Synthesis of Functionalized Heterocycles *via* Pd-Catalyzed Aminocarbonylation using $Mo(CO)_6$ as Alternative CO-Source and Tandem Cyclisation-Condensation to access Dihydroquinazolinones

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Ich habe eine Dissertation zum Thema

“Synthesis of Functionalized Heterocycles *via* Pd-Catalyzed Aminocarbonylation using Mo(CO)$_6$ as Alternative CO-Source and Tandem Cyclisation-Condensation to access Dihydroquinazolinones”

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Abstract

The aim of this work was the development of synthetical strategies for the convenient access of heterocyclic building blocks. First, Pd-catalyzed aminocarbonylative cross coupling reactions were developed to obtain amide scaffolds. These syntheses were performed with the use of molybdenum hexacarbonyl as alternative CO source to avoid the application of gaseous carbon monoxide. The second part of the work focused on tandem condensation-cyclisation reactions of 2-amino-benzonitriles with aldehydes to give access to 1,2-dihydroquinazolinones. The condensation-cyclisation was furthermore performed using 2-amino-benzothioamides to allow for the synthesis of 1,2-dihydro-quinazolinthiones.

Abstract

Das Ziel dieser Arbeit war die Entwicklung praktischer Strategien für die Synthese von heterozyklischen Buildingblocks. Zunächst lag der Fokus auf der Entwicklung Pd-katalysierter aminocarbonylierneder Kreuzkupplungsreaktionen zur Synthese von Amiden. Die Reaktionen wurden unter Einsatz von Molybdänhexacarbonyl als alternative CO-Quelle zu gasförmigen Kohlenmonoxid durchgeführt. Der zweite Teil der Arbeit galt tandem kondensation-zyklisieruns Reaktionen von 2-Amino-benzonitrilen mit Aldehyden zur Synthese von 1,2-Dihydrochinazolinonen. Die Tandemreaktionen wurden weiterhin ausgehend von 2-Aminobenzothioamiden durchgeführt, um 1,2-Dihydrochinazolinthione zu erhalten.

Contents

Index of Abbreviations

Ar	arylgroup
Bn	benzylgroup
Bu	butylgroup
n-BuPAd$_2$	di(adamantly)-*n*-butylphosphine
Bz	benzoylgroup
Cy	cyclohexylgroup
CNS	central nervous system
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DMF	*N*,*N*-dimethylformamide
EDG	electron donating group
eq.	equivalents
EI	electron ionization
ESI	electron spray ionization
Et	ethylgroup
EWG	electron withdrawing group
FGI	functional group interchange
fig.	figure
GC	gaschromatography
h	hours
IC$_{50}$	half maximal inhibitory concentration
IR	infrared

L	ligand
m	*meta*
Me	methylgroup
Mp.	melting point
MS	mass spectroscopy
NMR	nuclear magnetic resonance
o	*ortho*
OMe	methoxygroup
p	*para*
Ph	phenylgroup
py	pyridylgroup
R	rest
R-M	metal organyl
rt	room temperature
R-X	organo halide
TBHP	*tert*-butyl hydroperoxide
TLC	thin layer chromatography
UHP	urea hydroperoxide adduct

NMR-abbreviations:

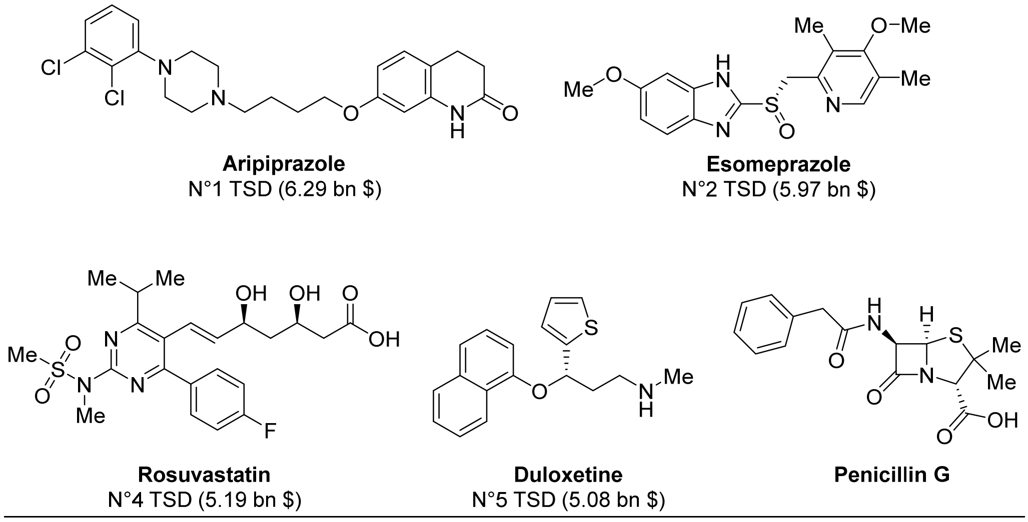
COSY	correlated spectroscopy
HMBC	heteronuclear multiple bond correlation
HSQC	heteronuclear multiple quantum correlation

NOESY	nuclear overhauser enhanced spectroscopy
ppm	parts per million
s	singlet
d	doublet
t	triplet
m	multiplet
J	coupling constant
δ	chemical shift

> *"I have been frequently asked why I invented the name "Penicillin". I simply followed perfectly orthodox lines and coined a word which explained that the substance penicillin was derived from a plant of the genus P*ENICILLIUM *[...]"*
>
> −Sir Alexander Fleming in his Nobel lecture, 1945

1. Introduction

The ability and the affinity of carbon to form stable chains and complex ring systems, involving "inorganic" elements to form functional groups such as exemplarily penicillin, discovered by Sir Alexander Fleming, introducing the “age of antibiotics”. Hydrocarbons are the base of a vast range of manifold organic compounds which led ultimately to life and its complex biochemical processes. Heterocycles play a superior role in metabolic action, the development of pharmaceuticals and in the design of new materials. It is therefore hardly surprising that four of the five top-selling drugs (TSD) in the US in 2013 are heterocyclic scaffolds with a seemingly astonishing low complexity (fig. 1)[i].[1]



Aripiprazole
N°1 TSD (6.29 bn $)

Esomeprazole
N°2 TSD (5.97 bn $)

Rosuvastatin
N°4 TSD (5.19 bn $)

Duloxetine
N°5 TSD (5.08 bn $)

Penicillin G

Figure 1: Top selling drugs in the US (2013) and structure of penicillin G.

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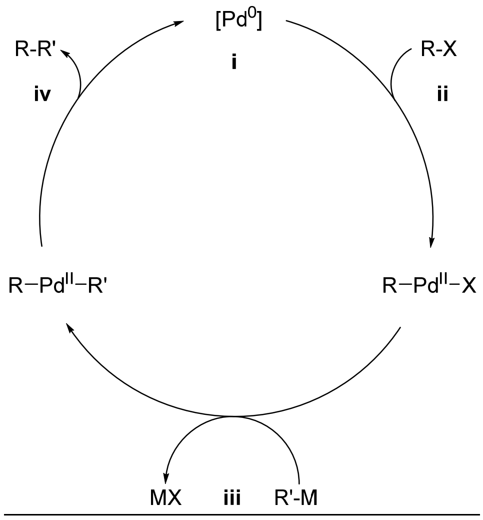
[i] N°3, adalimurab, is a human antibody, which can be regarded as a more complex scaffold

Owing to the importance of heterocycles, big efforts are made to develop new synthetical methodologies for the convenient access of these scaffolds in lab scale and industrial processes. Catalysis plays a big role in synthesis of heterocycles. The use of catalysts benefits a decrease of the reaction energy and a high atom economy, since the catalyst loading is usually in the range of some few mol% of the substrates. Artificial or naturally occurring catalysts, depending from the choice of the catalyst, allow for high functional group selectivity. Furthermore, many efforts have been made in the last decades in the field of ligand design and in developing new catalytical systems, resulting in a broad library of applications. The importance of the research in the field of catalysis has been acknowledged by the Nobel-Prize committee. From 1901 until 2014, 15 Nobel Prizes have been awarded in the field of chemical and enzymatical catalysis, lately for Richard Heck, Ei-Ichi Negishi and Akira Suzuki in 2010, honoring their work in the field of homogenous catalysis.

One of the most important protocols for homogeneous catalysis is using palladium complexes as catalysts. Palladium has been shown appropriate for a wide range of different catalytical cross-coupling reactions of haloarenes, such as the HECK-, SUZUKI-, BUCHWALD-HARTWIG-, SONOGASHIRA- or STILLE-coupling. Depending on the choice of ligand, many different substrates can be used in this still growing field.[2]



Scheme 1: Simplified mechanism for homogeneous cross coupling; ligands not shown

Scheme 1 displays a general overview of the catalytic circular process for Pd-catalysis. The Pd^0 species, frequently *in situ* formed by the reaction of a Pd precatalyst and a reductive (**i**), such as a posphine, forms a palladium(II)-aryl complex *via* oxidative addition of the aryl halide species (**ii**). The next step is the ligand exchange of the halide by the coupling partner *via* transmetallation[i] (**iii**). Finally, the product forms *via* reductive elimination and the palladium-catalyst is regenerated, whereas the cycle may start over again (**iv**). The reactivity differs for the aryl halides whereas iodides are the most reactive and fluorides are the least. However, the reactivity may be altered by different substituents attached on the aryl halide. For unreactive haloarenes, such as aryl chlorides, the rate determining step is usually the oxidative addition, whereas the rate of reaction for reactive iodides, is limited by the transmetallation.[3]

Furthermore, an interesting application for transition metal catalyzed coupling reactions is the three-component coupling, using carbon monoxide or its derivatives as C1 building block, introducing an additional functionality into the coupling product. The first part of this work concerns with palladium catalyzed carbonylative cross coupling for the easy access of functionalized hetero organyls. Pd-catalyzed carbonylations is a complex topic and will be discussed more detailed in the next chapter.

Another important approach to synthesize complex hydrocarbon scaffolds are tandem- or domino reactions. This concept is based on the *in situ* formation of a highly reactive species from a precursor, which subsequently undergoes a series of intra- or intermolecular reactions, leading to the assembly of complex polycyclic organic structures. The principle benefits usually from a high atom economy, fast reaction speed and the avoidance of the isolation and purification of the intermediates. Domino reactions contain usually a cascade of cyclisation- or addition reactions, frequently combined with transition metal catalysis. Cascade reactions are a powerful tool in the synthesis of poly-(hetero)cycles, hence this reaction type is extensively used in biochemical processes.[4]

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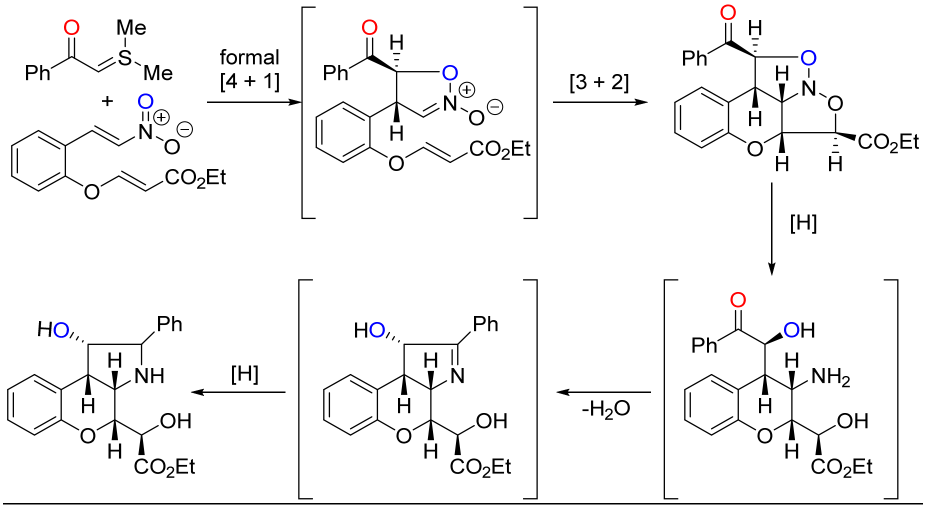
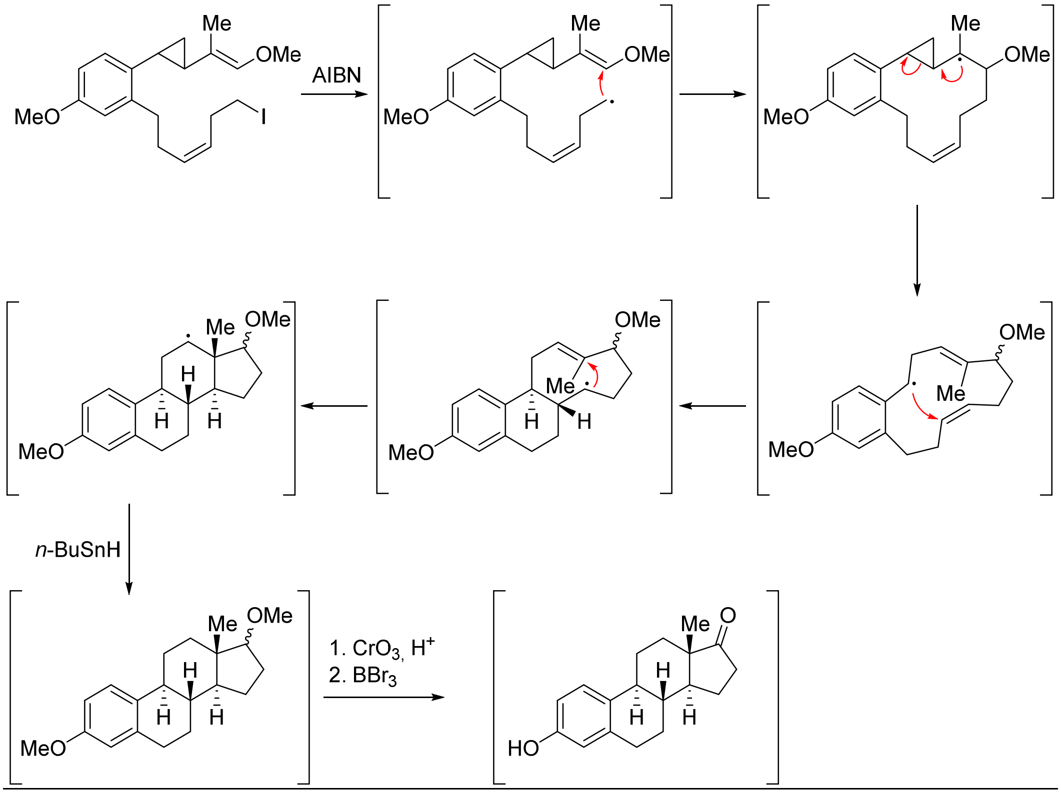
[i] For the HECK-reaction, no actual transmetallation takes part but the formation of a Pd-alkene π-complex. The BUCHWALD-HARTWIG reaction uses alkoxides for transmetallation, which are subsequently exchanged by the nucleophile amine.

One example among many is the synthesis of chromanes, which can easily be performed by the Michael-addition of a sulfur ylide and a nitro olefin with subsequently a formal [4+1]/[3+2] cascade, followed by Raney Ni assisted hydrogenolysis, as given in scheme 2.[5]



Scheme 2: Cascade reaction to access chromanes



Scheme 3: Overview for the radical cascade cyclisation pathway for the synthesis of (±)-estrone

Furthermore, domino reactions are a tool often used in total synthesis of complex natural compounds. A prominent example is the (±)-estrone cascade synthesis. Funk and Volhardt reported about a domino estrone synthesis from bis(trimethylsilyl)acetylene and a diyne under cobalt-catalysis.[6]

Another interesting approach has been realized by Pattenden and coworkers in 2004 using a radical cascade for the diastereoselective formation of (±)-estrone (scheme 3). However, the cascade suffers from a relatively low yield in the formation of the makrocycle due to the reaction with the *n*-Bu_3SnH and formation of the hydrocarbon out of the iodide. But when the initial step of the reaction proceeded, the cascade unhampered proceeds to the tetracycle.[7]

These examples show representatively the significance and the possible simplification for the synthesis of polycyclic structures *via* domino reactions. However, a general overview for tandem-reactions is hard to give, since every single synthetic problem requires detailed consideration of the target structure and retrosynthetic analysis.

The second chapter of this work focuses on the imine-condensation of amines with aldehydes followed by a cyclisation to form dihydroquinazolinone scaffolds in an easy one pot manner. Furthermore, the protocol can be extended for the synthesis of the corresponding thiones, which additionally have used as building-block for further derivatization *via* sulfur extrusion reactions.

2. Carbon Monoxide-Free Pd-Catalyzed Amino carbonylation

2.1. Three Component Carbonylative Pd-Catalyzed Coupling Reactions

2.1.1. Coupling in the Presence of CO

Carbonylative cross coupling reactions are an important and versatile method for the direct functionalization and chain elongation of organic compounds. In the 1970's, Richard Heck (who is widely known for the coupling of aryl iodides and styrenes, the Heck-reaction) and co-workers reported about their seminal work on palladium-catalyzed carbonylative coupling reactions (fig. 2). This reaction is nowadays known as the so called Heck-carbonylation.[8]

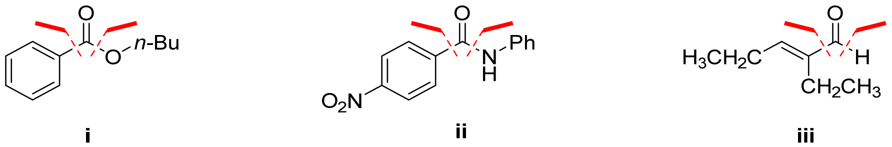
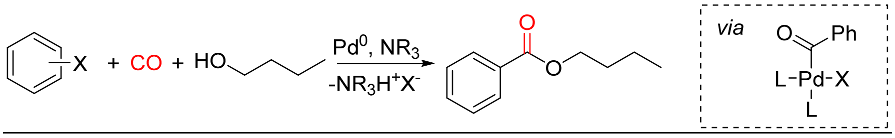


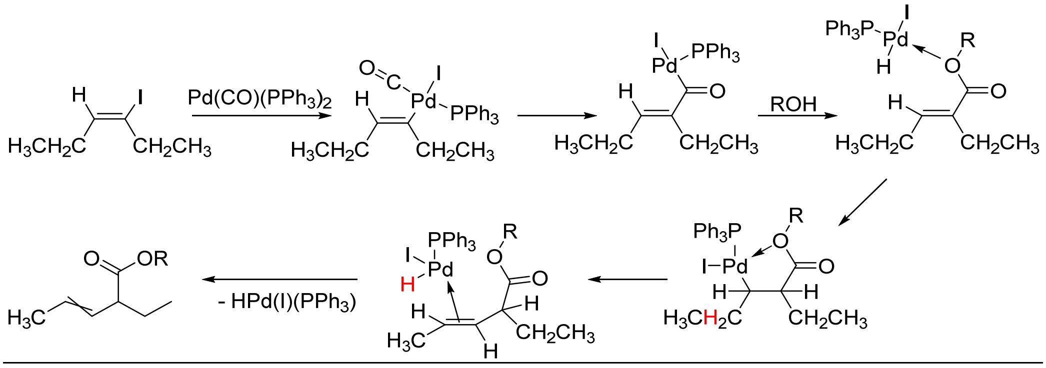
Figure 2: Alkoxylation- (**i**), amidation- (**ii**) and formylation- (**iii**) products by Heck-carbonylation

Heck and Schönberg assumed for the mechanism a reaction of organopalladium complexes with carbon monoxide to form an acyl species. This acyl may subsequently undergo either elimination to form the acyl halide or furthermore react with alcohols to form esters and a Pd-hydride complex which may undergo reductive elimination to reform the catalytical active species. Initial experiments showed the reaction of different C(sp^2)-X-moieties (aromatic and vinylic) with *n*-butanol in the presence of CO (scheme 4). The reaction of aryl iodides already was catalyzed by $Pd(OAc)_2$ but bromides did not react unless they were activated with strong electron withdrawing substituents. Using dihalo bis(triphenyl-phosphine)palladium(II) as precatalyst or adding PPh_3 to the $Pd(OAc)_2$ enabled the reaction of unactivated aryl bromides. Notably, the addition of phosphine ligands decreased the reaction rate of iodobenzene but raised the rate for bromobenzene. Electron withdrawing groups attached to the Ar-X moiety showed generally a higher reactivity.



Scheme 4: Reaction scheme for the butoxycarbonylation by Heck

The $PdX_2(PPh_3)_2$-catalyzed reaction of vinyl halides showed considerable stereospecifity at 60°C - 80°C. (*E*)-2-Iodo-hex-4-ene gave 74 % of the (*E*)-product and 6 % (*Z*)-isomer. Interestingly, they also reported on the formation of the 4-hexene-3-carboxylate *via* the butoxy carbonylation of (*Z*)-2-Iodo-hex-4-ene. This can be explained by the formation of the π-complex *via* exocyclic hydride elimination which gives a noncyclic intermediate without the ring strain of the pentacyclic complex (scheme 5**Scheme 5**).



Scheme 5: Overview for the isomerization in the HECK-carbonylation

Moreover, the group of Heck successfully applied the use of amines[9] for Pd-catalyzed formylations in the presence of H_2-atmosphere.[10] These three-component reactions easily give access to esters, amides and aldehydes, depending on the nucleophile. A major advantage of this reaction type is the easy access and stability of halogenated aromates and vinyl halides and therefore the vast range of target compounds.

Due to the broad spectrum of applications of palladium catalyzed carbonylation, extensive research has been made in the field of CO-insertion. As palladium catalyst precursors, a range of Pd(II)-salts such as $Pd(dba)_2$, $Pd(OAc)_2$ or $Pd(TFA)_2$ showed to be appropriate to form the catalyst *in situ*, but also separately formed catalysts can be applied. Most studies focused on the use of bidentate ligands, e.g. xantphos **i** (fig. 3), (*S*)-BINAP **ii** (fig. 3), dppb **iii** (fig. 3) or ferrocenylphosphines **iv** (fig 3). But also monodentate ligands such as $P(Ph)_3$, PCy_3, or *n*-$BuPAd_2$ **v** (Cata*CX*ium A, fig. 3) showed activity for carbonylation of bromo- and iodoarenes, though monodentate ligands such as *n*-$BuPAd_2$ do not activate chloroarenes for carbonylation.[11]

Milstein *et al*. reported that the initial oxidative addition is the rate limiting step in the carbonylation reactions of aryl chlorides. They studied the influence of an increased electron density on the palladium-atom by using bidentate $(alk)_2P(CH_2)_nP(alk)_2$-type ligands and obtained 89 % *n*-butyl benzoate using $(i\text{-}Pr)_2P(CH_2)_3P(i\text{-}Pr)_2$.[12] Interestingly, the catalytically active species appears to be Pd-complex **vi** (fig. 3) with one bidentate and one monodentate bound ligand.

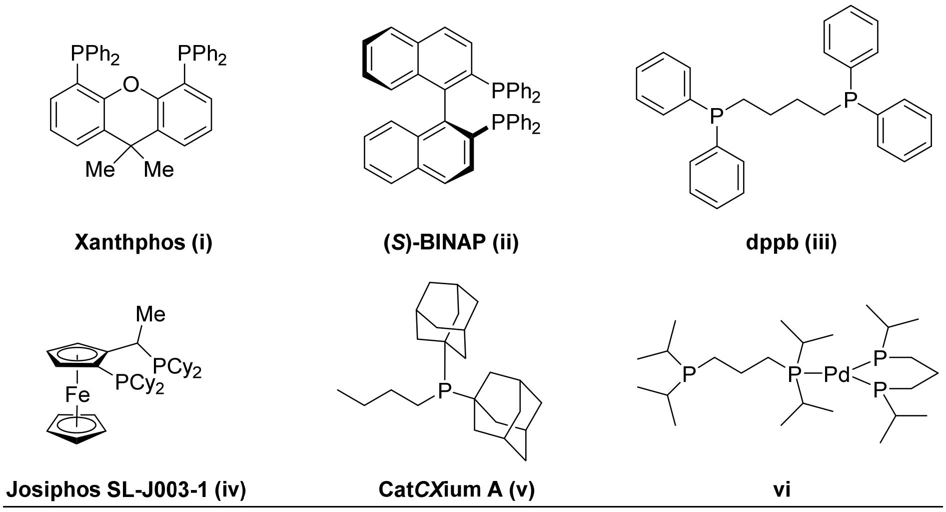
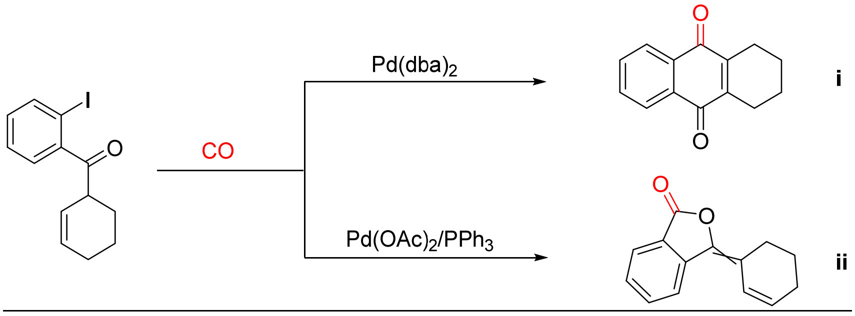


Figure 3: Selected ligands for carbonylative cross coupling reactions

Usually, intramolecular carbonylative coupling (two-component reaction) is more facile than intermolecular carbonylation (three-component reaction). As an example for intramolecular carbonylative coupling reactions, Ei-ichi Negishi *et al.*[13] and

Gagnier/Larock[14] reported on the carbonylative HECK-reaction[i] to form cyclized products. Notably, the outcome of the HECK-reaction of *o*-iodophenyl-cyclohexenyl ketones in the presence of CO depends on the choice of the catalyst. Quinones **i** (scheme 6) were formed in the presence of Pd(dba)$_2$ but when the reaction was performed with a Pd(OAc)$_2$/PPh$_3$ catalyst, isobenzofuranones **ii** (scheme 6) were formed.[15] This shows exemplarily the importance of the choice of the catalyst for these reactions.



Scheme 6: Intramolecular carbonylative HECK-reaction on *o*-iodophenylcyclohexyl ketones

Since the Pd-catalyzed carbonylations allow for the terminal, mid-chain and endocyclic formation of carbonyl groups, many protocols for different carbonylative cross coupling reactions have been established. The field of nucleophiles has been extended to carbon-nucleophiles such as boronic acids[16] or organometallics such as organomercury or aryltin derivatives.[17] Furthermore, protocols for carbonylative HIYAMA-,[18] HECK-,[19] and NEGISHI-reactions,[20] inter- as well as intramolecular, have been developed. Besides, carbonylative SONOGASHIRA-reactions have been reported to access alkynones,[21] which afterwards may undergo cyclisation to access heterocylces, e.g. oxazoles.[22] This methodology is advantageous against the method to synthesize alkynones *via* the cross coupling of acid chlorides and alkynes[23] due to the instability of the acid chlorides and the selectivity of this procedure.

Moreover, many transition metals such as iron, rhodium or iridium show activity for CO insertion reactions and a number of other carbonylative coupling reactions have

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[i] Not to be confused with HECK-carbonylation. The carbonylative HECK-reaction is the carbonylative coupling of aryl halides with alkenes whilst the HECK-carbonylation uses N- or O-nucleophiles.

been developed, but to discuss these reactions in detail would be beyond the scope of this study.

2.1.2. Why Does CO Undergo Carbonylative Coupling?

What gives CO the ability to undergo this insertion into the M-C bond of metal organyls?

Carbon monoxide is not only an interesting C1 building block but also a very special ligand. To understand the mechanism of the Pd catalyzed carbonylation, one has to take a look on metal carbonyls. Nearly all transition metals form carbonyl complexes and mostly in or close to the oxidation state ±0, e.g. $Mo(CO)_6$, $Tc_2(CO)_{10}$, $Ni(CO)_4$ and $Fe(CO)_5$. These complexes are remarkably stable, though CO cannot be considered as a strong LEWIS-base.[24] A prominent example for such a stable complex is the coordination of CO to the central iron atom in the heme B-complex, which leads to a much stronger bond compared to the oxygen complex and is therefore the reason for the high toxicity of carbon monoxide.[25]

The reason to form these steady complexes comes from the ability of the CO-ligand to accept electron density from the central metal atom *via* its π^*-orbitals. Therefore, CO acts as σ-donor but additionally as π-acceptor (fig. 4, **i**). Both effects reinforce themselves synergistically to such a strong bond that by the way of example metallic nickel reacts with CO to form $Ni(CO)_4$ already at moderate temperatures.[26] The M-CO bond length in exemplarily $Re(CH_3)(CO)_5$ is ~200 pm, which is ~24 pm less compared to the M-CO single bond (~224 pm).[27] This double bond character is underpinned by the outcome of the exchange reaction of one CO with a phosphine ligand in $Cr(CO)_6$ and comparing the length of the *trans*-bond of CO-Cr-PR_3. Both ligands compete for the same *d*-orbital of the chromium atom. Due to the fact that CO is the better π-acceptor compared to the phosphine ligand, the axial CO-M bond is shorter compared to the equatorial bonds and shorter compared to $Cr(CO)_6$.[28]

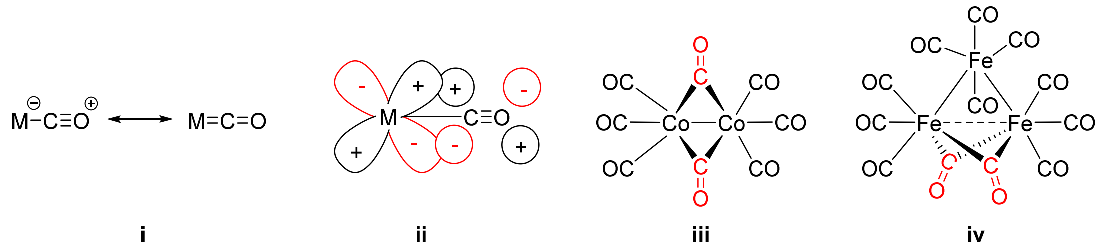


Figure 4: Bonding in metal carbonyl complexes

An additional method to investigate the bonding character in carbonyls is IR-spectroscopy. The non-bonding electron pair of gaseous CO is located in the 3σ-MO (HOMO). When one electron is excited to the nonbonding π*-orbital, the wavenumber decreases drastically from $\tilde{\nu}$ = 2143 cm^{-1} to $\tilde{\nu}$ = 1489 cm^{-1} in free carbon monoxide. This means that a delocalization of electron density leads to a decrease in wavenumbers and this is exactly what can be observed in metal carbonyls (e. g. $Cr(CO)_6$ at $\tilde{\nu}$ = 2000 cm^{-1}, $Mo(CO)_6$ at $\tilde{\nu}$ = 2003 cm^{-1} and $W(CO)_6$ at $\tilde{\nu}$ = 1998 cm^{-1}). CO-ligands are able to take over electron density from the metal atom *via* back donation (fig. 4, **ii**) of the metal *d*-orbital and the CO π*-orbital which leads to a strong double bond character.[29]

Furthermore, the σ-lonepair and the unoccupied π*-orbital allow for the formation of bridged complexes such as $Co_3(\mu_2\text{-}CO)_2(CO)_6$ (fig. 4, **iii**) or $Rh_6(\mu_3\text{-}CO)_4(CO)_{12}$, though in these cases additional M-M-bonds occur, which may lead eventually to multicore carbonyl clusters.[30] An interesting example is iron tetracarbonyl (fig. 4, **iv**) which exists in an trimeric form with two different iron sites and only two bridging carbonyl ligands.[31]Moreover, transition metal carbonyls are able to form hydride complexes, which is crucial for many catalytical processes such as the hydroformylation of alkenes with $Co_2(CO)_8$.[32]

Despite being considered as stable complexes, metal carbonyls can also be decomposed to release carbon monoxide. $Mo(CO)_6$ and $Fe_3(CO)_{12}$ decompose to the metal and CO above 150°C. $Co_2(CO)_8$ and $Ni(CO)_4$ decompose under ambient pressure already at 60°C and 50°C, respectively.[33] In general, it can be said that 18 VE carbonyl complexes are more stable than species with less valence electron shells. This fact is also represented in the formation of multicore carbonyls to form the 18 VE shell. Furthermore, carbonyl ligands can easily be exchanged by other ligands such as PPh_3, sulfur organyls or amines. The reactions of $Mo(CO)_6$ with imidazoline-2-thione[34] and of $W(CO)_6$ with piperidine,[35] each under UV irradiation, show replacement of only one carbonyl group, even if the reaction was carried out with an excess of ligand. Interestingly, when piperidine or pyridine are introduced, the ligand is N bonded to the metal while imidazoline-2-thione and corresponding structures are S bonded. Wannberg and Larhed showed in addition the CO exchange of $Mo(CO)_6$ with 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) at 100°C *via* microwave heating.[36] In this case a $Mo(DBU)_2(CO)_4$ complex is formed.

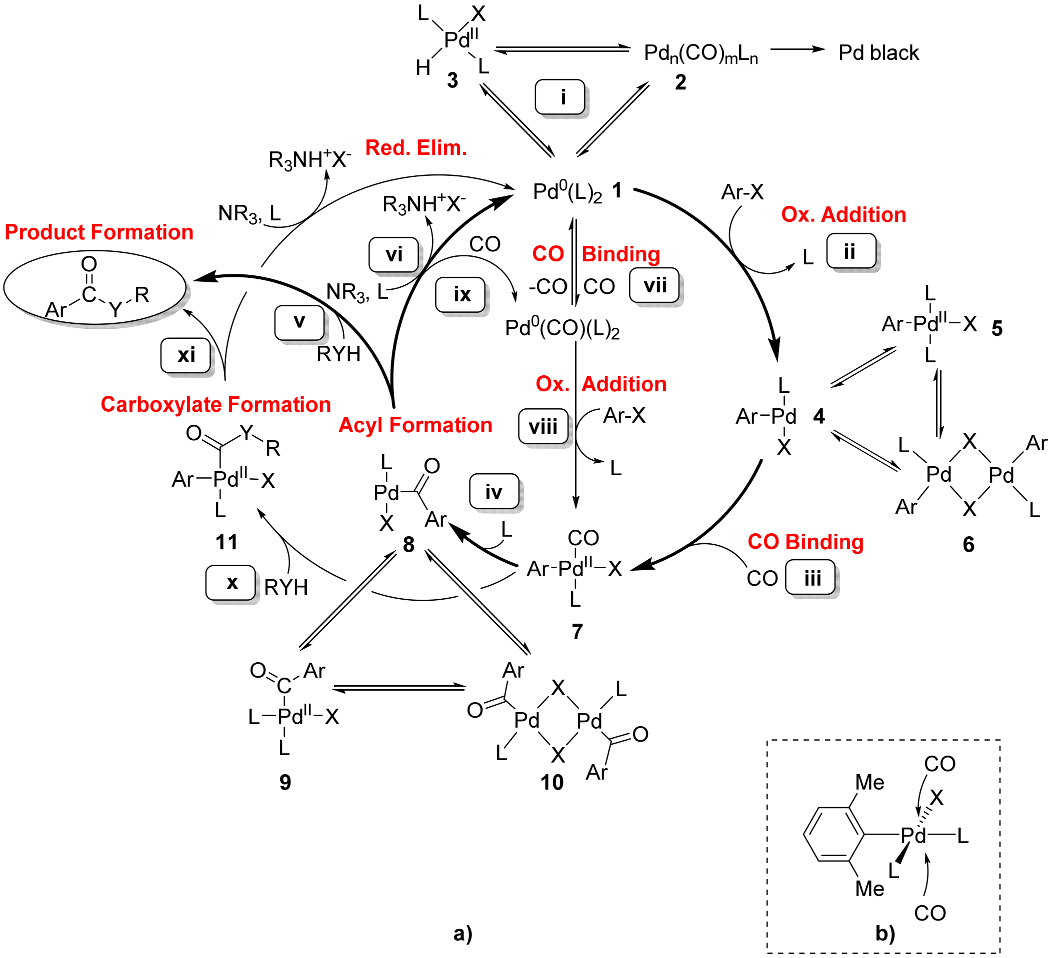
In summary, carbon monoxide is a ligand with extraordinary properties, allowing for a range of different applications.

