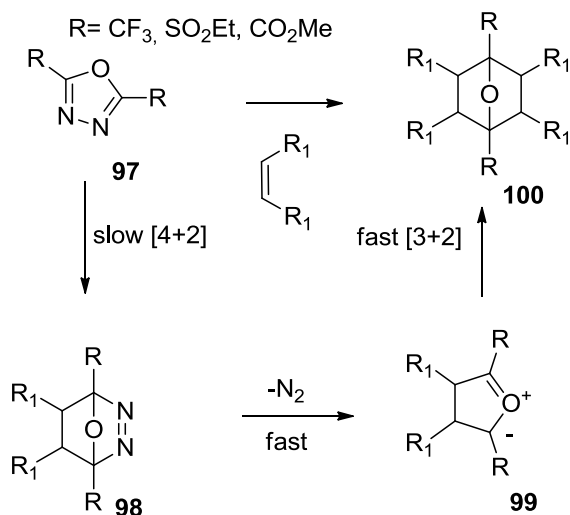
Scheme 27. *Inter-molecular Diels-Alder reaction of electron deficient 1,3,4-oxadiazoles and with electron-rich olefins.*

4.4 Conclusions and future perspectives.

To be able to combine the investigated single steps (MCR/Amidation/IMDA) or (MCR/IMDA) an appropriate choice of the solvent is crucial. As for the IMDA a high boiling solvent such as *ortho*-dichlorobenzene (*o*-DCB) is requested, next step toward the optimization of the one-pot procedure was performing the Ugi/Aza-Wittig MCR in such a solvent. To our delight Ugi/Aza-Wittig MCR affording **85** (Scheme 20) in *o*-DCB and ammonium chloride[26] gave oxadiazole derivatives in comparable yields while MCR with amines **10** and **11** remained to be optimized. Amidation reaction on purified oxadiazole **85** in *o*-DCB seemed to work as nice as in DCM. A full-sequence MCR/Amidation/IMDA one-pot reaction for the obtainment of **93** (Scheme 24) is now under investigations. The project in progress aims to demonstrate that 1,3,4-oxadiazoles, as already reported for oxazoles, could be a chemical platform for the synthesis of a wide range of *N*-containing multi-functionalized heterocycles. The Ugi/Aza-Wittig reaction with primary amines and the observation of a non-competitive Mumm rearrangement opened to interesting mechanistic considerations about the reaction pathway. The Intra-Molecular Diels-Alder reaction of oxadiazole **92** (Scheme 23) raised an intriguing question about its nature. The study of stronger or weaker

electron-withdrawing group on the dienophile moiety could be, e.g., a useful approach to get new insights. Last but not least, IMDA with oxadiazole **75** failed to yield the desired dihydro-furopyrrol **78** affording an unexpected major adduct which needs to be fully characterized. Studies on the reproducibility of the reaction as well are in progress. IMDA of oxadiazoles **76** successfully gave the desired tetrahydro-furopyrrole **79**, but yields remain to be further improved.

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26) For the role of ammonium chloride in MCRs see: ref 10

EXPERIMENTAL SECTION

PART I

General informations.

Commercially available reagents and solvents were used without further purification and were purchased from Fluka-Aldrich or Lancaster. Melting points were determined in open glass capillary with a Stuart scientific SMP3 apparatus and are uncorrected. All the compounds were checked by IR (FT-IR THERMO-NICOLET AVATAR); 1H and 13C APT (JEOL ECP 300 MHz) and mass spectrometry (Thermo Finningan LCQ-deca XP-*plus*) equipped with an ESI source and an ion trap detector. Chemical shifts are reported in part per million (ppm). Column chromatography was performed on silica gel (Merck Kieselgel 70-230 mesh ASTM) using the indicated eluants. Thin layer chromatography (TLC) was carried out on 5 x 20 cm plates with a layer thickness of 0.25 mm (Merck Silica gel 60 F254).When necessary they were developed with KMnO4. Elemental Analysis of all the 1-aryl-5-aroyl tetrazoles (C, H, N) are within ± 0.4 % of the calculated values unless otherwise noted. Isocyanides (**5**, **19**, **28**-**33**) are described in literature. We synthesized them in two steps starting from the aromatic anilines, forming the formamide and dehydrating it with POCl$_3$.

1-(ethylamino)-1-oxobutan-2-yl 2-iodobenzoate (2). Procedure: to a solution of heptanal (1 eq) in DCM (1M), 2-iodobenzoic acid (1eq) and 1-pentyl isocyanide (0.05g, 0.515 mmol), were added and stirred overnight. After completion of the reaction, the reaction mixture was evaporated and purified by silica gel chromatography (Petroleum ether/ AcOEt 4:1, Rf = 0.3), yield 69%. 1H-NMR (300 MHz, CDCl3) δ 7.97 (d, *J*= 9 Hz, 1-H), 7.79 (d, *J*= 9 Hz, 1-H), 7.42 (t, *J*= 15 Hz, 1-H), 7.17 (t, *J*= 15 Hz, 1-H), 6.31 (bs, NH), 5.38 (t, *J*= 12 Hz, 1-H), 3.29-3.22 (m, 2-H), 2.00-1.92 (m, 2-H), 1.52-1.22 (m, 14-H), 0.85-0.81 (m, 6-H); 13C-NMR (75 MHz, CDCl3) δ 168.88, 164.97, 140.93, 134.47, 132.61, 130.77, 127.71, 93.21, 75.25, 38.82, 31.50, 31.14, 28.75, 28.58, 28.48, 24.44, 22.07, 21.85, 13.57, 13.52. C$_{13}$H$_{16}$INO$_3$
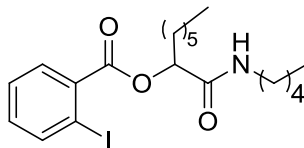
General procedure for the preparation of 1-aryl-5-aroyl tetrazoles.

Equimolar amounts of aromatic isocyanide, aromatic aldehyde, *N*-benzylamine and trimethylsilylazide were dissolved in dry methanol (2M) under a nitrogen atmosphere. The resulting solution was stirred at room temperature for three days. The solid formed was filtered off and washed with cold methanol. For oily products, the reaction mixture was evaporated and purified by column chromatography using PE/EtOAc as eluants. The obtained tetrazole intermediate was then stirred in methanol under a hydrogen atmosphere in the presence of Pd/C 10 % heating at 60 °C for 24 h. The crude reaction was filtered through a Celite pad and evaporated to give the free amine enough pure for the following step. The amine was dissolved in CH2Cl2/DMF 3:1 and 4-formyl-1- methylpyridinium benzenesulfonate (1.2 eq) was added. The reaction mixture was stirred at room temperature for 8 h, then treated with triethylamine (1.0 eq) and stirred for 15-20 min. The reaction was finally quenched with a cold saturated aqueous solution of oxalic acid and stirred overnight. The reaction was then diluted with water and CH2Cl2. After extraction with CH2Cl2 (x3) the combined organic phases were washed with brine (x1), dried over sodium sulphate, filtered, and evaporated under reduced pressure. The carbonyl compound was purified by column chromatography using PE/AcOEt as eluant.

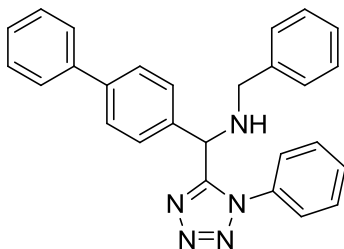**N-benzyl-1-(1-(4-methoxyphenyl)-1*H*-tetrazol-5-yl)-1-(3,4,5-trimethoxyphenyl)methanamine (20).** The crude material was filtered under vacuum, washed with cold methanol and evaporated to give a white solid (59 %). IR (KBr) 3290,

2943, 1591, 1323, 1256, 1131, 834 cm^{-1}; 1H-NMR (300 MHz, CDCl3) δ 7.24-7.23 (m, 5-H), 7.01 (d, *J*= 9 Hz, 2-H), 6.87 (d, *J*= 9 Hz, 2-H), 6.35 (s, 2-H), 4.88 (s, 1-H), 3.82 (s, 3-H), 3.78 (s, 3-H), 3.72 (s, 8-H); 13CNMR (75 MHz, CDCl3) δ 161.5, 160.4, 156.3, 155.5, 152.8, 137.9, 137.2, 127.8, 127.7, 126.7, 126.4, 125.3, 124.1, 113.9, 103.9, 60.1, 55.5, 55.41, 55,0 , 50.5; MS (ESI) *m/z* 462 (M+H)$^+$; Mp = 112-116°C. C$_{25}$H$_{27}$N$_5$O$_4$
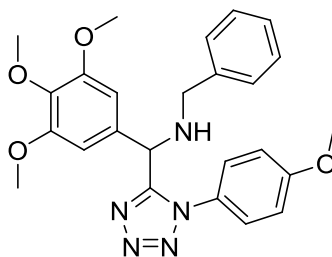
N-benzyl-1-(1-(4-methoxyphenyl)-1*H*-tetrazol-5-yl)-1-(3,4,5-trimethoxyphenyl)methanamine (36) The crude material was purified by column chromatography, using petroleum ether/EtOAc 6:4 as eluant to give a yellowish oil (70 %). IR (KBr) 3288, 2326, 1275, 1128, 749, 764 cm^{-1}; 1H-NMR (300 MHz, CDCl3) δ 7.12-7.04 (m, 5-H), 7.01 (d, *J*= 9 Hz, 2-H), 6.70 (d, *J*= 9 Hz, 2-H), 6.23 (s, 2-H), 4.93 (s, 1-H), 3.75 (s, 3-H), 3.764 (s, 3-H), 3.55 (s, 8-H); 13C-NMR (75 MHz, CDCl3) δ 159.1, 155.8, 153.0, 138.8, 138.5, 128.6, 127.9, 127.7, 126.7, 113.7, 102.6, 60.4, 55.7, 54.9, 54.7, 50.5; MS (ESI) *m/z* 462 (M+H)$^+$. C$_{25}$H$_{26}$N$_5$O$_4$.
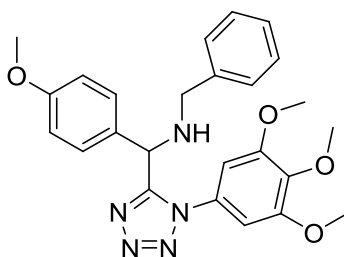
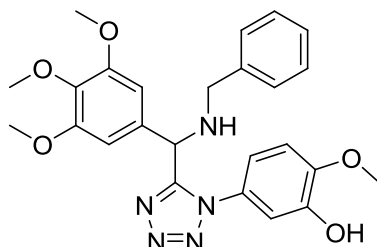**N-benzyl-1-(biphenyl-4-yl)-1-(1-(4-phenoxyphenyl)-1*H*tetrazol-5-yl)methanamine (37).**
The crude material was purified by column chromatography, using petroleum ether/EtOAc
8:2 as eluant to give a brown oil (74 %). IR (KBr) 3291, 2360, 2341, 1521, 1237, 733, 788,
699 cm^{-1}; 1H-NMR (300 MHz, CDCl3) δ 7.59-6.97 (m, 23-H), 5.12 (s, 1-H), 3.80 (s, 2-H);
13C-NMR (75 MHz, CDCl3) δ 159.5, 156.4, 155.8, 141.5, 140.3, 138.9, 137.0, 130.3,
129.0, 128.6, 128.5, 128.4, 127.7, 127.2, 124.8, 120.0, 118.7, 55.6, 51.2; MS (ESI) *m/z* 510
(M+H)$^{+}$. C$_{33}$H$_{27}$N$_5$O.
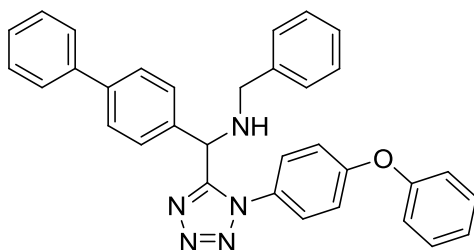
1-(1-(benzo[d][1,3]dioxol-5-yl)-1*H*-tetrazol-5-yl)-N-benzyl-1-(3,4,5,-trimethoxyphenyl)
**methanamine (38)** The crude material was filtered under vacuum, washed with cold
methanol and evaporated to give a pale yellow solid (78 %). IR (KBr) 3278, 2925, 1502,
1323, 1131, 894, 747 cm^{-1}; 1H-NMR (300 MHz, CDCl3) δ 7.25-7.23 (m, 5-H), 6.78 (d, *J* =
9 Hz 1-H), 6.61-6.56 (m, 2-H), 6.41 (s, 2-H), 6.05 (s, 2-H), 4.89 (s, 1-H), 3.79 (s, 3-H),
3.75 (s, 6- H), 3.72 (s, 2-H); 13C-NMR (75 MHz, CDCl3) δ 156.3, 153.6, 149.5, 148.4,
138.7, 138.1, 133.4, 128.6, 128.5, 127.5, 127.0, 119.8, 108.4, 106.9, 104.9, 102.5, 60.9,
56.4, 56.3, 51.3; MS (ESI) *m/z* 476 (M+H)$^{+}$; Mp = 123-126 °C. C$_{25}$H$_{25}$N$_5$O$_5$.
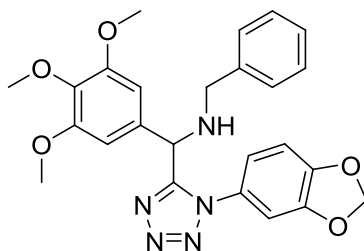
_N_-benzyl-1-(1-(4-phenoxyphenyl)-1_H_-tetrazol-5-yl)-1-(3,4,5,-trimethoxyphenyl)methanamine (39). The crude material was filtered under vacuum, washed with cold methanol and evaporated to give a pale yellow solid (86 %). IR (KBr) 3420, 1617, 1509, 1242, 1132, 700 cm^{-1}; 1H-NMR (300 MHz, CDCl3) δ 7.36-6.92 (m, 16-H), 6.38 (s, 2-H), 4.92 (s, 1-H), 3.76 (s, 2-H), 3.71 (s, 3-H); 13C-NMR (75 MHz, CDCl3) δ 159.6, 156.4, 155.6, 153.6, 138.9, 138.1, 133.4, 130.3, 128.6, 128.5, 127.9, 127.5, 127.4, 124.9, 120.0, 118.4, 104.9, 60.9, 56.3, 56.2, 51.2; MS (ESI) _m/z_ 524 (M+H)$^{+}$; Mp = 126-130 °C. C$_{30}$H$_{29}$N$_5$O$_4$.
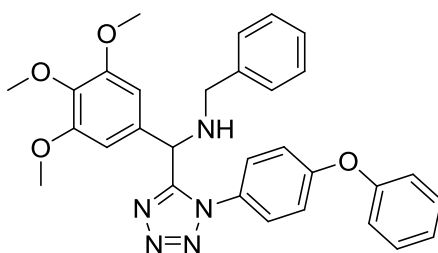
5-((1-(benzo[d][1,3]dioxol-5-yl)-1_H_-tetrazol-5-yl)(benzylamino)methyl)-2-methoxyphenol (40). The crude material was purified by column chromatography, using petroleum ether/EtOAc 6:4 as eluant to give a colourless oil (53 %). IR (KBr) 3290, 2361, 1505, 1246, 1270, 1033, 743, 730, 699, cm^{-1}; 1H-NMR (300 MHz, CDCl3) δ 7.22-7.16 (m, 5-H), 6.79 (d, _J_ = 3Hz, 1-H), 6.73 (s, 1-H), 6.70 (s, 1-H), 6.64 (dd, _Jo,m_= 9Hz, 6Hz, 1-H), 6.54 (m, 1-H), 6.51(d, _J_ = 3Hz, 1-H), 5.99 (s, 2-H), 4.86 (s, 1-H), 3.78 (s, 3-H), 3.67 (s, 2-H); 13C-NMR (75 MHz, CDCl3) δ 156.6, 149.6, 148.6, 147.2, 146.4, 138.9, 131.0, 128.6, 128.6, 127.5, 127.0, 119.7, 119.6, 114.5, 111.2, 108.5, 106.8, 102.6, 60.6, 56.2, 55.5, 51.2; MS (ESI) _m/z_ 432 (M+H)$^{+}$. C$_{23}$H$_{21}$N$_5$O$_4$.
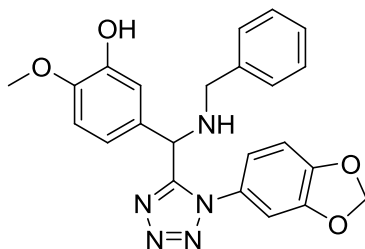
1-(1-(benzo[d][1,3]dioxol-5-yl)-1*H*-tetrazol-5-yl)-N-benzyl-1-(4-chlorophenyl)-methan amine (41). The crude material was purified by column chromatography, using petroleum ether/EtOAc 8:2 as eluant to give a colourless oil (87 %). IR (KBr) 3283, 1505, 1244, 1035, 811, 732, 699 cm^{-1}; 1H-NMR (300 MHz, CDCl3) δ 7.20-7.12 (m, 9-H), 6.68 (dd, $J_{o,m}$= 12Hz, 6Hz, 1-H), 6.54-6.48 (m, 3-H), 5.96 (s, 2-H), 4.93 (s, 1-H), 3.62 (s, 2-H); 13C-NMR (75 MHz, CDCl3) δ 156.2, 149.6, 148.7, 138.8, 136.7, 134.5, 129.5, 129.2, 128.9, 128.5, 127.5, 126.9, 119.7, 108.5, 106.7, 102.7, 60.5, 55.2, 51.2; MS (ESI) *m/z* 420 (M+H)$^{+}$. C$_{22}$H$_{18}$ClN$_5$O$_2$.
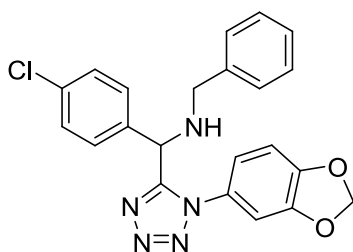
***N*-benzyl-1-(4-chlorophenyl)-1-(1-phenyl-1*H*-tetrazol-5-yl)- methanamine (42).** The crude material was purified by column chromatography, using petroleum ether/EtOAc 9:1 as eluant to give a colourless oil (65 %). IR (KBr) 3295, 1492, 1091, 1015, 702, 762, 736, 691 cm^{-1}; 1H-NMR (300 MHz, CDCl3) δ 7.46-7.34 (m, 3-H), 7.23-7.09 (m, 11-H), 4.99 (s,

1-H), 3.67 (s, 2-H); 13C-NMR (75 MHz, CDCl3) δ 156.5, 139.2, 137.1, 134.9, 133.9, 131.3, 130.3, 129.9, 129.6, 129.5, 129.1, 128.9, 128.4, 127.9, 125.9, 55.7, 51.6; MS (ESI) *m/z* 389 (M+H)$^{+}$. $C_{21}H_{18}ClN_5$.
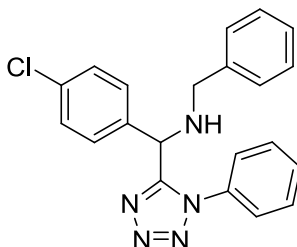
N-benzyl-1-(4-morpholinophenyl)-1-(1-phenyl-1*H*-tetrazol-5-yl)methanamine **(43).** The crude material was filtered under vacuum, washed with cold methanol and evaporated to give an off-white solid (71 %). IR (KBr) 3238, 2812, 1513, 1263, 1112, 921, 699 cm^{-1}; 1H-NMR (300 MHz, CDCl3) δ 7.40-7.29 (m, 3-H), 7.17-7.05 (m, 8-H), 6.73 (d, *J*= 9Hz, 2-H), 4.89 (s, 1-H), 3.69 (t, *J*= 9Hz, 4-H), 3.62 (s, 2-H), 3.01 (t, *J*= 9Hz, 4-H); 13C-NMR (75 MHz, CDCl3) δ 157.2, 151.9, 139.7, 134.2, 131.2, 130.4, 129.4, 129.1, 129.1, 127.9, 126.0, 116.2, 67.4, 55.9, 51.7, 49.5; MS (ESI) *m/z* 450 (M+Na)$^{+}$; Mp= 89-93°C. $C_{25}H_{26}N_6O$.
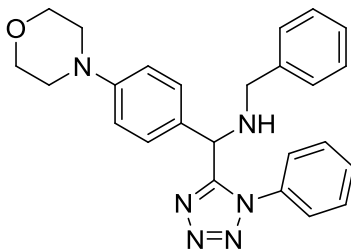
N-benzyl-1-(2-(3-methoxyphenyl)-2*H*-tetrazol-5-yl)-1-(3,4,5-trimethoxyphenyl)
methanamine (44). The crude material was purified by column chromatography, using
petroleum ether/EtOAc 6:4 as eluant to give a yellow oil (63 %). IR (KBr) 3288, 1592,
1460, 1235, 1124, 729, 688 cm^{-1}; 1H-NMR (300 MHz, CDCl3) δ 7.20-7.12 (m, 6-H), 6.97
(dd, $J_{o,m}$ = 12Hz,6Hz, 1-H), 7.69 (dd, $J_{o,m}$ = 9Hz,6Hz, 1-H), 6.60 (t, , J= 3Hz, 1-H), 6.36 (s,
2-H), 4.92 (s, 1- H), 3.73 (s, 3-H), 3.67 (s, 8-H), 3.64 (s, 3-H); 13C-NMR (75 MHz,
CDCl3) δ 161.3, 157.1, 154.5, 139.8, 138.9, 135.4, 134.4, 131.4, 129.5, 129.3, 128.3,
118.6, 117.6, 112.2, 105.8, 61.7, 57.4, 57.1, 56.6, 52.2; MS (ESI) *m/z* 462 (M+H)$^+$.
$C_{25}H_{27}N_5O_4$.
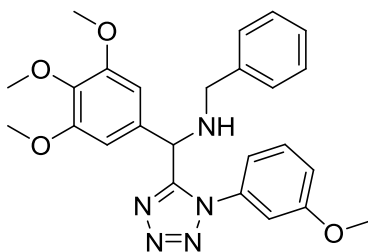
N-benzyl-1-(biphenyl-4-yl)-1-(2-phenyl-2H-tetrazol-5-yl)methanamine (45). The crude
material was purified by column chromatography, using petroleum ether/EtOAc 8:2 as
eluant to give a colourless oil (69 %). IR (KBr) 3286, 1597, 1453, 1101, 1008, 761, 733,
692 cm^{-1}; 1H-NMR (300 MHz, CDCl3) δ 7.57- 7.16 (m, 18-H), 5.11 (s, 1-H), 3.76 (s, 2-H);
13C-NMR (75 MHz, CDCl3) δ 157.0, 142.1, 141.0, 139.6, 137.7, 134.2, 131.4, 130.5,
129.7, 129.3, 129.2, 129.1, 128.6, 128.4, 128.4, 128.1, 127.8, 126.1, 56.3, 51.9; MS (ESI)
m/z 418 (M+H)$^+$. $C_{27}H_{23}N_5$.