2.1.3. Mechanistical Considerations on the Pd-Catalyzed Reductive Carbonylation

The general mechanism for the HECK-carbonylation is shown in scheme 7. The assumed catalytical cycle is highlighted in bold. The first step, after formation of the catalyst (**i**), is the oxidative addition (**ii**) to form the Pd-aryl species (**4**), which exists in an equilibrium with the four coordinated complex (**5**) and its dimeric form (**6**).[37] Subsequently, the insertion of the carbonyl ligand (**iii**) into the metal sphere takes place to form (**8**).

Notably, the introduction of the carbonyl ligand is highly sensitive to the sterical properties of the Pd-aryl moiety based on the plane arrangement of the complex. Arenes with steric substituents in *ortho* position to the C-Pd-bond, as given in a *m*-xylene group, hinder the coordination of the CO on the Pd and therefore the activation energy is increased due to the required twisting of the xylene out of the plane (scheme 7, **b**)).[38]

After the binding of the CO ligand, the formation of the acyl species takes place (**iv**). Garrou and Heck investigated the formation of the acyl species and proposed an indirect route with initial formation of a threefold coordinated intermediate (**8**).[39] This intermediate reacts reversibly to the four coordinated complex (**9**) and the *trans*-dimer (**10**) which leads to an equilibrium mixture.[40] Afterwards, the nucleophile R-YH (e.g. alcohols, amines, H_2) attacks the carbonyl carbon to form the final carbonyl product (**v**) and the palladium hydrido complex (**3**). Finally, reductive elimination (**vi**) with base promoted loss of HX regenerate the catalyst.



Scheme 7: Mechanistical overview for the HECK-carbonylation. The assumed pathway is highlighted in bold. **vii** and **viii** show the initially proposed mechanism by Heck. **x** and **xi** show the alternatively proposed pathway by Yamamoto.

In their initial work, Heck and co-workers proposed a mechanism with a Pd(CO)L_2 complex (**vii**) as catalytically active species and an oxidative addition that proceeds after CO binding (**viii**).[8] This pathway would be in agreement with the primal equilibrium (**i**). However, the electron density of the Pd in such a species is heavily reduced due to the back donation of the carbonyl ligand and therefore this complex is in general not active for the crucial oxidative addition of the aryl halide.[41] Hence, the oxidative addition must take place before the CO coordination, especially in the case of aryl bromides. Iodides behave in a different manner due to the much weaker C-I-bond and the known ability of iodide to inhibit Pd-catalyst.

Furthermore, in 1987 Yamamoto *et al.* proposed a different pathway to form the product from the Pd-aryl-carbonyl-complex (**7**). They reported about their investigation on the formation of esters and proposed a premonitory attack on the carbonyl ligand by the alcohol (**x**) to form an intermediate carboxylate complex (**11**) which gives the ester *via* reductive elimination of the aryl group and the carboxylate (**xi**).[42] Their suggestion is based on investigations on the reaction of acyl palladium halide complexes and CO with amines, which lead to α-keto amides.

Another interesting aspect is the formation of the catalyst. The cluster (**2**) and the hydrido complex (**3**) are considered as the source of the [PdL_2] moiety (**1**) which may also dissociate into the highly active [PdL] complex. *In situ* ^{31}P-NMR studies show the existence of **2** and **3** and free *n*-$BuPAd_2$ which indicate that these species are reservoirs for the active Pd complex. This equilibrium retains the concentration of the catalyst at a low level for which the oxidative addition (**ii**) becomes the rate-determining step of the reaction.[40]

2.1.4. Methyl-Migration *versus* CO-Insertion

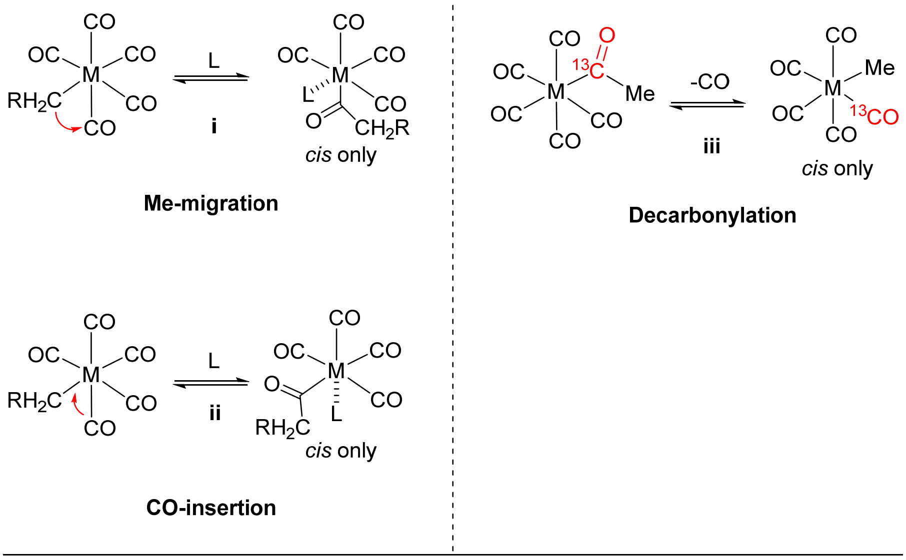
Insertion reactions are widely spread and a good example is the insertion into a covalent bond, the oxidative addition to a metal complex, whereby the coordination number and the oxidative state of the metal increase by two. However, classical insertion reactions preserve both coordination and oxidation number of the metal, as seen in scheme 8. The insertion of CO into a metal alkyl bond is known for decades.[43]

$$\text{R-Mn(CO)}_5 \rightleftharpoons \left[\text{RCO-Mn(CO)}_4\right] \overset{\text{CO}}{\rightleftharpoons} \text{RCO-Mn(CO)}_5$$

Scheme 8: General M-C bond insertion by CO

In 1967, K. Noack and F. Calderazzo reported an interesting study on the mechanistically aspects of this reaction. In general, two different pathways can be assumed: the insertion of the CO into the M-organyl bond (scheme 9, **i**), and the migration of the organyl to the carbonyl ligand (scheme 9, **ii**). Both would lead to an acyl-metal complex.

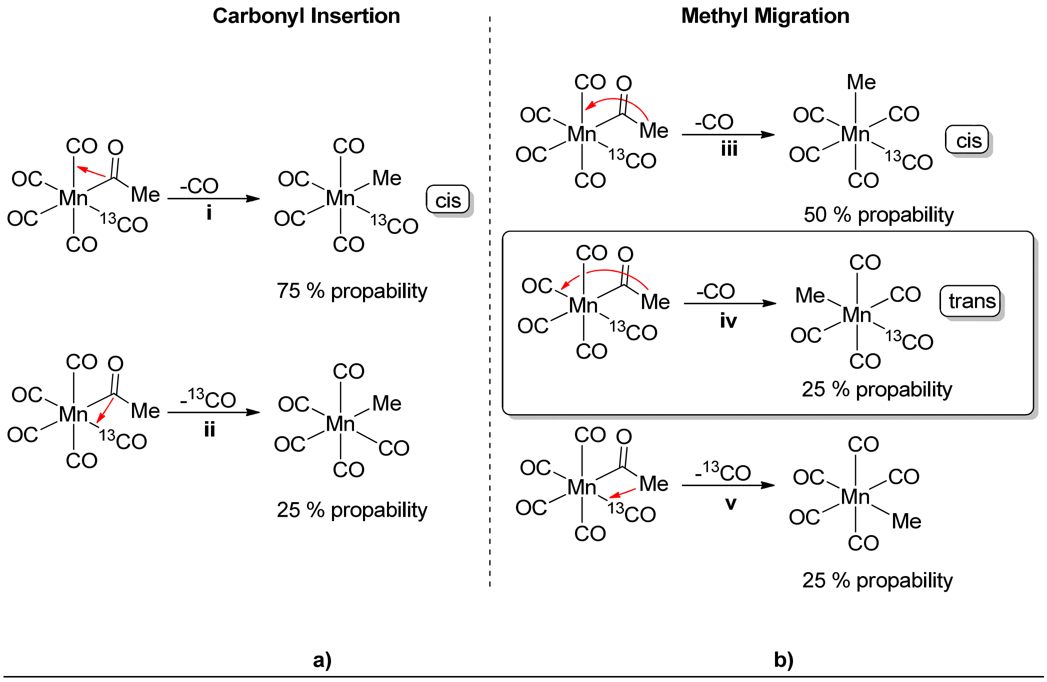
To determine whether insertion or migration takes place, Noack and Calderazzo investigated the outcome of the back reaction of $(MeCO)Mn^{13}CO(CO)_4$ to $Mn(Me)(^{13}CO)(CO)_4$ (scheme 9, **iii**, L = ^{13}CO) due to the fact that the formation of the acyl species will lead to *cis* products in any case (scheme 9 **i**, **ii**). Initially, they have shown that the decarbonylation of a labeled acetyl group containing complex gives *cis*-only products (scheme 9, **iii**). Therefore, both, the insertion and deinsertion, follow the principle of microscopic reversibility and no dissociative pathway takes part.



Scheme 9: Me-migration *versus* CO-insertion

Afterwards, the decarbonylation of the *cis*-^{13}CO acetyl complex was investigated and the *cis-trans* ratio determined. Depending on the mechanism, different ratios can be expected as shown in scheme 10.

Contrary to the Me-migration mechanism, no labeled *trans* complex should be formed when the decarbonylation follows the deinsertion pathway (scheme 10, **a)**). But the formation of the *trans* isomer (scheme 10, **b)**, **iv**) is exactly what could be detected in IR in a 2:1 *cis-trans* ratio. *Vice versa*, a Me-migratory mechanism can be assumed for carbonylative coupling reactions.[44]



Carbonyl Insertion

Methyl Migration

Scheme 10: Overview of the different outcome of the insertion and migration mechanism

2.1.5. Alternative Carbonyl Sources – No Need for Carbon Monoxide Gas

Carbonylative cross coupling has become an important and versatile tool for the lab-scale synthesis of carbonyl compounds and also for industrial scale, albeit the work with gaseous carbon monoxide suffers from several issues. CO gas is toxic and flammable, and its handling, storage and transport demands high requirements in working safety. Thus, several efforts have been made in the search for alternative CO-sources and how to transfer carbonyl groups from such substitutes, whereas only a few will be mentioned here.

A wide field is the use of organic carbonyl compounds and their decarbonylation to generate CO *in situ* and therefore avoid handling of pure carbon monoxide. A group of easy to handle CO precursors are formic acid derivatives. First examples are formates, which are known to decarbonylate fairly easy *via* transition metal catalysis. Sneeden and co-workers showed the ruthenium-catalyzed formation of methyl propionate by the use of ethylene and methyl formate.[45] First, ethylene is carbonylated by CO, which is formed by the decarbonylation of the formate, giving the ester by reaction with the released methanol (fig. 5, **a)**). Additionally, formates can decompose to give carbon monoxide in the presence of strong bases such as sodium ethoxide. Changing to potassium *tert*-butoxide as base led to a violently decarbonylation already at 0°C. Mortreux *et al.* used the NaOEt catalyzed decarbonylation of ethyl formate for the carbonylative coupling of vinyl- and aryl halides at room temperature to obtain esters (fig. 5, **b)**).[46] Furthermore, the decarbonylation of aqueous methyl formate by the catalysis of [Ru$_3$(CO)$_{12}$] and PCy$_3$ and subsequent hydroformylation-hydrogenation of alkenes has been reported (fig. 5, **c)**).[47]

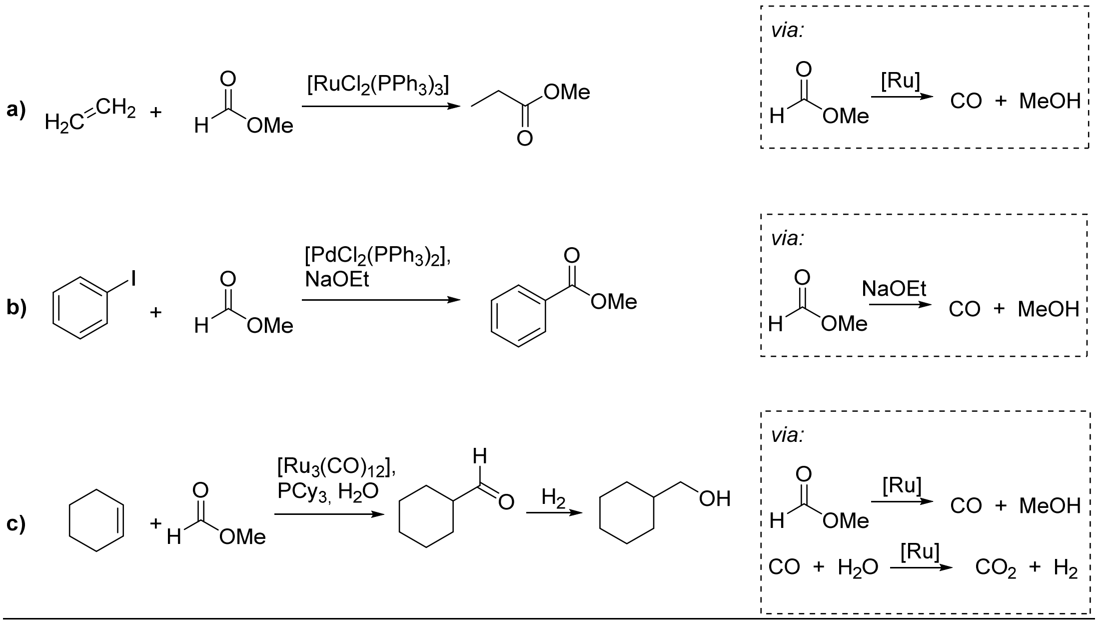
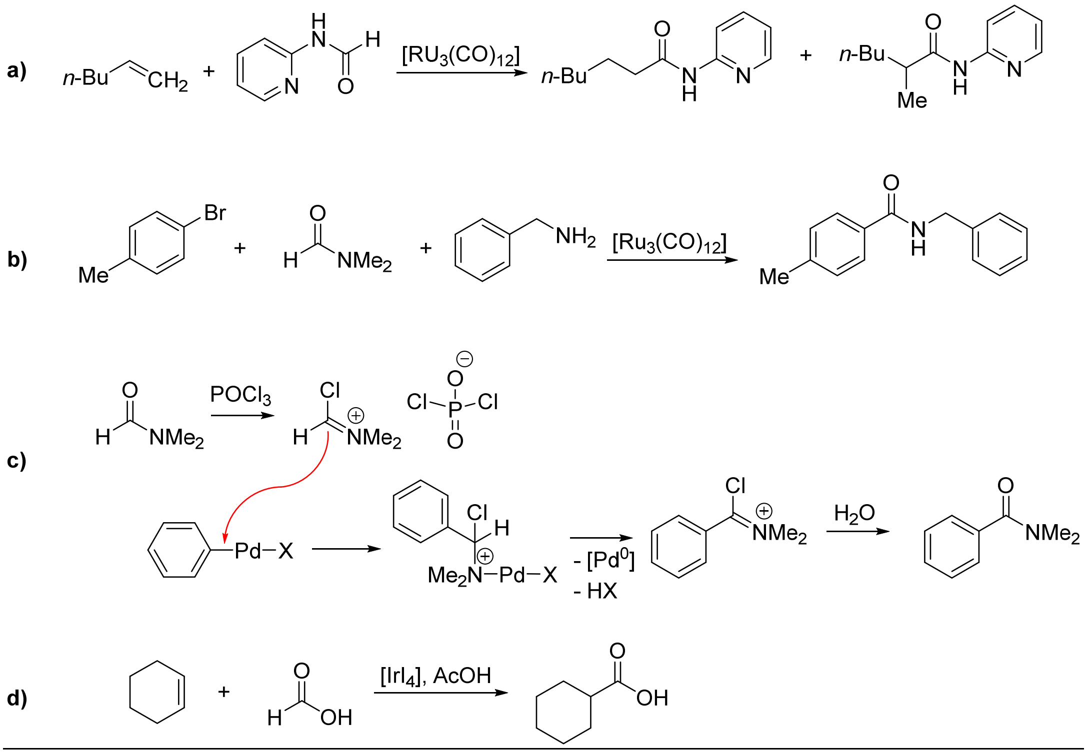


Figure 5: Carbonylation reactions using formates as CO-source

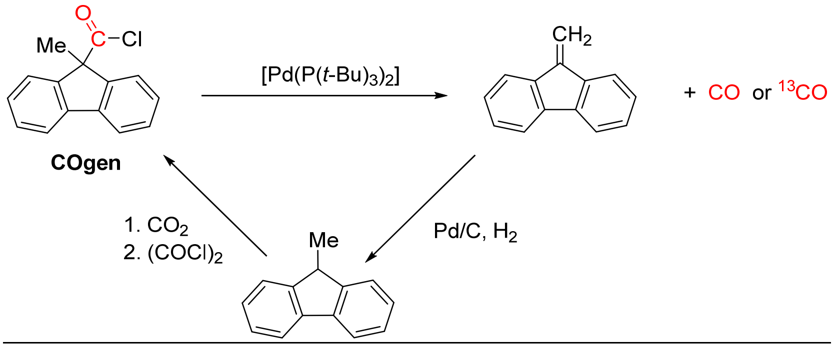
Moreover, formamides can also provide CO for carbonylation reactions. Formamide with an attached pyridyl group, which may undergo coordination onto the metal, gives the hydroamidation product with alkenes under Ru-catalysis (scheme 11, **a)**).[48] The mechanism can be understood analogous to the decarbonylation of formates as mentioned above and gives CO and the corresponding amine. A very convenient CO-precursor is DMF, which may release carbon monoxide in the presence of a strong base such as KO^{t}Bu. An aminocarbonylative procedure using DMF as CO-precursor to obtain amides has been reported by the group of Alterman (scheme 11, **b)**).[49]

In addition, Nozaki *et al.* presented a method to obtain amides using DMF in the presence of $POCl_3$.[50] In this case, no carbon monoxide is formed, but a VILSMEYER-iminium-ion which gives, after insertion into the Ar-Pd bond and β-hydride elimination, the amide (scheme 11, **c)**). Furthermore, formic acid shows the ability to decompose into water and carbon monoxide and therefore is an appropriate source for CO. The carbonylative formation of acids under IrI_4-catalysis using CO gained from the acid catalyzed decomposition of formic acid has been reported by Simonato and co-workers in 2001 (scheme 11, **d)**).[51]



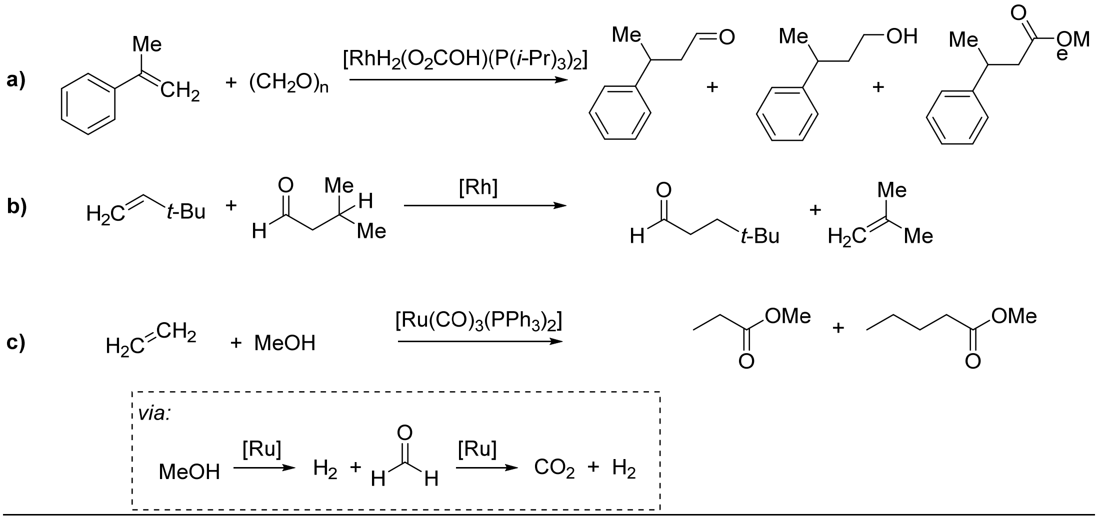
Scheme 11: Amides and formic acid as CO-precursors in carbonylative coupling chemistry

An interesting, easy to handle solid carbon monoxide source has been introduced by the group of Skrydstrup.[52] Ongoing from the Pd-catalyzed decarbonylation of pivalyl chloride, they developed an acid chloride scaffold based on 9-fluorenone, brand named COgen. This moiety provides the advantage of forming a non-volatile byproduct and furthermore an isotope-labeled carbonyl group can be introduced at a late stage of the synthesis by this scaffold. Lastly, this carbonyl source can be easily resynthesized from the produced alkene (scheme 12). Skrydstrup *et al.* showed the application of this compound as appropriate CO source in a two-chamber setup for a range of carbonylative cross-coupling reactions, e.g. the synthesis of diketones.[53]



Scheme 12: Decarbonylation and regeneration of COgen

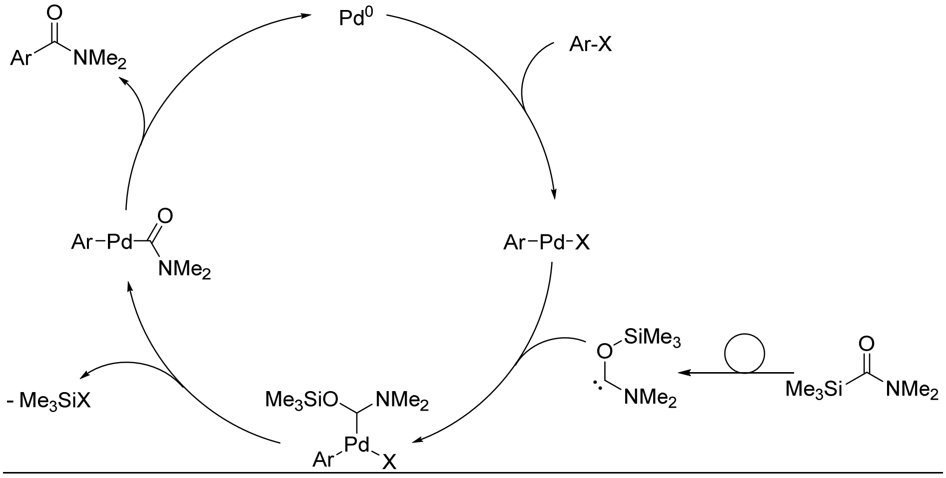
In addition, the transition metal catalyzed decarbonylation of aldehydes has found its way into organic synthesis as well. Formaldehyde can formally be regarded as syn gas (CO/H_2), and the rhodium catalyzed reaction of alkenes in the presence of paraformaldehyde leads to the hydroformylation product (scheme 14, **a)**).[54] This syngas-behavior is also known for *β*-hydrogen containing aldehydes, and Brookhart and Lenges showed the successful hydroformylation of 3,3-dimethyl butene with isovaleraldehyde (scheme 13, **b)**).[55]



Scheme 73: Aldehydes as CO-precursors in carbonylative coupling reactions

Primary alcohols can be used as carbon monoxide source as well, though in this case the alcohol, such as methanol, *a priori* undergoes dehydrogenation to form the aldehyde which subsequently decarbonylates (scheme 13, **c)**).[56]

Other interesting CO-precursors are organo silanes and -stannanes (scheme 14). Cunico and co-workers showed the use of carbamoylsilanes for the Pd-catalyzed formation of amides. Although no transmetallation of the carbamoyl group can be assumed, the suggested mechanism shows the formation of a carbene by dyotropic rearrangement, which subsequently forms a complex with the palladium species. Loss of the silyl halide and reductive elimination form the amide.[57]



Scheme 84: Simplified mechanism for the Pd-catalyzed aminocarbonylation using carbamoylsilane

Lastly, metal carbonyls as described previously play a significant role in the *in situ* generation of CO. They are even more favorable, since the cleavage of a C-C-bond in organo carbonyls requires much more energy compared to the extrusion of a carbonyl ligand. Metal carbonyls represent easy to handle and relatively stable carbonyl sources. As mentioned before, the release of CO can even be promoted by simple ligand exchange reaction with amines such as DBU. A range of protocols has been developed using [Cr(CO)$_6$], [Mo(CO)$_6$] and [W(CO)$_6$] as CO-precursors. Especially the group of Larhed put great effort in investigations on the Pd-catalyzed carbonylative cross coupling.[58]

In conclusion, a range of alternative CO-sources have been reported. Though industrial scale processes may have advantages in the use of gaseous carbon monoxide, the presented alternatives are convenient and easy to handle reagents for the lab-scale synthesis of carbonyl compounds avoiding the hazards by using CO.

2.1.1. Bulky Phosphine Ligands in Pd-Catalyzed Cross Coupling

The choice of ligand has significant influence on the outcome of a transition metal catalyzed reaction. Two different properties of the phosphine influence the reactivity: 1.) the influence on the electron density on the metal atom and 2.) the demand on the steric volume. These properties can be characterized by the Tolman cone angle θ*[59]* (fig. 6, **a)**) and the Tolman electronic parameter. Bidentate ligands are furthermore characterized *via* the bite-angle, which, in the end, influences the electronic- and steric properties of the catalyst. These characteristics in turn have different influence on each single step in the catalytic cycle, promoting and impeding.

In 1989, Osborn stated that significant catalytic activity is on the one hand found only with phosphines which are strongly basic and on the other hand with certain steric bulkiness with a cone angle larger than 160°.[60] Electron rich ligands are usually understood to facilitate oxidative addition. The Pd^0-species can be understood as electron donor and the organo halide as electron acceptor. Therefore, electron rich ligands increase the electron density and promote the oxidation to form a Pd^{II}-species. Furthermore, electron rich ligands are believed to stabilize the Pd^0-species and to prevent the formation of “palladium black”.[61] However, the counterpart of this step, the reductive elimination to form the product and regenerate the catalytic Pd^0-species requires exactly the opposite properties, whereas electron donating ligands impede this step. Transmetallation processes are believed to be less dependent from the electronic effects of the ligand.[62]

The other parameter is the bulkiness of the ligand. In the case of aryl bromides, the oxidative addition may occur *via* two different pathways. The first is the reaction with a PdL_2-species to form the aryl complex by ligand exchange. The other possible pathway which occurs generally for steric bulky ligands is the initial dissociation of the PdL_2-scaffold to form the monophosphine complex, which may subsequently underwent oxidative addition of the bromoarene to form a $[ArPdL_1X]$-complex. Depending on the steric demand of the ligand, one or the other pathway is preferred. It is generally believed, that the PdL_1-species shows the highest activity for the oxidative addition.[3] Therefore, it is strongly evident that the steric demand of the ligand is more important than the electronic properties for the oxidative addition. As one would expect, the reductive elimination is promoted for steric demanding ligands, which comes from liberation of the more strained Pd^{II}-complex. Furthermore, Clarke and Heydt assumed that the transmetallation is favored for less steric complexes.[63]

Based on the higher influence of steric demand comparing to the electronic properties, many efforts have been made to introduce bulky phosphines as ligands for Pd-catalyzed coupling chemistry. Notably, Buchwald *et al.* showed the excellent catalytic properties of steric dicyclohexylphosphino biphenyl ligands, such as SPhos (fig. 6, **b)**) and XPhos. They demonstrated that minor modifications on the ligand may lead to significant differences in the catalytic activity for different substrates. Whereas the exemplarily XPhos shows high activity for the reaction of aryl chlorides with amines, the Buchwald-Hartwig-amination,[64] SPhos gives high yields and TONs for Suzuki-coupling of aryl chlorides[65]. Furthermore, the group of Hartwig developed a procedure for the CH-activated coupling of malonates with aryl bromides and -chlorides using bulky ligands based on ferrocene scaffolds, such as QPhos (fig. 6, **b)**).[66]

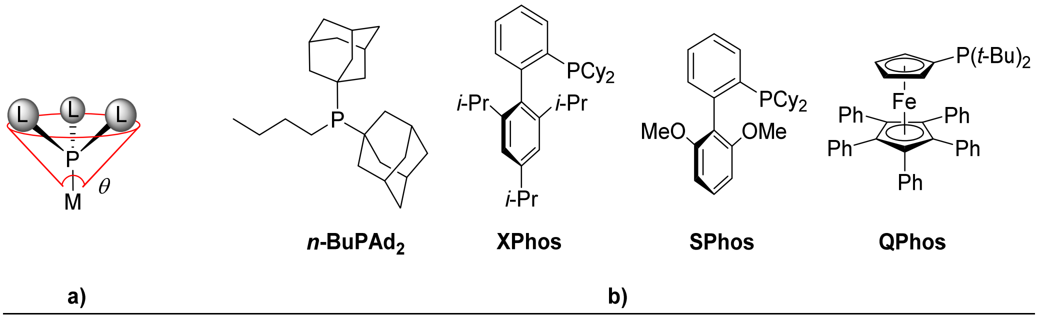
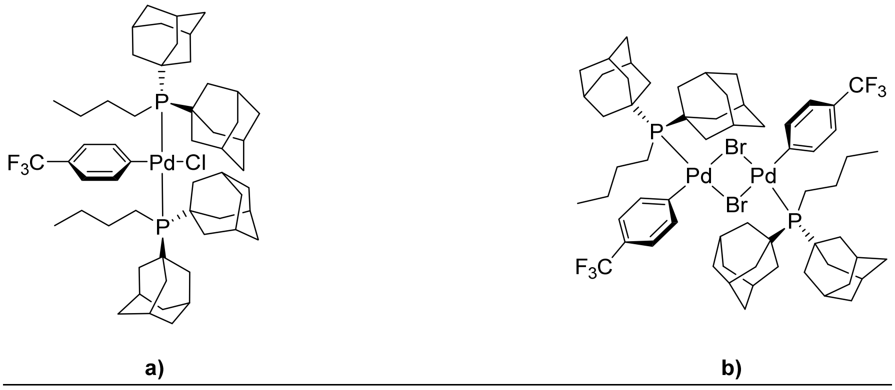


Figure 6: Illustration of the Tolman cone angle θ **a)** and selected sterically demanding ligands **b)**

Another steric demanding ligand is the air and moisture stable phosphine *n*-$BuPAd_2$, developed in the group of Beller at LIKAT in Rostock around the year 2000. Compared to the similar tri-*tert*-butyl-phosphine ligand, which is pyrophoric, *n*-$BuPAd_2$ does not make special requirements in storing or handling.[67] The *n*-$BuPAd_2/Pd(OAc)_2$ catalytic system has shown high TONs for SUZUKI-cross coupling of *o*-cyano-chlorobenzene with phenyl boronic acid.[68]. So far, *n*-BuPAd$_2$ has been applied for a wide range of different cross coupling reactions beside Suzuki-reaction, such as BUCHWALD-HARTWIG-,[69] MIZOROKI-HECK-[70] and ketone arylation-reactions,[71] to name only a few. In addition, *n*-BuPAd$_2$ has shown superior activity for carbonylations compared to PCy$_3$, P(*t*-Bu)$_3$ or bidentate ligands such as Josiphos or bis-diphenylphosphino-alkyl ligands.[72]

The palladium catalyzed three-component syntheses in this work were performed using an *in situ* formed [Pd(*n*-BuPAd$_2$)$_n$]-catalyst.[i] Interestingly, the Pd(*n*-BuPAd$_2$)$_2$ shows nearly linear geometry with a L-P-L-angle of 172.2° and eclipsed conformation along the P-Pd-P axis.[37] Studies on different derivatives of di-adamantly butyl phosphine showed a crucial dependency of the catalytical activity from the alkyl group. By exchanging the *n*-butyl group with an aryl moiety, the catalytical activity drops drastically. This can be explained by an arrangement of the alkyl chain lying over the aryl- or acyl-ligand attached to the palladium,[40] whereas aryl moieties or more steric demanding steric groups would distort this assembly and therefore the stability of an Ar-Pd-X complex (fig. 7).



a)

b)

Figure 7: Structures of the monomeric and dimeric [ArPd(*n*-BuPAd$_2$)X]- complexes as reported by Beller

Moreover, Beller *et al.* showed that the dimeric [Pd(*n*-BuPAd$_2$)Br]$_2$-complex easily reacts with CO to form a isolatable analogue dimeric acyl analogue. This may be based

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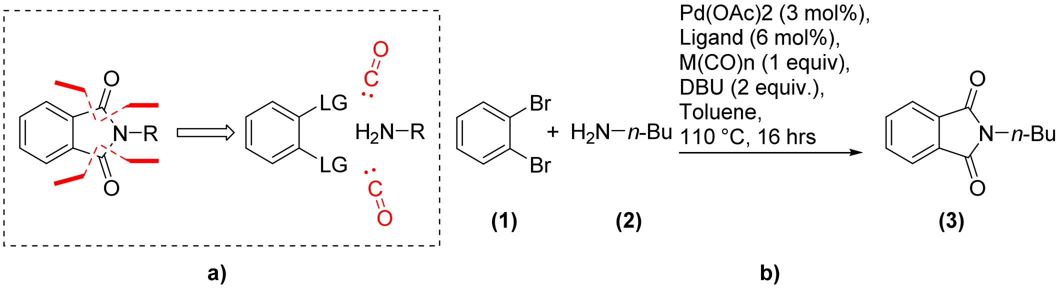
[i] Several species are assumed to be present in the reaction mixture. The equilibrium between the palladium-ligand-complexes has been shown in scheme 7 for the mechanism of the HECK-carbonylation.

on the relatively high electron density on the Pd-atom and the promoted coordination of a carbonyl ligand to the metal sphere. The formed acyl species can easily undergo elimination with appropriate nucleophiles (e.g. alcohols, amines, but also hydrogen) to form a [$HPdL_2X$]-complex, which regenerates the catalyst as shown in scheme 7.[40]

Summarizing, the electron rich and steric demanding Cata*CX*ium A ligand has shown excellent properties not only for standard cross coupling reactions but in addition also for three-component palladium catalyzed carbonylative coupling reactions. The catalytic active species can be easily formed using $Pd(OAc)_2$ as precatalyst.

2.2. Bis-Aminocarbonylative Synthesis of Phthalimides[i,73]

The first part of this work focuses on application of Pd-catalyzed aminocarbonylation for chemically interesting substrates and on the development of procedures for the synthesis of biologically and pharmaceutically interesting heterocycles *via* HECK-carbonylation. The first aim was the synthesis of *N*-substituted phthalimides *via* Pd catalyzed bis-aminocarbonylation as given in scheme 15, **a)**.



Scheme 15: Overview for the synthesis of phthalimides

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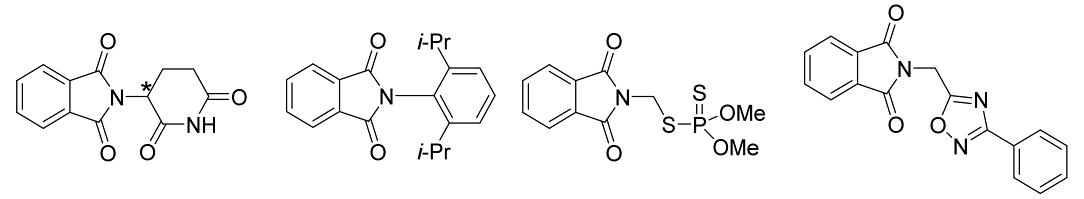
[i] The helpful work of *cand.* M.Sc. Anika Flader in this project is gratefully acknowledged.

2.2.1. Preface

Phthalimides represent an important class of biologically active and chemical relevant molecules. The most famous phthalimide structure is α-phthalimido glutarimide, commonly known as *Thalidomide* (fig. 8, (**4**)).