N-benzyl-1-(4-chlorophenyl)-1-(1-(4-morpholinophenyl)-1Htetrazol-5-yl)methan

amine (46). The crude material was purified by column chromatography, using petroleum ether/EtOAc 6:4 as eluant to give a yellow oil (82 %). IR (KBr) 3290, 1521, 1450, 1236, 1120, 926, 823, 699 cm^{-1}; 1H-NMR (300 MHz, CDCl3) δ 7.24-7.12 (m, 9-H), 6.92 (d, $J=$ 9Hz, 2-H), 6.77 (d, $J=$ 9Hz, 2-H), 4.94 (s, 1-H), 3.75 (m, 4-H), 3.62 (s, 2-H), 3.13 (m, 4-H); 13CNMR (75 MHz, CDCl3) δ 156.8, 153.2, 139.5, 137.6, 134.9, 130.1, 129.7, 129.3, 129.1, 128.1, 127.1, 124.8, 115.8, 67.3, 55.9, 51.8, 48.9; MS (ESI) m/z 461 (M+H)$^{+}$. $C_{25}H_{25}ClN_6O$.
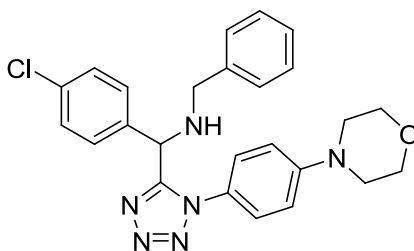
5-((benzylamino)(1-(3,4,5-trimethoxyphenyl)-1H-tetrazol-5-yl)methyl)-2-methoxy

phenol (47). The crude material was filtered under vacuum, washed with cold methanol and evaporated to give a yellow solid (75 %). IR (KBr) 3284, 2835, 1509, 1465, 1232, 1133, 999 cm^{-1}; 1H-NMR (300 MHz, CDCl3) δ 7.25-7.12 (m, 5- H), 6.77 (s, 1-H), 6.68 (d, $J=$ 9Hz, 1-H), 6.59 (dd, $Jo,m=$ 12Hz, 6Hz, 1-H), 6.29 (s, 2-H), 4.89 (s, 1-H), 3.85 (s, 3-H),

3.77 (s, 3-H), 3.66 (s, 6-H), 3.36 (s, 2-H); 13C-NMR (75 MHz, CDCl3) δ 156.8, 154.1, 147.7, 146.9, 139.9, 139.3, 131.4, 129.2, 129.1, 128.9, 127.9, 120.1, 115.1, 111.6, 103.7, 61.6, 56.9, 56.6, 56.2, 51.6, 51.0; MS (ESI) *m/z* 478 ; Mp = 130-134 °C. $C_{25}H_{27}N_5O_5$.

N-benzyl-1-(3-methoxyphenyl)-1-(1-(3,4,5-trimethoxyphenyl)-1H-tetrazol-5-yl) methanamine (48). The crude material was purified by column chromatography, using petroleum ether/EtOAc 7:3 as eluant to give a colourless oil (81 %). IR (KBr) 3286, 1508, 1232, 1131, 1126, 735, 698 cm^{-1}; 1H-NMR (300 MHz, CDCl3) δ 7.07-7.01 (m, 5-H), 6.66-6.60 (m, 3-H), 6.22 (s, 2-H), 4.93 (s, 1- H), 3.68 (s, 3-H), 3.59 (s, 2-H), 3.55 (s, 3-H), 3.49 (s, 6-H); 13C-NMR (75 MHz, CDCl3) δ 160.6, 156.6, 154.1, 140.2, 140.0, 139.4, 130.5, 128.9, 128.8, 127.8, 120.7, 114.5, 114.1, 103.9, 61.4, 60.8, 56.8, 56.7, 55.8, 51.6; MS (ESI) *m/z* 475 (M+H)$^+$. $C_{25}H_{27}N_5O_4$.
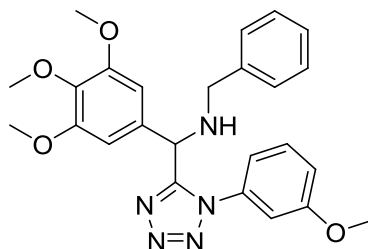
N-(4-methoxybenzyl)-1-(2-phenyl-2H-tetrazol-5-yl)-1-(3,4,5-trimethoxyphenyl) methanamine. (49) The crude material is purified by column chromatography, using petroleum ether/EtOAc 5:5 as eluant to give a yellowish amorphous solid (39%). IR 1464.32, 1240.65, 1132.24, 763.90, 694.09 cm^{-1}; 1H-NMR (300 MHz, CDCl$_3$) δ 7.48-7.35 (m, 3-H), 7.12-7.05 (m, 4-H), 6.70 (d, J= 9Hz, 2-H), 6.29 (s, 2-H), 4.86 (s, 1-H), 3.70 (s, 3-H), 3.67 (s, 3-H), 3.66 (s, 3-H), 3.62 (s, 3-H), 3.59 (s, 2-H); 13C-NMR (75 MHz, CDCl$_3$) δ 159.60, 156.91, 154.17, 138.60, 134.26, 134.10, 131.45, 131.29, 130.26, 126.32, 114.55, 105.39, 61.44, 56.79, 55.95, 51.26; MS (ESI) m/z 462.8 (M+H)$^+$. C$_{25}$H$_{27}$N$_5$O$_4$.
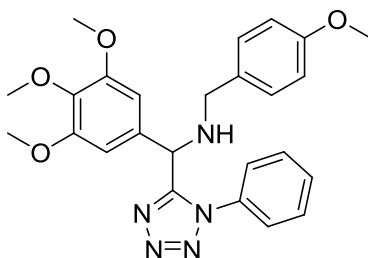
1-(2-(3-(tert-butyldimethylsilyloxy)-4-methoxyphenyl)-2H-tetrazol-5-yl)-1-(4-methoxy phenyl)-N-(3,4,5-trimethoxybenzyl)methanamine. (50a) The crude material is purified by column chromatography, using petroleum ether/EtOAc 6:4 as eluant to give a yellowish amorphous solid (67%). IR 2933.50, 1516.82, 1241.77, 1131.93, 948.40, 840.71 cm^{-1}; 1H-NMR (300 MHz, CDCl$_3$) δ 7.05 (d, J= 9Hz, 2-H), 6.79-6.72 (m,3-H), 6.63 (dd, $J_{o,m}$ = 9Hz,6Hz, 1-H), 6.52 (d, J= 3Hz, 1-H), 6.39 (s, 2-H), 4.89 (s, 1-H), 3.77 (s, 3-H), 3.72 (s, 6-H), 3.71 (s, 3-H), 3.68 (s, 2-H), 0.84 (s, 9-H), 0.01 (s,3-H), 0.00 (s, 3-H); 13C-NMR (75 MHz, CDCl$_3$) δ 160.44, 157.20, 154.04, 153.53, 146.37, 137.86, 135.51, 131.03, 129.82, 126.73, 119.52, 118.77, 115.10, 112.52, 105.95, 61.57, 56.89, 56.44, 56.22, 56.05, 52.28, 26.35, 19.14, -3.90, -3.95; MS (ESI) m/z 620.3 (M-H)$^-$. C$_{32}$H$_{43}$N$_5$O$_6$Si
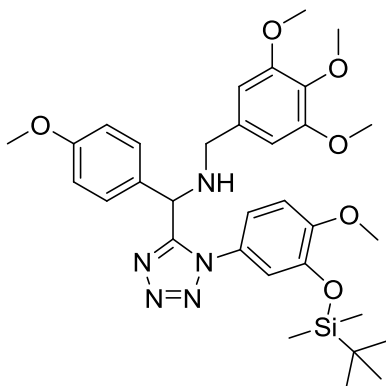
2-methoxy-5-(5-((4-methoxyphenyl)(3,4,5-trimethoxybenzylamino)methyl)-2H-tetrazol-2-yl)phenol. **(50)** The crude material is purified by column chromatography, using petroleum ether/EtOAc 6:4 and then 2:8 as eluant to give a yellowish oil (67%). IR 1509.25, 1459.95, 1247.86, 1124.82, 731.79, 764.17 cm^{-1}; 1H-NMR (300 MHz, CDCl$_3$) δ 7.11 (d, J= 9Hz, 2-H), 6.78-6.74 (m,3-H), 6.69 (d, J= 3Hz, 1-H), 6.51 (dd, $J_{o,m}$ = 9Hz,6Hz, 1-H), 6.42 (s, 2-H), 4.92 (s, 1-H), 3.83 (s, 3-H), 3.75 (s, 3-H), 3.73 (s, 9-H), 3.71 (s, 2-H); 13C-NMR (75 MHz, CDCl$_3$) δ 160.48, 157.22, 154.05, 149.37, 147.43, 137.87, 135.35, 130.78, 129.84, 127.13, 117.82, 115.13, 112.98, 111.52, 106.06, 61.63, 56.99, 56.91, 56.14, 56.03, 52.30; MS (ESI) m/z 506.27 (M-H)$^-$. C$_{25}$H$_{29}$N$_5$O$_6$
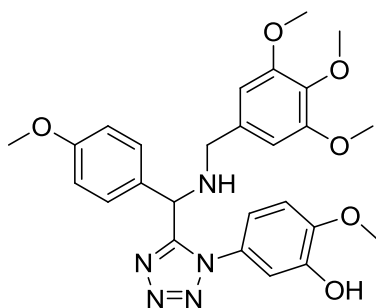
5-((benzylamino)(1-(3,4,5-trimethoxyphenyl)-1H-tetrazol-5-yl)methyl)-2-methoxy phenol. (51) The crude material is purified by column chromatography, using petroleum ether/EtOAc 3:7 as eluant to give a light yellow solid (72%). IR 2838.31, 1474.75, 1326.79, 1251.55, 1024.47, 879.43 cm^{-1}; 1H-NMR (300 MHz, CDCl$_3$) δ 7.26 (t, J= 15Hz, 1-H), 6.95 (dd, $J_{o,m}$ = 12Hz,6Hz, 1-H), 6.78 (d, J= 3Hz, 1-H), 6.70-6.66 (m, 3-H), 6.63 (s, 1-H), 6.40 (s, 2-H), 4.88 (s, 1-H), 3.75 (s, 3-H), 3.73 (s, 3-H), 3.70 (s, 6-H), 3.64 (s, 3-H), 3.60 (s, 2-H); 13C-NMR (75 MHz, CDCl$_3$) δ 161.30, 157.16, 154.17, 147.98, 147.20, 137.94, 135.49, 135.23, 131.85, 131.39, 120.40, 118.09, 117.63, 115.33, 111.89, 111.67, 106.13, 61.78, 61.41, 57.03, 56.93, 56.52, 56.41, 52.45; MS (ESI) m/z 507.9 (M+H)$^+$. C$_{26}$H$_{29}$N$_5$O$_6$.
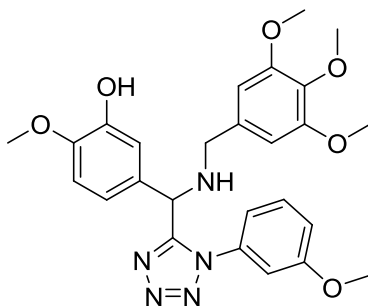
(1-(4-methoxyphenyl)-1*H*-tetrazol-5-yl)(3,4,5-trimethoxyphenyl)methanamine (21). Yellow-brown solid (91%). IR (KBr) 3372, 3290, 2359, 1517, 1257, 1122, 834, 764 cm^{-1}; 1H-NMR (300 MHz, CD3OD) δ 7.01 (d, J= 9Hz, 2-H), 6.84 (d, J= 9Hz, 2-H), 6.26 (s, 2-H), 5.14 (s, 1-H), 3.75 (s, 3-H), 3.68 (s, 3-H), 3.62 (s, 6-H); 13C-NMR (75 MHz, CD3OD) δ 160.4, 156.9, 152.8, 137.1, 134.8, 126.4, 126.1, 125.2, 113.9, 103.2, 60.0, 55.8, 55.3, 50.6; MS (ESI) m/z 372 (M+H)$^+$; Mp = 123-125°C. C$_{18}$H$_{21}$N$_5$O$_4$.
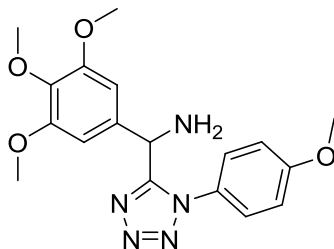
(4-methoxyphenyl)(1-(3,4,5-trimethoxyphenyl)-1*H*-tetrazol-5-yl)methanamine (52).
White solid (72 %). IR (KBr) 3335, 3276, 2999, 1601, 1242, 1128, 1002, 848 cm-1; 1H-NMR (300 MHz, CD$_3$OD) δ 7.12 (d, *J*= 9Hz, 2-H), 6.81 (d, *J*= 9Hz, 2-H), 6.35 (s, 2-H), 5.24 (s, 1-H), 3.86 (s, 3-H), 3.76 (s, 3-H), 3.68 (s, 6-H); 13C-NMR (75 MHz, CD$_3$OD) δ 159.1, 153.1, 138.9, 128.3, 127.9, 113.9, 102.7, 60.5, 55.8, 54.9, 50.4; MS (ESI) *m/z* 394.2 (M+Na)$^+$; Mp = 132-135°C. C$_{18}$H$_{21}$N$_5$O$_4$.
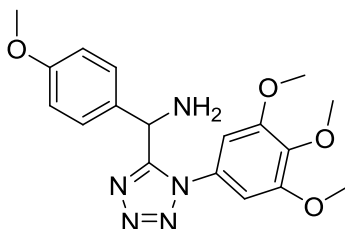
biphenyl-4-yl(1-(4-phenoxyphenyl)-1*H*-tetrazol-5-yl)methanamine (53). White solid (95 %). IR (KBr) 3420, 3330, 2852, 1588, 1240, 1166, 1008, 758 cm-1; 1H-NMR (300 MHz, CD$_3$OD) δ 7.64-7.56 (m, 3-H), 7.47-7.14 (m, 8-H), 6.99-6.94 (m, 3-H), 6.12 (s, 1-H); 13C-NMR (75 MHz, CD$_3$OD) δ 159.9, 155.8, 152.8, 143.4, 139.4, 130.4, 129.9, 129.1, 128.8, 127.9, 127.7, 127.2, 126.7, 124.4, 119.4, 118.5, 49.8, 48.5; MS (ESI) *m/z* 420 (M+H)$^+$; Mp = 234-236°C. C$_{26}$H$_{21}$N$_5$O.
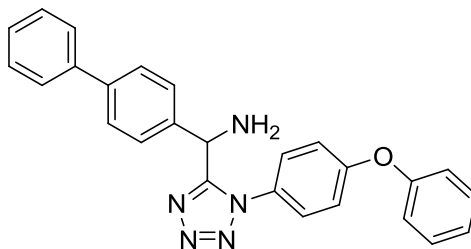
(1-(benzo[d][1,3]dioxol-5-yl)-1*H*-tetrazol-5-yl)(3,4,5,-trimethoxyphenyl)methanamine (54) White solid (93 %). IR (KBr) 3323, 3280, 2901, 1425, 1463, 1252, 1119, 1002, 860 cm^{-1}; 1H-NMR (300 MHz, CD$_3$OD) δ 6.90 (d, *J* = 9 Hz 1-H), 6.78 (dd, *Jo,m* = 9Hz,6Hz, 1-H), 6.70 (s, 1-H), 6.46 (s, 2-H), 6.06 (s, 2-H), 5.41 (s, 1-H), 3.71 (s, 6-H), 3.68 (s, 3-H); 13C-NMR (75 MHz, CD$_3$OD) δ 157.6, 153.5, 149.7, 148.5, 138.1, 134.3, 126.9, 120.2, 108.2, 106.8, 104.9, 102.8, 59.9, 55.5, 51.0; Mp = 95-98 °C. MS (ESI) *m/z* 386 (M+H)$^+$; Mp = 234-236°C. C$_{18}$H$_{19}$N$_5$O$_5$.
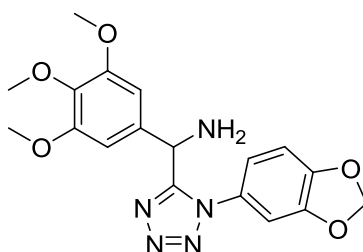
(1-(4-phenoxyphenyl)-1*H*-tetrazol-5-yl)(3,4,5,-trimethoxyphenyl)methanamine (55). White solid (70 %). IR (KBr) 3370, 3280, 2838, 1512, 1462, 1244, 1125, 1009, 839 cm^{-1}; 1H-NMR (300 MHz, CD$_3$OD) δ 7.42-6.98 (m, 9-H), 6.47 (s, 2-H), 5.64 (s, 1-H), 3.69 (s, 6-H), 3.67 (s, 3-H); 13C-NMR (75 MHz, CD$_3$OD) δ 171.7, 159.7, 156.5, 155.8, 153.6, 138.3, 130.1, 127.9, 127.7, 124.6, 119.7, 118.4, 105.1, 60.3, 59.9, 55.5; Mp = 75-79 °C. MS (ESI) *m/z* 434 (M+H)$^+$. C$_{23}$H$_{23}$N$_5$O$_4$.
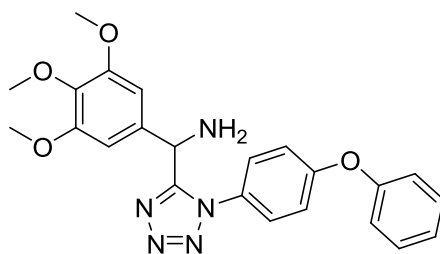
5-(amino(1-(benzo[d][1,3]dioxol-5-yl)-1*H*-tetrazol-5-yl)methyl)-2-methoxyphenol (56)

Dark yellow amorphous solid (68 %). IR (KBr) 3368, 3300, 2602, 1852, 1508, 1256, 1028, 931, 890 cm^{-1}; 1H-NMR (300 MHz, CD$_3$OD) δ 6.89-6.83 (m, 2-H), 6.73-6.59 (m, 4-H), 6.06 (s, 2-H), 5.56 (s, 1-H), 3.80 (s, 3-H); 13C-NMR (75 MHz, CD$_3$OD) δ 155.7, 150.0, 148.9, 148.8, 147.1, 128.0, 126.6, 119.9, 119.5, 114.6, 111.9, 108.3, 106.5, 102.9, 55.4, 50.2; MS (ESI) *m/z* 342 (M+H)$^+$. C$_{16}$H$_{15}$N$_5$O$_4$.
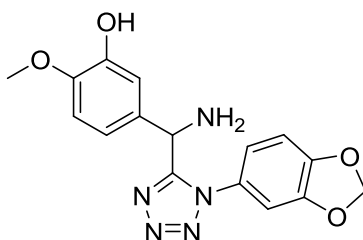
1-(1-(benzo[d][1,3]dioxol-5-yl)-1*H*-tetrazol-5-yl)(4-chlorophenyl)methanamine (57)

Off-white solid (77 %). IR (KBr) 3350, 3255, 2851, 1491, 1225, 1107, 893, 697 cm^{-1}; 1H-NMR (300 MHz, CD$_3$OD) δ 7.41-7.38 (m, 2-H), 7.22-7.26 (m, 2- H), 6.86 (d, *J* = 9 Hz, 1-H), 6.72-6.67 (m, 2-H), 6.05 (s, 2-H), 6.01 (s, 1-H); 13C-NMR (75 MHz, CD$_3$OD) δ 152.9, 150.2, 148.9, 131.8, 130.6, 129.5, 128.6, 126.2, 119.8, 108.3, 106.3, 102.9, 50.0; MS (ESI) *m/z* 330 (M+H)$^+$; Mp = 238-241 °C. C$_{15}$H$_{12}$ClN$_5$O$_2$.
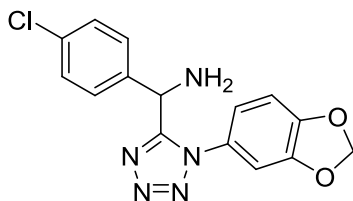
(4-chlorophenyl)(1-phenyl-1*H*-tetrazol-5-yl)-methanamine (58). Off-white solid (77 %). IR (KBr) 3300, 3278, 2853, 1560, 1458, 1258, 1075, 759, 530 cm^{-1}; 1H-NMR (300 MHz, CD$_3$OD) δ 7.59-7.19 (m, 9-H), 5.98 (s, 1-H); 13C-NMR (75 MHz, CD$_3$OD) δ 153.9, 136.4, 133.5, 133.3, 131.5, 130.7, 130.4, 130.3, 129.9, 128.8, 125.8, 50.1; MS (ESI) *m/z* 286 (M+H)$^+$; Mp = 229-232°C. C$_{14}$H$_{12}$ClN$_5$.
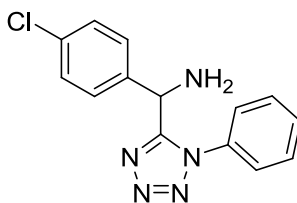
(4-morpholinophenyl)(2-phenyl)-2*H*-tetrazol-5-yl)methanamine (59). Yellowish oil (92 %). IR (KBr) 3367, 3296, 2360, 1515, 1231, 1118, 925, 749 cm^{-1}; 1H-NMR (300 MHz, CD$_3$OD) δ 7.54-7.46 (m, 3-H), 7.27 (d, *J*= 6 Hz, 2-H), 7.02 (d, *J*= 9 Hz, 2-H), 6.81 (d, *J*= 6 Hz, 2-H), 5.46 (s, 1H), 3.73 (t, *J* = 9Hz, 4-H), 3.05 (t, *J* = 9Hz, 4-H); 13C-NMR (75 MHz, CD$_3$OD) δ 157.7, 152.4, 134.1, 131.4, 130.4, 129.0, 126.1, 125.9, 116.4, 67.2, 50.8, 49.3. MS (ESI) *m/z* 337 (M+H)$^+$. C$_{18}$H$_{20}$N$_6$O.
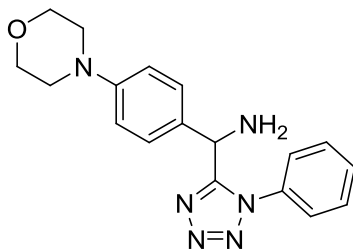
(3-methoxyphenyl)(1-(3,4,5-trimethoxyphenyl)-1*H*-tetrazol-5-yl)methanamine **(60)**.
Dark yellow oil (71 %). IR (KBr) 3376, 3289, 1601, 1463, 1125, 996, 774, 696 cm^{-1}; 1H-
NMR (300 MHz, CD$_3$OD) δ 7.21 (t, *J*= 15 Hz, 1-H), 6.86- 6.74 (m, 3-H), 6.55 (s, 2- H),
5.64 (s, 1H), 3.77 (s, 3-H), 3.70 (s, 9-H); 13C-NMR (75 MHz, CD$_3$OD) δ 160.8, 157.1,
154.3, 140.2, 139.4, 130.8, 129.3, 120.3, 115.0, 114.2, 113.2, 104.4, 60.7, 56.4, 55.3, 51.4;
MS (ESI) *m/z* 372 (M+H)$^{+}$. C$_{18}$H$_{21}$N$_5$O$_4$.
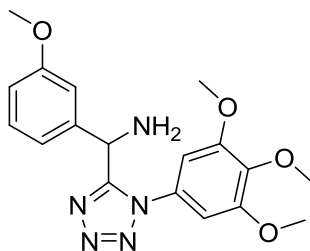
Biphenyl-4-yl(2-phenyl-2*H*-tetrazol-5-yl)methanamine (61). The reaction mixture was
filtered through a Celite pad, evaporated under vacuum and purified by column
chromatography, using petroleum ether/EtOAc 3:7 and then EtOAc as eluant to give a
yellow amorphous solid (60 %). IR (KBr) 3410, 3300, 1617, 1116, 760, 692 cm^{-1}; 1H-
NMR (300 MHz, CD$_3$OD) δ 7.44-7.10 (m, 14-H), 5.36 (s, 1H); 13C-NMR (75 MHz,
CD$_3$OD) δ 158.9, 141.7, 140.8, 139.6, 134.2, 131.3, 130.4, 129.4, 128.1, 127.9, 127.7,
127.4, 126.3, 51.2. MS (ESI) *m/z* 328 (M+H)$^{+}$. C$_{20}$H$_{17}$N$_5$.
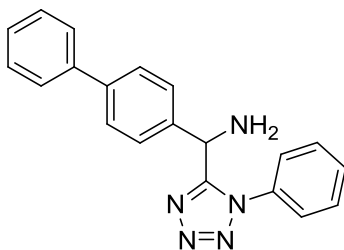
(4-chlorophenyl)(2-(4-morpholinophenyl)-2*H*-tetrazol-5-yl)methanamine (62). Off-white solid (92 %). IR (KBr) 3371, 3290, 2859, 2630, 1523, 1451, 1237, 1126, 926, 697 cm^{-1}; 1H-NMR (300 MHz, CD$_3$OD) δ 7.42-7.34 (m, 2-H), 7.22 (d, *J*= 9 Hz, 2-H), 7.09-7.01 (m, 5-H), 5.98 (s, 1-H), 3.84 (t, *J* = 9Hz, 4-H), 3.24 (t, *J* = 9Hz, 4-H); 13C-NMR (75 MHz, CD$_3$OD) δ 153.6, 152.4, 132.5, 131.3, 130.3, 129.3, 127.2, 125.6, 117.1, 66.9, 50.8, 50.0; Mp= 231-234 °C. MS (ESI) *m/z* 371 (M+H)$^+$. C$_{18}$H$_{19}$ClN$_6$O.
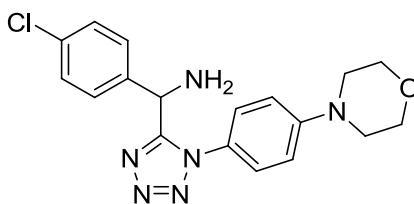
5-(5-(amino(3,4,5-trimethoxyphenyl)methyl)-2*H*-tetrazol-2-yl)-2-methoxyphenol (63). Colourless oil (66 %). IR (KBr) 3400, 3300, 2839, 1507, 1464, 1126, 1017, 904, 867 cm^{-1}; 1H-NMR (300 MHz, CD$_3$OD) δ 7.00 (d, *J*= 9 Hz, 1-H), 6.70 (dd, *J$_{o,m}$* = 12Hz,6Hz, 1-H), 6.60 (s, 1-H), 6.49 (s, 2-H), 5.89 (s, 1-H), 3.90 (s, 3-H), 3.72 (s, 9-H); 13C-NMR (75 MHz, CD$_3$OD) δ 154.6, 153.9, 150.7, 148.1, 140.0, 128.1, 126.3, 117.9, 113.3, 112.3, 106.6, 60.8, 56.3, 51.2; MS (ESI) *m/z* 386.1 (M-H)$^-$; Mp= 138- 140°C. C$_{18}$H$_{21}$N$_5$O$_5$.
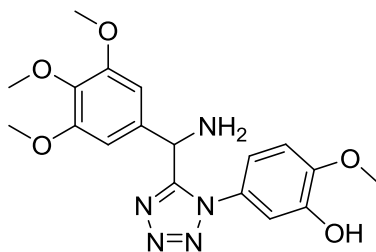
(1-(3-methoxyphenyl)-1*H*-tetrazol-5-yl)(3,4,5-trimethoxyphenyl)methanamine (64). Brownish solid (92 %).IR (KBr) 3370, 3296, 2623, 1599, 1129, 1035, 988, 843 cm^{-1}; 1H-NMR (300 MHz, CD$_3$OD) δ 7.43 (t, *J*= 18 Hz, 1-H), 7.12 (dd, *Jo,m* = 12Hz,6Hz, 1-H), 6.91(d, *J*= 6 Hz, 1-H), 6.77 (s, 1-H), 6.54 (s, 2-H), 6.03 (s, 1-H), 3.75 (s, 3-H), 3.71 (s, 6-H), 3.69 (s, 3-H); 13CNMR (75 MHz, CD$_3$OD) δ 161.6, 154.8, 153.7, 140.2, 134.8, 131.6, 127.9, 118.6, 117.8, 112.2, 106.9, 60.8, 56.5, 56.1, 51.1; Mp= 227-230 °C. MS (ESI) *m/z* 372 (M+H)$^+$; Mp= 138-140°C. C$_{18}$H$_{21}$N$_5$O$_4$.
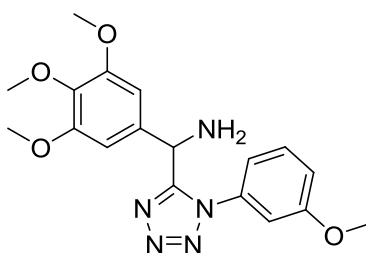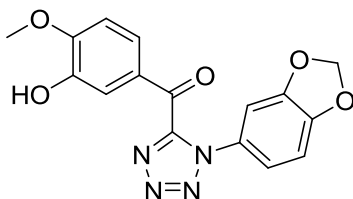