(**4**) has been developed as sedative by Grünethal in the late 1950's.[74] Its ability to additionally treat morning sickness and nausea during pregnancy resulted in its wide application for pregnant women. However, as one can see, *Thalidomide* exists in two different stereo isomers which interchange into each other *in vivo* in a way that even if the pure enantiomer is applied it turns into a racemic mixture.[75] It is assumed that the sedative effect is caused only by the (+)-(*R*)-enantiomer. Unfortunately, the (-)-(*S*)-form leads to at that point unknown phocomelia and other development disorders in the fetus. Frighteningly, it took several years to discover the correlation of these child birth defects and the usage of *Thalidomide*, which resulted in its withdrawal in 1961. Lately, these terrible effects caused by such a small change in the pharmaceutical led to tighter controls in the drug development. However, this compound is still relevant due to its high immunomodulatory properties in the treatment of severe illnesses such as plasma cell myeloma,[76] AIDS[77] and leprosy.[78]

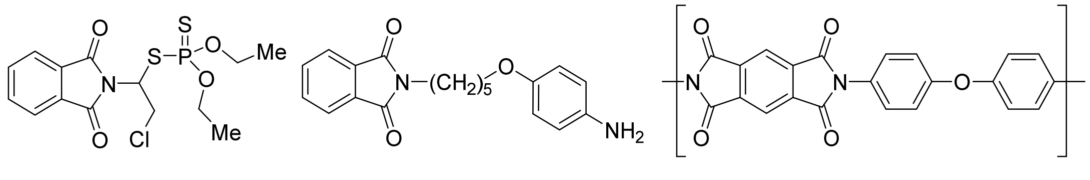


Thalidomide (4)
sedative, antiinflammatory, antineoplastic,angiogenesis inhibition

PP-33 (5)
α-TNF-inhibition

Phosmet (6)
insecticide, acaride

Oxadizole-phthalimide (7)
antiinflamatory, analgesic



Dialifor (8)
insecticide, acaricide

Amphotalide (9)
anthelmintic

Repeat unit of **Kapton (10)**

Figure 8: Selected examples of phthalimide containing structures

Moreover, other phthalimide derivatives show potentially biological activities. Oxadizole-phthalimides show anti-inflammatory and analgesic effects.[79] α-Tumor necrosis factor-inhibition has been reported for the phthalimide analogue PP-33 (fig. 8, **5**).[80] Furthermore, phosmet[81] (**6**) and dialifor[82] (**8**) are used in plant protection. In material science, phthalimide-like structures such as pyromellitic diimide (**10**) play an important role as structural element in high-performance polymers, e.g. Kapton®, which was used as thermal insulation layer in the Apollo lunar module and has been considered as material for solar sails.[83] Amphotalide (**9**) is used in the treatment of parasitic worm infections.[84]

2.2.2. Motivation

Concerning the importance of phthalimides, several methods for their preparation have been developed. Beside classic methodologies such as the condensation of phthalic anhydride with primary amines[85] (fig. 9, **a)**) or the GABRIEL-synthesis,[86] only few examples for a palladium catalyzed carbonylative synthesis have been reported. These carbonylations were usually applied for more reactive diiodobenzenes such as in the procedure reported by Perry and Turner starting from primary amines giving phthalimides *via* palladium catalysis under CO pressure (~6.2 bar, fig. 9, **b)**).[87] In 2010, Cao and Alper reported an interesting Pd-catalyzed carbonylative synthesis of phthalimides under atmospheric pressure of CO using ionic liquids as solvent (fig. 9, **c)**).[88] Furthermore, the group of Larock reported about a Pd-catalyzed procedure using *o*-halo benzoates and amines with atmospheric CO-pressure (fig. 9, **d)**).[89]

The objective of this project was the development of a carbonylative procedure starting from 1,2-dibromoarenes. The use of bromoarenes benefits from a broadened spectrum of substrates and the starting materials can be furthermore considered as "low-energy" compounds. Additionally, metal carbonyls should be applied as carbonyl source to avoid the usage of CO gas and high pressure equipment. A protocol fitting such demands was a convenient tool for the lab scale synthesis of phthalimides as a pharmacological relevant substance class and an interesting building block in organic synthesis.

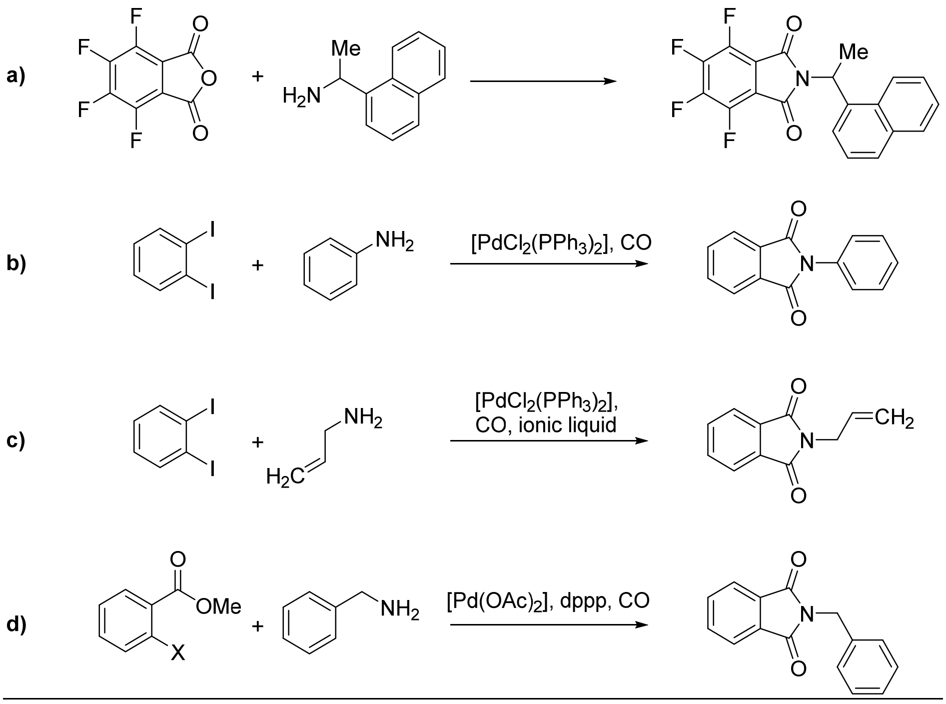


Figure 9: Examples for phthalimide synthesis

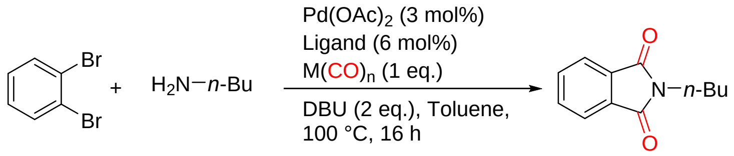
2.2.3. Development of a Synthetic Procedure

A model reaction was carried out using 3 mol% of $Pd(OAc)_2$ as precatalyst and *n*-butylamine as a simple N-nucleophile. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) has been used as base of choice in twofold excess to the arene due to its ability to additionally promote the release of CO from metal carbonyls *via* ligand exchange as aforementioned. Different ligands and carbonyl complexes have been tested as shown in table 1.

Initial experiments were carried out using different ligands and molybdenum hexacarbonyl as it has been applied successfully before as CO precursor. *n*-$BuPAd_2$ (entry 6) showed the best yield for this reaction, even better than bidentate xanthphos or dppf. This coheres with the results on other carbonylation reactions performed in the group of Beller whereby *n*-$BuPAd_2$ showed in general high TONs and yields.[40] Subsequently, the screening of different metal carbonyls was performed. Interestingly, using $Cr(CO)_6$ as CO source (entry 8) resulted in higher yields compared to the molybdenum complex (entry 6). However, due to the toxicity of chromium, the decision was to carry on further investigations on this reaction using $Mo(CO)_6$.

The target compound **(3)** has been identified *via* NMR-spectroscopy. The ^{1}H-NMR-spectrum shows only two signals in the low field area which relate to the four protons attached to the phenyl ring. Accordingly, the ^{13}C-NMR shows only four signals, which is even the half amount of signals due to the symmetry of the molecule. The introduction of the carbonyl groups has been proven by the strong low field shifted signal at δ = 168.5 ppm. No broad N*H*-signal is detectable, which would indicate only a monocarbonylation. The distinct identification of the signal was performed using 2D-NMR-spectroscopie.

Table 1: Screening of metal-carbonyls and ligands



(1) **(2)** **(3)**

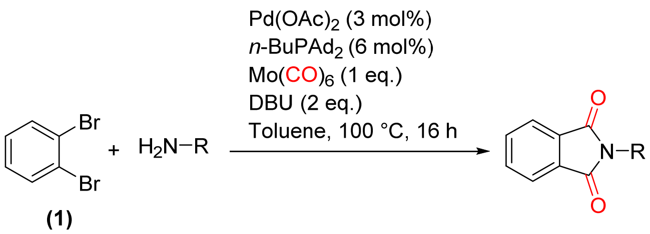
entry	ligand	CO-Source	yield (%)[a]
1	PPh_3	$Mo(CO)_6$	6
2	Xantphos	$Mo(CO)_6$	72
3	dppf	$Mo(CO)_6$	72
4	PCy_3	$Mo(CO)_6$	8
5	P(*o*-Tolyl)$_3$	$Mo(CO)_6$	10
6	*n*-BuPAd$_2$	$Mo(CO)_6$	84[b]
7	*n*-BuPAd$_2$	$Fe(CO)_5$	16
8	*n*-BuPAd$_2$	$Cr(CO)_6$	86
9	*n*-BuPAd$_2$	$Co_2(CO)_8$	2
10	*n*-BuPAd$_2$	$W(CO)_6$	56

Reaction conditions: 0.5 mmol dibromobenzene, 0.6 mmol *n*-butylamine, 1 eq. $M(CO)_n$, 2 eq. DBU, 3 mol% $Pd(OAc)_2$, 6 mol% ligand, 3 ml toluene, 100°C, 16 h
[a]: GC-yields [b]: isolated yield

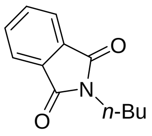
With a well working procedure in hand, the substrate scope was carried out to investigate the limiting effects for different substituents attached to the bromoarene and the amines. First, the focus was on the reaction of simple 1,2-dibromobenzen (**1**) with different amines as given in table 2.

Short chain aliphatic amines gave a better yield (**3**). In the case of *tert*-butylamine, only the formation of the amide could be observed, which may be due to the steric hindrance of the alkyl group and therefore a suppressed second CO-insertion to the Pd-complex. Unsubstituted aniline led only to the mono carbonylation product (**33**) as well. This can be explained by the general lower nucleophilicity owing to the delocalization of the lone pair with the benzene ring. Hence, after formation of the first amide species, dehalogenation of the bromoarene takes part which leads to the amide, as discussed before. On the other hand, electron donating substituents attached to the phenyl ring, such as *p*-methoxy (**18**), increased the reactivity of aniline and gave the desired phthalimide in 66 % yield. The electron donating effect is much weaker with *p*-ethylaniline, but still the phthalimide is formed in acceptable yield (**19**).

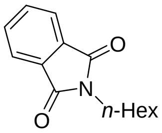
Table 2: Palladium catalyzed bis-aminocarbonylation of 1,2-dibromobenzene with different amines.



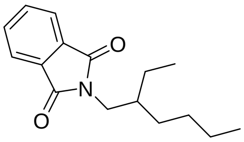
yield^{a}/entry



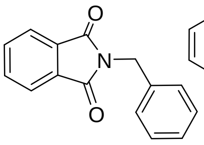
84% **(3)**



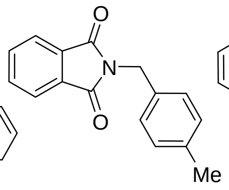
55% **(11)**



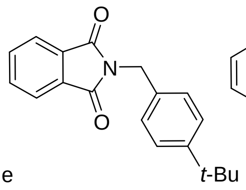
55% **(12)**



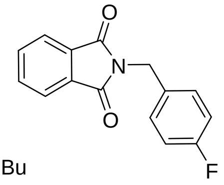
84% **(13)**



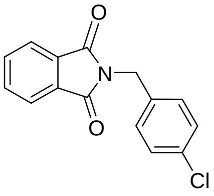
79% **(14)**



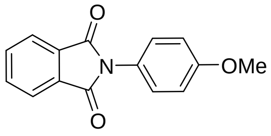
68% **(15)**



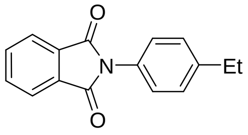
78% **(16)**



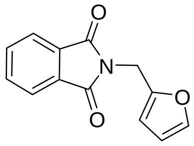
48% **(17)**



66% **(18)**



26% **(19)**

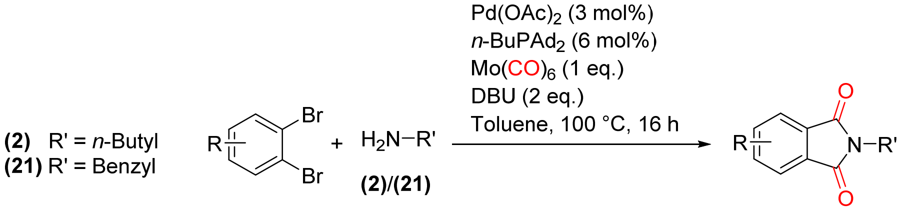


74% **(20)**

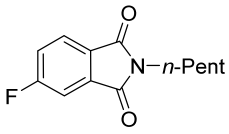
Reaction conditions: 0.5 mmol dibromobenzene **(1)**, 0.6 mmol amine, 1 eq. $Mo(CO)_6$, 2 eq. DBU, 3 mol% $Pd(OAc)_2$, 6 mol% *n*-$BuPAd_2$, 3 ml toluene, 100°C, 16 h, ^{a}: isolated yield

Furthermore, the scope was extended to different substituted 1,2-dibromobenzenes (tab. 3). In case of single fluorine (**22**) as electron withdrawing substituent, a slight decrease of the yield could be observed. 1,2-Dibromo-3,5-difluorobenzene gave only the amidation on position 1 and elimination of the residual bromine (**30**). However, electron rich dibromobenzenes (**23 - 27**) gave significant lower yields. This can be explained with a deactivation of the Ar-Br-bond and has been observed for similar systems before.[88]

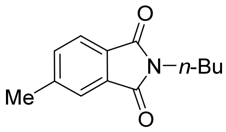
Table 3: Substituent influence for the aminocarbonylation of 1,2-dibromobenzene



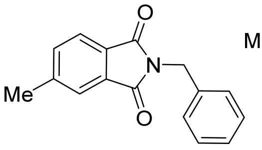
yield[a]/entry



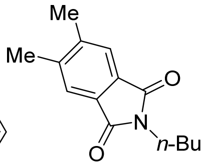
60% **(22)**[b]



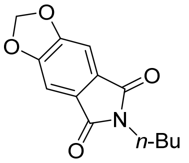
80% **(23)**



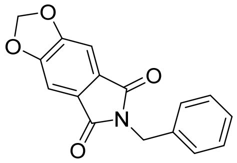
45% **(24)**



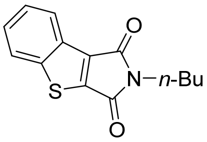
15% **(25)**



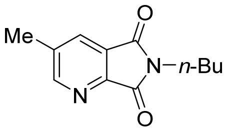
38% **(26)**



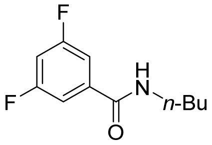
28% **(27)**



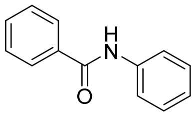
7%[c, d] **(28)**



2%[c, d] **(29)**



(30)



(31)

Reaction conditions: 0.5 mmol dibromobenzene, 0.6 mmol amine, 1 eq. Mo(CO)$_6$, 2 eq. DBU, 3 mol% Pd(OAc)$_2$, 6 mol% *n*-BuPAd$_2$, 3 ml toluene, 100°C, 16 h, [a]: isolated yield, [b]: the reaction was carried out using *n*-pentyl-amine, [c]: main product is the amide, [e]: reaction time 32 h.

Compared to the reaction of *n*-butylamine with 1,2-dibromobenzene, the yield decreased slightly for 4-methyl-1,2-dibromobenzene to 80 % (**23**) and decreased drastically for 4,5-dimethyl-1,2-dibromobenzene to 15 % (**26**). The general very low yields for heteroarenes such as benzo[*b*]thiophene (**28**) or pyridine (**29**) can be explained by the high rate of the halo elimination of the intermediate Ar-Pd-Br complex. *n*-Butylamine and benzylamine show for the reaction with unsubstituted dibromobenzene similar reactivity (**3** + **13**). However, arenes substituted with electron donating groups, show in general lower yields for the reaction with benzylamine compared to the use of *n*-butyl amine (**23** and **24**, **26** and **27**).

In summary, a convenient procedure to obtain phthalimides has been developed. Using inorganic metal carbonyls as CO source is a convenient way to perform aminocarbonylations in a lab scale without the need of special equipment such as autoclaves when using CO gas. This palladium catalyzed method uses 1,2-dibromo benzenes as substrates which allows for a broad functionalization of the products.

Though aliphatic amines showed the best yields, the developed conditions can be applied for activated anilines. Unfortunately, heterocyclic dibromoarenes showed significant low yields.

2.2 Synthesis of *N*-Benzoylindoles *via* Aminocarbonylative Coupling of Bromobenzenes with Indole

2.2.1 Preface

Ongoing, the objective was to develop a strategy for the weak nucleophilic indole for Pd-catalyzed aminocarbonylation.

Indole is an outstanding important scaffold in pharmaceuticals, fragrances, dyes,[i] agrochemicals and in material science. Indole is a crucial building block in naturally occurring alkaloids, proteins and hormones. As an example, tryptophan (fig. 10, (**32**)),

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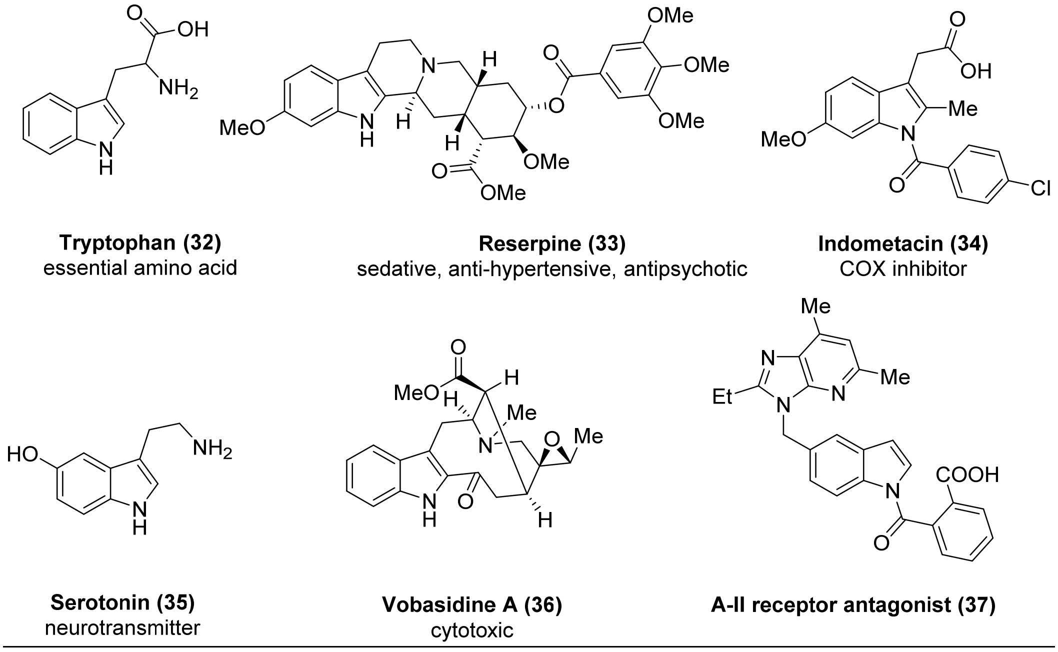
[i] The name indole originates from the first procedure to obtain this scaffold from the treatment of indigo with oleum.

an essential amino acid, contains the indole moiety and is necessary for the biosynthesis of neurotransmitters such as serotonin (fig. 10, (**35**)) and melatonin. Thus, justified by its importance and wide applications, indole has even been addressed as "the lord of the rings of aromatic compounds".[90]

A privileged indole containing scaffold is reserpine (fig. 10, (**33**)). This scaffold occurs naturally in a range of *Rauwolfia* species. These plants were used as sedative for mental diseases or in the treatment of snake bites and fever for several hundred years in India. Studies revealed that reserpine blocks post-ganglionic nerve fibers and therefore inhibits the accumulation of serotonin and catecholamines.[91] Reserpine itself was firstly isolated by Schlittler *et al.* in the mid 1950's, and soon after, it was applied for hypertension and psychiatric disorders, such as schizophrenia. [92]



Tryptophan (32)
essential amino acid

Reserpine (33)
sedative, anti-hypertensive, antipsychotic

Indometacin (34)
COX inhibitor

Serotonin (35)
neurotransmitter

Vobasidine A (36)
cytotoxic

A-II receptor antagonist (37)

Figure 10: Selected pharmacologically relevant indole derivatives

Intense investigations on the mechanism of action of reserpine led to a fundamental understanding of the metabolization of catecholamines, such as dopamine, and their related physiological and neurological influence.[93] Hence, it is said that reserpine, though it lost its importance nowadays due to numerous side effects, lead to an era of modern psychiatric medication. The first total synthesis of the quite complex reserpine was successfully achieved in the group of Woodward in the late 1950's.[94]

An overview of pharmacological and biological relevant indoles is huge and a vast number of articles and reviews address this topic. By the way of example, an essential *N*-acyl indole containing representative is the non-steroidal anti-inflammatory drug (non-selective COX-1 and -2 inhibitor) indomethacin (**34**). This scaffold is applied as analgesic and beyond in the treatment of unilateral headache and rheumatic diseases such as gout or arthritis.[95] Another example is vobasidine A (**36**), an alkaloid naturally occurring in *tabernaemontana* species, which shows cytostatic effects.[96] Structure (**37**) acts as non-peptide angiotensin-II receptor antagonist and may be applied in the treatment of hypertension.[33]

Due to the importance of indole containing structures, various different methodologies have been developed for the direct synthesis of functionalized indoles. A prominent example is the FISCHER-indole synthesis[97] starting from phenylhydrazine and aldehydes. Other examples are the LAROCK-synthesis[98] *via* palladium catalyzed coupling of *o*-iodo aniline with alkines, or the FUKUYAMA-method,[99] starting from *o*-isocyanostyrenes, to name only a few (fig. 11).

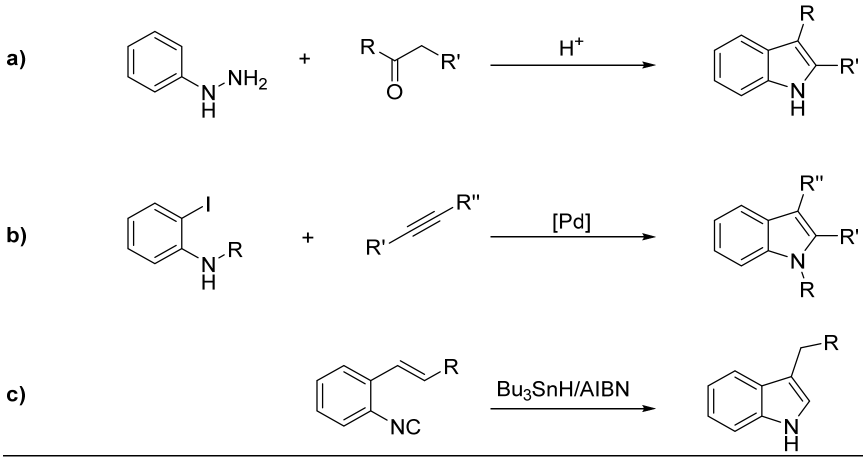


Figure 11: FISCHER- (**a**)), LAROCK- (**b**)) and FUKUYAMA-indole-synthesis (**c**))

Whereas these methodologies focus on the synthesis of a complete indole scaffold, other approaches target for the direct functionalization of an already present indole-structure. Owing to the extensive field on these reactions, only some examples for the direct *N*-functionalization will be given here. Notably, though indole can be seen as an electron rich heteroarene with an enhanced reactivity for electrophilic aromatic substitutions, the NH-group is not the most reactive center for electrophilic reactions. The most reactive position for electrophilic reactions is the carbon on position 3, about 10^{13} times more reactive compared to benzene, which makes indole an appropriate substrate for a range of transition metal catalyzed CH-activation reactions.[100] Also, the C2-position shows considerable reactivity.

In addition, the N*H*-acidity is rather low for unsubstituted indole, with a range of $pK_s = 16.97$ in water to $pK_s = 21.0$ in DMSO. Therefore, to elude the inertness of the NH-group, strong bases are required for the preliminary conversion into an indolyl anion to access *N*-alkylated indoles. However, the ambident character of this species does not only promote the *N*-alkylation, but in addition the C-alkylation and the C-N-double alkylation. The outcome of this kind of reaction depends strongly on the solvent and the structure of the alkylation reagent. Though high selectivity can be achieved, specific optimization in each concrete case remains required.[101]

The *N*-alkylation is a standard protocol for methyl-[102] and benzyl[103] substituents in most cases using strong bases such as NaH or KOH for the N*H*-deprotonation. Still, the MITSUNOBU-protocol[104] requires additional electron withdrawing groups on the indole system for activation of the NH-group to access more branched *N*-alkyl derivatives (fig. 12, **b)**). Furthermore, a protocol for the MORITA-BAYLIS-HILLMAN-reaction[105] on indoles has been developed to obtain *N*-allyl indoles (fig. 12, **a)**). Transition metal catalyzed *N*-functionalization plays a significant role, and synthetic procedures using copper-[106] or palladium[107] catalysts (fig. 12, **c)**) have been elaborated by the way of example in the group of Buchwald to obtain the *N*-arylation product.

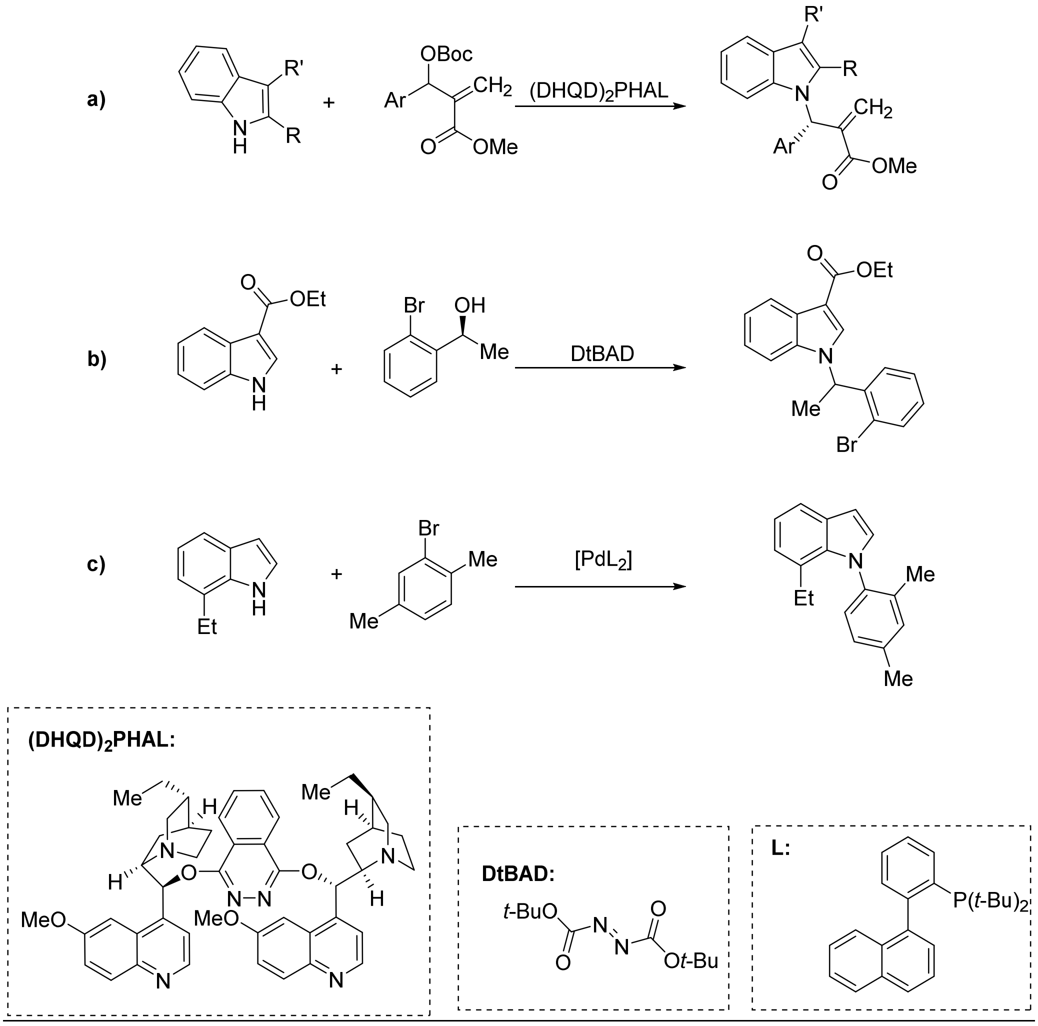


Figure 12: Examples for the *N*-functionalization of indoles

2.2.2 Motivation

In addition to the *N*-alkylation and *N*-arylation, several procedures for the *N*-benzoylation have been elaborated. The probably most frequently used protocol is the reaction of indole with benzoyl chloride. However, the high reactivity of acid chlorides may result in selectivity issues when multiple functional groups are present. Therefore, catalyzed C-N-formation reactions appear to be a convenient and selective alternative. As an example, Bremner and co-workers elaborated a protocol using dimethylamino pyridine as catalyst and dicyclohexylcarbodiimide as coupling agent to access the amide (fig. 13, **a)**).[108]

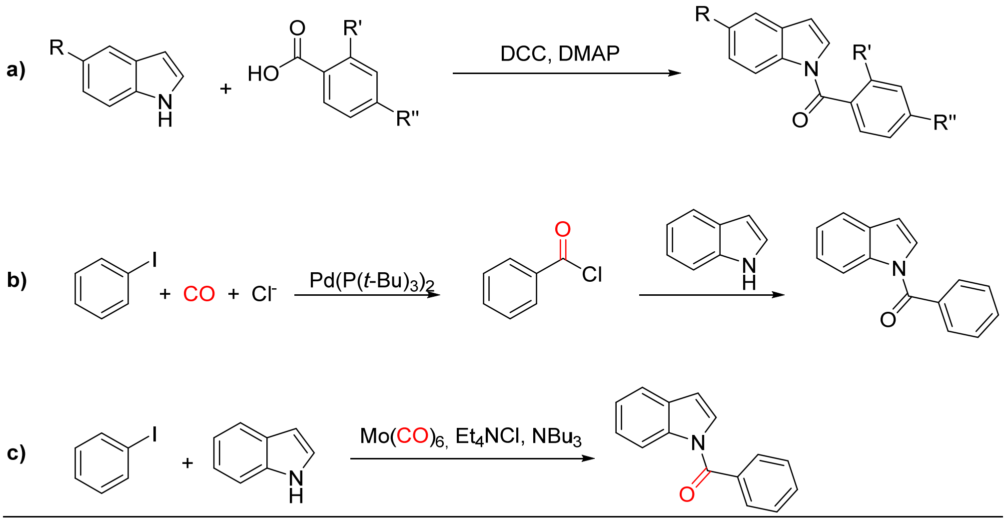


Figure 13: Reported carbonylative syntheses of *N*-benzoylindole

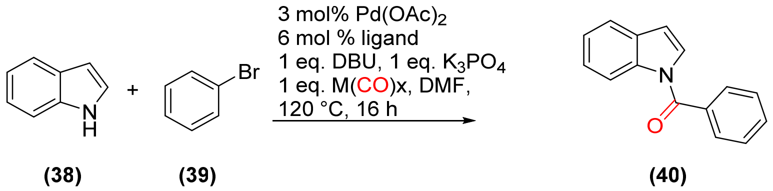
Moreover, transition metal aminocarbonylations have been reported. Interestingly, Quesnel and Arndtsen reported on a Pd-catalyzed *in situ* generation of an acid chloride species from iodobenzenes, which subsequently reacted with the indole. The reaction took place under 1 atm. of CO-gas, giving 85% benzoyl indole (fig. 13, **b)**).[109] However, this approach cannot be considered as a "real" aminocarbonylation. Another approach was published by Ren and Yamane, using $Mo(CO)_6$ as CO-source and catalyst at once, yielding 60 % benzoylindole from the aminocarbonylation of iodobenzene (fig. 13, **c)**).[110]

Based on the results previously presented in this work, the consideration was on a Pd-catalyzed HECK-carbonylation type synthesis of *N*-benzoylindoles with aryl bromides. Bromobenzenes provide a wide range of different substituted substrates, which allow for easy and convenient further derivatization of the target benzoyl indole. Moreover, a method should be developed, which enables a carbonylative C-N-coupling of non-activated indole. Lastly, the pursued protocol should proceed without the use of CO-gas or higher pressures, but with $Mo(CO)_6$ as alternative CO-source for lab scale carbonylation reactions.

2.2.3 Synthetic Procedure for the Synthesis of *N*-Benzoylindoles

An initial experiment was carried out using the already elaborated conditions for the bis-carbonylation of dibromo benzenes. *n*-BuPAd$_2$ was chosen as ligand and DBU as base due to its ability to promote the CO-release. Unfortunately, neither conversion to the target *N*-benzoyl-indole nor formation of the normal arylation product was detected (tab. 4, entry 1). Due to the known inertness of the NH-group in indole, another experiment was performed adding an equimolar amount of K_3PO_4 to deprotonate the indole and therefore increase its reactivity. Delightfully, this reaction gave the desired *N*-benzoylindole (**42**) in 90 % yield.

Table 4: Optimization table for the aminocarbonylative coupling of indole



entry	Ligand	CO-Source	yield (%)[a]
1[b]	*n*-BuPAd$_2$	$Mo(CO)_6$	0
2	*n*-BuPAd$_2$	$Mo(CO)_6$	90
3	$P(Ph_3)_3$	$Mo(CO)_6$	0
4	$P(Cy)_3$	$Mo(CO)_6$	0
5	dppp	$Mo(CO)_6$	0
6[c]	*n*-BuPAd$_2$	$Mo(CO)_6$	0
7	*n*-BuPAd$_2$	$Co_2(CO)_8$	85
8	*n*-BuPAd$_2$	$W(CO)_6$	68
9	*n*-BuPAd$_2$	$Cr(CO)_6$	95

Reaction conditions: 0.5 mmol indole, 0.5 mmol bromobenzene, 0.5 mmol DBU, 0.5 mmol K_3PO_4, 0.5 mmol CO-source, 3 mol% $Pd(OAc)_2$, 6 mol% Ligand, 3 ml DMF, Ar-atmosphere, 120°C, 16 h. [a]:GC-yields with hexadecane as internal standard. [b]: reaction was carried out without K_3PO_4. [c]: reaction was carried out without DBU.

Subsequently, the influence of different ligands has been investigated as well as the applicability of different metal carbonyls as CO-source. Interestingly, Cata*CX*ium A is the only ligand among the tested, giving any product formation, contrary to the previous experiments using dibromobenzenes, where other ligands such as PPh_3 show a mediocre conversion of the aroylation product (tab. 1). Not even the arylation product was found using other ligands than *n*-$BuPAd_2$ (tab. 4, entries 2 - 5).

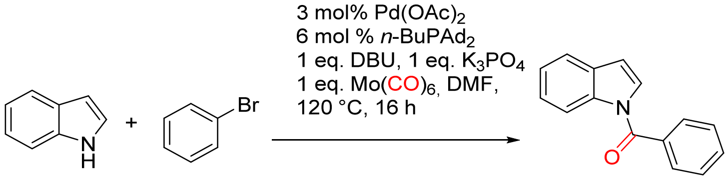
Using different metal carbonyls gave similar results as mentioned above and in the literature.[58] Again, the focus was on molybdenum hexacarbonyl. Though the usage of chromium hexacarbonyl resulted in higher yields, the decision was to use $Mo(CO)_6$ due to its lesser toxicity. The reaction did not proceed without the addition of DBU to facilitate the CO-release.