(1-(4-methoxyphenyl)-1*H*-tetrazol-5-yl)(3,4,5-trimethoxyphenyl)methanone (22). The crude material was purified by column chromatography, using petroleum ether/EtOAc 7:3 as eluant to give a yellowish solid (50 %). IR (KBr) 2945, 1655, 1472, 1339, 1133, 833, 775 cm^{-1}; 1H-NMR (300 MHz, CDCl3) δ 7.58 (s, 2-H), 7.40 (d, *J* = 9 Hz, 2-H), 7.01 (d, *J*

= 9 Hz, 2-H), 3.97 (s, 3-H), 3.90 (s, 6-H), 3.86 (s, 3-H); 13C-NMR (75 MHz, CDCl3) δ 179.4, 160.7, 152.8, 149.6, 144.5, 129.1, 126.5, 126.0, 114.2, 108.0, 60.7, 55.9, 55.2; MS (ESI) *m/z* 371 (M+H)⁺; Mp=156-159°C. $C_{18}H_{18}N_4O_5$ (370,1): calcd. C 58.37, H 4.90, N 15.13; found C 58.30, H 5.10, N 15.30.
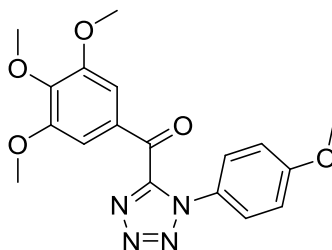
(1-(4-methoxyphenyl)-1*H*-tetrazol-5-yl)(3,4,5-trimethoxyphenyl)methanone (65). The crude material was purified by column chromatography, using petroleum ether/EtOAc 7:3 as eluant to give a yellowish solid (50 %). IR (KBr) 2930, 1600, 1512, 1280, 1173, 1026, 926, 843 cm⁻¹; 1H-NMR (300 MHz, CDCl3) δ 7.58 (s, 2-H), 7.40 (d, *J* = 9 Hz, 2-H), 7.01 (d, *J* = 9 Hz, 2-H), 3.97 (s, 3-H), 3.90 (s, 6-H), 3.86 (s, 3-H); 13C-NMR (75 MHz, CDCl3) δ 179.7, 165.3, 153.2, 149.9, 139.2, 133.0, 129.1, 127.5, 114.1, 102.3, 60.6, 56.0, 55.4; MS (ESI) *m/z* 392 (M+Na)⁺; Mp=134-135 °C. $C_{18}H_{18}N_4O_5$ (370,1): calcd. C 58.37, H 4.90, N 15.13; found C 58.60, H 5.15, N 15.00.
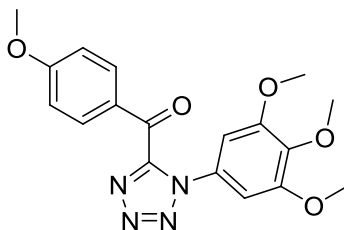
Biphenyl-4-yl(2-(4-phenoxyphenyl)-2*H*-tetrazol-5-yl)methanone **(66).** The crude material was purified by column chromatography, using petroleum ether/EtOAc 7:3 as eluant to give an amorphous orange solid (44 %). IR (KBr) 2860, 1630, 1452, 1121, 1049, 734, 697 cm^{-1}; 1H-NMR (300 MHz, CDCl3) δ 8.33 (d, *J* = 9 Hz, 2-H), 7.76 (d, *J* = 9 Hz, 2-H), 7.65 (d, *J* = 6Hz, 2-H), 7.51-7.37 (m, 5-H), 7.19 (t, *J* = 15Hz, 1-H), 7.08 (d, *J* = 9 Hz, 2-H); 13C-NMR (75 MHz, CDCl3) δ 181.0, 159.8, 155.7, 150.1, 148.3, 139.4, 133.6, 131.7, 130.3, 129.2, 128.9, 128.6, 127.7, 127.5, 126.78, 124.8, 120.2, 118.5. MS (ESI) *m/z* 419 (M+H)$^+$; C$_{26}$H$_{18}$N$_4$O$_2$ (418,1): calcd. C 74.63, H 4.34, N 13.39; found C 74.80, H 4.50, N 13.40.
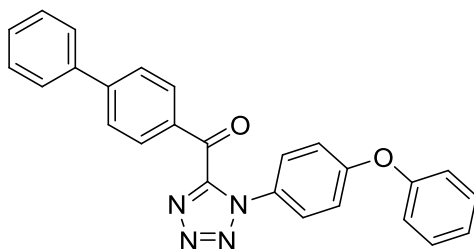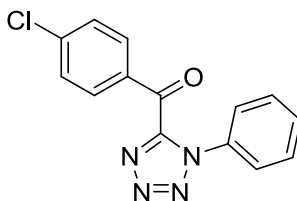

(2-(benzo[d][1,3]dioxol-5-yl)-2*H*-tetrazol-5-yl)(3,4,5,-trimethoxyphenyl)methanone (67). The crude material was purified by column chromatography, using petroleum ether/EtOAc 7:3 as eluant to give a yellowish solid (63 %). IR (KBr) 2894, 1620, 1504, 1474, 1336, 1124, 995, 860 cm^{-1}; 1H-NMR (300 MHz, CDCl$_3$) δ 7.55 (s, 2-H), 6.93-6.88 (m, 3-H), 6.07 (s, 2-H), 3.95 (s, 3-H), 3.89 (s, 6-H); 13C-NMR (75 MHz, CDCl$_3$) δ 179.8, 153.3, 150.1, 149.6, 148.4, 145.0, 129.6, 127.8, 119.3, 108.5, 108.4, 106.4, 102.6, 61.2, 56.4; MS (ESI) *m/z* 385 (M+H)$^+$; Mp = 109- 112 °C. C$_{18}$H$_{16}$N$_4$O$_6$ (384,1): calcd. C 56.25, H 4.20, N 14.58; found C 55.90, H 4.00, N 14.70.
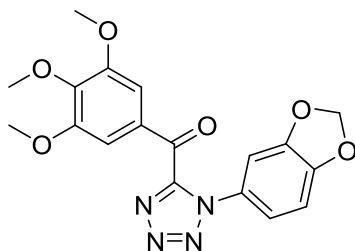
(2-(4-phenoxyphenyl)-2*H*-tetrazol-5-yl)(3,4,5,-trimethoxyphenyl)methanone (68). The crude material was purified by column chromatography, using petroleum ether/EtOAc 8:2 as eluant to give a yellowish solid (50 %). IR (KBr) 2831, 1630, 1507, 1414, 1383, 1244, 1127, 837 cm^{-1}; 1H-NMR (300 MHz, CDCl$_3$) δ 7.59 (s, 2-H), 7.44-7.39 (m, 4-H), 7.18 (t, *J* = 12Hz, 1-H), 7.10-7.05 (m, 4-H), 3.97 (s, 3-H), 3.90 (s, 6-H); 13CNMR (75 MHz, CDCl$_3$) δ 18.00, 159.9, 155.7, 153.4, 150.2, 145.2, 130.4, 129.7, 128.7, 126.8, 124.9, 120.3, 118.5, 108.7, 61.3, 56.6; MS (ESI) *m/z* 433.06 (M+H)$^+$; Mp = 183-185°C. C$_{23}$H$_{20}$N$_4$O$_5$ (432,1): calcd. C 63.88, H 4.66, N 12.96; found C 64.05, H 4.80, N 12.90.
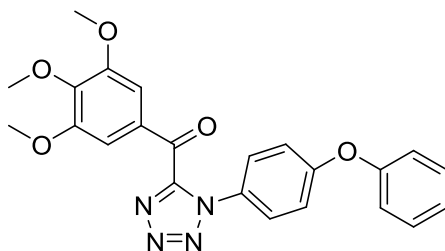
(2-(benzo[d][1,3]dioxol-5-yl)-2*H*-tetrazol-5-yl)(3-hydroxy-4-methoxyphenyl) methanone (69) The crude material was purified by column chromatography, using EtOAc as eluant to give a light yellow solid (46 %). IR (KBr) 1645, 1505, 1282, 1126, 1036, 778 cm^{-1}; 1H-NMR (300 MHz, DMSO-d6) δ 7.68 (d, *J*= 9Hz, 1-H), 7.54 (s, 1-H), 7.27 (s, 1-H), 7.12-7.06 (m, 3-H), 6.16 (s, 2-H), 3.88 (s, 3-H); 13C-NMR (75 MHz,

DMSO-d6) δ 180.5, 155.2, 150.9, 149.7, 148.5, 147.5, 128.3, 128.1, 126.1, 120.3, 116.4, 112,3, 109.0, 107.4, 103.2, 56.7; MS (ESI) *m/z* 339.0 (M-H)⁻ ; Mp = 220- 223 °C. $C_{16}H_{12}N_4O_5$ (340,1): calcd. C 56.47, H 3.55, N 16.46; found C 56.60, H 3.70, N 16.70.

(2-(benzo[d][1,3]dioxol-5-yl)-2*H*-tetrazol-5-yl)(4-chloro-3-methylphenyl)methanone (70). The crude material was purified by column chromatography, using petroleum ether/EtOAc 7:3 as eluant to give a yellow solid (40%). IR (KBr) 2920, 1635, 1471, 1383, 1035, 922, 616 cm-1; 1H-NMR (300 MHz, CDCl₃) δ 8.22 (m, 2-H), 7.71 (t, *J*= 18Hz, 1-H), 7.58-7.52 (m, 2-H), 6.95-6.89 (m, 2-H), 6.09 (s, 2-H); 13C-NMR (75 MHz, CDCl₃) δ 181.7, 149.8, 148.6, 135.7, 135.0, 132.5, 131.1, 129.3, 127.3, 119.6, 108.6, 102.7; Mp = 117-121 °C. MS (ESI) *m/z* 329 (M+H)⁺. $C_{15}H_9ClN_4O_3$ (328,0): calcd. C 54.81, H 2.76, N 17.04; found C 55.00, H 2.90, N 16.90.
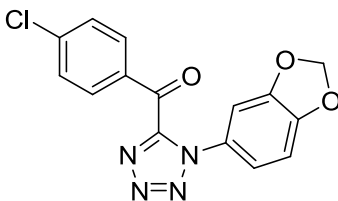
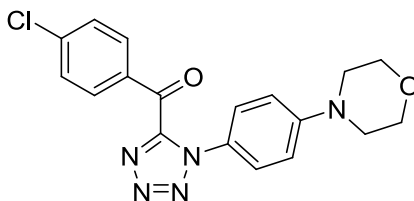**(4-chlorophenyl)(2-phenyl-2*H*-tetrazol-5-yl)methanone (71).** 2,2 eq of 4-formyl-1-methylpyridinium benzenesulfonate were used. The crude material was purified by column

chromatography, using petroleum ether/EtOAc 9:1 as eluant to give a white solid (38 %). IR (KBr) 1675, 1503, 1303, 918, 767 cm^{-1}; 1H-NMR (300 MHz, CDCl$_3$) δ 8.25-8.22 (m, 2-H), 7.70 (t, J= 15Hz, 1-H), 7.57- 7.46 (m, 6-H); 13C-NMR (75 MHz, CDCl$_3$) δ 182.2, 150.6, 136.2, 135.4, 134.8, 133.7, 133.0, 131.6, 131.4, 130.3, 130.1, 129.7, 125.8, 125.6; Mp = 85-87 °C. MS (ESI) m/z 285 (M+H)$^+$. C$_{14}$H$_9$ClN$_4$O (284,0): calcd. C 59.06, H 3.19, N 19.68; found C 59.30, H 3.40, N 19.30.

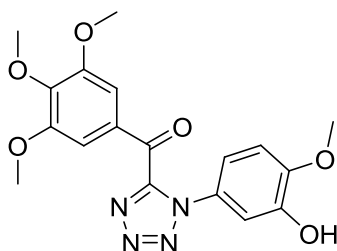
(4-morpholinophenyl)(2-phenyl-2*H*-tetrazol-5-yl)methanone (72). The crude material was purified by column chromatography, using petroleum ether/EtOAc 7:3 as eluant to give a yellow solid (61%). IR (KBr) 1610, 1395, 1250, 1191, 929 cm^{-1}; 1H-NMR (300 MHz, CDCl$_3$) δ 8.09 (d, J= 9Hz, 2-H), 7.51-7.46 (m, 5-H), 6.86 (d, J= 9Hz, 2-H), 3.82 (t, J = 9Hz, 4-H), 3.39 (t, J = 9 Hz, 4-H); 13C-NMR (75 MHz, CDCl$_3$) δ 179.6, 156.3, 151.3, 135.1, 134.2, 131.2, 130.3, 125.7, 125.5, 113.6, 67.2, 47.6; MS (ESI) m/z 336.2 (M+H)$^+$; Mp = 164-167 °C. C$_{18}$H$_{17}$N$_5$O$_2$ (335,1): calcd. C 64.47, H 5.11, N 20.88; found C 64.45, H 5.30, N 20.80.
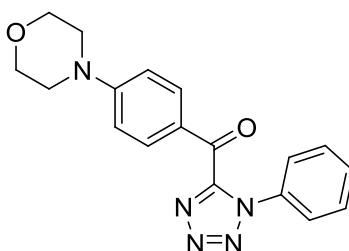
3-methoxyphenyl)(2-(3,4,5-trimethoxyphenyl)-2*H*-tetrazol-5- yl)methanone (73). 2,2 eq of 4-formyl-1-methylpyridinium benzenesulfonate were used. The crude material was purified by column chromatography, using petroleum ether/EtOAc 7:3 as eluant to give a yellow solid (41 %). IR (KBr) 1632, 1506, 1339, 1277, 1127, 942 cm⁻¹; 1H-NMR (300 MHz, CDCl₃) δ 7.73-7.76 (m, 1-H), 7.66 (t, J = 6Hz, 1-H), 7.42 (t, J= 15Hz, 1-H), 7.25-7.05 (m, 1-H), 6.71 (s, 2-H), 3.86 (s, 3-H), 3.84 (s, 3-H), 3.81 (s, 6-H); 13C-NMR (75 MHz, CDCl₃) δ 182.7, 161.1, 154.6, 151.1, 137.0, 131.2, 130.4, 125.0, 123.6, 123.5, 115.0, 103.8, 62.0, 57.5, 56.6; MS (ESI) *m/z* 371 (M+H)⁺ ; Mp = 94-99 °C. $C_{18}H_{18}N_4O_5$ (370,1): calcd. C 58.37, H 4.90, N 15.13; found C 58.45, H 5.10, N 15.13.
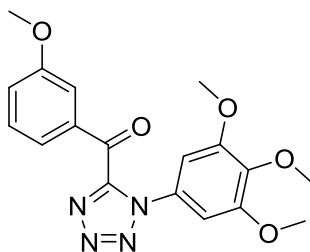
Biphenyl-4-yl(2-phenyl-2*H*-tetrazol-5-yl)methanone (74). The crude material was purified by column chromatography, using petroleum ether/EtOAc 9:1 as eluant to give a white solid (39 %). IR (KBr) 1668, 1600, 1481, 1306, 924 cm⁻¹; 1H-NMR (300 MHz, CDCl₃) δ 8.32 (d, J= 9Hz, 2-H), 8.76 (d, J= 9Hz, 2-H), 7.65 (d, J= 6Hz, 2-H), 7.56-7.43 (m, 8-H); 13C-NMR (75 MHz, CDCl₃) δ 181.7, 150.8, 148.9, 140.0, 134.2, 132.3, 131.7, 131.5, 130.4, 129.9, 129.6, 128.4, 128.2, 125.7; MS (ESI) *m/z* 327 (M+H)⁺ ; Mp = 129-132 °C. $C_{20}H_{14}N_4O$ (326,1): calcd. C 73.61, H 4.32, N 17.17; found C 73.80, H 4.56, N 17.43.
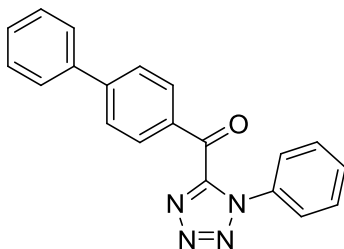
(4-chlorophenyl)(2-(4-morpholinophenyl)-2*H*-tetrazol-5-yl)methanone (75). The crude material was purified by column chromatography, using petroleum ether/EtOAc 6:4 as eluant to give a yellow solid (46 %). IR (KBr) 1640, 1520, 1447, 1303, 1113, 927, 819. cm^{-1}; 1H-NMR (300 MHz, CDCl$_3$) δ 8.21 (d, *J*= 6Hz, 2-H), 7.54 (d, *J*= 6Hz, 2-H), 7.35 (d, *J*= 9Hz, 2-H), 7.93 (d, *J*= 9Hz, 2-H), 3.84 (t, *J* = 9Hz, 4-H), 3.23 (t, *J* = 9 Hz, 4-H); 13CNMR (75 MHz, CDCl$_3$) δ 182.6, 153.3, 150.7, 136.2, 135.7, 131.7, 129.8, 126.89, 126.8, 126.0 115.8, 67.5, 49.0; Mp = 124- 128 °C. MS (ESI) *m/z* 370 (M+H)$^{+}$. C$_{18}$H$_{16}$ClN$_5$O$_2$ (369,1): calcd. C 58.46, H 4.36, N 18.94; found C 57.92, H 4.24, N 19.10.

(2-(3-hydroxy-4-methoxyphenyl)-2*H*-tetrazol-5-yl)(3,4,5-trimethoxyphenyl) methanone (76). The crude material was purified by column chromatography, using petroleum ether/EtOAc 7:3 as eluant to give a yellow solid (46 %). IR (KBr) 1643, 1514, 1255, 1124, 1021, 865 cm^{-1}; 1H-NMR (300 MHz, CDCl$_3$) δ 7.55 (s, 2-H), 7.01 (d, *J*= 3Hz, 1-H), 7.97 (d, *J*= 3Hz, 1-H), 6.94 (s, 1- H), 3.97 (s, 3-H), 3.94 (s, 3-H), 3.89 (s, 6-H); 13C-NMR (75 MHz, CDCl$_3$) δ 181.0, 154.2, 151.0, 149.4, 147.4, 145.9, 130.6, 128.3, 117.8,

112.7, 111.6, 109.4, 62.1, 57.4, 57.2; MS (ESI) *m/z* 385 (M-H)⁻ ; Mp = 166-169 °C. $C_{18}H_{18}N_4O_6$ (386,1): calcd. C 55.96, H 4.70, N 14.50; found C 56.22, H 4.83, N 14.30.