To investigate the influenceof additional substituents, different bromoarenes were tested under the examined conditions as given in table 5 to investigate the influence of additional substituents. In general, the reaction proceeds very well for electron donating substituents attached to the bromobenzene in *para* or *ortho* position, ranging from 87 % yield for *o*-methoxybromobenzene (**46**) to 97 % for *p*-bromtoluene (**41**). Electron donating groups in *m*-positon to the bromine still result in acceptable yields (**42 + 45**). The lower yields of bromo-mesitylene (**43**) can be explained by the steric hindrance due to the two neighbouring methyl groups and therefore suppressed CO-insertion.

Fortunately, the brominated derivatives of heteroaromatic pyridine (**49** + **50**) and thiophene (**51**) proved to be suitable coupling agents for the aminocarbonylation and gave access to the desired amide in acceptable yields, though no conversion was observed for the isoquinoline scaffold (**55**). Electron withdrawing substituents attached to the bromobenzene gave lower yields compared to electron donating due to the deactivation of the C-Br-bond.

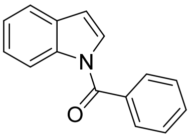
Interestingly, when using 1,2-dibromo-4,5-dimethylbenzene, only 18 % of the *N*-benzoyl scaffold (**53**) were isolated. However, when changing to 1,2-dibromo-4,5-dimethoxybenzene (**56**) neither the acylation product nor the cyclized form was observed. This leads to the necessity of ongoing studies and optimization for these scaffolds.

Table 5: Scope for the synthesis of *N*-benzoylindoles using different bromoarenes

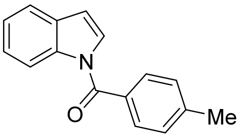


(38) **(39)** **(40)**

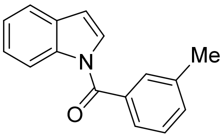
yield^a/entry



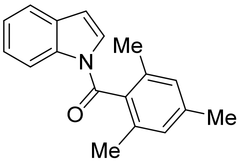
89 % **(40)**



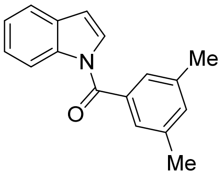
97 % **(41)**



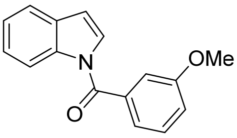
23 % **(42)**



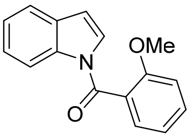
42 % **(43)**



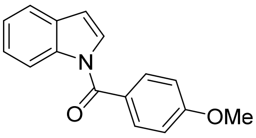
80 % **(44)**



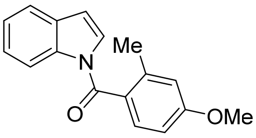
38 % **(45)**



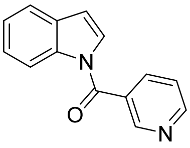
87 % **(46)**



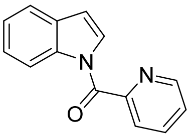
94 % **(47)**



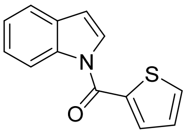
98 % **(48)**



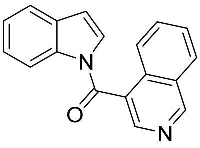
50 % **(49)**



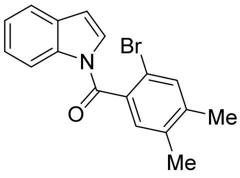
28 % **(50)**



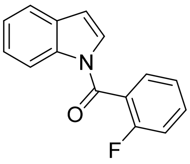
39 % **(51)**



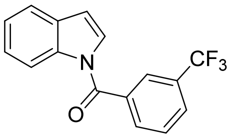
0 % **(52)**



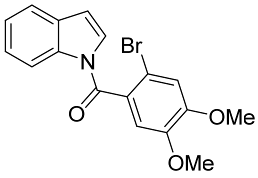
18 % **(53)**



25 % **(54)**



49 % **(55)**



0 % **(56)**

Reaction conditions: 0.5 mmol indole, 0.5 mmol bromoarene, 0.5 mmol DBU, 0.5 mmol K_3PO_4, 0.5 mmol $Mo(CO)_6$, 3 mol% $Pd(OAc)_2$, 6 mol% *n*-BuPAd$_2$, 3 ml DMF, Ar-atmosphere, 120°C, 16 h. ^{a} isolated yields

An interesting noteworthiness is the appearance of a characteristic shift difference of proton signal C*H*(2) in ^{1}H-NMR spectra of the different substituted *N*-benzoylindoles. Although the arene moiety is fairly far away from the proton attached on position 2, there is an influence on the chemical shift of this hydrogen atom. This effect is shown in fig. 14 for the model compound, *N*-benzoylindole (**40**, **a**)), compared to the xylene derivative (**44**, **b**)) and the thiophene containing scaffold (**51**, **c**)).

Whereas the C*H*(2)-signal appears around δ = 7.3 ppm[i] for the *N*-benzoyl compound (fig. 14, **a**)), the signal is high-field shifted for the 2,4,5-trimethylbenzoyl substituent to δ = 6.81 ppm (fig. 14, **b**)). The nucleus gives a distinct doublet with ^{3}J = 3.8 Hz, showing the coupling with proton C*H*(3). On the other hand, the signal for C*H*(2) is low field shifted for the thiophenyl moiety, and appears at around δ = 7.7 ppm[ii] (fig. 14, **c**)). This change in the chemical shift leads to the assumption of a different arrangement of the acyl substituents.

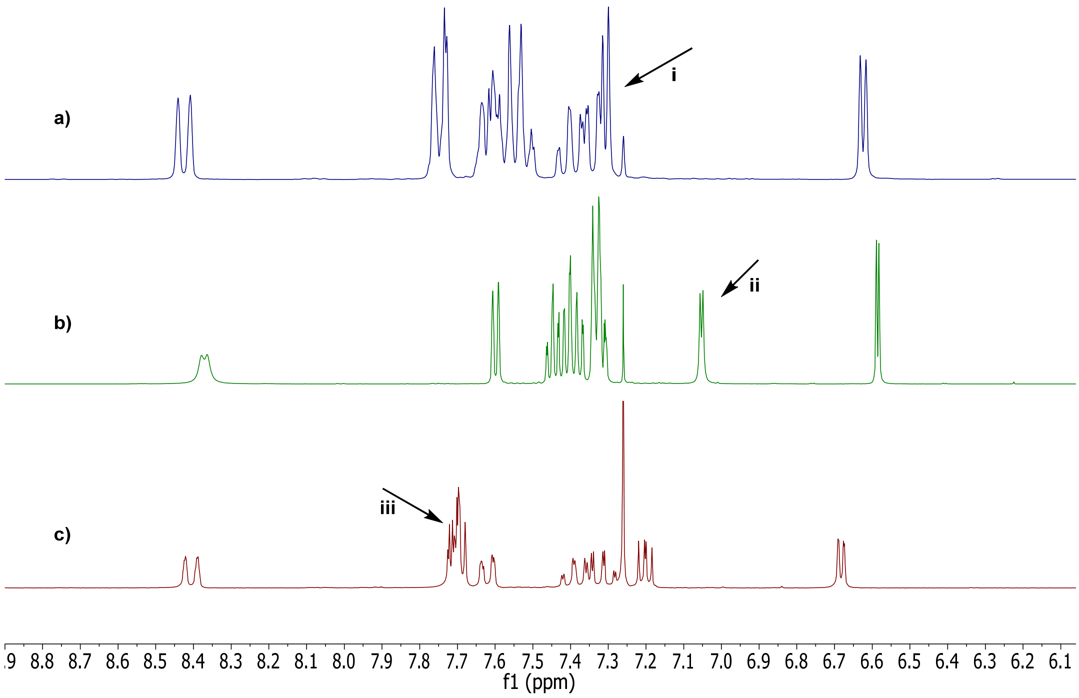


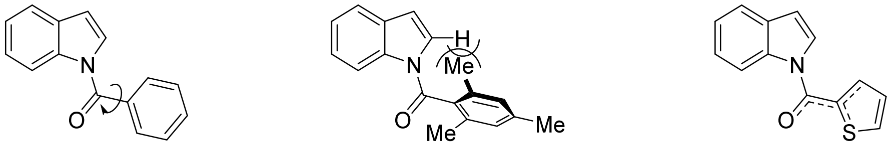
Figure 14: ^{1}H-NMR segment for *N*-benzoylindole (**40**, **a**)), *N*-(2,4,6-trimethyl)-benzoyl-indole (**44**, **b**)) and *N*-2-thiophenoyl-indole (**51**, **c**))

---

[i] The signal overlaps with the signal from the C*H*(5)-proton. However, it was identified *via* the correlation with C*H*(3) in the H-H-COSY-spectrum and the correlation in the HMBC-spectrum

[ii] The signal overlaps in this case as well.

Whereby the phenyl ring for benzoyl indole (fig. 15, **a)**) may rotate freely, there is no strong anisotropic effect of the arene moiety on the neighboring protons. For the 2,4,5-trimethylbenzoyl a stacked conformation has to be assumed (fig. 15, **b)**) due to the steric hindrance of the methyl groups and the suppressed rotation. This orthogonal arrangement results in a stronger influence of the anisotropy of the phenyl ring and therefore a shielding of the nucleus, which leads to a high-field shift. Contrary to this, the thiophene-containing moiety can be considered as a push-pull system, at which a partial double bond character between the thiophene ring and the carbonyl group is expressed (fig. 15, **c)**). Thus, the thiophene ring is arranged in plane with the indole system and the hydrogen on position 2 is not affected by the anisotropic effect of the arene. Hence, proton C*H*(2) is not shielded, resulting in no high-field shift shift.



(40), a) **(44)**, b) **(51)**, c)

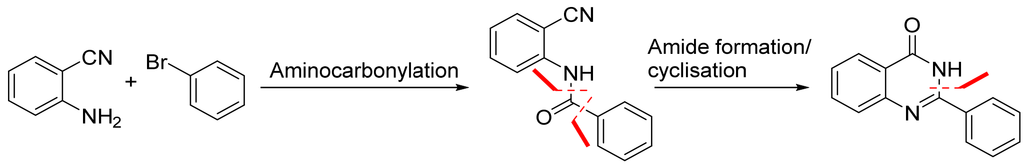
Figure 15: Schematic image for the arrangement of the *N*-aroylindoles

To summarize, an aminocarbonylative synthesis of *N*-benzoylindoles has been developed. The usage of $Mo(CO)_6$ as alternative CO-source avoids the handling of highly toxic CO-gas and the need for high pressure equipment such as autoclaves. A broad range of functionalized benzenes can be used in the developed protocol, allowing for further derivatization of the amide scaffold.

2.3 Synthesis of *N*-(*o*-Cyanoaryl)-benzamides with Subsequent Radziszewski-Reaction and Dimroth-Type Cyclisation[111]

2.3.1 Motivation

With a working procedure for the bis-aminocarbonylation to access phthalimides and *N*-benzoylindoles, the next aim of the work on deactivated nucleophiles for palladium catalyzed carbonylative cross coupling focused on *o*-cyano aniline. Therefore, the developed procedure for the aminocarbonylation was applied for simple bromobenzene and 2-amino benzonitrile as nucleophile. The strong electron withdrawing cyano group in *ortho* position deactivates the NH_2-group, but on the other hand gives the possibility for further derivatization. The aim for subsequent functionalization was the conversion of the nitrile into an amide *via* the Radziszewski-reaction followed by Dimroth-rearrangement to obtain quinazolinones in a one-pot-two-step manner. A brief summary of this project is given in scheme 16.



(57) **(39)** **(58)** **(59)**

Scheme 16: Synthesis of *N*-cyanoaryl benzamides and quinazolinones

2.3.2 Preface

Functionalized benzamides are an important class of bioactive structures. A concise overview of some pharmaceuticals based on benzamide is shown in fig. 16. For instance, niclosamide (**60**), a teniacide against parasitic flatworms in humans,[112] is listed as essential medicine by WHO (state 2015). Vismodegib (**65**) is used in the treatment of basal cell carcinoma[113] *via* hedgehog inhibition.[i] An extraordinary representative of benzamides is methaqualone[114] (**62**) with its lactam structure. Originally developed as an alternative sedative to barbiturates, it is now illicit and withdrawn due to its high addiction potential and the widespread abuse.[115] Cruciferane (**64**) is a naturally occurring alkaloid isolated from *isatis indigotica.*[116]

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[i] Hedgehog refers to a gene firstly discovered in drosophilae by later Nobel laureates C. Nüsslein-Volhard and E. Wieschaus. No actual hedgehogs are inhibited.

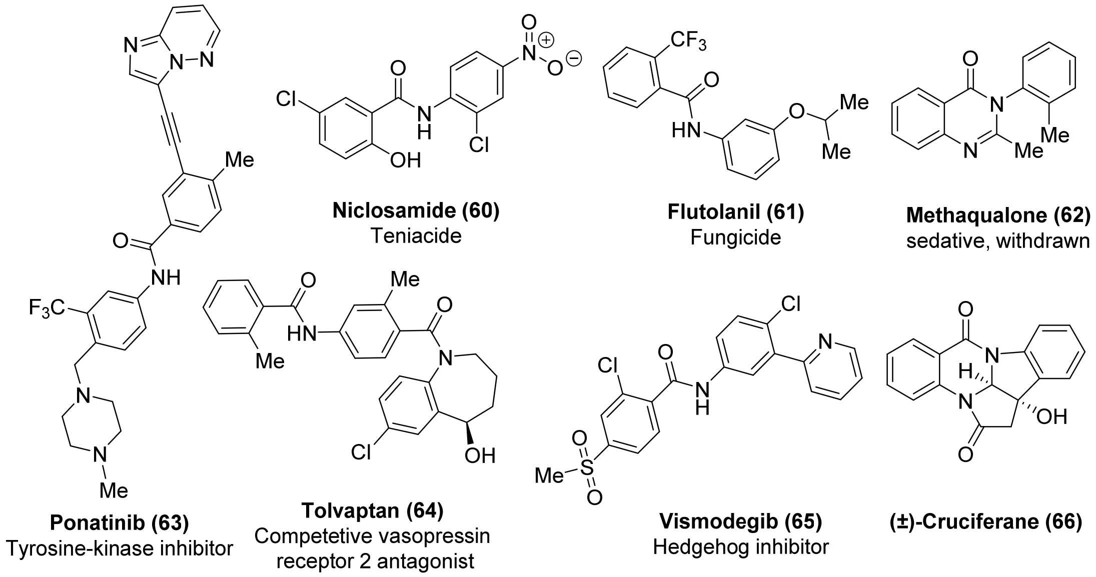


Figure 16: A selection of biological relevant benzamides

Though benzamides can be easily synthesized from the reaction of amines with acid chlorides, this methodology suffers from selectivity issues due to the high reactivity of the acid chloride species and in the case that several reactive centers are present in the substrate moiety. Thus, a wide range of catalyzed amide formation reactions have been elaborated in recent times and only a few will be mentioned here.

An interesting approach is the transamidation. In such a case, a primary or secondary amide undergoes usually an *H*-substitution on the nitrogen atom. As a noteworthy example, the group of Williams used hydroxyl amine as catalyst as well as amines and primary amides to access secondary and tertiary amides (fig. 17, **a)**).[117] Furthermore, Xu and Wolf developed a copper(II) oxide catalyzed coupling of bromo- and iodoarenes with amides for a carbon-nitrogen bond formation (fig. 17, **b)**).[118] Moreover, our group reported about the use of amines in the Zn(II)-catalyzed oxidative amidation of benzyl alcohols under solvent free conditions (fig. 17, **c)**).[119]

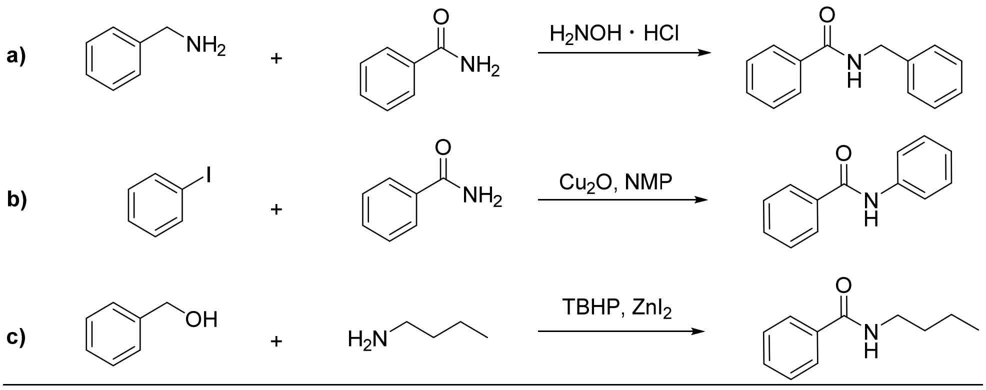


Figure 17: Selected examples for benzamide synthesis

The background idea of the aminocarbonylative synthesis of benzamides was that palladium catalyzed reactions allow for the use of less active substrates such as bromobenzenes and allow for chemo- and regio-selective reactions. The objective was to extend the applicability of the Pd-catalyzed amide synthesis from deactivated amines to anthranilamide, which offers in addition the possibility for further derivatization.

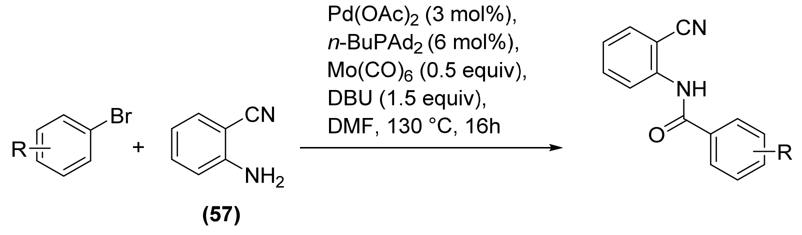
2.3.3 Synthesis of *N*-(*o*-Cyanoaryl)-benzamides *via* Pd-Catalyzed Aminocarbonylation

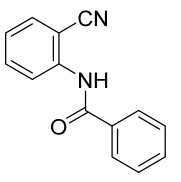
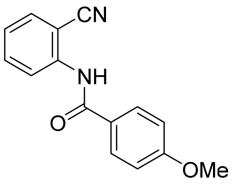
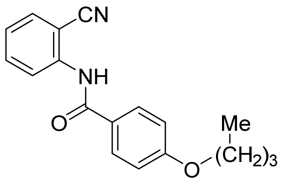
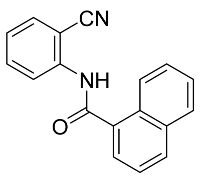
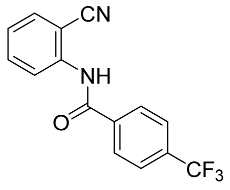
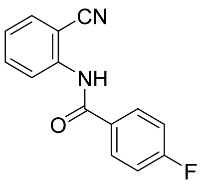
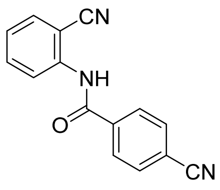
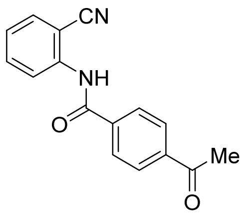
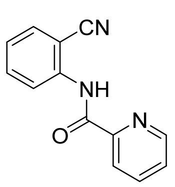
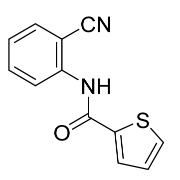
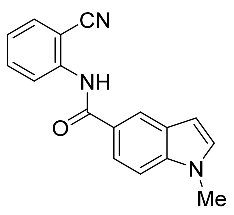
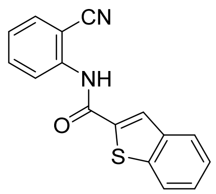
Initially, the procedure for the aminocarbonylation of dibromobenzene was applied for anthranilonitrile to obtain *N*-(2-cyanophenyl)-benzamide with reduced amount of the CO source since only single aminocarbonylation is desired. Fortunately, the formation of the amides could be observed. However, at 110°C with toluene as the solvent, the reaction showed mediocre conversion. Fortunately, when shifting to DMF and 130°C, the yield increased to 79 %. The higher temperatures were required due to the decrease of the nucleophilicity of the amino group caused by steric hindrance and the strong -*m* effect of the CN group (scheme 17, page 47). *n*-BuPAd$_2$ already showed to be an appropriate ligand for aminocarbonylation of bromoarenes with aniline moieties, which is why this system was applied here as well.

^{1}H-NMR-spectroscopical analysis of the product showed a broad low-field shifted signal at $\delta = 10.63$ ppm, which indicates the successful formation of an amide. Furthermore, three distinct signals in the aromatic area can be found, which belong to the *N*-phenyl ring. The three signals for the benzamide ring overlap together with the proton attached *ortho* to the N-atom, resulting in a multiplet. The carbon-NMR shows a single signal at δ = 162.3 ppm which relates to the newly introduced carbonyl group. Further identification of the CH-signals was carried out using HMBC- and HSQC-experiments.

Since the test reaction showed good yield, following reactions were carried out with various bromobenzenes to investigate the limiting effects of different substituents. The substrate-scope for arylbromides is shown in table 6.

Table 6: Synthesis of *N*-(2-cyanoaryl)-benzamides with different bromoarenes



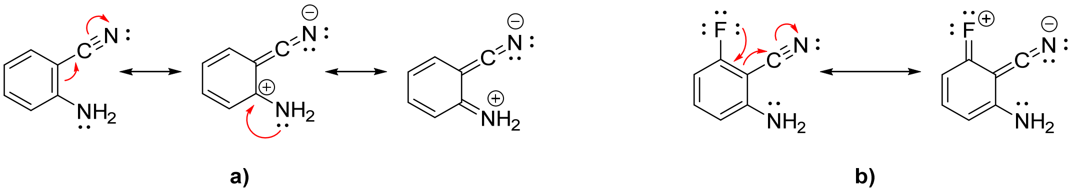
yield^a/entry			
 79 % **(58)**	 36 % **(67)**	 31 % **(68)**	 82 % **(69)**
 66 % **(70)**	 40 % **(71)**	 61 % **(72)**	 68 % **(73)**
 49 % **(74)**	 39 % **(75)**	 61 % **(76)**	 43 % **(77)**

Reaction conditions: 1 eq. 2-aminobenzonitrile, 1.2 eq. bromoarene, 0.5 eq. $Mo(CO)_6$, 1.5 eq. DBU, 3 mol% $Pd(OAc)_2$, 6 mol% Cata*CX*ium *A*, 4 ml DMF, 130°C, 16 h.; ^{a}: isolated yields

Bromobenzenes with additional electron withdrawing substituents (**70** - **73**) showed in general higher yields compared to the model substrate. This can be explained by the additional positivation effect of the intermediate acyl species which promotes the nucleophilic attack of the amine. Electron donating substituents such as *p*-methoxy (**67**) should foster the oxidative addition. The yields are significant lower compared to the model substrate. This underlines the significance of the two other steps, the CO insertion and the product formation *via* nucleophilic attack of the amine species, as aforementioned (scheme 7, page 13) and indicates that the oxidative addition is not the, at least not the *only one*, rate determining step.

Fortunately, heterocyclic bromoarenes are also able to give amides under these conditions (**74** - **77**). However, the yield was lower for these moieties compared to the model substrate which may be explained by the decreased stability of the intermediate Pd-aryl species, leading to dehalogenation. Still, the yields are appropriate and this method accesses even more functionalized compounds.

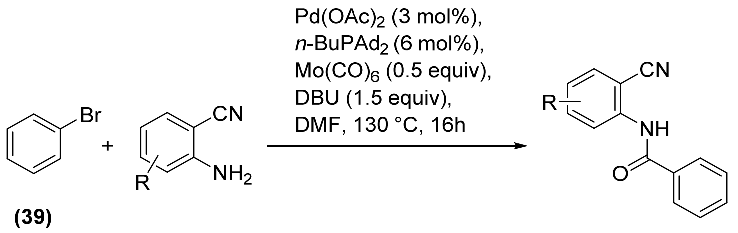
Subsequently, the optimized conditions were applied for different substituted *o*-cyano anilines (tab. 7). Since the nitrile group is electron withdrawing itself and already deactivates the amine, an additional *-I* substituent in *para*-position to the amino function should lead to a decrease of the yield, which was actually observed for the reaction of 5-chloro-2-amino benzonitrile (**81**). The additional decrease of the nucleophilicity led to only 21 % of the desired product. When fluorine as electron withdrawing substituents was attached in *meta* position to the NH_2-group (**79**), an increase of the yield could be observed. This may be explained by the electron donating ability of halides and therefore a decrease of the takeover of electron density from the amine by the CN-group. However, the amine is still weakened in its nucleophilicity. Thus, one cannot speak of a good nucleophile but of a less weakened reactant. A short overview of the resonance structure is given in scheme 17.



Scheme 17: Some resonance structures of 2-amino benzonitriles

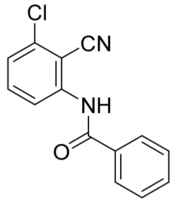
When chlorine was attached *meta* to the amine, one would expect the same result compared to the fluorine substituent or even better. However, the reaction showed a decreased yield (**82**, 66%). An explanation for this may be the fact that chlorine itself may undergo oxidative addition onto the palladium catalyst. This is even favored by the neighboring CN group, which weakens the C-Cl-bond and promotes the coordination to the Pd.

Table 7: Synthesis of *N*-(2-cyanoaryl)-benzamides with different *o*-cyano-anilines

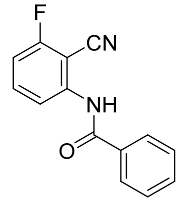


(39)

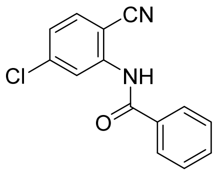
yield[a]/entry



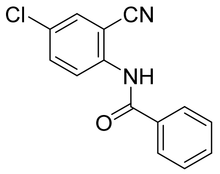
66 % **(78)**



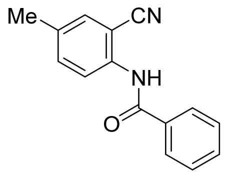
92 % **(79)**



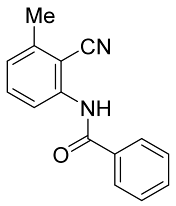
0[b] % **(80)**



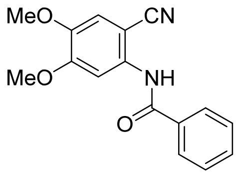
21 % **(81)**



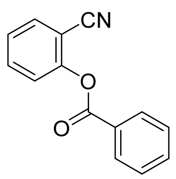
42 % **(82)**



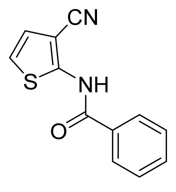
64 % **(83)**



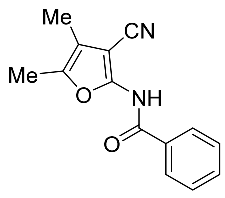
71 % **(84)**



54 % **(85)**



44 % **(86)**



50 % **(87)**

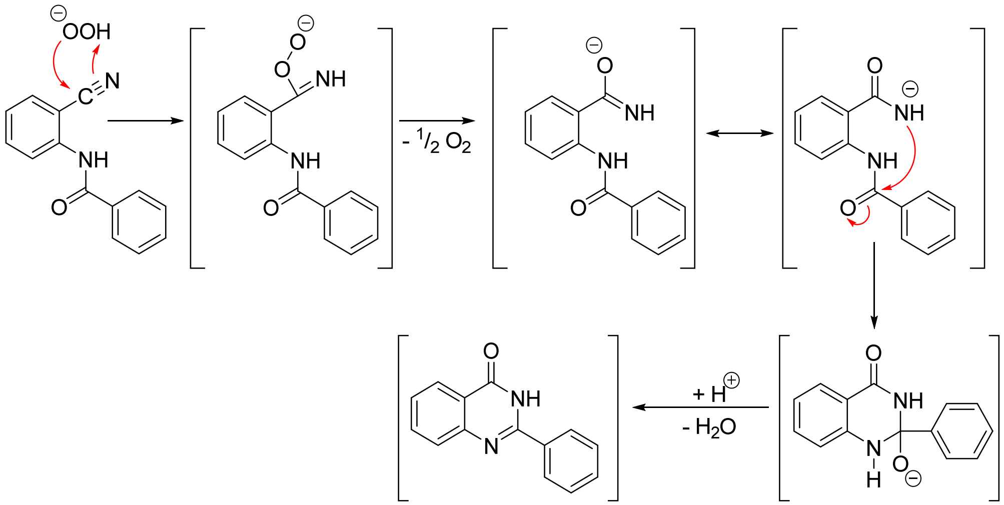
Reaction conditions: 1 eq. 2-aminobenzonitrile, 1.2 eq. bromoarene, 0.5 eq. $Mo(CO)_6$, 1.5 eq. DBU, 3 mol% $Pd(OAc)_2$, 6 mol% *n*-$BuPAd_2$, 4 ml DMF, 130°C, 16 h.; [a] isolated yields; [b] traces in GC/MS

Actually, GC/MS analysis of the crude reaction mixture showed the formation of *N*-(2-cyanophenyl)-benzamide as side product. This indicates the successful oxidative addition of the C-Cl-bond, but followed by dehalogenation, a well-known side reaction for carbonylations. 2-amino-4-chloro-benzonitrile showed almost no conversion to the amide. Electron donating substituents showed appropriate to good yields (**82** (42 %), **83** (64 %), **84** (71 %)), which may be explained by the higher electron density on the NH_2-nitrogen. Interestingly, also corresponding 2-amino-3-cyano-thiophene (86) and -furan (**87**) gave the benzamides although in lower yields (44 % and 50 %). The reaction conditions were additionally tested with the use of the corresponding alcohol as nucleophile to obtain the ester (**85**).

2.3.4 RADZIZEWSKI-Reaction and DIMROTH-Type Cyclization to obtain Quinazolin-4(3*H*)-ones

Based on the synthesis of the cyanoaryl benzamides, the focus lay on a subsequent transformation to cyclized lactams in a one-pot manner. As mentioned before, quinazolinones play an important role in medicine and occur as natural compounds. Therefore, a one-pot procedure offers many synthetic benefits. The idea was to transform the nitrile group into a primary amide which may undergo a subsequent cyclisation to form the pyrimidone ring. In 2006, Bandgar[120] reported about the synthesis of quinazolin-4(3*H*)-ones in acetone *via* RADZISZEWSKI-reaction[121] using urea hydroperoxide (UHP) as a safe and non-hazardous reagent, which was now applied for the one-pot-two-step transformation.

An overview for the reaction is shown in scheme 18. To the crude mixture of the aminocarbonylation was added UHP. This did not act as an oxidant but is deprotonated to form peroxide anions. This moiety is much more reactive than hydroxide ions and undergoes nucleophilic attack on the nitrile group whereby the amidate is formed. Subsequently, intramolecular attack on the secondary amide proceeds to form the hydroxyl quinazolinone moiety, which gives the quinazolin-4-(3*H*)-one after elimination of water in a DIMROTH[122]-type cyclisation.

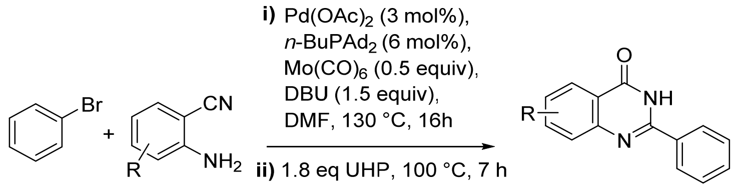


Scheme 18: Mechanism for the UHP mediated quinazolinone synthesis from *N*-(2-cyanophenyl)-benzamides

The intermediate *N*-(2-amidophenyl)-benzamide was not observed in the reaction mixture. Hence, it can be concluded that the intramolecular attack performs very easily due to the resonance stabilization of the final quinazolinone product and the limiting step is the formation of the primary amide form from the nitrile.

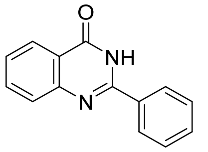
A first test was carried out for simple 2-aminobenzonitrile and bromobenzene. The cyclisation worked well and gave 2-phenyl-quinazolin-4-(3*H*)-one (**59**) in 76 % yield. The structure was confirmed by NMR-spectroscopy. A noticeable change can be seen in the shift of the endocyclic CON*H*-group to δ = 12.55 ppm compared to quianzolin-4(3*H*)-ones. The rest of the signals also underwent a change in the shift, resulting in two broad multiplets and only two distinct signals. Furthermore, 2D-NMR analysis shows the correlation of the carbonyl carbon with the formerly anthranilonitrile phenyl ring, but not with the phenyl ring attached on position 2.

Table 8: One-pot-two-step synthesis of quinazoline-4-(3*H*)-ones

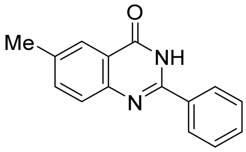


(39)

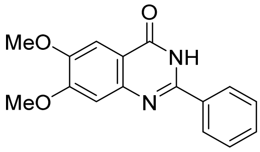
yield^a/entry



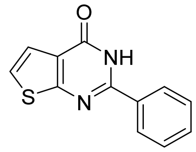
76 % (96 %) **(59)**



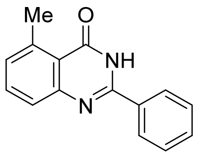
41 % (98 %) **(88)**



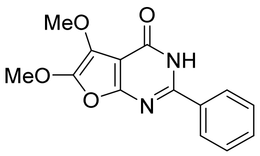
29 % (41 %) **(89)**



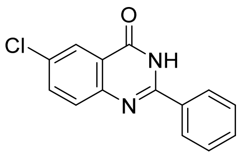
25 % (57%) **(90)**



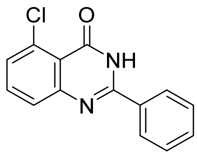
0 % **(91)**



0 % **(92)**



0 % **(93)**



0 % **(94)**

Reaction conditions: 1 eq. 2-aminobenzonitrile, 1.2 eq. bromoarene, 0.5 eq. $Mo(CO)_6$, 1.5 eq. DBU, 3 mol% $Pd(OAc)_2$, 6 mol% *n*-$BuPAd_2$, 4 ml DMF, 130°C, 16 h., addition of 1.8 eq. UHP, 100°C, 7 h.; ^{a}: isolated yields; values in parenthesis give the yield in relation to aminocarbonylative benzamide formation

Afterwards, the UHP mediated transformation was tested for amides with different substituents attached on the nitrile containing phenyl ring as shown in table 8. With a methyl substituent *meta* to the nitrile (**88**), the quinazolinone was obtained in moderate yield over these two steps, though it has to be considered that the carbonylation gave the intermediate amide in only 42 %. Using methoxy substituents (**89**) or the heterocyclic thiophene moiety (**90**), the quinazolinones were obtained in acceptable yields.

Performing this sequential transformation with amides containing electron donating substituents in *ortho* position to the cyano group did unfortunately not give any quinazolinone nor showed the formation of the amide from the nitrile (**91** - **49**). An explanation for this may be the steric hindrance of the substituents which suppresses the attack of the peroxide anion to the nitrile-carbon. Moreover, when using electron poor nitriles, for instance the chlorine substitutedarenes, no cyclisation was observed.