(1-(3-methoxyphenyl)-1*H*-tetrazol-5-yl)(3,4,5-trimethoxyphenyl)methanone (77). 2,2 eq of 4-formyl-1- methylpyridinium benzenesulfonate were used.he crude material was purified by column chromatography, using petroleum ether/EtOAc 6:4 as eluant to give a yellowish amorphous solid (38 %). IR (KBr) 1610, 1578, 1237, 1134, 842, 684 cm⁻¹; 1H-NMR (300 MHz, CDCl₃) δ 7.55 (s, 2-H), 7.40 (t, *J*= 15Hz, 1-H), 7.08- 6.97 (m, 3-H), 3.97 (s, 3-H), 3.89 (s, 3-H), 3.88 (s, 6-H); 13CNMR (75 MHz, CDCl₃) δ 180.9, 161.3, 154.3, 154.2, 151.1, 131.4, 130.5, 118.0, 117.9, 117.5, 109.4, 62.2, 57.5, 57.4, 56.7; MS (ESI) *m/z* 371 (M+H)⁺; $C_{18}H_{18}N_4O_5$ (370,1): calcd. C 58.37, H 4.90, N 15.13; found C 58.62, H 4.95, N 15.30.
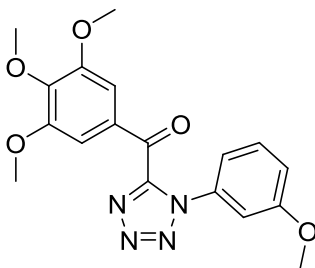
EXPERIMENTAL SECTION

PART II

General informations.

Melting points were recorded using Reichert melting point apparatus. Mass spectra were obtained either from an AEI MS-50 instrument using electron impact ionization (EI), from an AEI MS-9 using electron spray (ES), or from a MALDI-TOF type of instrument for the high resolution mass spectra (HRMS). Proton NMR (1H) spectra were recorded at 300 MHz or at 500 MHz. Carbon NMR (13C) spectra were similarly recorded at 75 MHz on a Bruker AC-300 spectrometer, using a broadband decoupled mode with the multiplicities obtained using a JMOD or DEPT sequence. Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane. NMR experiments were carried out in deuterochloroform ($CDCl_3$). The following abbreviations are used for the multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, brs: broad singlet for proton spectra. Coupling constants (*J*) are reported in Hertz (Hz).

Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer. Flash chromatography was performed using Kieselgel Si 60, 40-63 µm particle sized silica gel (200-400 mesh). Visualization was achieved under a UVP mineralight UVGL-58 lamp, and by developing the plates with phosphomolybdic acid reagent or potassium permanganate ($KMnO_4$). All reagents were obtained from commercial suppliers unless otherwise stated. Where necessary, organic solvents were routinely dried and/or distilled prior to use and stored over molecular sieves under nitrogen. Other solvents were dried by distillation from the following: tetrahydrofuran (sodium/benzophenone); dichloromethane (calcium hydride); toluene (CaH_2). All reactions requiring anhydrous conditions were performed in flame-dried apparatus under a nitrogen atmosphere. Organic extracts were, in general, dried over anhydrous magnesium sulfate ($MgSO_4$) or sodium sulfate (Na_2SO_4).

1,1-bis(5-phenyl-1,3,4-oxadiazol-2-yl)ethanol (31). Procedure: A 50 mL round-bottom flask equipped with a magnetic stir bar and charged with 2-phenyl-1,3,4-oxadiazole (0.03 g,

0.2 mmol) and THF (0.5 mL) are allowed to cool to -78 °C for five min prior to addition of *n*-BuLi (1.6 M solution in hexanes, 0.13 mL, 0.21 mmol). The reaction mixture was allowed to stir at the same temperature for 1.5 h. The acid chloride (0.21 mmol) was added dropwise to the solution. The solution was stirred for additional 2 h. The reaction mixture was poured onto a mixture of AcOEt (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic layer was washed with water (2 x 5 mL), dried, and concentrated *in vacuo*. The resulting residue was purified by silica gel flash column chromatography (2:1 *n*-heptane/ AcOEt) and the organics concentrated *in vacuo* to provide the title compounds. IR: 3211, 2362, 1731, 1558, 1448, 1155 cm^{-1}; 1H-NMR (300 MHz, CDCl$_3$) δ 7.93 (d, *J*= 9 Hz, 4-H), 7.47-7.18 (m, 6-H), 2.23 (s, 2-H); 13C-NMR (75 MHz, CDCl$_3$) δ 166.1, 132.6, 129.4, 127.3, 123.6, 68.3, 25.6. $C_{18}H_{14}N_4O_3$
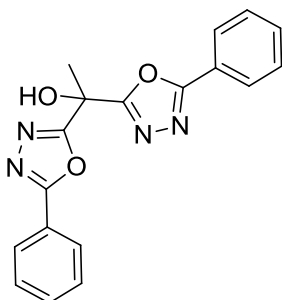
N-(3-isopropylquinazolin-4(3H)-ylidene)propan-2-amine (45). Procedure: To a solution of 2-iodophenyl isocyanide (336 mg, 1.47 mmol) in anhydrous tetrahydrofuran (15 mL), kept in an oven-dried 25 mL- flask under an atmosphere of dry argon, was added dropwise with stirring a 1.35 M solution of *n*BuLi in hexane (1.1 mL, 1.47 mmol) at −78 °C over a period of 5 min. The mixture was stirred at −78 °C for an additional 10 min, then diisopropylcarbodiimide (1.47 mmol) in anhydrous THF (1.47 mL) was added dropwise. The mixture was stirred at −78 °C for 3 h, and the reaction was quenched with saturated NH$_4$Cl solution (1.47 mL). The mixture was warmed to r.t., diluted with AcOEt (35 mL), the organic phase washed with water (2 × 10 mL), brine (20 mL) and dried over anhydrous

Na$_2$SO$_4$. The solvents were removed under reduced pressure to give a crude product, which was purified by flash chromatography on silica gel (2:1 n-heptane/ AcOEt), (14 %). IR: 2963, 2359, 1596, 1471, 1272, 1135 cm^{-1}; 1H-NMR (300 MHz, CDCl$_3$) δ 7.85 (d, J= 8 Hz, 1-H), 7.79 (s, 1-H), 7.27 (d, J= 6 Hz, 2-H), 7.26-7.22 (m, 2-H), 5.15 (m, 1-H), 4.39 (m, 1-H), 1.31 (d, J= 7 Hz, 6-H), 1.21(d, J= 6 Hz, 6-H). C$_{14}$H$_{19}$N$_3$
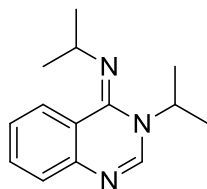
N-(2-butyl-3-isopropylquinazolin-4(3H)-ylidene)propan-2-amine (46). The following product is the second spot isolated from the previous reaction. (7%). IR: 2963, 2359, 1635, 1579, 1556, 1239 cm^{-1}; 1H-NMR (300 MHz, CDCl3) δ 7.67 (d, J= 8 Hz, 1-H), 7.43-7.38 (m, 2-H), 7.17-7.11 (m, 1-H), 4.27-4.23 (m, 1-H), 4.16-4.12 (m, 1-H), 1.57-1.55 (m, 2-H), 1.23-1.05 (m, 19-H); 13C-NMR (75 MHz, CDCl$_3$) δ 146.09, 142.58, 131.19, 127.24, 126.99, 124.51, 120.34, 53.92, 49.03, 24.98, 23.46. C$_{18}$H$_{27}$N$_3$
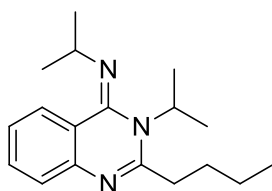
***tert*-butyl(2-(N,N'-diisopropylcarbamimidoyl)phenyl)carbamate (55). Procedure:** The reaction mixture was purified by flash chromatography (9:1 *n*-heptane/ AcOEt, R_f= 0.4) (11 %). IR: 2960, 1631, 1594, 1474, 1241, 1136 cm^{-1}; 1H-NMR (300 MHz, CDCl$_3$) δ 7.38-7.37 (m, 2-H), 7.20-7.15 (m, 2-), 4.55-4.53 (m, NH), 4.04-3.97 (m, 1-H), 1.64 (s, 1-NHBoc), 1.27-1.12 (m, 21-H). C$_{18}$H$_{29}$N$_3$O$_2$
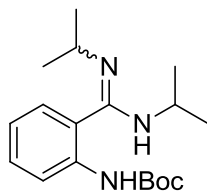
N-(3-isopropyl-2-(trimethylsilyl)quinazolin-4(3H)-ylidene)propan-2-amine (61).
Procedure: A 50 mL round-bottom flask equipped with a magnetic stir bar and charged with **45** (0.05 g, 0.2 mmol) and THF (0.5 mL) are allowed to cool to -78 °C for five min prior to addition of *n*-BuLi (1.35 M solution in hexanes, 0.15 mL, 0.24 mmol). The reaction mixture was allowed to stir at the same temperature for 0.5 h. Trimethylsylil-chloride (0.24 mmol) was added dropwise to the solution. The solution was stirred for additional 0.5 h. The reaction mixture was poured onto a mixture of AcOEt (5 mL) and saturated aqueous NaHCO$_3$ (5 mL). The organic layer was washed with water (2 x 5 mL), dried, and concentrated *in vacuo*. The crude 1H-NMR spectrum is reported (98 % conversion) (300 MHz, CDCl$_3$) δ 7.91-7.88 (m,1-H), 7.54-7.52 (m,1-H), 7.43-7.40 (m,1-H), 7.34-7.29 (m,1-H), 5.18-5.09 (m,1-H), 4.43-4.36 (m,1-H), 1.41 (d, *J*= 7 Hz, 6-H), 1.28 (d, *J*= 6 Hz, 6-H) ; C$_{17}$H$_{27}$N$_3$Si
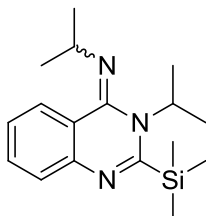
ethyl 4-(benzylamino)but-2-ynoate (10). Procedure: to the N-Boc protected amine (0.2 g, 0.63 mmol) TFA (1.26 mL) was added at 0°C, and the solution was stirred for 0.5h. The reaction mixture was then diluted with DCM (5 mL), and saturated aqueous NaHCO$_3$ (5 mL), and extracted DCM (x3). The organic phases were washed with brine (10 mL) and concentrated *in vacuo*. The reaction mixture was purified by flash chromatography (2:1 *n*-heptane/ AcOEt, R$_f$= 0.4) (52 %). 1H-NMR (300 MHz, CDCl$_3$) δ 7.38-7.27 (m, 5-H), 4.27 (q, *J*= 21.4 Hz, 2-H), 3.90 (s, 2-H), 3.58 (s, 2-H), 1.69 (bs, NH), 1.35 (t, *J*= 14.2 Hz, 3-H). C$_{18}$H$_{23}$NO$_4$.
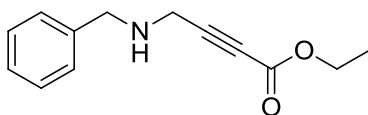
General procedure for the Multi-Component Ugi/Aza-Wittig Reaction (75-77): to a 1mL round-bottom flask the aldehyde (1 eq) was added to a solution of amine (1eq) in *ortho*-dichlorobenzene (*o*-DCB), followed by the carboxylic acid (1 eq), N-isocyanoiminotriphenylphosphorane (0.05 g, 0.165 mmol) and ammonium chloride (1.5 eq). After completion of the reaction, monitored by TLC, the solvent was filtered over silica equilibrated with *n*-heptane; the crude was then eluted with AcOEt, dried *in vacuo* and purified by flash chromatography.
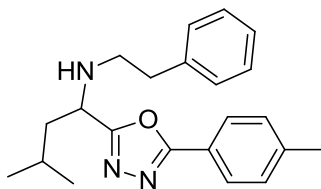
Ethyl 4-(benzyl(3-methyl-1(5-(*p*-tolyl)-1,3,4-oxadiazol-2-yl)butyl)amino)but-2-ynoate (75). The reaction mixture was purified by flash chromatography (9:1 *n*-heptane/ AcOEt, R_f=0.2) (27 %). Yellowish amorphous solid. IR: 2956, 1709, 1498, 1242, 1053 cm^{-1}; 1H-NMR (300 MHz, CDCl$_3$) δ 7.98 (d, *J*= 9 Hz, 2-H), 7.41-7.28 (m, 7-H), 4.33 (t, *J*= 14.9 Hz, 1-H), 4.08 (d, *J*= 13 Hz, 1-H), 4.08 (q, *J*= 21.3 Hz, 2-H), 3.73 (d, *J*= 13 Hz, 1-H), 3.59 (s, 2-H), 2.45 (s, 2-H), 2.07-2.02 (m, 1-H), 1.88-1.80 (m, 2-H), 1.13 (t, *J*= 14.4 Hz, 3-H), 0.99 (d, *J*= 6.2 Hz, 3-H), 0.91(d, *J*= 6.2 Hz, 3-H) ; 13C-NMR (75 MHz, CDCl$_3$) δ 165.27, 164.97, 153.03, 142.15, 137.67, 131.35, 129.69, 129.05, 128.52, 127.58, 126.97, 121.35, 83.37, 61.97, 54.67, 39.37, 39.11, 24.63, 22.81, 21.95, 21.65, 13.79; MS (ESI) *m/z* 446.2 (M+H)$^+$; HRMS: 468.2242 (calc: 468.2263). C$_{27}$H$_{31}$N$_3$O$_3$
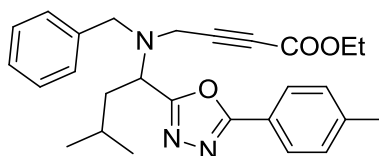
**Ethyl 5-(benzyl(3-methyl-1(5-(*p*-tolyl)-1,3,4-oxadiazol-2-yl)butyl)amino)pent-2-ynoate (76).** The reaction mixture was purified by flash chromatography (4:1 *n*-heptane/ AcOEt, R_f=0.3) (48 %). Yellow amorphous solid. IR: 2924, 1706, 1438, 1254, 1117 cm^{-1}; 1H-NMR (300 MHz, CDCl$_3$) δ 8.03-7.95 (m, 2-H), 7.44-7.27 (m, 7-H), 4.26-4.13 (m, 3-H), 3.97 (d, *J*= 14Hz, 1-H), 3.55 (d, *J*= 14Hz, 1-H), 3.10-3.01 (m, 1-H), 2.74-2.65 (m, 1-H), 2.52-2.44 (m, 2-H), 2.46 (s, 3-H), 2.00-1.75 (m, 3-H), 1.31 (t, *J*= 14Hz, 3-H), 0.93 (d, *J*= 6Hz, 3-H), 0.79 (d, *J*= 6Hz, 3-H) ; 13C-NMR (75 MHz, CDCl$_3$) δ 165.79, 164.96, 153.65, 142.33, 138.64, 130.23, 129.81, 129.19, 128.99, 128.43, 127.39, 126.92, 121.12, 87.30, 74.04, 61.80, 55.57, 53.90, 48.44, 39.61, 24.44, 22.94, 21.82, 21.67, 19.33; MS (ESI) *m/z* 460.2 [M+H]$^+$; HRMS: 483.2463 (calc: 483.2420). C$_{28}$H$_{33}$N$_3$O$_3$
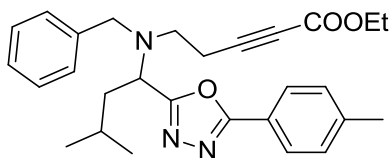
3-methyl-1(5-(*p*-tolyl)-1,3,4-oxadiazol-2-yl)butan-1-ol (77). The reaction mixture was purified by flash chromatography (4:1 *n*-heptane/ AcOEt, R_f=0.4) (37%). Yellowish oil. IR: 2956, 1688, 1612, 1499, 1176, 1138 cm^{-1}; 1H-NMR (300 MHz, CDCl$_3$) δ 8.04-7.95 (m, 2-H), 7.34-7.27 (m, 2-H), 5.14-5.09 (m, 1-H), 2.45 (s, 3-H), 1.99-1.81 (m, 3-H), 1.11-1.01 (m, 6-H); 13C-NMR (75 MHz, CDCl$_3$) δ 170.74, 167.94, 144.30, 142.50, 130.22, 129.77, 129.16, 126.97, 120.82, 64.42, 43.92, 24.37, 23.01, 21.85, 21.66; MS (ESI) *m/z* 247.1 [M+H]$^+$; HRMS: 247.1444 [M+H]$^+$; (calc: 247.1447). C$_{14}$H$_{18}$N$_2$O$_2$
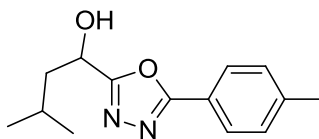
3-methyl-*N*-phenethyl-1-(5-(*p*-tolyl)-1,3,4-oxadiazol-2-yl)butan-1-amine   (87).   The reaction mixture was purified by flash chromatography (7:1 DCM/ AcOEt, R_f=0.3) (74 %). Yellowish oil. IR: 2955, 1610, 1499, 1451, 1259, 1079 cm^{-1}; 1H-NMR (300 MHz, CDCl$_3$) δ 7.82 (d, *J*= 9 Hz, 2-H), 7.23-7.06 (m, 7-H), 4.03 (t, *J*= 15Hz, 1-H), 2.81-2.66 (m, 4-H), 2.35 (s, 3-H), 1.65 (t, *J*= 12 Hz, 1-H), 1.57-1.50 (m, 2-H), 0.86 (d, *J*= 6 Hz, 3-H), 0.80 (d, *J*= 6Hz, 3-H); 13C-NMR (75 MHz, CDCl$_3$) δ 167.79, 164.96, 142.17, 139.42, 129.67, 128.63, 128.47, 126.88, 126.24, 121.17, 52.98, 48.54, 43.16, 36.18, 24.90, 22.45, 22.43; MS (ESI) *m/z* 350.2 [M+H]$^+$; HRMS: 350.2239 (calc: 350.2232). C$_{22}$H$_{27}$N$_3$O