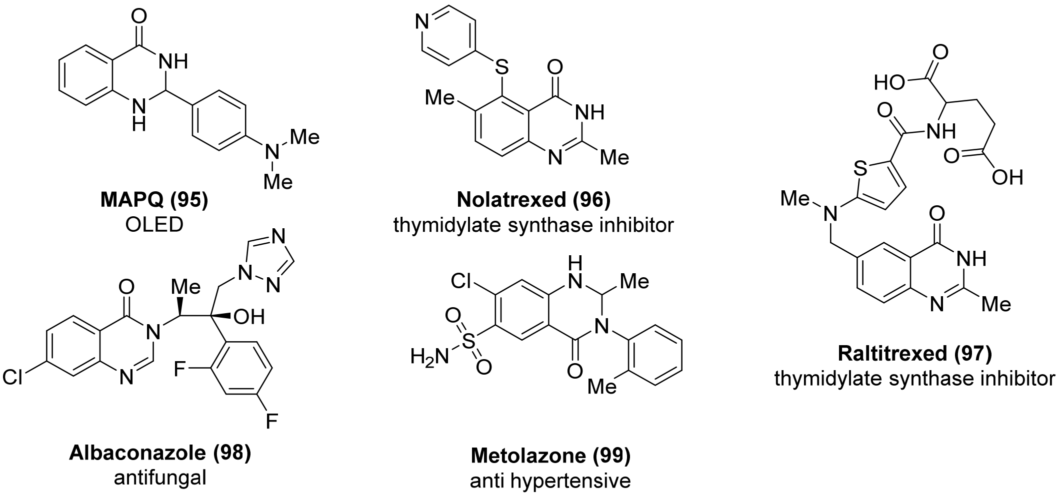
In conclusion it can be stated that the aminocarbonylation of deactivated anilines with phenyl bromide proceeds with acceptable to good yields. A subsequent transformation to quinazolinones can be performed using UHP as hydratization agent. However, the RADZIZEWSKI-reaction does not proceed for electron poor or steric hindered nitriles under the deployed conditions.

3. Synthesis of Dihydroquinazoline-Scaffolds *via* Tandem Imine Condensation-Cyclisation-Reaction in Water

3.1. Base Mediated Synthesis of Dihydroquinazolin-4-(1*H*)-ones[123]

3.1.1. Preface

As aforementioned, quinazolinones are an important heterocyclic structure class. They show a variety of applications in pharmacy and in material science. Beside the sedative effect of previously mentioned methaqualone (fig. 18, **62**), compounds containing the quinazolinone structure are used as antihypertensive, such as metolazone (**99**). Furthermore, raltitrexed[124] (**97**) or nolatrexed[125] (**96**) are used as thymidylate synthase inhibitor drugs in cancer therapy. Another example is albaconazole[126] (**98**) which shows antifungal properties. Moreover, 2-(4-*N*,*N*-dimethylaminophenyl)-quiazolinone (MAPQ, **95**) can be used as emitting layer in organic electroluminescent devices.[127] These are just a few examples of the wide applications of quinazolinone-like moieties.



MAPQ (95)
OLED

Nolatrexed (96)
thymidylate synthase inhibitor

Raltitrexed (97)
thymidylate synthase inhibitor

Albaconazole (98)
antifungal

Metolazone (99)
anti hypertensive

Figure 18: Selected examples of quinazolinone structures

Based on the importance of quinazolinones, many different synthetic approaches have been reported, whereby only a few will be mentioned here. A frequently used method is the NIEMENTOWSKY quinazolinone synthesis by the fusing of anthranilic acid and amides at 130 - 150°C *via* an amido benzamide intermediate. Another useful tool is the

N-alkylation of amines with alcohols *via* hydrogen transfer. The group of Yokoyama demonstrated the formation of quinazolinones *via* Pd-catalyzed domino reaction of benzyl alcohols and anthranilamide.[128] The mechanism of this reaction can be understood as oxidative addition of the alcohol to the Pd^0-species, giving a (η^3-benzyl) palladium complex after elimination of water.

Analogously, Zhou and co-workers used a $[Cp^*IrCl_2]_2$-catalyst for the C-N-bond formation of amines with primary alcohols.[129] Another approach was reported by Deng *et al.*, who showed the quinazolinone synthesis starting from *o*-nitrobenzamide using nontoxic iron as catalyst.[130] Furthermore, Alper and co-workers developed an aminocarbonylative method, starting from *o*-iodo anilines and imidoyl chlorides.[131] In 2014, our group reported an oxidative cyclisation of anthranilamide and benzyl alcohols using TBHP and ZnI_2 in DMSO .[132]

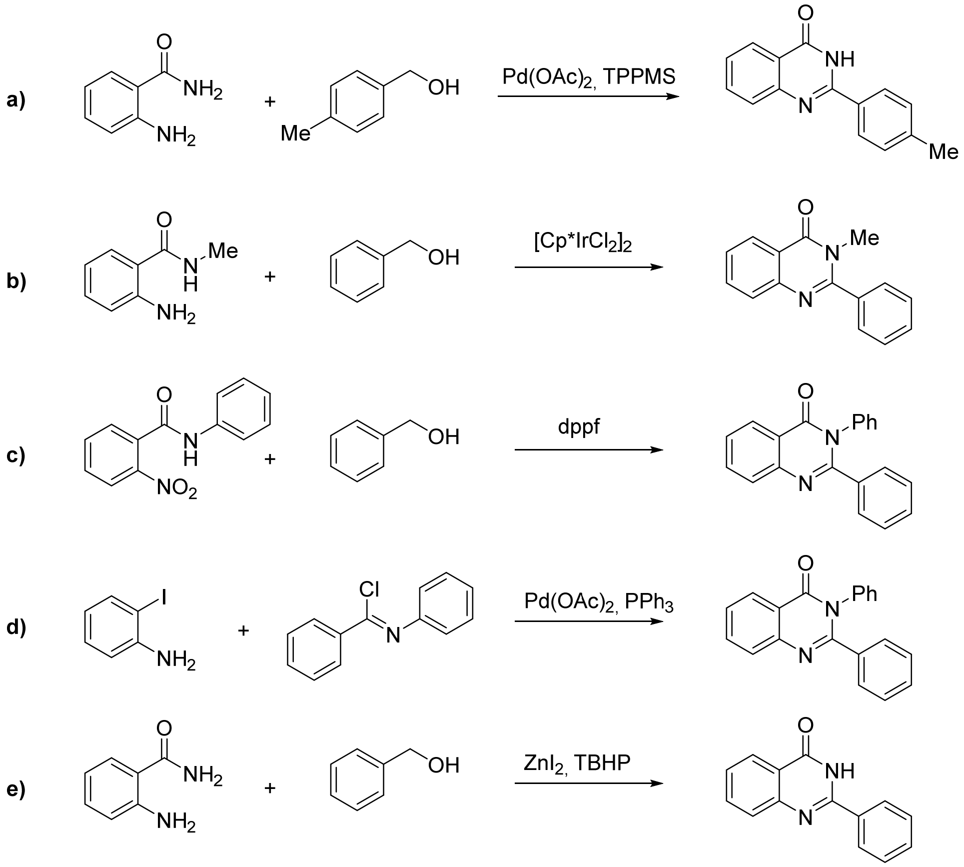
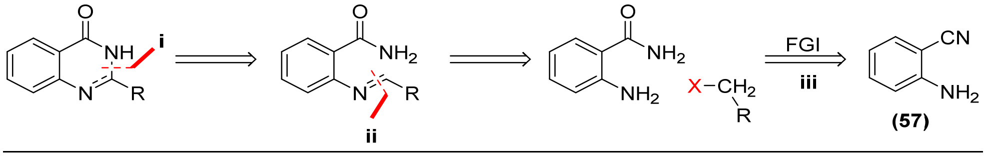


Figure 19: Exemplary reactions for the synthesis of quinazolinones

3.1.2. Motivation

Though the aminocarbonylative synthesis of *N*-(2-cyanoaryl)-benzamides with subsequent transformation to quinazolinones by using UHP was successful, the scope has been shown to be limited to electron donating substituents and non-steric hindered substrates. Additionally, the reaction was carried out in DMF, a toxic and teratogenic solvent, and with harsh conditions. Hence, a different and more convenient procedure for the synthesis of quinazolinones should be developed. The focus lay on anthranilonitriles as starting materials, which are cheap, stable and a broad library of these arenes with different substituents is commercially available. Additionally, the solvent should be changed from DMF to a more convenient solvent such as water and to less drastic reaction conditions.

The quinazolinone synthesis consists of two crucial steps. First, the cyclisation step (**i**), followed by the formation of the C-N-bond (**ii**), and the transformation of the nitrile into a reactive species (**iii**), such as an amide (scheme 19).



Scheme 19: Retrosynthetic approach for the formation of quinazolinones

As C-N bond formation, the reaction of an amine with an aldehyde to give an imine or an intermediate PINNER-salt, respectively, is a convenient method. Indeed, Kesavan and Parakash reported about the enantioselective synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones from 2-amino-benzamides with aldehydes using a Sc(III) catalytical system.[133] Furthermore, Li *et al.* published the formation of 2,3-dihydro-quinazolin4(1*H*)-ones from 2-aminobenzonitriles and carbonyl compounds using $ZnCl_2$ as Lewis acid in DMF.[134] This indicates that the C-N linking *via* the reaction of an amine with an aldehyde is a considerable possibility. However, the aim was to obtain quinazolinones without the use of LEWIS acids or other catalysts, such as iron[135] or TRIP[i].[136]

3.1.3. Synthetic Procedure of the Tandem Condensation-Cyclisation of Anthranilonitrile and Aldehydes with subsequent Nitrile Hydrolysis

The attempt of this project was to achieve the hydrolysis of the nitrile *via* nucleophilic attack of a hydroxide anion likewise the hydroperoxide anion. The C-N-bond formation could be achieved by condensation of the NH_2-group with an aldehyde and subsequent cyclisation should give the target compound. Fortunately, the reaction of anthranilonitrile with benzaldehyde gave the 2,3-dihydro-quinazolin-4-(1*H*)-one in 33 % yield only in the presence of K_2CO_3 as base in water. A side advantage of using water in this reaction is the fact that the product simply precipitates and can be filtered off, which immensely facilitates the workup.

In their work for the Zn(II)-catalyzed formation of quinazolinones, Li and co-workers proposed a mechanism (scheme 20, **a)**) whereat an hemiaminal (**100**) is formed (**i**), which subsequently attacks the nitrile group (**ii**) to give the benzoxazin-4-imine (**101**), which may finally undergo DIMROTH-rearrangement (**iii**) to give the quinazolinone (**102**). This pathway could also be considered for the base catalyzed cyclisation as performed in the work presented here, *via* a deprotonated hemiaminal. However, analysis of the crude reaction mixture showed the presence of the imine (**103**) as the condensation product of the amine and the aldehyde, but no hemiaminal. This indicates a pathway different to the one under LEWIS acid catalysis proposed by Li.

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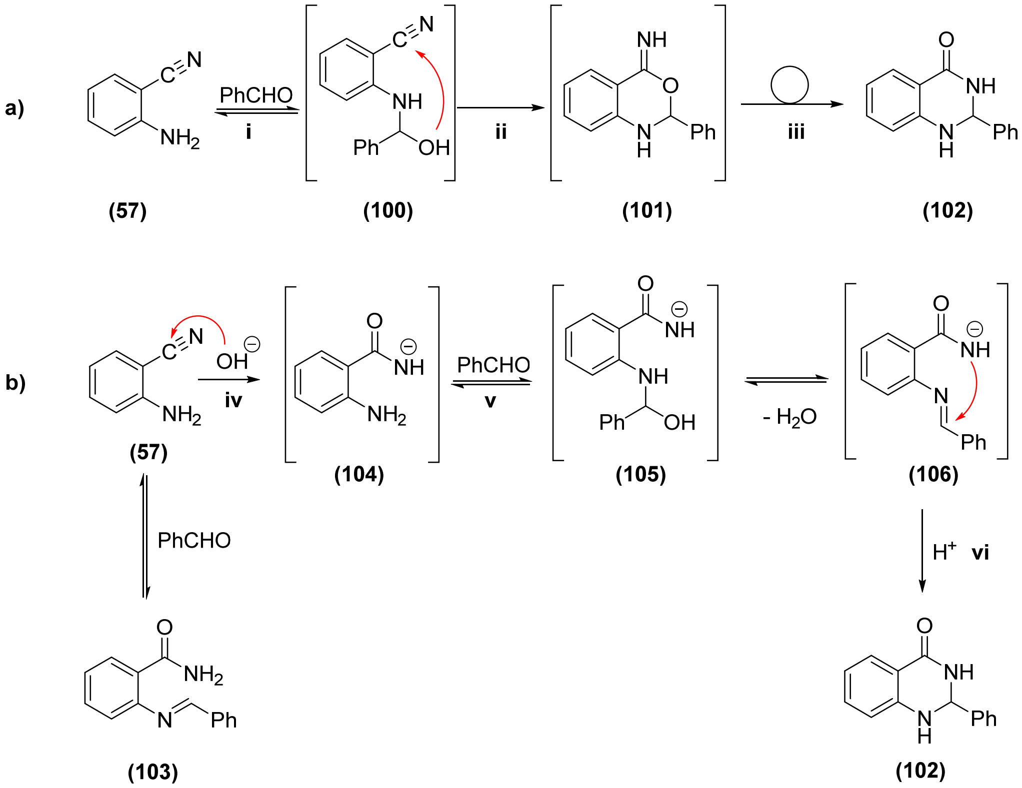
[i] 3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate



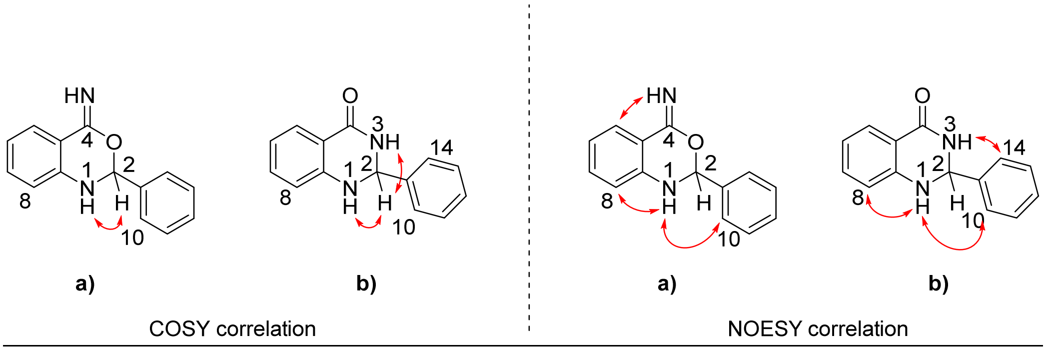
Scheme 90: a) Mechanistical suggestion by Li *et al*; b) mechanistical proposal for the base mediated condensation of 2-aminobenzonitril with aldehydes

The 2-(benzylideneamino)-benzonitrile (**103**) exists in an equilibrium state between the free amine (**57**) and the aldehyde. This equilibrium should be far more on the side of the uncondensed form, since water is used as reaction medium. Eventually, the imine condensation proceeds with the *in situ* formed amide (**iv**) to give **102** (**v**). This may then undergo a nucleophilic attack on the double bond to irreversibly form the cyclized product (**vi**). Therefore, the crucial step is the base catalyzed hydrolysis of the nitrile. To underpin this mechanistical suggestion, a control reaction was performed using only 2-aminobenzonitril and K_3PO_4 at 100°C in water. After 4 hours, nearly all nitrile is converted into the corresponding amide as was monitored by TLC[i]. Thus, a mechanism *via* amide formation and subsequent cyclisation can be assumed as given in scheme 20, **b)**.

---

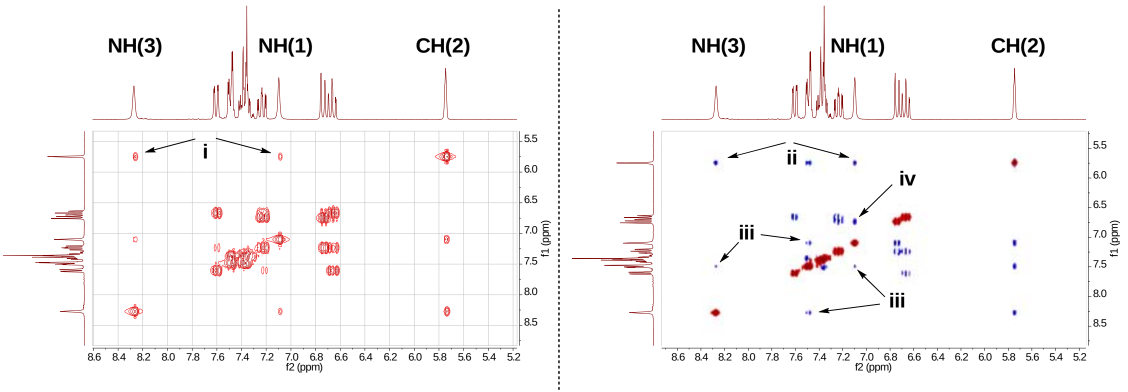
[i] Commercially available anthranilamide was used as reference

Furthermore, it was intended to ensure the structure of the product as the quinazolinone moiety (**102**) and not the isomer benzoxazin-4-imine in that an analogous synthesis for both moieties has been reported.[134, 137] To analyze the structure, 2-D NMR experiments were performed due to the fact that both isomers show differences in the correlation pattern (scheme 21). Contrary to the imine benzoxazin-4-imine **a)**, which gives only an interaction of N*H*(1) and C*H*(2), the quinazolinone **b)** should show a correlation between both of the N*H*-protons and the hydrogen on position 2 in the H-H-COSY spectrum. Additionally, the imine proton should show an interaction in the NOESY-spectrum with C*H*(5) of the annulated phenyl ring, but for the imine structure not with the phenyl ring originating from the aldehyde.



Scheme 21: COSY-/NOESY-correlation of the isomer benzoxazin-imine (**101**), **a)** and quinazolinone (**102**), **b)**

In the ^{1}H-NMR, the N*H*(3) signal appears at δ = 8.28 ppm and the N*H*(1) at δ = 7.11 ppm. Furthermore, a distinct *pseudo*-triplet for the C*H*(2)-proton can be found at δ = 5.75 ppm. The carbon NMR shows a strong low field shifted signal for the carbonyl atom at δ = 163.6 ppm. The H-H-COSY-spectrum shows a correlation for both of the NH-groups with the C(2)-proton (fig. 20, **a)**, **i**). This can be also seen in the NOESY (fig. 20, **b)**, **ii**). Additionally, the NOESY shows an interaction for both of the N*H*-protons with the C*H*(14 + 15)-signal of the phenyl ring attached on position 2 (**iii**), but only the N*H*(1) interacts with the proton C*H*(8) of annulated benzene ring (**iv**). The NMR-spectra for all the further synthesized derivatives follow the same pattern, by what it can be assumed that the quinazolinone was formed in all cases.



a) b)

Figure 20: a) COSY-spectrum for 2-phenyl-2,3-dihydro-quinazolin-4-(1H)-one; **b)** NOESY-spectrum for 2-phenyl-2,3-dihydro-quinazolin-4-(1*H*)-one

Moreover, the structure has been confirmed for the 2-(4-isopropyl-phenyl)-2,3-dihydro-quinazolin-4-(1*H*)-one (**112**) derivative by X-ray analysis (fig. 21). These analytical data prove for the successful formation of the 2,3-dihydro-quinazolinone and not the isomer benzoxazin-4-imine derivative.

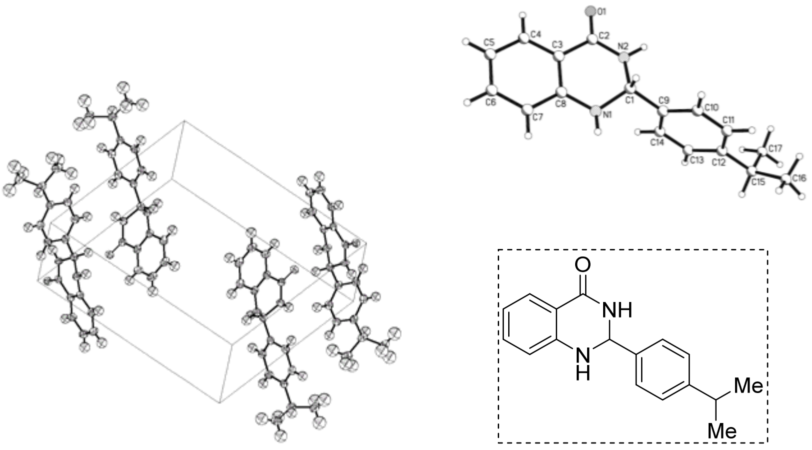
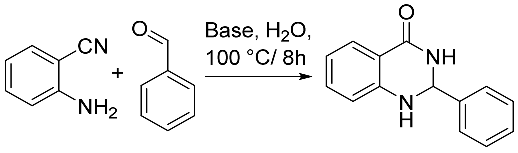


Figure 21: Crystal structure and packing diagram of 2-(4-isopropyl-phenyl)-2,3-dihydro-quinazolin-4-(1*H*)-one (**112**)

After ensuring the structure, different bases and base-concentrations have been tested to improve the yield, as shown in table 9. The best yields (73 - 75 %) were obtained using strong bases such as KOH or K_3PO_4 in equimolar amounts (entries 4 + 6). However, catalytical amounts of these bases did not lead to any product at all (entries 3 + 5). This indicates a strong pOH-dependency for the nitrile hydrolysis to give the primary amide.

Table 9: Base screening for the synthesis of dihydroquinazolinones



(61) **(107)** **(102)**

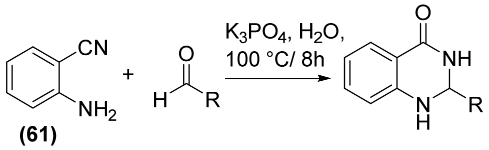
entry	base	amount	yield (%)^a
1	K_2CO_3	1 equiv.	33
2	$CsCO_3$	1 equiv.	0
3	K_3PO_4	0.01 equiv.	0
4	K_3PO_4	1 equiv.	73
5	KOH	0.01 equiv.	0
6	KOH	1 equiv.	75

Reaction conditions: 1 eq. 2-aminobenzonitrile, 1 eq. benzaldehyde, base, 3 ml H_2O, 100°C, 8 h., ^{a} isolated yields

Afterwards, the scope was carried out using different 2-aminocyanoarenes and aldehydes. Though KOH showed comparable yield, the reactions were carried out using K_3PO_4 as base since it is not as hygroscopic as KOH and therefore easier to handle. Satisfyingly, many different substituted 2,3-dihydroquinazolinones can be obtained by the developed method.

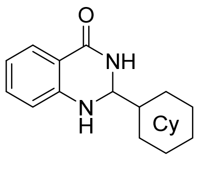
In general, electron withdrawing substituents attached to the aldehyde gave the best yields, though lower compared to the model substrate. However, fluorine attached in *para*-position led to a much decreased yield (**115**). *o*-Methyl benzaldehyde did not give any product. A reason for this may be the bulkyness of the methyl group and therefore a reduced reactivity. Using *p*-methoxy benzaldehyde (**113**) resulted in the highest yields which may be explained by a higher solubility of the aldehyde in water. Fortunately, the reaction is suitable for the easy synthesis of MAPQ (**95**) which, as mentioned before, can be used in electroluminescent layers. In a general sense, this method is not suitable for *α*–H-acidic aldehydes (**109)**. The reaction of 2-aminobenzonitrile with hexanal showed no formation of the quinazolinone, but the aldol-reaction product of the aldehyde, which was the anticipated side reaction under these conditions. However, *iso*-butyraldehyde (**110**) and cyclohexanecarbaldehyde (**108**) gave the cyclized compound in 64 % and 43 % yield, respectively.

Table 10: Scope for the synthesis of 2,3-dihydroquinazolinones with anthranilonitrile and different aldehydes

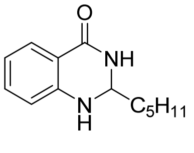


(61)

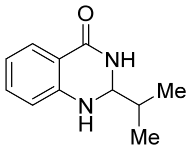
yield^a /entry



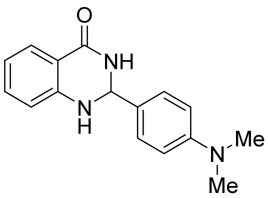
43 % **(108)**



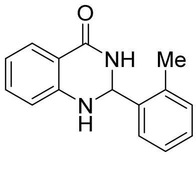
0 % **(109)**



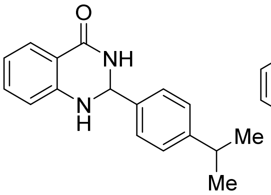
64 % **(110)**



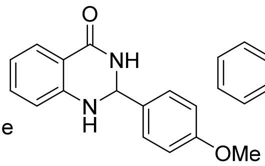
22 % **(95)**



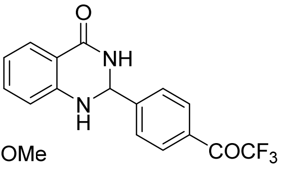
0 % **(111)**



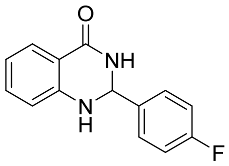
26 % **(112)**



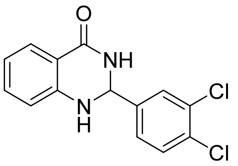
80 % **(113)**



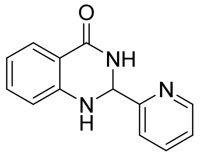
49 % **(114)**



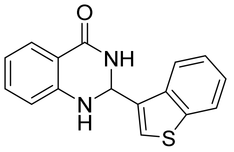
37 % **(115)**



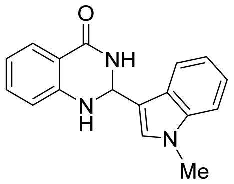
58 % **(116)**



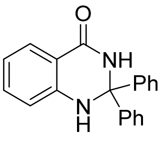
64 % **(117)**



28 % **(118)**



0 % **(119)**

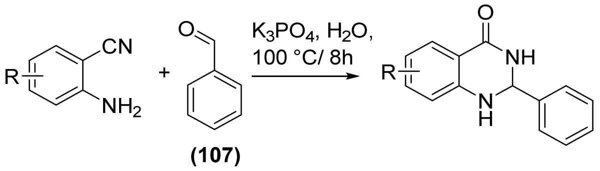


0 % **(120)**

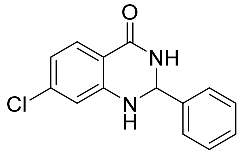
Reaction conditions: 1 eq. 2-aminobenzonitrile, 1 eq. aldehyde, 1 eq. K_3PO_4, 3 ml H_2O, 100°C, 8 h., ^{a}: isolated yields

The success of the reaction for the last-named aldehydes though the presence of an α-proton can be explained by steric hindrance, which suppresses the deprotonation and therefore the formation of the aldol. Benzophenone (**120**) and *N*-methylindole-3-carbaldehyde (**119**) did neither show the formation of the imine nor the quinazolinone, albeit the reaction worked out for benzo[*b*]thiophen-3-carbaldehyde (**118**) with 28 % yield.

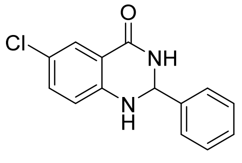
Table 11: Base mediated synthesis of 2,3-dihydroquinazolinones using different 2-amino-cyano-arenes



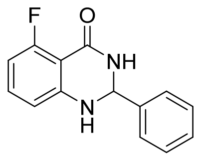
yield^a/entry



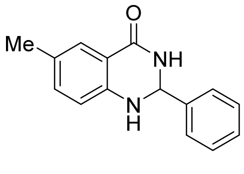
58 % **(121)**



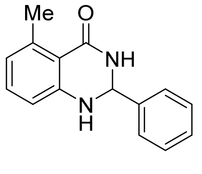
23 % **(122)**



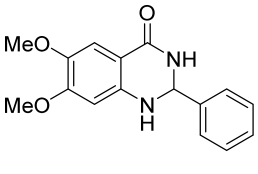
41 % **(123)**



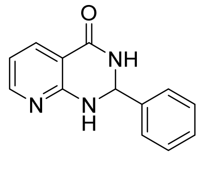
14 % **(124)**



0 % **(125)**



43 % **(126)**

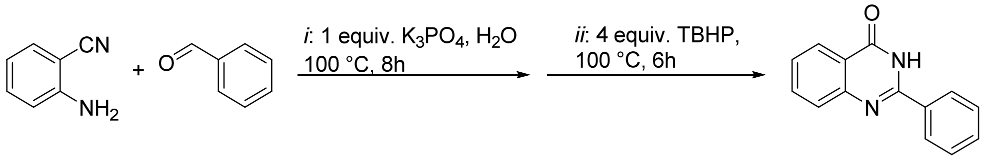


66 % **(127)**

Reaction conditions: 1 eq. 2-aminobenzonitrile, 1 eq. aldehyde, 1 eq. K_3PO_4, 3 ml H_2O, 100°C, 8 h., ^{a}: isolated yields

After performing the reaction with various aldehydes, different 2-amino-cyanoarenes were tested (tab. 11). A methyl group in position 5 (**124**) decreased the yield to 14 %. No conversion was observed when the methyl group was attached *ortho* to the nitrile (**125**), which may be explained by steric hindrance and therefore a decreased formation of the amide. The reaction worked well for 2-amino-3-cyano-pyridine (**127**) and gave 66 % of the pyridopyrimidone.

Following, the sequential one-pot oxidation to obtain 2-phenyl-quinazolin-4-(3*H*)-one (**59**) was carried out exemplarily for the reaction of (**57**) and (**107**) (scheme 22). By adding *tert*-butyl hydroperoxide (TBHP) to the crude reaction mixture and heating it to 100°C, the oxidized form could be obtained in 60 % yield. When using H_2O_2 as oxidant or decreasing the amount of TBHP, less conversion was observed as was monitored by TLC. The NMR-data of the structure are similar to 2-phenylquinazolinone obtained by aminocarbonylation of anthranilonitrile with bromobenzene and subsequent cyclisation.



(57) **(107)** 60 % **(59)**

Scheme 22: Oxidation of 2-phenyl-2,3-dihydroquinazolin-4-(1*H*)-one

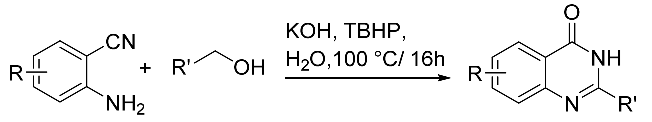
3.1.4. *In situ* Oxidation of Alcohols to Aldehydes for the Synthesis of Dihydroquinazolinones

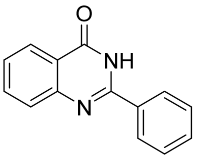
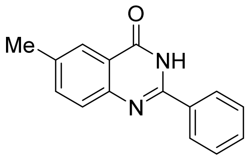
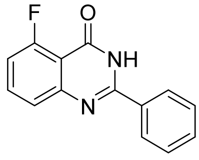
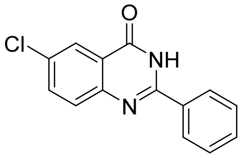
The base-mediated condensation-cyclisation showed to be a convenient method to obtain quinazolinones from aldehydes and anthranilonitriles. Following, the aim was to expand the procedure for a transformation of nitrile to the amide and a simultaneously oxidation of alcohols to aldehydes. The *in situ* formed aldehyde may subsequently undergo condensation with the amine followed by cyclisation to give quinazolinones. As mentioned before, a procedure has been reported for the oxidation of alcohols in the presence of ZnI_2 using TBHP as oxidant followed by *in situ* condensation-cyclisation with anthranilamide to obtain quinazolinones.

Fortunately, the reaction of 2-aminobenzonitrile with benzyl alcohol in the presence of only TBHP and KOH result in the formation of 2-phenyl-quinazolin-4-(3*H*)-one (**92**), but the desired product was obtained only in 35 % yield. When using different additives such as ZnI_2 or $ZnCl_2$, as reported before for similar reactions, or changing to H_2O_2 as oxidant did not lead to any product formation at all. Furthermore, using DMSO as solvent did not give quinazolinones. NMR-data for the isolated compound was similar to the data collected for the products described before.

An explanation for the moderate yields may be the use of TBHP and therefore the radical oxidation process which may lead directly to benzoic acid, albeit analysis showed mediocre presence of aldehyde and only traces of benzoic acid in the reaction mixture but plenty of unconverted alcohol. This may come from the incomplete conversion of benzyl alcohol into the aldehyde but the formation of an α-hydroxybenzyl radical, which is rather unreactive. This inhibitory effect of benzylalcohol has been shown by Hutchings *et al.* in 2014 for the autoxidation of benzaldehyde whereas different additives, such as $PhCH_2OH$, inhibit the radical oxidation.[138] Due to the use of water as solvent, the alcohol is reformed from the radical by re-protonation and for this the condensation does not proceed.

Table 12: Synthesis of quinazolin-4-(3*H*)-ones from anthranilonitriles and alcohols



yield^a/entry	
 35 % **(59)**	 33 % **(88)**
 34 % **(128)**	 31 % **(93)**

Reaction conditions: 1 eq. 2-amino-benzonitrile, 1 eq. alcohol, 2 eq. KOH, 4 eq. TBHP, 3 ml H_2O, 100°C, 16 h., ^{a} isolated yields

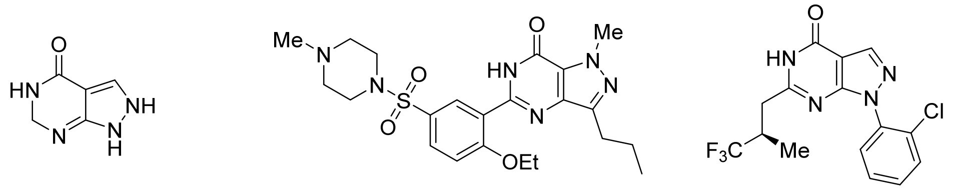
However, 2-phenyl-quinazolin-4-(3*H*)-ones can be synthesized in mediocre yields from the reaction of anthranilonitrile with benzyl alcohol in with the use of TBHP as oxidant (table 12).

In summary, the developed protocol offers a convenient and environmental friendly access to dihydroquinazolinones. This substance class plays a crucial role in pharmaceuticals and the development of materials. The methodology can be extended for the one-pot-two-step oxidation to quinazolinone scaffolds. Furthermore, benzyl alcohol can be applied as aldehyde source by the addition of oxidant, though the employment of alcohol requires further optimization.

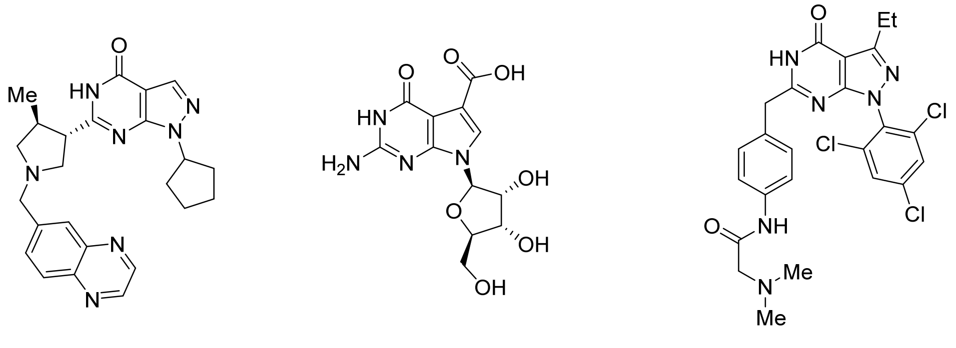
3.2. Base-mediated Condensation-Cyclisation to form Pyrazolo-Pyrimidones

3.2.1. Preface

Though quinazolinones are important representatives of pyrimidone based alkaloids, this structure can be found in many other pharmacologically active compounds. By exchanging the annulated phenyl ring with pyrazole, one comes to 1*H*-pyrazolo[3,4-*d*]-pyrimidin-4(5*H*)-ones, a crucial structural element in a range of pharmaceuticals.



Allopurinol (129) Xanthine oxidase inhibitor | **Sildenafil (130)** PDE5 inhibitor | **BAY 73-6691 (131)** PDE9 A inhibitor



PF-4181366 (132) PDE9 A inhibitor | **Cadeguomycin (133)** Antibiotic | **(134)** CDK/Cyclin inhibitor

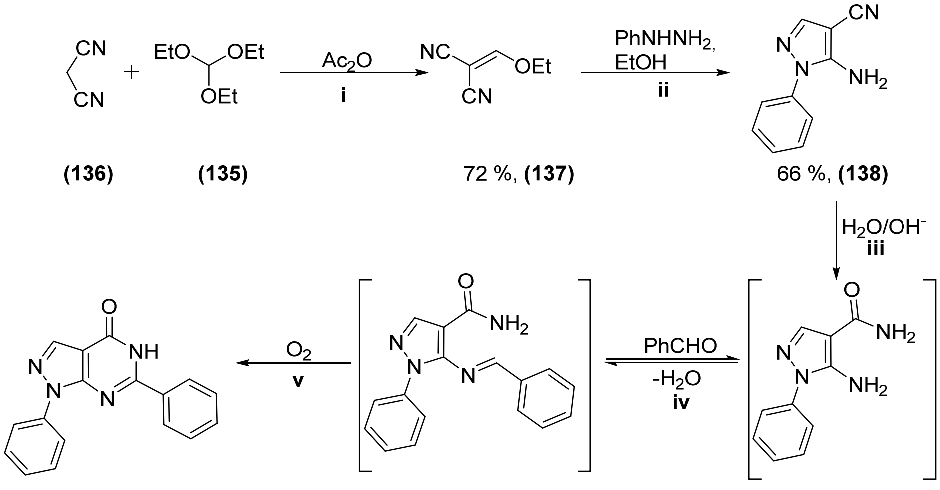
Figure 22: Selected pharmacologically relevant pyrazolopyrimidones

The most simple representative of this class itself, allopurinol (fig. 22, **129**), a xanthine oxidase inhibitor, is listed as an essential medicine by the WHO.[139] This compound is used as uricostatic in the treatment of hyperuricemia and, in addition, in the treatment of life-threatening tumor lysis syndrome.[140] Another prominent compound of this league is sildenafil (**130**), a phosphodiesterase inhibiting drug. Originally developed for the treatment of pulmonary arterial hypertension, it became more famous in the shape of a blue rhombic pill for the treatment of erectile dysfunction by inhibiting cGMP-specific phosphodiesterase type 5, which regulates the blood flow in male genitals.[141] Moreover, the derivatives BAY 73-6691 (**131**)[142] and PF-4181366

(**132**)[143] inhibit the phosphodiesterase subtype PDE9A and are under investigation for the treatment of Alzheimer's disease. A naturally occurring alkaloid, isolated from *streptomyces hygroscopicus*, the ribofuranoside cadeguomycin (**133**), shows antibiotic, anti-viral and cytostatic activities.[144] Furthermore, Markwalder *et al.* reported about the CDK-inhibition of several 1-aryl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]-pyrimidin-4-one derivatives, e.g. compound **(134)**.[145]

3.2.2. Synthesis of Pyrazolo-Pyrimidones

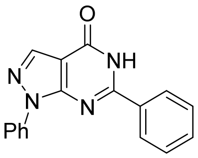
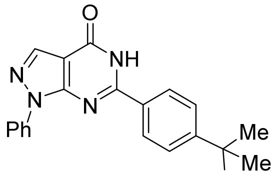
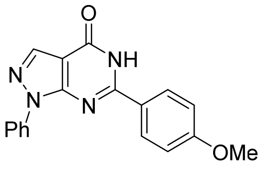
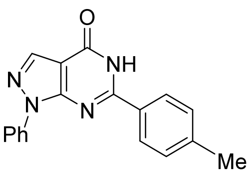
Ongoing from the successful development of a convenient procedure for the synthesis of 1,2-dihydroquinazolin-4-(1*H*)-ones, the scope of this reaction should be extended for the use of 2-amino-3-cyano-pyrazole as substrate. Though this scaffold is not commercially available, it can be easily synthesized (scheme 23). The reaction of trietylorthoformate (**135**) with malonitrile (**136**) in acetic anhydride (**i**) accesses 2-(ethoxymethylene)-malonitrile (**137**).[146] The subsequent reaction of this moiety with phenyl hydrazine (**ii**) gives 5-amino-1-phenyl-pyrazolo-4-carbonitrile (**138**) in moderate yield (66 %) as prescribed in the literature.[147] The *ortho*-cyano-amine was allowed to react with benzaldehyde in water in the presence of base as prescribed before for anthranilonitrile (**iv**). Delightfully, this reaction gave the 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**141**) in 57 % yield



Scheme 23: Reaction overview for the synthesis of 1-phenyl-1*H*-pyrazolo[3,4-*d*]-pyrimidin-4(5*H*)-one (**141**)

Structure (**141**) was identified by NMR-spectroscopy. The proton spectrum shows a broad signal for the N*H*-proton at δ = 12.55 ppm. Furthermore, a distinct singlet for the CH(1)-group can be found at δ = 8.32 ppm. The signals for the two phenyl substituents overlap, resulting in two multiplets.

Table 13: Synthesis of 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones

yield^a/entry	
 57 % **(141)**	 15 % **(142)**
 0 % **(143)**	 0 % **(144)**

Reaction conditions: 1 equiv. 5-amino-1-phenyl-pyrazolo-4-carbo-nitrile, 1 equiv. aldehyde, 1 equiv. K_3PO_4, 3 ml H_2O, 100°C, 16 h. ^{a}: Isolated yields

Contrary to the results for the reaction of anthranilonitrile with aldehydes, no dihydro-pyridopyrimidone was detected, but only the oxidized form. Thus, it can be assumed that the cyclisation product is oxidized *in situ* by air (**v**) to form (**141**), which should be stabilized by conjugation. Different aldehydes were tested for this reaction as shown in tab. 13. In general, the reactivity was significant lower lower compared to the reaction of 2-aminobenzonitrile with aldehydes, and only the desired product of the reaction with *p*-*tert*-butyl-benzaldehyde (**142**) could be isolated. This decrease can on the one hand be explained with the lower solubility of the amine scaffold and on the other hand with a decreased nucleophilicity of the amine. Therefore, the formation of the imine with the aldehyde is decreased due to the electron withdrawal by the endocyclic nitrogen atoms. The last issue is underpinned by detection of unreacted pyrazoloamide, which leads to the conclusion that the hydrolysis of the nitrile takes place in a good manner but the limiting step is either the condensation or the cyclisation. Due to the reversibility of the condensation reaction, which is even promoted by the presence of water, and the dependency of the subsequent nucleophilic attack, no distinct statement which step is the reason for the low conversion can be made. Further investigation on different solvents or performing the reaction in different solvent in the presence of desiccants or LEWIS-acids may lead to higher yields and a more broaden product scope.

3.3. Synthesis of 1,2-Dihydroquinazolin-4(1*H*)-thiones[i,148]

3.3.1. Preface

Organo sulfur compounds represent an interesting and important structure class not only for pharmacologically active substances but also for materials, e.g. OLEDs. Compared to oxygen organyls, the introduction of sulfur in a hydrocarbon moiety coheres with essential changes in the biological behavior and the physicochemical properties of the compound.

Although sulfur is the next homologue of oxygen, the ability to occupy *d*-shells and the different electronegativity (3.5 for oxygen vs. 2.5 for sulfur) result in different bond lengths and dipole moment as well as a varying ability to form hydrogen bonds. Exemplarily, some properties of δ-valerolactam (2-piperidone) are compared to δ-valerothiolactam as reported by Lee and Kummler:[149] whilst the lactam possesses a covalent radius for oxygen of 0.73 Å, the radius is bigger for sulfur in the thio-analogue with 1.02 Å. Furthermore, the dipole moment differs with 3.83 for the lactam and 5.15 for the thiolactam. This change in the dipole moment indicates that the ionic C^+-S^- structure is more present in thiolactams than in lactams which has crucial impact on the reactivity. This is even underpinned by infrared data, which show a more single bond character (88.5 % single bond length) or, in other words, a lower stretching frequency compared to lactams in the area of $\tilde{\nu} = 1110\ cm^{-1}$.[150]

Though these changes may appear small, they result in a significantly different biological behavior. Examples for these changes are the structural related ζ-enantholactam (azocanone) and ζ-enanthothiolactam (fig. 23, **145**). Whereas the oxygen compound shows a toxicity in the range of LD_{50} = 270 mg/kg and a logP = 0.24, the corresponding azocane-2-thione, LD_{50} = 23 mg/kg, is more toxic by around a factor 10 and less soluble in water, with logP = 1. Both show strong effects on the CNS, though it has been reported that thiolactams cause clonic and tonic convulsions a few seconds after injection.[151]

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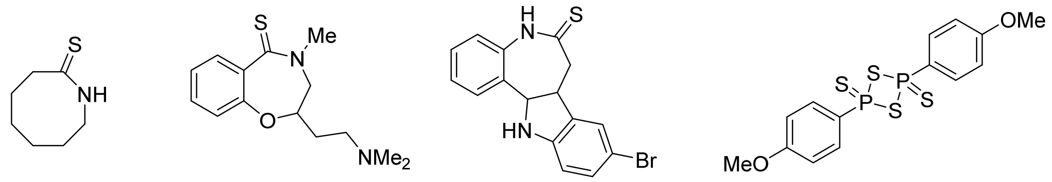
[i] The project was realized with the gratefully acknowledged help of B.Sc. Tom Brunzel



Azocane-2-thione (145) **Rocastine (146)** Histamine antidot **9-Bromo-thiopaullone (147)** GSK-3inhibition **Lawessons reagent (148)**

Figure 23: A selection of thiones and LAWESSONS Reagent for thiation

Moreover, extreme differences can found comparing urea and thiourea. Urea shows no hazards and appears as important metabolite in mammals. It is widely applied in cosmetics as ceratolytic and moisturizer, and in agriculture as nitrogen containing fertilizer or animal feed. Furthermore, urea is used as food additive E 927b, e.g. in bubble gum. Contrary to this, thiourea shows acute oral toxicity with LD_{50} = 125 mg/kg and is classified as goitrogenetic and carcinogenic group 3.[152] However, thiourea is a valuable reagent, e.g. in the synthesis of pyrimidines[153] or in the synthesis of aldehydes from alkenes *via* ozonolysis.[154]

Several thione structures have been reported to show beneficial properties. Examples are rocastine (**146**), which shows protection against histamine induced lethality contrary to the lactam analogue,[155] and thiopaullone (**147**), which, although the inhibition of glycogen synthase kinase-3 is decreased compared to the lactam, shows an increase in the inhibition of cyclin dependent kinase-1 and -5.[156] In proteins, sulfur is a crucial element for the structural composition, e.g. in insulin two chains linked together by two cysteine scaffolds *via* a disulfide bridge.[157] Last, sulfur organyls play an important role in organic synthesis, e.g. in the ESCHENMOSER-sulfide-contraction in the total synthesis of vitamin B12,[158] the RAMBERG-BÄCKLUND-reaction[159] or in the COREY-SEEBACH-reaction.[160] Summarizing, it can be said that the exchange of oxygen by sulfur can be addressed as "small cause, great impact".

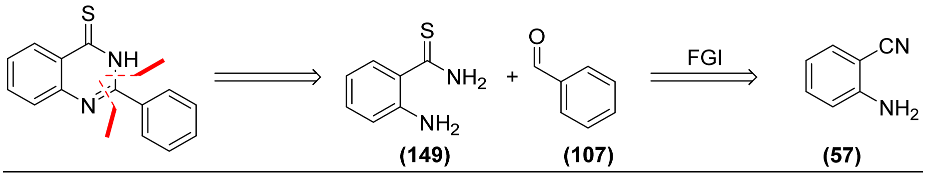
For synthetic aspects, the formation of thioamides and thiolactams is usually limited to thionation reagents such as phosphorus pentasulfide[161] or LAWESSONS reagent (**148**).[162] Furthermore, gaseous H_2S played a role in the formation of thiones.[163]

However, working with these compounds is usually related with disadvantages due to the foul smell and the very high toxicity of the hydrogen sulfide. In addition, these methodologies suffer from selectivity issues if further carbonyl functionalities are present in the substrate moiety. An interesting approach to access thiones has been made by Zhang and co-workers. They were able to synthesize quinazoline dithiones by capturing CS_2 at room temperature.[164] Nonetheless, carbon disulfide is toxic and long exposure may end in nerve damages.

3.3.2. Motivation

Since quinazoline- and quinazolinone-structures play a crucial role in many pharmaceutical active compounds and the exchange of oxygen by sulfur may lead to essentially different biological properties, further considerations of this work focused on the formation of quinazolinthiones.

Regarding the approved synthesis of quinazolinones from 2-amino benzamide, the approach was to obtain the pyrimidine-thione ring *via* cyclisation of the related thioamide in order to avoid the use of classical thionation reagents (scheme 24). Albeit, no data could be found for the reactivity of thioamides with such double bond systems and it was unsure if the thione species is stable against water. Another concern was the pathway of the reaction. If the reaction proceeds as suggested by Li for corresponding 2-amino benzamides it would lead to the formation of quinazolinones by nucleophilic attack of the hemiaminal oxygen, followed by sulfur extrusion (as shown on page 56). In such a case, the product would be the dihydroquinazolinone scaffold and not the desired thione species.

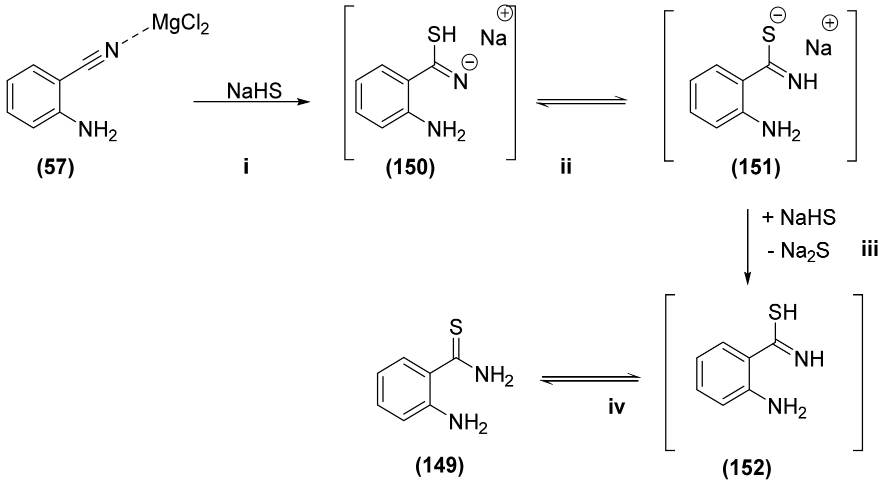


Scheme 24: Synthetic consideration to access thiolactams

3.3.3. Synthesis of 2-Aminobenzothioamides from Anthranilonitrile

A priori, 2-amino benzothioamides were synthesized. In 2005, Manaka and Sato reported on the formation of thioamides from aromatic nitriles using $MgCl_2$ as LEWIS-acid and NaHS to avoid the handling of hazardous hydrogen sulfide. Fortunately, a modification of their procedure led to the formation of 2-amino-benzothioamide (**149**) from anthranilonitrile (**57**) at room temperature in 88 % yield. However, higher temperatures led to a drastic decrease of product formation.

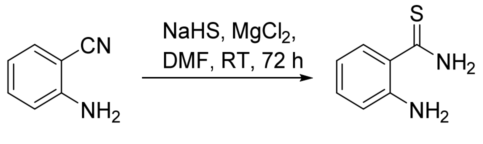
The mechanism of the thioamide formation may be as follows (scheme 25): The magnesium chloride activates the nitrile (**57**), which is attacked by the nucleophile hydrosulfide anion in the first step (**i**) to form the sodium thioamidate (**150**). After rearrangement (**ii**) and protonation (**iii**) by another NaHS, the final thioamide (**149**) is formed (**iv**). The driving force of this reaction is assumed to be the formation of the Na_2S.



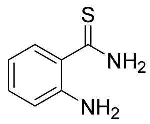
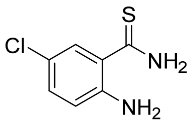
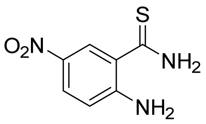
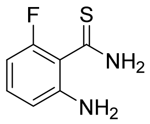
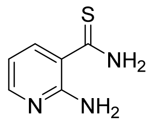
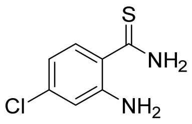
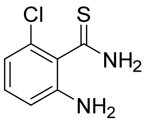
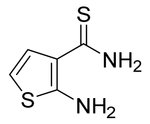
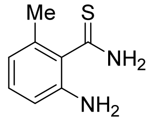
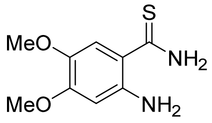
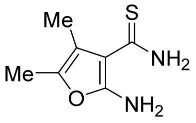
Scheme 25: Proposed mechanism for the thiolysis of the nitrile

The ^1H-NMR-spectrum of (**149**) shows two broad N*H*-signals in the low-field area at $\delta = 9.63$ ppm and $\delta = 9.29$ ppm. These relate to the newly formed thioamide, giving one signal for each proton due to the distinct double bond character of the C-N-group, resulting in magnetic inequivalence of the protons. Furthermore, the signals of the aromatic H-nuclei and the two protons of the amino group are visible. The ^{13}C-NMR shows a significant low-field signal at δ = 200.1 ppm, indicating the successful transformation of the nitrile into a thioamide.

Table 14: Thiation of different 2-amino-benzonitriles



(57) **(149)**

yield^a/entry			
 88 % **(149)**	 96 % **(153)**	 80 % **(154)**	 97 % **(155)**
 93 % **(156)**	 78 % **(157)**	 62 % **(158)**	 85 % **(159)**
 0 % **(160)**	 0 % **(161)**	 0 % **(162)**	

Reaction conditions: 0.5 mmol nitrile, 2 eq. NaHS·H_2O, 1 eq. $MgCl_2$, 2 ml DMF, 20°C, 72 h. ^{a}: isolated yields

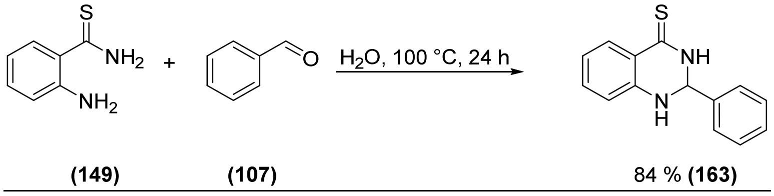
In the following, different 2-amino-cyanoarenes were tested for the formation of the corresponding thioamide. The conditions showed to be appropriate for a range of electron withdrawing substituents and for the heterocyclic 2-amino-3-cyano-thiophene (**159**) as well as the pyridine derivative (**156**). However, electron donating substituted nitriles did not show any thioamide formation (tab. 14, **160** – **162)**.

Notably, the thioamides proved to be unstable against heating and to undergo the elimination of H_2S to reform the anthranilonitrile. This may be the reason for the low yields when the reaction with NaHS was performed at higher temperatures.

3.3.4. Synthesis of 1,2-Dihydroquinazolin-4-(1*H*)-thiones

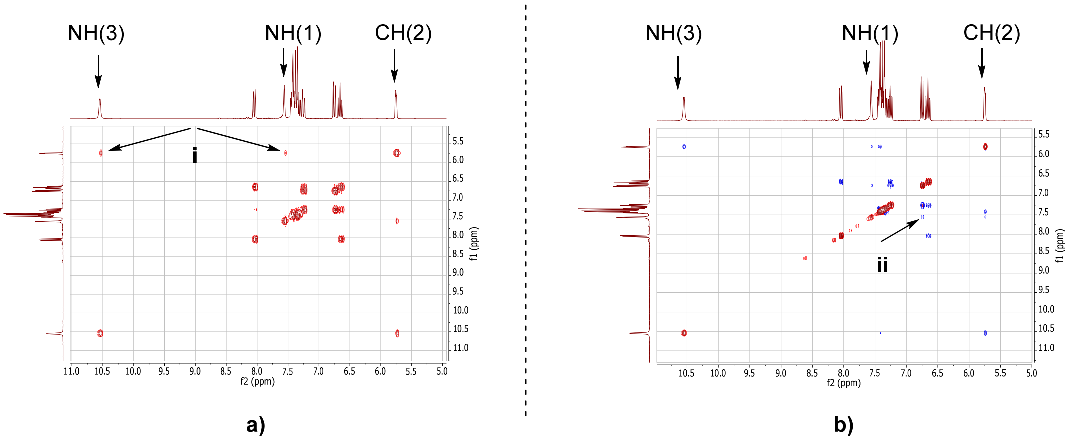
In the following, the reaction of the previously synthesized thioamides with aldehydes was investigated. Fortunately, the reaction of anthranilothioamide with benzaldehyde gave the dihydroquinazolinthione (**163**) in very good yield even without the use of a base or an additive just in water (scheme 26). Only slight increase of the reaction time to 24 hours was required.

Delightfully, the thioamide seemed to be stable against hydrolysis and showed a higher reactivity compared to the amide. The outcome of this reaction underpins the suggested mechanism for the formation of dihydroquinazolinones (page 56), whereas a nucleophilic attack of the NH_2-group nitrogen was assumed and not a formation of a hemiaminal followed by cyclisation *via* attack of the OH-group to the nitrile carbon. As discussed above, a mechanism such as the latter would result in an sulfur extrusion.



Scheme 26: Synthesis of 2-phenyl-1,2-dihydroquinazolin-4(1*H*)-thione (**163**)

The structure (**172**) has been identified by NMR-analysis. The ^{1}H-NMR-spectrum shows two clear N*H*-signals at $\delta = 10.45$ ppm and $\delta = 7.56$ ppm. The signal for N*H*(3) is high field shifted compared to the oxygen analogue (**102**), which gave a signal at $\delta = 8.28$ ppm. The signal for the C*H*(2)-nucleus appears at $\delta = 5.75$ ppm, giving a dd due to the couplings with both N*H*-protons, as shown below. The coupling constants are $^3J = 3.7$ Hz and $^3J = 1.9$ Hz. A strongly low-field shifted signal was detected in ^{13}C-NMR-analysis at $\delta = 189.2$ ppm. Again, the shift differs compared to the lactam species (**102**), which gave a signal at more high-field shifted at $\delta = 163.6$ ppm. This indicates the preservation of the thione species and the formation of the desired thiolactam. Furthermore, the successful ring closure was proved by H-H-COSY- (fig. 24, **a)**, **i**) and NOESY-experiments (fig. 24, **b)**, **ii**) which both show the correlation of both of the endocyclic N*H*-groups with the proton on position 2 (in accordance with the oxygen-derivative, page 52).



a)

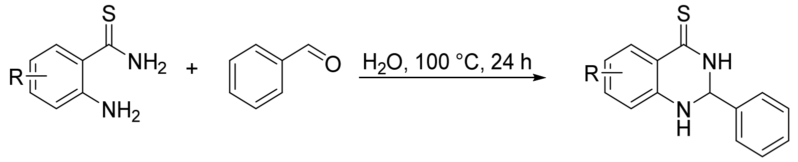
b)

Figure 24: H-H-COSY- (**a)**) and NOESY-spectra (**b)**) for 2-phenyl-1,2-dihydroquinazolin-4(1*H*)-thione (**163**)

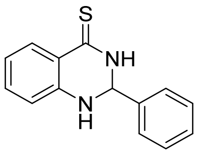
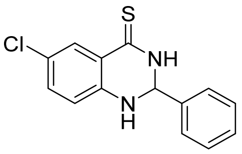
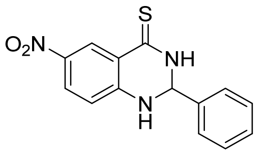
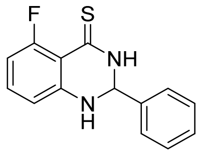
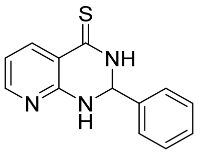
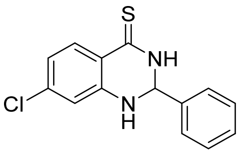
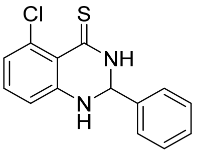
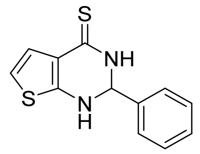
Subsequently, the scope of the reaction was extended to different aldehydes and the previously synthesized thioamides (tab. 15). Generally, the reaction worked with high yields and tolerates a broad range of substituents. Only the 6-chloro anthranilothioamide (**169**) and the 2-amino-3-thioamido-thiophene (**170**) showed decomposition during the purification process. Due to the limitations of the prior thioamide synthesis, only electron withdrawing substituents attached to the amine were tested. Fortunately, most of the substrates show only a slight decrease in the yield, whereas the strongest effect can be observed for chlorine attached *para* to the thioamide group (**168**). This reduction in yield can be explained by the withdrawal of electron density from the thioamide and therefore a decrease in the nucleophilicity.

In addition, electron donating as well as withdrawing substituents on the benzaldehyde are tolerated for this reaction (tab. 16)). Using ethanal (**177**) resulted in a fair yield which may be explained by the lower boiling point compared to benzaldehyde and therefore accumulation in the gaseous phase. Other aliphatic aldehydes (**178**, **179**, and **180**) gave yields above 80 %, and since no base is used for this reaction, the procedure is additionally applicable for *α*-protic aldehydes. The lowest yield was obtained for benzo[*b*]thiophene-3-carbaldehyde (**182**). This can be due to the low solubility in water.

Table 15: Synthesis of 1,2-Dihydro-quinazolin-4(1*H*)-thiones from different thioamides



(107)

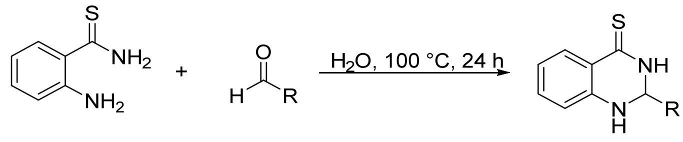
yield[a]/entry			
			
84 % **(163)**	68 % **(164)**	79 % **(165)**	88 % **(166)**
			
73 % **(167)**	57 % **(168)**	0 %b) **(169)**	< 50%b) **(170)**

Reaction conditions: 0.5 mmol thioamide, 1 eq. benzaldehyde, 2 ml H_2O, 100°C, 24 h. [a]: isolated yields, [b]: product decomposed during purification

Noteworthy, the thiolactams showed to be unstable when solved and eliminate sulfur fairly easy whilst standing in solution. This may be due to the more distinct single bond character. Therefore, the sulfur may easily undergo oxidation and extrusion of sulfur oxides to give the quinazoline. Still they are stable enough to be purified *via* recrystallization and show no such decomposition when isolated.

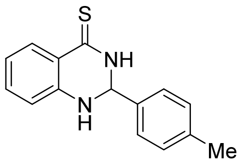
In summary, a convenient and environmental friendly procedure for the synthesis of 1,2-dihydroquinazolin-4(1*H*)-thiones has been elaborated. The required thioamides were synthesized using NaHS as solid HS-source avoiding the use of gaseous hydrogen sulfide. Notably, the thioamides have been shown to be more reactive compared to the amides, hence no addition of base or LEWIS-acid is required for the tandem cyclisation-condensation. A range of functionalized thiones can be easily synthesized by this protocol.

Table 16: Synthesis of 1,2-Dihydro-quinazolin-4(1*H*)-thiones from different aldehydes

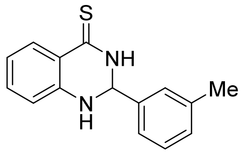


(149)

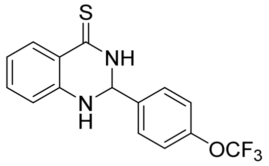
yield[a]/entry



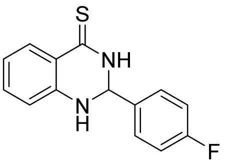
93 % **(171)**



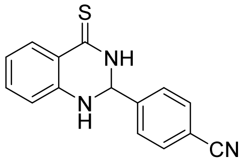
82 % **(172)**



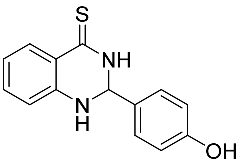
74 % **(173)**



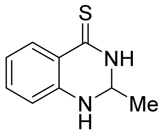
75 % **(174)**



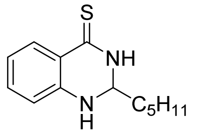
80 % **(175)**



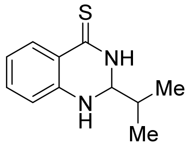
75 % **(176)**



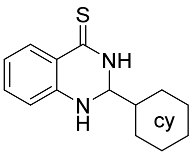
57 % **(177)**



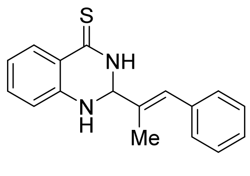
85 % **(178)**



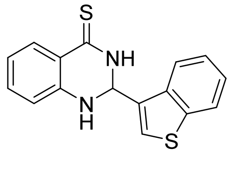
82 % **(179)**



84 % **(180)**



71 % **(181)**



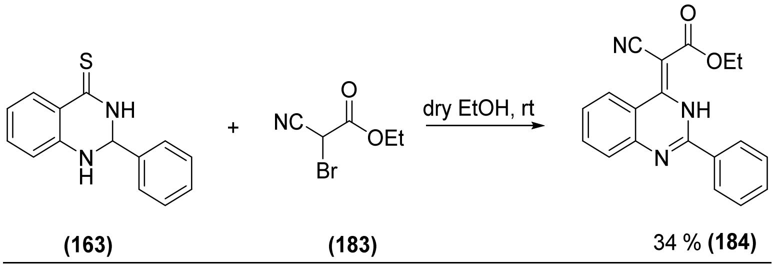
46 % **(182)**

Reaction conditions: 0.5 mmol anthranilothioamide, 1 eq. aldehyde, 2 ml H_2O, 100°C, 24 h. [a]: isolated yields

3.3.5 Derivatization of the Thiones *via* Sulfur Exchange Reactions

In the end, ongoing from the thione species, further possibilities to obtain derivatives of quinazolines have been in the focus of investigation. As mentioned above, the thiones are more sensitive for substitution reactions compared to carbonyl compounds.

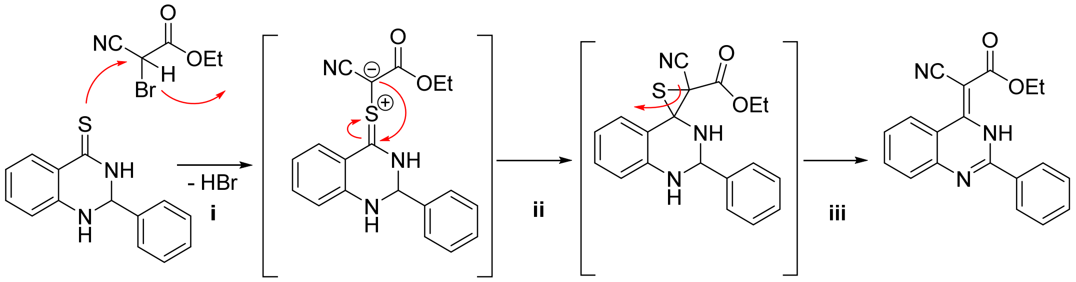
Therefore, two different procedures have been applied. First, the thiones were reacted with *o*-bromo-cyanoethyl acetate in an electrocyclic sulfur extrusion reaction (scheme 27). This S_N2-type reaction follows the principle of the aforementioned ESCHENMOSER-reaction. The bromo ester is easily accessible by bromination of commercially available ethyl cyanoacetate.



Scheme 27: ESCHENMOSER sulfide contraction of 2-phenyl-1,2-dihydro-quinazolin-4(1*H*)-thione

Subsequently, the ester reacts with the thiolactam as given in scheme 28. The thiones show remarkable reactivity whereas the reaction already takes place at room temperature without the need of a promoting agent such as a base.

The mechanism can be understood as an initial nucleophilic attack of the sulfur, forming an S-ylid (scheme 28, **185**) and releasing HBr. The ylide undergoes rearrangement to form the thiirane (1**86**). The thiirane may subsequently undergo elimination of elemental sulfur to form the more stable alkene as the final product. The *in situ* formed sulfur is believed to be responsible for the oxidation of the endocyclic amine moiety to form the quinazolin (**184**). Unfortunately, due to the high tendency of the thione to eliminate sulfur, as discussed above, the reaction proceeds only in mediocre yield. The elimination product was found to be the main side product. Trials for a subsequent decarboxylation of the ester following the KRAPCHO-protocol failed so far. However, the scaffold accessed by the sulfur substitution shows the potential for further derivatization on the nitrile functionality.



(149) **(185)** **(186)** **(184)**

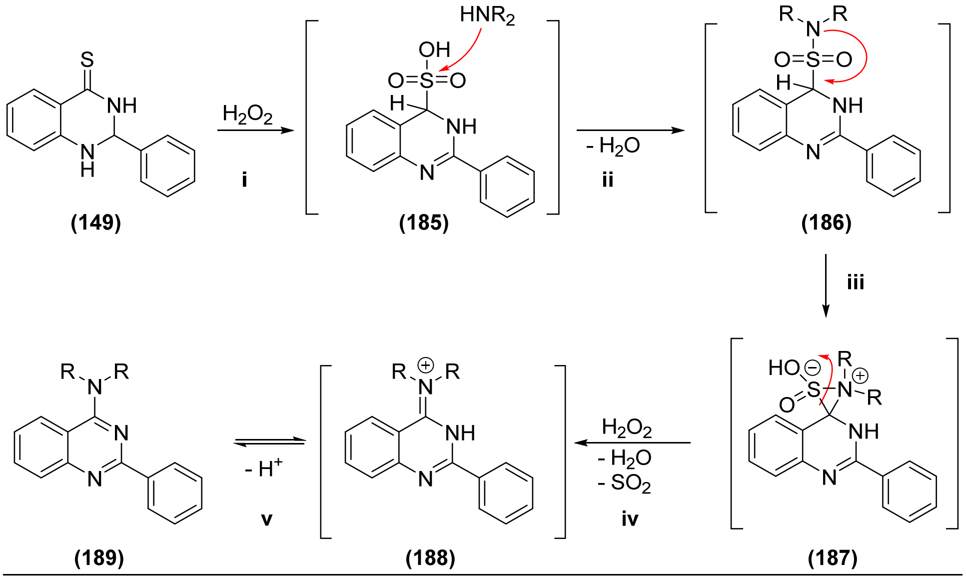
Scheme 28: Assumed mechanism for the sulfur substitution *via* ESCHENMOSER sulfide contraction

Interestingly, when performing the reaction with 2-bromo malonethylester, no sulfur substitution product was detected but the quinazoline formed by sulfur elimination.

As a second derivatization, sulfur substitution has been performed following a protocol developed by Langer and co-workers.[165] They showed the reaction of 1,2,4-triazolo[1,5-*c*]quinazoline-5(6*H*)-thiones with secondary amines to give 5-substituted quinazolines. The objective was now to obtain 4-substituted quinazolines by a similar protocol.

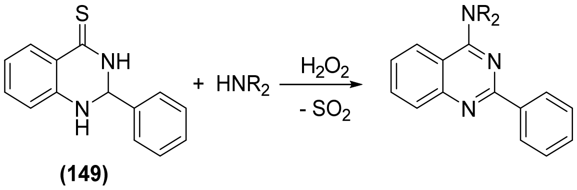
Fortunately, the reaction of 1,2-dihydroquinazolin-4(1*H*)-thione with amines under assistance of H_2O_2 resulted in the substitution of sulfur to obtain the desired functionalized scaffolds. The reaction was carried out with morpholine as secondary amine, and *n*-butylamine and allylamine as primary amine. The reaction showed the best yields for *n*-butylamine, but still fair formation of the products for morpholine and allylamine. Again, the main side product is 2-phenylquinazolin due to the elimination.

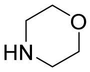
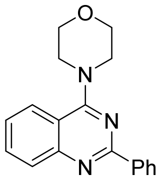
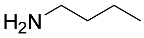
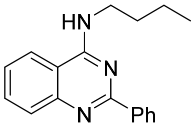
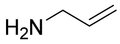
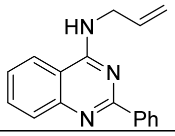
The reaction of thiones with amines under the presence of H_2O_2 can be understood in similar to the RAMBERG-BÄCKLUND-reaction in analogy to the ESCHENMOSER-reaction. The oxidant initially oxidizes the sulfur to form a sulfonic acid (**185**, **i**). By reaction with the amine (**ii**), an intermediate sulfonamide (**186**) is formed which subsequently forms an episulfon derivative (**187**, **iii**). Elimination of SO_2 (**iv**) gives the imine (**188**), which tautomerizes to the amine (**189**, **v**, scheme 29). Due to the presence of a strong oxidant, the dihydroquinazoline moiety is transformed into the quinazoline.