N-(3-methyl-1(5-(*p*-tolyl)-1,3,4-oxadiazol-2-yl)butyl)-N-phenethyl-3-phenylpropiolamide (92). Procedure: TEA (1.5 eq) and 3-phenylpropioloyl chloride (1.3 eq) were added at 0°C to a DCM solution (0.5 mL) of the starting MCR adduct **87** (0.05 mmol). The reaction is stirred for two hours at 0°C. The reaction was then diluted with DCM (2 mL) washed with water (3 mLx2), brine and the organic phase was evaporated under vacuum. The resulting mixture was purified by flash chromatography (4:1 *n*-heptane/ AcOEt, R_f=0.4) (63%). Off-white amorphous solid. IR: 2941, 2206, 1629, 1495, 1405 cm^{-1}; 1H-NMR (300 MHz, CDCl$_3$) 1:1 mixture of rotamers. δ 7.88-7.80 (m, 2-H), 7.55-7.47 (m, 2-H), 7.39-7.30 (m, 3-H), 7.23-7.02 (m, 7-H), [6.12 (t, *J*= 15Hz); 5.91 (t, *J*= 15Hz) 1-H], 3.74-3.67 (m, 1-H), 3.47 (t, *J*= 16Hz, 1-H), 2.91-2.74 (m, 1-H), 2.56-2.47 (m, 1-H), 2.34 (s, 3-H), 2.19-1.91 (m, 2-H), 1.75-1.55 (m, 1-H), 1.02-0.95 (m, 6-H); 13C-NMR (75 MHz, CDCl$_3$) δ 165.57 and 165.54, 164.71 and 164.31, 155.23 and 154.83, 142.73 and 142.59, 138.43 and 137.77, 132.56 and 132.49, 130.43, 129.80 and 129.76, 128.80, 128.66 and 128.53, 127.06 and 127.03, 126.76 and 126.50, 120.69 and 120.58, 120.15 and 120.07, 91.29 and 91.03, 81.75 and 81.24, 53.24, 47.38, 46.92, 44.74, 39.24, 38.79, 36.90, 34.17, 24.76 and 24.47, 22.76 and 22.71, 22.27 and 22.24, 21.65; MS (ESI) *m/z* 478.3 [M+H]$^+$; HRMS: 500.2301 [M+Na]$^+$; (calc: 500.2314). C$_{31}$H$_{31}$N$_3$O$_2$
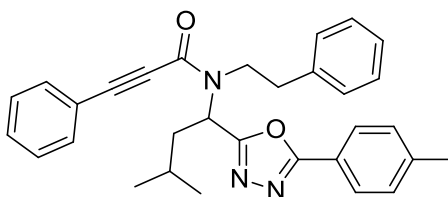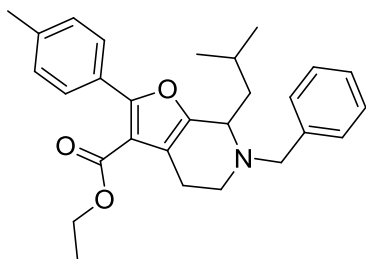
6-isobutyl-5-phenethyl-3-phenyl-2-(*p*-tolyl)-5,6-dihydro-4*H*-furo[2,3-c]pyrrol-4-one (93). Procedure: the starting MCR adduct **92** is dissolved in *o*-DCB (0.1M) and the reaction is stirred at 180°C overnight. The reaction mixture was purified by flash chromatography (9:1 *n*-heptane/ AcOEt, R_f=0.3) (87%). Yellowish amorphous solid. IR: 2925, 1688, 1454, 1352, 1178 cm^{-1}; 1H-NMR (300 MHz, CDCl$_3$) δ 7.64-7.60 (m, 2-H), 7.37-7.33 (m, 2-H), 7.29-7.13 (m, 8-H), 7.09-7.05 (m, 2-H), 4.14-4.01 (m, 2-H), 3.26-3.18 (m, 1-H), 2.90-2.84 (m, 2-H), 2.29 (s, 2-H), 1.90-1.82 (m, 1-H), 1.68-1.37 (m, 3-H), 0.89-0.80 (m, 6-H); 13C-NMR (75 MHz, CDCl$_3$) δ 169.62, 164.66, 154.32, 139.23, 138.54, 130.98, 129.27, 129.21, 128.79, 128.65, 128.44, 128.11, 127.55, 127.27, 126.48, 118.55, 55.56, 42.12, 39.43, 35.45, 24.45, 23.88, 21.84, 21.36; MS (ESI) *m/z* 450.3 [M+H]$^+$; HRMS: 472.2230 [M+Na]$^+$; (calc: 472.2252). C$_{31}$H$_{31}$NO$_2$
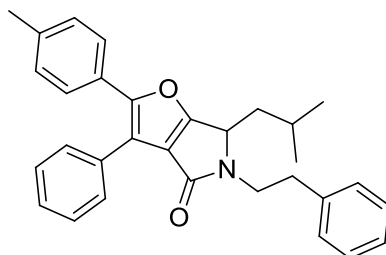
Ethyl 6-benzyl-7-isobutyl-2-(*p*-tolyl)-4,5,6,7-tetrahydrofuro[2,3-c]pyridine-3-carboxylate (79). Procedure: the starting MCR adduct **76** is dissolved in *o*-DCB (0.1M) and the reaction is stirred at 210°C for 28h. The reaction mixture was purified by flash chromatography (4:1 *n*-heptane/ AcOEt, R_f=0.3) (16%). 1H-NMR (300 MHz, CDCl$_3$) δ 7.78 (d, *J*= 8 Hz, 2-H), 7.41-7.22 (m, 7-H), 4.30 (q, *J*= 22 Hz, 2-H), 3.74 (s, 2-H), 3.63 (t, *J*= 13 Hz, 1-H), 3.15-3.05 (m, 2-H), 2.89-2.86 (m, 2-H), 2.63-2.56 (m, 2-H), 2.40 (s, 3-H), 1.96-1.87 (m, 1-H), 1.68-1.53 (m, 2-H), 1.34 (t, *J*= 14 Hz, 3-H), 0.93 (d, *J*= 6 Hz, 3-H), 0.76 (d, *J*= 6 Hz, 3-H). C$_{28}$H$_{33}$NO$_3$

Acknowledgements