Scheme 29: Assumed mechanism for the oxidative sulfur substitution by amines

Table 17: Oxidative sulfur substitution by amines



amine	product	yield^a/entry
		30% **(190)**
		69% **(191)**
		30%^{b} **(192)**

Reaction Conditions: 1 eq. Thiolactam, 1 eq. amine, 4 eq. H_2O_2, 80°C, finished after addition of H_2O_2, ^{a}: isolated yields, ^{b}: reaction was carried out at rt.

The reaction using primary amines may in principle lead to two isomer products, containing the imine exocyclic or with an endocyclic C-N double bond. The presence of an exocyclic imine was confirmed for (**192**) by NOESY NMR-experiment, showing the correlation between the N*H*-proton and the signal for the CH(7) nucleus (fig. 25,, **i**). The signals have been identified *via* HMBC-, HSQC- and H-H-COSY experiments.

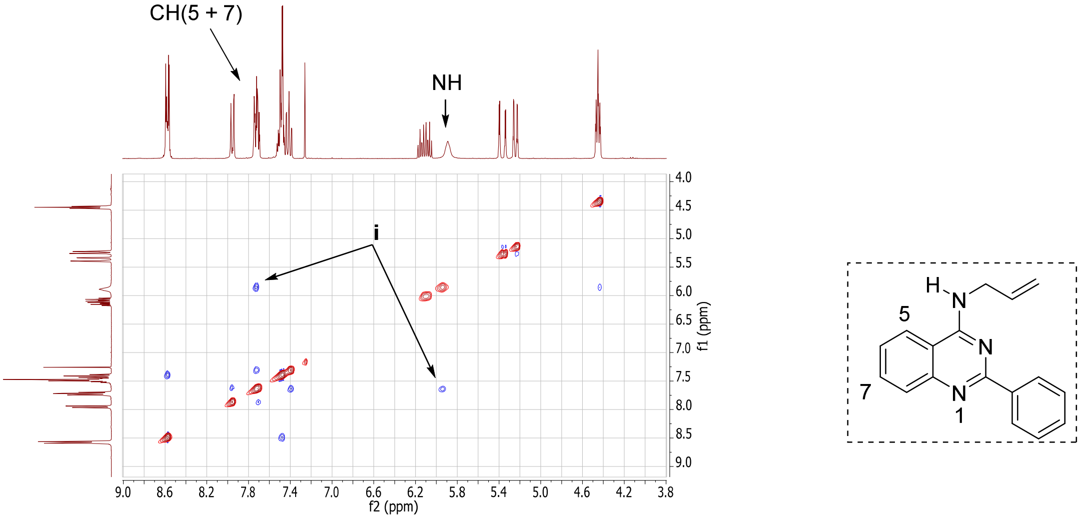


Figure 25: NOESY-spectrum for (**196**)

In conclusion, sulfur derivatives of quinazolinones are interesting precursors for the synthesis of 4-substituted quinazolines. Two different sulfur substitution reactions have been applied on preliminary synthesized 1,2-dihydroquinazolin-4(1*H*)-thiones. By the reaction with *o*-bromo-cyanoethyl acetate, further substitution of the scaffolds is enabled, regarding the nitrile moiety or the ester functionality. Moreover, oxidant supported substitution with amines extends the cycle with another *N*-scaffold. The use of functionalized amines may lead to a range of possibilities for further modifications such as cyclisation or the linkage to another molecule.

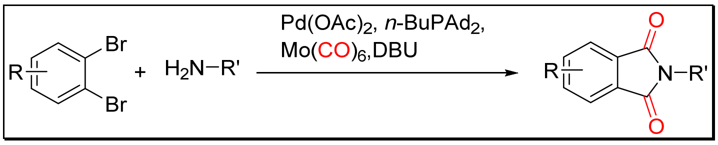
4. Summary and Outlook

The synthesis of heterocycles is an important and challenging topic in synthetic organic chemistry. The development of new pharmaceuticals, agrochemicals and materials demands for new synthetic strategies for the lab scale synthesis and easy and convenient access to variously functionalized compounds. Especially in the screening of new compounds regarding their applications (bioactive or in material science), clean reactions are required for the cost-efficient synthesis of a broad range of derivatives. Moreover, industrial processes require ecologically and economically efficient procedures which allow for the targeted synthesis of such hetero organyls. The use of catalysts in such processes offers big advantages regarding the atom economy and the selectivity in micro and industrial scale. By the choice of the catalyst, high yields with better selectivity and functional group tolerance can be achieved.

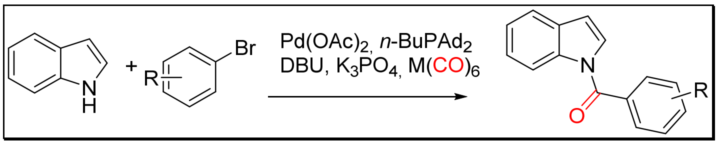
A particular interesting method is the use of catalyzed three-component reactions using carbon monoxide as C1 building block. This method allows for the direct functionalization and chain elongation of various scaffolds. By the development of CO-gas free protocols, carbonylative Pd-catalyzed reactions are an even more powerful tool for the lab-scale synthesis of heteroarenes and heterocycles avoiding the need of special equipment such as autoclaves or special safety regulations as are required for the use of gaseous carbon monoxide.

Furthermore, tandem reactions play a significant role in the synthesis of heterocycles. The *in situ* transformation of the substrate into a “high” reactive species, which may undergo a cascade of follow up reactions, offers the benefit that the isolation of several intermediate products can be bypassed. This reduces the amount of time and solvents, which is in particular important regarding the aim for a greener and sustainable chemistry, though the demand for high performance materials and high selective drugs steadily grows.

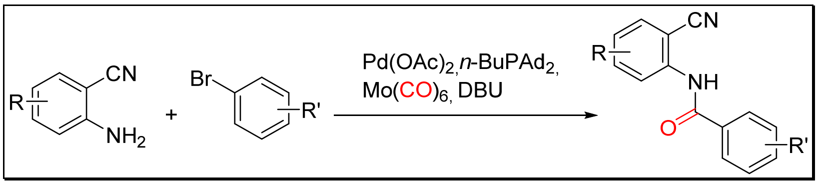
The first objective of the work presented here was to develop synthetic strategies for the easy access of functionalized heterocycles *via* three-component carbonylative Pd-catalyzed coupling reactions. Initially, a protocol for the bis-aminocarbonylation of dibromoarenes has been elaborated to allow for the easy access of phthalimides. This structure plays significant role in a range of highly bioactive compounds, such as in the treatment of viral diseases or cancer. The developed procedure benefits from the use of bromoarenes, which may on the one hand be regarded as “low” energy compounds, and on the other hand, offer a wide range of substituted substrates.



Furthermore, a protocol for the direct aminocarbonylative synthesis of *N*-benzoyl indoles has been developed. Derivatives of indole play a superior role in natural compounds and the development of a range of pharmaceuticals. Hence, investigations on new derivatization strategies for this scaffold are still in the interest of research, though indole cannot be regarded as a newborn compound. By using K_3PO_4, the relatively inert amine of indole can be transformed into the indloyl anion, which may subsequently undergo the formation of the desired amides. The use of Pd-catalysis is a convenient alternative to the use of highly reactive substances such as acid chlorides, which usually coheres with selectivity issues.

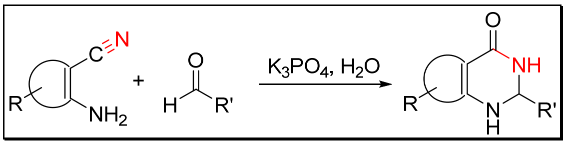


Another aminocarbonylative procedure has been developed using deactivated anilines as nucleophiles. A cyano-group attached *ortho* to the amine strongly decreases the nucleophilicity, albeit the emerging products are interesting regarding the possibilities of further functionalization. One possibility, the one-pot-two-step transformation into 2-phenyl-quinazolin-4(3*H*)-ones by RADZISZEWSKI-reaction/DIMROTH-type cyclisation, has been shown. The nitrile is possible to undergo *in situ* hydrolysis by the addition of urea hydroperoxide with subsequent cyclisation. The developed procedure benefits from the use of anthranilonitriles, which allow for the use of a broad scope of commercially available substrates.

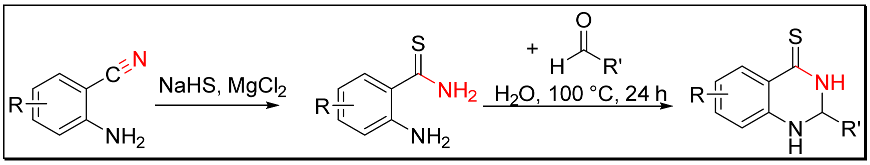


All the elaborated aminocarbonylations were realized using $Mo(CO)_6$ as alternative CO source, whereas the use of gaseous carbon monoxide can be avoided. The reactions were carried out in simple sealable glass tubes, and no high pressure equipment is required, which allow for the application in common organic synthesis laboratories.

Ongoing from the one-pot-two-step synthesis of quinazolinones, a different approach has been realized. By the *in situ* hydrolysis of anthranilonitrile followed by subsequent condensation/cyclisation with aldehydes, 2-phenyl-1,2-dihydroquinazolin-4(1*H*)-ones are accessible. The reactions were carried out using water as solvent according the understanding of a greener and sustainable chemistry. The obtained scaffolds are still in the interest of pharmaceutical research and have shown applicability in material science. 2-(4-dimethylaminophenyl)-1,2-dihydroquinazolin-4(1*H*)-one (MAPQ), which shows potential in the use for OLEDs, can be obtained using the developed tandem-reaction. An *in situ* oxidation of alcohols with *tert*-butyl hydroperoxide and subsequent reaction gives also access to dihydroquinazolinones, although the yields showed to be lower due to the incomplete conversion of the alcohol into the aldehyde. A variant of the developed protocol was used to synthesize pyrazolopyrimidones as another biorelevant lactam containing scaffold.



Delightfully, using the thioamide derivative of athranilonitrile, proved to be a convenient substrate for the synthesis of 1,2-dihydroquinazolin-4(1*H*)-thiones. Since sulfur containing scaffolds show significantly different properties compared to oxygen moieties, the presented pathway is an easy and hazardless access to the thione derivatives. A range of functionalities are tolerated and the synthesis of the thioamides takes place without the handling of highly toxic gaseous H_2S but instead NaHS as a solid and safe hydrosulfide source. The presented pathway is furthermore an appropriate alternative for thiation using LAWESSONS-reagent or P_4S_{10}, which may suffer from selectivity issues. The obtained thione scaffolds can also be regarded as precursors for 4-substituted quinazolines. Sulfur substitution reactions have been shown using *o*-bromo cyanoethyl acetate and amines, respectively.



Based on the presented results it can be said, that the research in the field of heterocyclic synthesis is far from being exhausted. In the three-component carbonylation, different substrates require different reaction conditions. Broadening the spectrum of possible starting substances may ease the access to important known scaffolds or even allows for the synthesis of so far unknown moieties. Regarding the synthesis of thiolactams, the option to introduce functionalities *via* sulfur substitution may open a field for follow up derivatizations and cyclisations to end up with complex structures from easily accessible small molecule starting materials.

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6. Appendix

1.1. Experimental section

1.1.1. General remarks

If not otherwise mentioned, the reactions were carried out using commercially available chemicals as received without further purification. Dry solvents were purchased in extra dry quality over molecular sieve and were stored under argon atmosphere. Dry solvents were used as received. Unless otherwise stated, the reactions were carried out following the conditions giving in the general experimental procedure.

NMR-data were recorded by Bruker ARX 300. Bruker ARX 400, Bruker Fourier 300, Bruker Avance 500, Bruker Avance 300 III and Bruker Avance 250 II NMR-spectrometer. ^{13}C- and ^{1}H-spectra were referenced to undeuterated rest signals of the deuterated solvents. Peaks were characterized as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), triplet of triplets (tt), quartet (q) and multiplet (m). NMR spectra were analyzed using MestreNova 8.0 processing program. Identification of the signals was perfomed using DEPT-, H-H-COSY-, NOESY-, HMBC- and HSQC-NMR spectra. The signals were furthermore identified by the help of SDBS online spectra database (http://sdbs.db.aist.go.jp/sdbs/cgi-bin/direct_frame_top.cgi) and Pretsch, Bühlmann, Affolter, "Structure Determination of Organic Compounds", 3. ed., Springer Berlin Heidelberg, 2000.

Gas-chromatography-mass-analysis was measured by an Agilent HP-5890 with Agilent HP-5973 Mass Selective Detector (EI) and HP-5-capillary column using helium as carrier gas. EI-mass analysis was carried out using a Finigan MAT 95-XP. ESI-spectra were measured using

IR-data were obtained by Nicolet 6700 FT-IR and Nicolet 380 FT-IR spectrometer. Signals were classified as weak (w), medium (m) and strong (s).

Melting points were measured on a Micro-Hot-Stage Galen™ III Cambridge Instrument and are uncorrected.

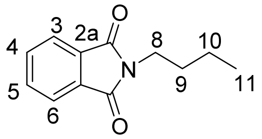
Elemental analysis was performed on a Flash EA 112 Series and a Leco Microanalysator TruSpec CHNS.

Column chromatography was carried out using Merck 60 Silica-Gel (0.043 – 0.006 mm) and distilled solvents were used.

1.1.2. Synthesis of phthalimides

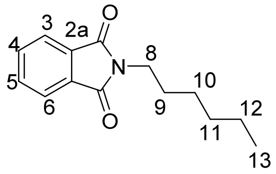
General experimental procedure: 1 mmol 1,2-dibromo-benzene (120 µl, **1**), 1.2 mmol *n*-butylamine (110 µl, **2**), 6.7 mg $Pd(OAc)_2$ (3 mol%), 21.5 mg Cata*CX*ium A (6 mol%), 1 mmol $Mo(CO)_6$ (264 mg), 2 mmol DBU (300 µl) and 5 ml toluene were given in an argon flushed pressure-tube which was subsequently sealed. The mixture was stirred for 16 hours at 100°C. Afterwards, the mixture was diluted with DCM and washed with water. The aqueous phase was extracted two times with DCM, the organic layers were combined and finally dried over Na_2SO_4. The solvent was removed under reduced pressure. Column chromatography (hexane/ethylacetate 1:0 → 4:1) gave 170 mg (0.84 mmol) *n*-butylphthalimide (**3**) as a yellow viscous liquid.

N-*n*-Butylphthalimide (3)



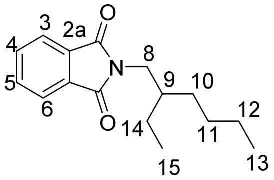
Liquid; **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 7.87–7.75 (m, 2H, CH(3 + 6)), 7.73–7.63 (m, 2H, CH(4 + 5)), 3.65 (t, ^3J = 7.2 Hz, 2H, CH_2(8)), 1.63 (tt, ^3J = 7.4 Hz, ^3J = 7.4 Hz, 2H, CH_2(9)), 1.42–1.24 (m, 2H, CH_2(10)), 0.91 (t, ^3J = 7.3 Hz, 3H, CH_3(11)) ppm; **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 168.5 (*C*=O(2 + 7)), 133.9 (CH(3 + 6)), 132.2 (C_{quart}(2a + 6a)), 123.2 (CH(4 + 5)), 37.84 (CH_2(8)), 30.7 (CH_2(10)), 20.1 (CH_2(9)), 13.7 (CH_3(11)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3389 (w), 2957 (m), 2930 (m), 1664 (s), 1590 (m), 1568 (m), 1522 (s), 1464 (m), 1433 (m), 1377 (w), 1285 (m), 1243 (m), 1164 (m), 1087 (m), 1042 (m), 997 (m), 820 (m), 748 (m), 691 (m), 620 (m); **MS (EI, 70 eV):** *m/z* (%) = 203 ($[M]^+$, 36), 161 (42), 169 (100), 133 (11), 130 (15), 104 (14), 77 (19), 76 (20); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{12}H_{13}O_2N_1$ 204.10191 ($[M+H]^+$), found 204.10185.

N-*n*-Hexylphthalimide (11)



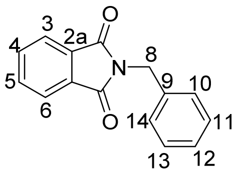
The compound was synthesized following the procedure for (**3**) starting from 1 mmol (**1**) and 1.2 mmol *n*-hexylamine, giving 55 % (**11**) as a viscous liquid; **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 7.82–7.72 (m, 2H, CH(3 + 6)), 7.65–7.53 (m, 2H, CH(4 + 5)), 3.60 (t, ^3J = 7.3 Hz, 2H, CH$_2$(8)), 1.59 (m, 2H, CH$_2$(9)), 1.32–1.11 (m, 6H, CH$_2$(10 + 11 + 12)), 0.80 (s, 3H, CH$_3$(13)) ppm; **^{13}C-NMR (75 MHz, CDCl$_3$):** δ = 168.5 (*C*=O(2 + 7)), 133.9 (CH(3 + 6)), 132.3 (C$_{quart}$(2a + 6a)), 123.2 (CH (4 + 5)), 38.2 (CH$_2$(8)), 31.5 (CH$_2$(9)), 28.7 (CH$_2$(11)), 26.6 (CH$_2$(10)), 22.61 (CH$_2$(12)), 14.1 (CH$_3$(13)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3460 (w), 3104 (w), 3030 (w), 2924 (m), 2851 (m), 1773 (m), 1696 (s), 1612 (m), 1463 (m), 1434 (m), 1395 (m), 1364 (m), 1332 (m), 1285 (m), 1222 (m), 1187 (m), 1120 (m), 1053 (m), 980 (m), 895 (m), 854 (m), 793 (m), 716 (s), 707 (s), 622 (m); **MS (EI, 70 eV):** *m/z* (%) = 231 ([M]$^+$, 41), 174 (11), 161 (50), 160 (100), 148 (12), 133 (12), 130 (19), 105 (10), 104 (13), 77 (15), 76 (14); **HRMS (EI):** *m/z* = calcd. for $C_{14}H_{17}O_2N_1$ 231.12538, found 231.12572.

N-(2-Ethylhexyl)-phthalimid (12)



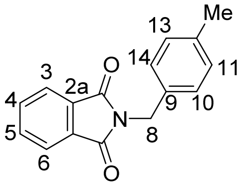
The compound was synthesized following the procedure for (**3**) starting from 1 mmol (**1**) and 1.2 mmol *n*-(2-ethyl)-hexylamine, giving 55 % (**12**) as a viscous liquid; **^{1}H-NMR (300 MHz, CDCl$_3$)**: δ = 7.88 – 7.77 (m, 2H, CH(3 + 6)), 7.74 – 7.64 (m, 2H, CH(4 + 5)), 3.56 (d, ^3J = 7.3 Hz, 2H, CH$_2$(6)), 1.82 (m, 1H, CH(7)), 1.39 – 1.20 (m, 8H, CH$_2$(8 + 9 + 10 + 12)), 0.90 (t, ^3J = 7.5 Hz, 3H, CH$_3$(13)), 0.86 (t, ^3J = 6.7 Hz, 3H, CH$_3$(11)) ppm; **^{13}C-NMR (75 MHz, CDCl$_3$):** δ = 168.8 (C=O(2 + 7)), 133.9 (CH(3 + 6)), 132.2 (C$_{quart}$(2a + 6a)), 123.2 (CH(4 + 5)), 42.0 (CH(8)), 38.4 (C$_{quart}$(9)), 30.6 (CH$_2$(14)), 28.6 (CH$_2$(10)), 23.9(CH$_2$(11)), 23.1 (CH$_2$(12)), 14.2 (CH$_3$(13)), 10.5 (CH$_3$(15)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3313 (m), 3066(w), 2957 (m), 2929 (m), 2872 (m), 2857 (m), 1717 (m), 1635 (s), 1603 (m), 1578 (m), 1540 (s), 1490 (m), 1458 (m), 1396 (w), 1378 (m), 1293 (m), 1185 (w), 1157 (m), 1074 (m), 1026 (m), 1001 (w), 926 (w), 801 (m), 765 (m), 692 (s), 668 (m), 616 (m); **MS (EI, 70 eV):** *m/z* (%) = 259 ([M]$^+$, 56),161 (97), 160 (100), 148 (31), 130 (21), 104 (21), 77 (23), 76 (19); **HRMS (EI):** *m/z* = calcd. for $C_{16}H_{21}O_2N_1$: 259.15668, found 259.15736.

N-Benzylphthalimide (13)



The compound was synthesized following the procedure for (**3**) starting from 1 mmol (**1**) and 1.2 mmol benzylamine, giving 84 % (**13**) as a solid **M.P.:** 117–119°C; **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 7.87–7.80 (m, 2H, CH(3 + 6)), 7.76–7.65 (m, 2H, CH(4 + 5)), 7.47–7.39 (m, 2H, CH(10 + 14)), 7.38–7.21 (m, 3H, CH(11 + 12 + 13)), 4.85 (s, 2H, CH$_2$(8)) ppm; **^{13}C-NMR (75 MHz, CDCl$_3$):** δ = 168.2 (C=O(2 + 7)), 136.5 (C$_{quart}$(9)), 134.1 (CH(4 +5)), 132.2 (C$_{quart}$(2a+ 6a)), 128.8 (CH(10 + 14)), 128.7 (CH(11 + 13)), 127.9 (CH(12)), 123.5 CH(3 + 6)), 41.7 (CH$_2$(8)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3458 (w), 3085 (w), 3059 (w), 3034 (w), 2947 (w), 1774 (w), 1764 (m), 1706 (m), 1602 (m), 1583 (m), 1491 (m), 1466 (m), 1452 (m), 1431 (m), 1389 (m), 1330 (m), 1310 (m), 1297 (m), 1276 (m), 1203 (m), 1184 (m), 1168 (m), 1157 (m), 1100 (m), 1086 (m), 1062 (m), 1029 (m), 1001 (m), 971 (w), 961 (w), 936 (m), 836 (w), 824 (m), 801 (m), 792 (m), 763 (m), 714 (m), 698 (m), 623 (m); **MS (EI, 70 eV):** *m/z* (%) = 237([M]+, 100), 219 (36), 209 (16), 208 (24), 180 (11), 105 (10), 104 (29), 77 (15), 76 (14); **HRMS (EI):** *m/z* = calcd. for $C_{15}H_{11}O_2N_1$ 237.07843, found 237.07867.

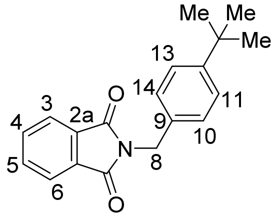
N-(4-Methylbenzyl)-phthalimide (14)



The compound was synthesized following the procedure for (**3**) starting from 1 mmol (**1**) and 1.2 mmol 4-methylbenzylamine, giving 79 % (**14**) as a solid; **M.P.:** 119–121°C; **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 7.87–7.80 (m, 2H, CH(3 + 6)), 7.73–7.66 (m, 2H, CH(4 + 5), 7.33 (d, ^3J = 8.0 Hz, 2H, CH(10 + 14)), 7.12 (d, ^3J = 7.8 Hz, 2H, CH(11 + 13)), 4.81 (s, 2H, CH$_2$(8)), 2.30 (s, 3H, CH$_3$(15)) ppm; **^{13}C-NMR (75 MHz, CDCl$_3$):** δ = 168.1 (C=O(2 + 7)), 137.6 (C$_{quart}$(12)), 134.0 (CH(4 + 5)), 133.4 (C$_{quart}$(9)), 132.2 (C$_{quart}$(2a+ 6a)), 129.4 (CH(10 + 14)), 128.7 (CH(11 + 13)), 123.3 (CH(3 + 6)), 41.4

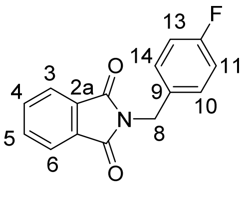
(CH_2(8)), 21.2 (CH_3(15)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3462 (w), 3093 (w), 3056 (w), 3029 (w), 3007 (w), 2939 (w), 2922 (w), 2849 (w), 1763 (w), 1711 (m), 1611 (w), 1510 (w), 1465 (w), 1427 (m), 1389 (m), 1331 (m), 1301 (m), 1180 (w), 1082 (m), 933 (m), 849 (w), 820 (w), 720 (m), 572 (m), 467 (m); **MS (EI, 70 eV):** *m/z* (%) = 251 ([M]$^+$, 100), 236 (55), 233 (26), 222 (18), 208 (12), 160 (11), 130 (16), 118 (25), 105 (17), 104 (24), 91 (13), 77 (25), 76 (21); **HRMS (EI):** *m/z* = calcd. for $C_{16}H_{13}O_2N_1$ 251.09408, found 251.09411.

N-(4-*tert*-Butylbenzyl)-phthalimide (15)



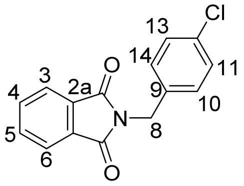
The compound was synthesized following the procedure for (**3**) starting from 1 mmol (**1**) and 1.2 mmol 4-*tert*-butylbenzylamine, giving 68 % (**15**) as a solid, **M.P.:** 99–101°C; **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 7.87–7.79 (m, 2H, CH(3 + 6)), 7.73–7.65 (m, 2H, CH(4 + 5)), 7.39–7.31 (m, 4H, CH(10 + 11 + 13 + 14)), 4.82 (s, 2H, CH_2(8)), 1.28 (s, 9H, CH_3) ppm; **^{13}C-NMR (75 MHz, CDCl$_3$):** δ =168.1 (*C*=O(2 + 7)), 150.8 (C_{quart}(12)), 134.0 (CH(4 + 5)), 133.4 (C_{quart}(9)), 132.2 (C_{quart}(2a + 6a)), 128.4 (CH(10 + 14)), 125.6 (CH(11 + 13)), 123.3 (CH(3 + 6)), 41.3 (CH_2(8)), 34.6 (C_{quart}(12)), 31.3 (CH_3(15 + 16 + 17)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$= 3464 (w), 3064 (w), 3025 (w), 2955 (w), 2905 (w), 2866 (w), 1768 (w), 1702 (m), 1612 (w), 1513 (w), 1465 (w), 1436 (w), 1393 (m), 1333 (w), 1305 (w), 1169 (w), 1086 (m), 939 (m), 841 (w), 808 (w), 717 (m), 621 (w), 578 (m), 529 (m); **MS (EI, 70 eV):** *m/z* (%) = 293 (M$^+$, 18), 279 (20), 278 (100), 236 (18), 160 (17), 131 (18); **HRMS (EI):** *m/z* = calcd.for $C_{19}H_{19}N_1O_2$ 293.14103, found 293.14141.

N-(4-Fluorobenzyl)-phthalimide (16)



The compound was synthesized following the procedure for (**3**) starting from 1 mmol (**1**) and 1.2 mmol 4-fluorobenzylamine, giving 76 % (**16**) as a solid, **M.P.:** 138–140°C; **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 7.90–7.78 (m, 2H, CH(3 + 6)), 7.76–7.66 (m, 2H, CH(4 + 5)), 7.46–7.33 (m, 2H, CH(10 + 14)), 7.04–6.95 (m, 2H, CH(11 + 13)), 4.81 (s, 2H, CH$_2$(8)) ppm; **^{13}C-NMR (75 MHz, CDCl$_3$):** δ = 168.0 (C=O(2 + 7)), 162.4 (d, ^{1}J = 246.4 Hz, C$_{quart}$(12)), 134.1 (CH(4 + 5)), 132.2 (d, ^{4}J = 3.5 Hz, C$_{quart}$(9)), 132.1 (C$_{quart}$(2a + 6a)), 130.6 (d, ^{3}J = 8.3 Hz, CH(10 + 14)), 123.4 (CH(3 + 6)), 115.6 (d, ^{2}J = 21.5 Hz, CH(11 + 13)), 40.9 (CH$_2$(8)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ =3458 (w), 3063 (w), 3032 (w), 2955 (w), 2920 (w), 2852 (w), 1770 (w), 1697 (s), 1605 (m), 1511 (m), 1425 (m), 1325 (m), 1225 (m), 1089 (m), 953 (m), 928 (m), 812 (m), 711 (s), 643 (m), 529 (m); **MS (EI, 70 eV):** *m/z* (%) = 255 ([M]$^+$, 100), 237 (25), 227 (20), 226 (27), 198 (11), 122 (32), 109 (12), 105 (12), 104 (14), 77 (14), 76 (21), 75 (10), 50 (10); **HRMS (EI):** *m/z* = calcd. for $C_{15}H_{10}F_1N_1O_2$ 255.06901, found 255.06879.

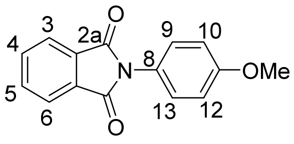
N-(4-Chlorobenzyl)-phthalimide (17)



The compound was synthesized following the procedure for (**3**) starting from 1 mmol (**1**) and 1.2 mmol 4-chlorobenzylamine, giving 48 % (**17**) as a solid, **M.P.:** 120–122°C; **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 7.88–7.80 (m, 2H, CH(3 + 6)), 7.76–7.68 (m, 2H, CH(4 + 5)), 7.41–7.34 (m, 2H, CH(10 + 14)), 7.31–7.26 (m, 2H, CH(11 + 13)), 4.81 (s, 2H, CH$_2$(8)) ppm; **^{13}C-NMR (75 MHz, CDCl$_3$):** δ = 168.0 (C=O(2 + 7)), 134.8 (C$_{quart}$(12)), 134.1 (CH(4 + 5)), 133.8 (C$_{quart}$(9)), 132.0 (C$_{quart}$(2a + 6a)), 130.1 (CH(10 + 14)), 128.9 (CH(11 + 13)), 123.5 (CH(3 + 6)), 41.0 (CH$_2$(8)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ =3461 (w), 3101 (w), 3046 (w), 3025 (w), 2923 (w), 2852 (w), 1770 (w), 1702 (s), 1488 (m), 1428 (m), 1392 (m), 1349 (m), 1328 (m), 1298 (m), 1174 (m), 1083 (s), 1013 (m), 935 (s), 850 (m), 795 (s), 736 (s), 711 (s), 530 (s); **MS (EI, 70 eV):** *m/z* (%) = 271 ([M]$^+$, 95), 253 (17), 242 (15), 236 (100), 208 (21), 138 (25), 130 (23), 125 (11), 105 (17), 104 (20), 89 (15), 77 (28), 76 (34), 50 (17). **HRMS (EI, 70 eV):** *m/z* = calcd. for

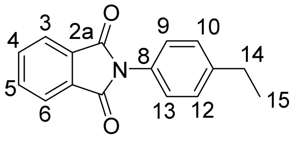
$C_{15}H_{10}{}^{35}ClN_1O_2$ 271.03946, found 271.03927. Calcd. for $C_{15}H_{10}{}^{37}ClN_1O$ 2 273.03651, found 273.03689.

N-(4-Methoxyphenyl)-phthalimide (18)



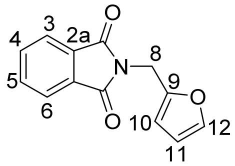
The compound was synthesized following the procedure for (**3**) starting from 1 mmol (**1**) and 1.2 mmol 4-methoxyaniline, giving 66 % (**18**) as a solid **M.P.:** 158 – 160°C; **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 7.99–7.91 (m, 2H, CH(3 + 6)), 7.80–7.77 (m, 2H, CH(4 + 5)), 7.37–7.31 (m, 2H, CH(9 + 13)), 7.05–7.00 (m, 2H, CH(10 + 12)), 3.85 (s, 3H, OMe) ppm; **^{13}C-NMR (75 MHz, CDCl$_3$):** δ = 167.6 (C=O(2 + 7)), 159.3 (C_{quart}(11)), 134.3 (CH(4 + 5)), 132.0 (C_{quart}(2a + 6a)), 128.0 (CH(9 + 13)), 123.7 (CH(3 + 6)), 114.5 (CH(10 + 12)), 100.0 (C_{quart}(8)), 55.6 (OMe) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3452 (w), 3358 (w), 3067 (w), 2991 (w), 2959 (w), 2945 (w), 2921 (w), 2844 (w), 1703 (m), 1610 (w), 1514 (m), 1386 (m), 1251 (m), 1101 (m), 1028 (m), 885 (m), 825 (m), 785 (m), 711 (s), 524 (m); **MS (EI, 70 eV):** *m/z* (%) = 253 ([M]$^+$, 100), 238 (51), 210 (13), 130 (12), 106 (11); **HRMS (EI):** *m/z* = calcd.for $C_{15}H_{11}N_1O_3$ 253.07334, found 253.07326.

N-(4-Ethylphenyl)-phthalimide (19)



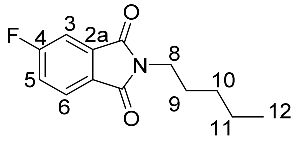
The compound was synthesized following the procedure for (**3**) starting from 1 mmol (**1**) and 1.2 mmol 4-ethylaniline, giving 26 % (**19**) as a solid; **M.P.:** 174–176°C; **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 7.93–7.83 (m, 2H, CH(3 + 6)), 7.75–7.67 (m, 2H, CH(4 + 5)), 7.34–7.33 (m, 4H, CH(9 + 10 + 12 + 13)), 2.63 (q, ^3J = 7.6 Hz, 2H, CH_2(14)), 1.20 (t, ^3J = 7.6 Hz, 3H, CH_3(15)) ppm; **^{13}C-NMR (75 MHz, CDCl$_3$):** δ = 167.5 (C=O(2 + 7)), 144.4 (C_{quart}(11)), 134.4 (CH(4 + 5)), 131.8 (C_{quart}(2a + 6a)), 129.1 (C_{quart}(8)), 128.7 (CH(10 + 12)), 126.5 (CH(9 + 13)), 123.7 (CH(3 + 6)), 28.6 (CH_2(14)), 15.5 (CH_3(15)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ =3331 (w), 3049 (w), 2960 (w), 2926 (w), 2852 (w), 1784 (w), 1702 (m), 1649 (m), 1514 (m), 1382 (m), 1100 (m), 1079 (m), 825 (s), 790 (m), 512 (s), 514 (s); **MS (EI, 70 eV):** *m/z* (%) = 251 ([M]$^+$, 62), 237 (18), 236 (100), 222 (5), 130 (18), 76 (17); **HRMS (EI):** *m/z* = calcd. for $C_{16}H_{13}N_1O_2$ 251.09408, found 251.09386.

N-Furfurylphthalimide (20)



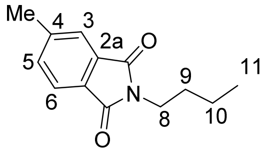
The compound was synthesized following the procedure for (**3**) starting from 1 mmol (**1**) and 1.2 mmol 2-aminomethylfuran, giving 74 % (**20**) as a solid; **M.P.:** 107–109°C; **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 7.90–7.82 (m, 2H, CH(3 + 6)), 7.75–7.68 (m, 2H, CH(4 + 5)), 7.33 (dd, ^3J = 1.9 Hz, ^4J = 0.9 Hz, 1H, CH(12)), 6.36 (dd, ^3J = 3.2 Hz, ^4J = 0.8 Hz, 1H, CH(10)), 6.30 (dd, ^3J = 3.3 Hz, ^3J = 1.9 Hz, 1H, CH(11)), 4.86 (s, 2H, CH_2(8)) ppm; **^{13}C-NMR (75 MHz, CDCl$_3$):** δ = 167.7 (C=O(2 + 7), 149.4 (C_{quart}(9)), 142.6 (CH(12)), 134.2 (CH(4 + 5)), 132.2 (C_{quart}(2a + 6a)), 123.6 (CH(3 + 6)), 110.6 (CH(10)), 108.9 (CH(11)), 34.4 (CH_2(8)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3142 (w), 3121 (w), 2928 (w), 1775 (w), 1701 (m), 1599 (w), 1507 (w), 1469 (w), 1434 (W), 1400 (w), 1390 (m), 1349 (w), 1307 (w), 1294 (w), 1238 (w), 1196 (w), 1174 (w), 1138 (w), 1105 (m), 1070 (w), 1021 (W), 1013 (w), 979 (w), 948 (m), 939 (m), 883 (w), 874 (w), 849 (w), 831 (w), 801 (w), 752 (m), 734 (m), 712 (m), 700 (w), 622 (w), 603 (w); **MS (EI, 70 eV):** *m/z* (%) = 227 ([M]$^+$, 100), 199 (30), 198 (41), 170 (26), 133 (17), 130 (10), 115 (10), 105 (20), 104 (27), 81 (10), 77 (12), 76 (23), 50 (11); **HRMS (EI):** *m/z* = calcd. for $C_{13}H_9O_3N_1$ 227.05769, found 227.05775.

N-Pentyl-5-fluoro-phthalimide (22)



The compound was synthesized following the procedure for (**3**) starting from 1.2 mmol 1,2-dibromo-4-fluoro benzene and 1 mmol *n*-pentylamine, giving 60 % (**22**) as a viscous liquid; **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 7.82 (dd, ^3J = 8.2 Hz, ^4J = 4.5 Hz, 1H, CH(6)), 7.48(dd, ^3J = 7.1 Hz, ^4J = 2.3 Hz, 1H, CH(3)), 7.35 (ddd, ^3J = 8.9 Hz, ^3J = 8.2 Hz, ^4J = 2.3 Hz, 1H, CH(5)), 3.64 (t, ^3J = 7.3 Hz, 2H, CH$_2$(8)), 1.64 (tt, ^3J = 8.4 Hz, ^3J = 7.1 Hz, 2H, CH$_2$(9)), 1.40–1.16 (m, 4H, CH$_2$(10 + 11)), 0.86 (t, ^3J = 6.7 Hz, 3H, CH$_3$(12)) ppm; **^{13}C-NMR (75 MHz, CDCl$_3$):** δ = 167.5 (C=O(7)), 167.10 (d, ^4J = 2.8 Hz, C=O(2)), 166.4 (d, ^1J = 256.7 Hz, CF(4)), 135.1 (d,^3J = 9.5 Hz, *C$_{quart}$*(2a), 128.0 (d,^4J = 2.9 Hz, C$_{\text{quart}}$(6a)) 125.6 (d, ^3J = 9.3 Hz, CH(6)), 120.9 (d,^2J = 23.6 Hz, CH(5)), 111.1 (d, ^2J = 24.8 Hz, CH(3)), 38.4 (CH$_2$(8)), 29.0 (CH$_2$(10)), 28.3 (CH$_2$(9)), 22.3 (CH$_2$(11)), 14.0 (CH$_3$(12)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3452 (w), 3109 (w), 3062 (w), 3035 (w), 2957 (m), 2930 (m), 2871 (m), 2858 (m), 1772 (m), 1694 (s), 1610 (s), 1548 (w), 1481 (m), 1439 (m), 1398 (m), 1363 (m), 1335 (m), 1280 (m), 1262 (m), 1228 (m), 1173 (m), 1141 (m), 925 (m), 911 (m), 846 (m), 789 (m), 746 (s), 669 (m), 623 (m); **MS (EI, 70 eV):** *m/z* (%) = 235 ([M]$^+$, 39), 179 (46), 178 (100), 166 (12), 151 (16), 148 (19), 123 (10), 122 (17), 95 (11), 94 (18); **HRMS (EI):** *m/z* = calcd. for $C_{13}H_{14}O_2N_1F_1$ 235.10031, found 235.10054.

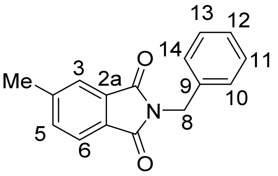
N-Butyl-5-methylphthalimide (23)



The compound was synthesized following the procedure for (**3**) starting from 1.2 mmol 1,2-dibromo-4-methyl benzene and 1 mmol (**2**), giving 80 % (**23**) as a solid, **M.P.:** 59–60°C; **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 7.71 (d, ^3J = 7.6 Hz, 1H, CH(6)), 7.63 (d, ^4J = 1.4 Hz, 1H, CH(3)), 7.48 (dd, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, CH(5)), 3.66 (t, ^{3}J = 7.3 Hz, CH$_2$(8)), 2.50 (s, 1H, CH$_3$(12)), 1.75–1.55 (m, 1H, CH$_2$(9)), 1.46–1.19 (m, 1H, CH$_2$(10)), 0.94 (t, ^3J = 7.3 Hz, 3H, CH$_3$); **^{13}C-NMR (75 MHz, CDCl$_3$):** δ = 168.7 (C=O), 168.6 (C=O), 145.1 (C$_{\text{quart}}$(4)), 134.4 (CH(5)), 132.6 (C$_{\text{quart}}$(2a)), 129.6 (C$_{\text{quart}}$(6a)), 123.7 (CH(3)), 123.1 (CH(7)), 37.8 (CH$_2$(8)), 30.7 (CH$_2$(9)), 22.0 (Me), 20.1 (CH$_2$(10)), 13.7 (CH$_3$(11)); **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3450 (w), 3040 (w), 2956 (m), 2941 (m), 2904 (m), 2873 (m), 2853 (w), 2729 (w), 1768 (m), 1692 (vs), 1613 (m), 1469 (m), 1394 (s), 1332 (s), 1048 (vs), 943 (s), 735 (vs), 545 (s), 504 (s); **MS (EI, 70**

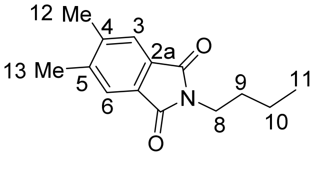
eV): *m/z* (%) = 217 ([M]$^+$, 37), 175 (39), 174 (100), 147 (7), 144 (11), 118 (11), 91 (11), 90 (10), 89 (15); **HRMS (EI):** *m/z* = calcd. for $C_{13}H_{15}N_1O_2$ 217.10973, found 217.10934.

N-Benzyl-5-methylphthalimide (24)



The compound was synthesized following the procedure for (**3**) starting from 1.2 mmol 1,2-dibromo-4-methyl benzene and 1 mmol (**23**), giving 45 % (**24**) as a solid, **M.P.:** 123–125 ° C; **^{1}H-NMR (400 MHz, CDCl$_3$):** δ = 7.72 (d, ^3J = 7.6 Hz, 1H, CH(6)), 7.64 (d, ^4J = 1.5 Hz, 1H, CH(3)), 7.49 (dd, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, CH(5)), 7.44–7.40 (m, 2H, CH(10 + 14)), 7.34–7.24 (m, 3H, CH(11 + 12 + 13), 4.83 (s, 2H, CH_2(8), 2.50 (s, 3H, CH_3) ppm; **^{13}C-NMR (101 MHz, CDCl$_3$):** δ = 162.0 (C=O), 161.7 (C=O), 44.9 (C_{quart}(4)), 134.5 (CH(5)), 132.4 (C_{quart}(2a)), 132.1 (C_{quart}(6a)), 128.7 (CH(10 + 14)), 128.6 (CH(11 + 13)), 127.8 (CH(12)), 123.9 (CH(3)), 123.3 (CH(6)), 122.7 (C_{quart}(9)), 41.6 (CH_2(8)), 21.9 (CH_3(15)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3457 (w), 3045 (w), 2927 (w), 1693 (vs), 1611 (m), 1496 (w), 1389(s), 1103 (s), 1076 (m), 955 (s), 885 (m), 847 (m), 736 (s), 716 (s), 699 (s), 493 (s); **MS (EI, 70 eV):** *m/z* (%) = 251 ([M]$^+$, 100), 234 (9), 233 (43), 223 (16), 222 (20), 208 (12), 119 (14), 118 (13), 104 (21), 91 (21), 90 (13), 89 (24), 77 (10), 65 (11), 63 (11); **HRMS (EI):** *m/z* = calcd. for $C_{16}H_{13}NO_2$ 251.09408, found 251.09396.

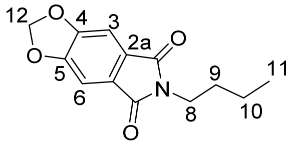
N-Butyl-5,6-dimethylphthalimide (25)



The compound was synthesized following the procedure for (**3**) starting from 1.2 mmol 1,2-dibromo-4,5-dimethyl benzene and 1 mmol (**2**), giving 15 % (**25**) as a solid, **M.P.:** 52–54°C; **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 7.58 (s, CH(3 + 6)), 3.64 (t, ^3J = 7.3 Hz, 2H, CH_2(8)), 2.39 (s, 6H, CH_3(12 + 13)), 1.69–1.56 (m, 2H, CH_2(9)), 1.42–1.21 (m, 2H,

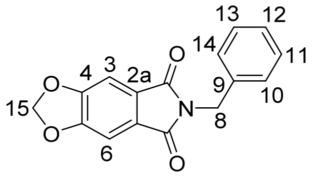
CH_2(10)), 0.93 (t, ^3J = 7.3 Hz, 3H, CH_3(11)) ppm; **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 168.9 (C=O(2 + 7)), 143.4 (C_{quart}(4 + 5)), 130.2 (C_{quart}(2a + 6a)), 124.2 (CH(3 + 6)), 37.7 (CH_2(8)), 30.7 (CH_2(9)), 20.6 (CH_3(12 + 13), 20.1 (CH_2(10)), 13.7 (CH_3(11)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3449 (w), 3050 (w), 3031 (w), 2955 (m), 2943 (w), 2931 (m), 2901 (w), 2872 (m), 2851 (w), 2732 (w), 1924 (w), 1698 (s), 1618 (m), 1395 (s), 1358 (s), 1333 (s), 1081 (s), 931 (m), 827 (m), 737 (s), 625 (m), 532 (m); **MS (EI, 70 eV):** *m/z* (%) = 231 ([M]$^+$, 34), 189 (38), 188 (100), 103 (11); **HRMS (EI, 70 eV):** *m/z* = calcd. for $C_{14}H_{17}N_1O_2$ 231.12538, found 231.12515.

N-Butyl-5,6-(methylenedioxy)-phthalimide (26)



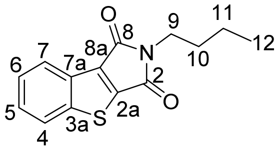
The compound was synthesized following the procedure for (**3**) starting from 1.2 mmol 5,6-dibromobenzo[d][1,3]dioxole and 1 mmol (**2**), giving 38 % (**26**) as a solid, **M.P:** 96–98°C; **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 7.20 (s, 2H, CH(3 + 6), 6.15 (s, 2H, CH_2(12)), 3.63 (t, ^3J = 7.3 Hz, 2H, CH_2(8)), 1.73–1.52 (m, CH_2(9)), 1.44–1.22 (m, CH_2(10)), 0.93 (t, ^3J = 7.3 Hz, CH_3(11)) ppm; **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 168.0 (C=O(2 + 7), 152.5 (C_{quart}(4 + 5)), 127.7 (C_{quart}(2a + 6a)), 103.7 (CH(3 + 6)), 102.9 (CH_2(12)), 37.9 (CH_2(8)), 30.8 (CH_2(9)), 20.1 (CH_2(10)), 13.7 (CH_3(11)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3448 (w), 3106 (w), 3077 (w), 3043 (w), 3010 (w), 2954 (w), 2916 (m), 2873 (w), 2782 (w), 1764 (m), 1701 (vs), 1598 (s), 1500 (m), 1431 (s), 1396 (s), 1635 (s), 1315 (s), 1170 (s), 1072 (s), 1026 (s), 923 (s), 824 (s), 748 (s), 604 (vs), 424 (s); **MS (EI, 70 eV):** *m/z* (%) = 247 ([M]$^+$, 37), 205 (31), 204 (100), 191 (16), 120 (10); **HRMS (EI):** *m/z* = calcd. for $C_{13}H_{13}N_1O_4$ 247.08391, found 247.08347.

N-Benzyl-5,6-(methylendioxy)-phthalimide (27)



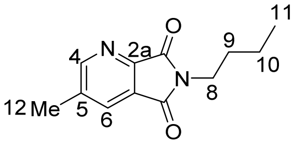
The compound was synthesized following the procedure for (**3**) starting from 1.2 mmol 5,6-dibromobenzo[d][1,3]dioxole and 1 mmol (**23**), giving 28 % (**27**) as a solid **M.P.:** 196–198°C; **^{1}H-NMR (400 MHz, CDCl$_3$):** δ = 7.47–7.44 (m, 2H, CH(10 + 14), 7.39–7.32 (m, 3H, CH(11 + 12 + 13)), 7.32 (s, 2H, CH(3 + 6)), 6.20 (s, 2H, CH_2(15)), 4.84 (s, 2H, CH_2(8)) ppm; **^{13}C-NMR (101 MHz, CDCl$_3$):** δ = 167.6 (C=O(2 + 7)), 152.6 (C-O(4 + 5)), 136.6 (C_{quart}(2a + 6)), 128.7 (CH(10 + 14)), 128.5 (CH(11 + 13)), 127.8 (CH(12)), 127.7 (C_{quart}(9)), 103.9 (CH(4 + 6)), 103.0 (CH_2(15)), 41.7 (CH_2(8)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3040 (w), 3008 (w), 2906 (w), 2102 (w), 1700 (s), 1684 (s), 1599 (m), 1587 (m), 1497 (m), 1424 (m), 131 (m), 1113 (s), 930 (s), 800 (m), 726 (s), 604 (s), 456 (m); MS (EI, 70 eV): *m/z* (%) = 281 ([M]$^+$, 100), 280 (12), 263 (19), 252 (12), 177 (10), 149 (26), 148 (11), 120 (12), 104 (14), 91 (15), 65 (10), 62 (10); **HRMS (EI):** *m/z* = calcd. for $C_{16}H_{11}N_1O_4$ 281.06826, found 281.06802.

N-Butyl-thianaphthene-3,11-dicarboximide (28)



The compound was synthesized following the procedure for (**3**) with increased reaction time to 32 hrs. starting from 1.2 mmol 2,3-dibromo-benzo[*b*]thiophene and 1 mmol (**2**), giving 7 % (**28**) as a solid, **M.P.:** 59–61°C; **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 8.25–8.19 (m, 1H, CH(4)), 7.97–7.91 (m, 1H, CH(7)), 7.58–7.47 (m, 2H, CH(5 + 6)), 3.66 (t, ^3J = 7.2 Hz, 2H, CH_2(9)), 1.73–1.61 (m, 2H, CH_2(10)), 1.46–1.33 (m, 2H, CH_2(11)), 0.95 (t, ^3J = 7.3 Hz, 3H, CH_3(12)) ppm; **^{13}C-NMR (75 MHz, CDCl$_3$):** δ = 164.5 (C=O(8)), 163.8 (C=O(2)), 147.1 (C_{quart}(3a)), 142.5 (C_{quart}(7a)), 138.1 (C_{quart}(8a)), 131.0 (C_{quart}(2a)), 127.5 (CH(5)), 126.8 (CH(6)), 124.1 (CH(4)), 124.0 (CH(7)), 38.2 (CH_2(9)), 30.9 (CH_2(10)), 20.0 (CH_2(11)), 13.7 (CH_3(12)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3448 (w), 2958 (m), 2928 (m), 2871 (m), 2854 (m), 1927 (w), 1701 (vs), 1346 (s), 1039 (s), 932 (s), 754 (vs), 741 (vs), 719 (vs), 486 (m), 415 (s); **MS (EI, 70 eV):** *m/z* (%) = 259 ([M]$^+$, 41), 217 (27), 216 (100), 189 (13), 161 (11), 160 (25), 132 (16); **HRMS (EI):** *m/z* = calcd. for $C_{14}H_{13}NO_2S$: 259.06615, found 259.06580.

N-Butyl-3-Methyl-5H-pyrrol-[3,4-*b*]-pyridin-5,7(6H)-dione (29)

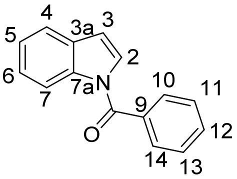


The compound was synthesized following the procedure for (**2**) with increased reaction time to 32 hrs. starting from 1.2 mmol 2,3-dibromo-5-methylpyridine and 1 mmol (**2**), giving 2 % (**29**) as a solid, **M.P.:** 133–135°C; **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 8.77 (d, ^4J = 2.1 Hz, 1H, CH(4)), 7.94 (d, ^4J = 2.1 Hz, 1H, CH(6)), 3.73 (t, ^3J = 7.3 Hz, 2H, CH_2(8)), 2.53 (s, 3H, CH_3(12)), 1.78–1.54 (m, 2H, CH_2(9)), 1.48–1.27 (m, 2H, CH_2(10)), 0.94 (t, ^3J = 7.3 Hz, 3H, CH_3(11)) ppm; **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 156.7 (C=O), 155.6 (C=O), 153.2 (CH(4)), 146.2 (C_{quart}(2a), 138.4 (C_{quart}(7a)), 131.2 (CH(6)), 38.1 (CH_2(8)), 30.6 (CH_2(9)), 20.1 (CH_2(10)), 19.2 (CH_3(12)), 13.7 (CH_3(11)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3469 (w), 3392 (w), 3021 (w), 2956 (w), 2930 (m), 2873 (w), 2859 (w), 1776 (m), 1702 (s), 1591 (m), 1398 (s), 1365 (s), 1333 (s), 1099 (m), 1054 (s), 809 (m), 748 (s), 682 (s), 556 (s); **MS (EI, 70 eV):** *m/z* (%) = 218 ($[M]^+$, 41), 189 (11), 176 (52), 175 (100), 163 (27), 148 (13), 145 (12), 120 (42), 119 (17), 93 (27), 92 (25), 91 (17), 65 (24), 64 (14), 39 (12); **HRMS (EI):** *m/z* = calcd. for $C_{12}H_{14}N_2O_2$ 218.10498, found 218.10542.

1.1.3. Synthesis of *N*-benzoylindoles

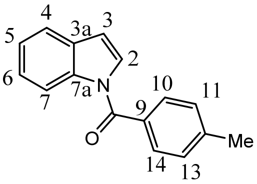
General procedure: An argon flushed pressure tube was charged with 0.5 mmol indole (59 mg, **38**), 0.5 mmol bromo benzene (62 µl, **39**), 0.5 mmol $Mo(CO)_6$ (132 mg), 0.5 mmol DBU (75 µl), 0.5 mmol K_3PO_4 (106 mg), 3 mol% $Pd(OAc)_2$ (3,4 mg), 6 mol% *n*-$BuPAd_2$ (10.8 mg) and 3 ml DMF. The tube was subsequently sealed and the mixture was stirred at 120°C for 16 h. Afterwards, the reaction mixture was diluted in dichloromethane and washed with water. The aqueous layer was extracted two times with dichloromethane, the combined organic phases were dried by sodium sulfate and the solvent was evaporated. The crude product was purified by column chromatography (pentane:ethyl acetate 4:1 with addition of 0.5 % NEt_3) giving 98 mg benzoylindole (89 %, **40**) as a viscous oil that solidified whilst standing.

N-Benzoylindole (40)



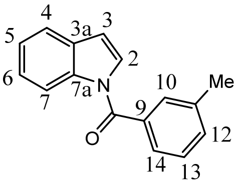
M.P.: 64–65°C, **^{1}H-NMR: (300 MHz, CDCl$_3$):** δ = 8.42 (d, ^3J = 8.0 Hz, 1H, CH(7)), 7.80–7.69 (m, 2H, CH(10 + 14)), 7.66–7.58 (m, 2H, CH(12 + 4)), 7.53 (dd, ^3J = 8.1 Hz, ^3J = 6.3 Hz, 2H, CH(11 + 13)), 7.45–7.28 (m, 3H, CH(2 + 5 + 6)), 6.62 (d, ^3J = 3.7 Hz, 1H, CH(3)) ppm; **^{13}C-NMR (63 MHz, CDCl$_3$):** δ = 168.8 (C=O), 136.2 (C$_{\text{quart}}$(7a)), 134.7 (C$_{\text{quart}}$(9)), 132.0 (CH(12)), 130.9 (C$_{\text{quart}}$(3a)), 129.3 (CH(10 + 14)), 128.7 (CH(11 + 13)), 127.7 (CH(4)), 125.0 (CH(2)), 124.1 (CH(5)), 121.0 (CH(6)), 116.5 (CH(7)), 108.7 (CH(3)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3145 (w), 3113 (w), 3049 (w), 1675 (s), 1600 (m), 1583 (m), 1533 (m), 1492 (w), 1471 (m), 1445 (s), 1377 (m), 1328 (s), 1245 (m), 1201 (m), 1184 (m), 1161 (m), 1150 (m), 1126 (m), 1065 (m), 939 (m), 886 (s), 868 (s), 793 (m), 765 (m), 746 (s), 728 (s), 698 (s), 682 (s), 629 (s); **MS (EI 70 eV):** *m/z* (%) = 221 (37, [M]$^+$), 116 (11), 105 (100), 89 (18), 77 (68), 63 (15), 51 (24), 50 (11); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{15}H_{11}N_1O_1$ 222.09134 ([M+H]$^+$), found 222.09119.

N-(4-Methylbenzoyl)-indole (41)



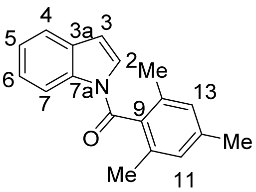
The compound was synthesized following the procedure for (**40**) starting from 0.5 mmol (**38**) and 0.5 mmol 4-methylbenzene, giving 97 % (**41**) as a solid. **M.P.:** 87–89°C, **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 8.44 – 8.33 (1H, m, CH(7)), 7.65 (2H, d, ^3J = 8.1 Hz, CH(10 + 14)), 7.43 – 7.28 (5H, m, CH(2 + 5 + 6 + 11 + 13), 7.13 (1H, dd, ^3J = 8.6 Hz, ^4J = 2.5 Hz, CH(4)), 6.99 (s, 1H), 6.61 (1H, dd, ^3J = 3.7 Hz, ^5J = 0.8 Hz, CH(3)), 1.43 (3H, s, CH$_3$) ppm; **^{13}C-NMR (75 MHz, CDCl$_3$):** δ = 168.9 (C=O), 142.7 (C$_{\text{quart}}$(9)), 136.2 (C$_{\text{quart}}$(7a)), 131.8 (C$_{\text{quart}}$(12)), 130.9 (C$_{\text{quart}}$(3a)), 129.5 (CH(10 + 14)), 129.4 (CH(11 + 13)), 127.8 (CH(4)), 124.9 (CH(2)), 123.9 (CH(5)), 121.0 (CH(6)), 116.5 (CH(7)), 108.4 (CH(3)), 21.8 (CH$_3$) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 2955 (w), 2918 (w), 2849 (w), 1678 (m), 1607 (w), 1542 (w), 1472 (w), 1450 (m), 1381 (m), 1341 m), 1206 (m), 1071 (s), 957 (m), 888 (m), 832 (m); 788 (m), 767 (m), 749 (s), 728 (m), 604 (m); **MS (EI 70 eV):** *m/z* (%) = 235 ($[M]^+$, 28), 119 (100), 116 (15), 91 (49), 90 (10), 89 (31), 65 (26), 63 (24), 39 (12); **HRMS (EI):** *m/z* = calcd. for $C_{16}H_{13}O_1N_1$ 235.09917, found 235.09928.

N-(3-Methylbenzoyl)-indole (42)



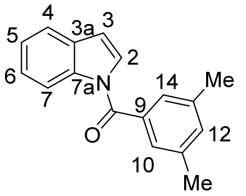
The compound was synthesized following the procedure for (**40**) starting from 0.5 mmol (**38**) and 0.5 mmol 3-methylbenzene, giving 23 % (**42**) as a viscous liquid. **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 8.45 – 8.35 (m, 1H, CH(7)), 7.64 – 7.49 (m, 5H, CH(4 + 10 + 12 + 13 + 14)), 7.46 – 7.28 (m, 3H, CH(2 + 5 + 6)), 6.61 (dd, ^3J = 3.8 Hz, ^4J = 0.8 Hz, 1H, CH(3)), 2.45 (s, 3H, CH_3) ppm; **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 169.1 (C=O), 138.7 (C_{quart}(11)), 136.2 (C_{quart}(7a)), 134.7 (C_{quart}(9)), 132.8 (CH(12)), 130.9 (C_{quart}(3a)), 129.8 (CH(10)), 128.5 (CH(13)), 127.8 (CH(4)), 126.4 (CH(14)), 125.0 (CH(2)), 124.0 (CH(5)), 121.0 (CH(6)), 116.6 (CH(7)), 108.6 (CH(3)), 21.52 (CH_3) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3268 (w), 2981 (m), 2927 (m), 2857 (w), 1734 (s), 1676 (s), 1604 (m), 1586 (m), 1532 (m), 1465 (m), 1449 (m), 1372 (m), 1336 (s), 1294 (m), 1236 (s), 1203 (s), 1161 (m), 1125 (m), 1096 (m), 1042 (s), 931 (m), 880 (m), 845 (m), 790 (m), 751 (s), 736 (s), 699 (m), 651 (m), 633 (m), 607 (m); **MS (EI 70 eV):** *m/z* (%) = 235 ($[M]^+$, 31), 119 (100), 91 (45), 89 (10), 65 (13); **HRMS (EI):** *m/z* = calcd. for $C_{16}H_{13}O_1N_1$ 235.09917, found 235.09928.

N-(2,4,6-Trimethylbenzoyl)-indole (43)



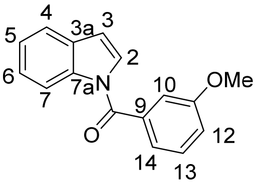
The compound was synthesized following the procedure for (**40**) starting from 0.5 mmol (**38**) and 0.5 mmol bromoxylene, giving 42 % (**42**) as a viscous liquid. **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 8.69 (dd, ^{3}J = 8.2 Hz, ^{4}J = 1.0 Hz, 1H, CH(7)), 7.59 (ddd, ^{3}J = 7.7 Hz, ^{4}J = 1.4 Hz, ^{4}J = 0.7 Hz, 1H, CH(4)), 7.43 (ddd, ^{3}J = 8.4 Hz, ^{3}J = 7.3 Hz, ^{4}J = 1.4 Hz, 1H, CH(6)), 7.38 – 7.30 (m, 1H, CH(5)), 6.93 (d, ^{4}J = 1.3 Hz, ^{4}J = 0.8 Hz, 2H, CH(11 + 13)), 6.81 (d, ^{3}J = 3.8 Hz, 1H, CH(2)), 6.54 (d, ^{3}J = 3.8 Hz, 1H, CH(3)), 2.35 (s, 3H, CH$_3$), 2.19 (d, ^{4}J = 0.7 Hz, 6H, CH$_3$) ppm; **^{13}C-NMR (63 MHz, CDCl$_3$):** δ = 162.1 (C=O), 139.7 (C$_{quart}$(9)), 134.7 (C$_{quart}$(7a)), 131.2(C$_{quart}$(10 + 14)), 129.7 (C$_{quart}$(3a)), 128.5 (CH(13 + 11)), 126.6 (CH(4)), 125.3 (CH(2)), 124.3 (CH(5)), 123.8 (C$_{quart}$(12)), 121.0 (CH(6)), 116.9 (CH(7)), 109.4 (CH(3)), 21.4 (CH$_3$), 19.3 (CH$_3$) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3117 (w), 3066 (w), 2954 (m), 2921 (m), 2852 (m), 1924 (w), 1732 (m), 1685 (s), 1611 (m), 1582 (m), 1533 (m), 1470 (m), 1449 (s), 1357 (m), 1364 (m), 1330 (s), 1293 (m), 1241 (m), 1207 (m), 1186 (m), 1157 (m), 1148 (m), 1121 (m), 1080 (m), 1056 (m), 1015 (m), 968 (m), 941 (m), 883 (m), 859 (m), 848 (s), 770 (m), 754 8s), 719 (s), 610 (m); **MS (EI 70 eV):** *m/z* (%) = 263 ([M]$^{+}$, 12), 148 (11), 147 (100), 119 (18), 91 (10); **HRMS (ESI-TOF):** *m/z* = Calcd. for $C_{18}H_{17}N_1O_1$ 264.13829 ([M+H]$^{+}$), found 264.13801.

N-(3,5-Dimethylbenzoyl)-indole (44)



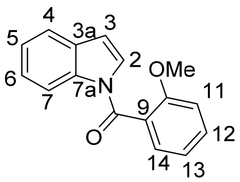
The compound was synthesized following the procedure for (**40**) starting from 0.5 mmol (**38**) and 0.5 mmol 3,5-dimethylbromobenzene, giving 80 % (**44**) as a solid. **M.P.:** 79–81°C; **^{1}H-NMR (250 MHz, CDCl$_3$):** δ = 8.40 (dd, ^{3}J = 8.1 Hz, ^{4}J = 1.0 Hz, 1H, CH(7)), 7.61 (ddd, ^{3}J = 7.6 Hz, ^{4}J = 1.5 Hz, ^{4}J = 0.8 Hz, 1H, CH(4)), 7.42 – 7.27 (m, 5H, CH(2 + 5 + 6 + 10 + 14)), 7.27–7.20 (m, 1H, CH(12)), 6.60 (dd, ^{3}J = 3.8 Hz, ^{4}J = 0.8 Hz, 1H, CH(3)), 2.44 – 2.36 (m, 6H, CH$_3$) ppm; **^{13}C-NMR (63 MHz, CDCl$_3$):** δ = 169.3 (C=O), 138.5 (C$_{quart}$(10 + 14)), 136.2 (C$_{quart}$(7a)), 134.7 (C$_{quart}$(9)), 133.6 (CH(12)), 130.9 (C$_{quart}$(3a)), 127.9 (CH(4)), 126.9 (CH(11 + 13)), 125.0 (CH(2)), 124.0 (CH(5)), 121.0 (CH(6)), 116.6 (CH(7)), 108.4 (CH(3)), 21.4 (CH$_3$) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3143 (w), 3120 (w), 3049 (w), 3004 (w), 2919 (m), 2852 (m), 1720 (w), 1684 (s), 1602 (m), 1582 (m), 1530 (m), 1470 (m), 1449 (s), 1438 (m), 1380 (m), 1366 (m), 1334 (s), 1287 (m), 1223 (m), 1199 (s), 1148 (m), 1123 (m), 1095 (m), 1073 (m), 1037 (m), 1013 (m), 934 (m), 890 (m), 882 (m), 859 (m), 784 (s), 771 (m), 754 (s), 740 (m), 686 (m), 644 (m), 618 (m); **MS (EI 70 eV):** *m/z* (%) = 249 ([M]$^+$, 26), 134 (10), 133 (100), 105 (28), 79 (11), 77 (12); **HRMS (ESI-TOF):** *m/z* = Calcd. for $C_{17}H_{15}N_1O_1$ 250.12264 ([M+H]$^+$), found 250.12263.

N-(3-Methoxybenzoyl)-indole (45)



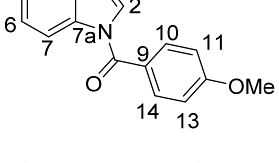
The compound was synthesized following the procedure for (**40**) starting from 0.5 mmol (**38**) and 0.5 mmol 3-methoxybromobenzene, giving 38 % (**45**) as viscous liquid. **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 8.46 (d, ^3J = 8.6 Hz, 1H, CH(7)), 7.58 (ddd, ^3J = 7.5 Hz, ^4J = 1.5 Hz, ^4J = 0.7 Hz, 1H, CH(11)), 7.51 (ddd, ^3J = 8.4 Hz, ^3J = 7.4 Hz, ^4J = 1.8 Hz, 1H, CH(6)), 7.45 (ddd, ^3J = 7.5 Hz, ^4J = 1.8 Hz, ^4J = 0.4 Hz, 1H, CH(4)), 7.42 – 7.35 (m, 1H, CH(2)), 7.31 (ddd, ^3J = 7.4 Hz, ^3J = 7.4 Hz, ^4J = 1.3 Hz, 1H, CH(5)), 7.13 – 7.05 (m, 2H, CH(12 + 13)), 7.03 (dd, ^3J = 8.4 Hz, ^4J = 0.9 Hz, 1H, CH(14)), 6.56 (dd, ^3J = 3.8, ^4J = 0.8 Hz, 1H, CH(3)), 3.78 (s, 3H, OMe) ppm; **^{13}C-NMR (63 MHz, CDCl$_3$):** δ = 168.6 (C=O), 159.8 (C-OMe), 136.1 (C$_{\text{quart}}$(7a)), 136.0 (C$_{\text{quart}}$(9)), 130.9 (C$_{\text{quart}}$(3a)), 129.8 (CH(13)), 127.7 (CH(4)), 125.1 (CH(2)), 124.1 (CH(5)), 121.5 (CH(14)), 121.0 (CH(6)), 118.16 (CH(12)), 116.6 (CH(7)), 114.2 (CH(10)), 108.7 (CH(3)), 55.65 (OMe) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3341 (w), 3142 (w), 3105 (w), 2999 (w), 2938 (w), 2834 (w), 1676 (s), 1597 (m), 1588 (m), 1531 (m), 1485 (m), 1472 (m), 1448 (s), 1425 (m), 1377 (m), 1320 (s), 1293 (m), 1262 (m), 1230 (m), 1202 (s), 1187 (m), 1170 (m), 1147 (m), 1124 (m), 1092 (m), 1033 (m), 1012 (m), 992 (m), 937 (m), 882 (m), 869 (m), 814 (m), 794 (s), 783 (s), 748 (s), 693 (m), 679 (m), 636 (m); **MS (EI 70 eV):** *m/z* (%) = 251 ([M]$^+$, 20), 135 (100), 116 (19), 92 (27), 89 (23), 77 (33), 64 (12), 63 (22); **HRMS (EI):** *m/z* = calcd. for $C_{16}H_{13}O_2N_1$: 251.09408, found 251.09451.

N-(2-Methoxybenzoyl)-indole (46)



The compound was synthesized following the procedure for (**40**) starting from 0.5 mmol (**38**) and 0.5 mmol 2-methoxybromobenzene, giving 87 % (**46**) as viscous liquid. **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 8.46 (d, ^{3}J = 8.6 Hz, 1H, CH(7)), 7.58 (ddd, ^{3}J = 7.5 Hz, ^{4}J = 1.5 Hz, ^{5}J = 0.7 Hz, 1H, CH(11)), 7.51 (ddd, ^{3}J = 8.4 Hz, ^{3}J = 7.4 Hz, ^{4}J = 1.8 Hz, 1H, CH(12)), 7.45 (ddd, ^{3}J = 7.5 Hz, ^{4}J = 1.8 Hz, ^{4}J = 0.4 Hz, 1H, CH(4)), 7.42 – 7.35 (m, 1H, CH(6)), 7.31 – 7.05 (m, 3H, CH(2 + 5 +13), 7.03 (dd, 1H, ^{3}J = 8.4 Hz, ^{4}J = 0.9 Hz, 1H, CH(14)), 6.56 (dd,^{3} J = 3.8 Hz, ^{4}J = 0.8 Hz, 1H, CH(3)), 3.78 (s, 3H, CH$_3$) ppm; **^{13}C-NMR (63 MHz, CDCl$_3$):** δ = 167.3 (C=O), 156.4 (C-OMe), 135.7 (C$_{\text{quart}}$(7a)), 132.2 (CH(12), 131.1 (C$_{\text{quart}}$(3a)), 129.1 (CH(13)), 127.5 (CH(4)), 124.9 (CH(2)), 124.9 (C$_{\text{quart}}$(9)), 124.0 (CH(5)), 120.9 (CH(14)), 120.8 (CH(6)), 116.6 (CH(7)), 111.5 (CH(11)), 108.7 (CH(3)), 55.7 (OMe) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3409 (m), 3052 (w), 2873 (w), 1676 (s), 1599 (s), 1583 (m), 1535 (m), 1488 (m), 1449 (s), 1434 (s), 1379 (s), 1335 (s), 1283 (s), 1250 (s), 1205 (s), 1179 (m), 1163 (m), 1150 (m), 1131 (m), 1114 (m), 1042 (m), 1016 (s), 939 (m), 918 (m), 887 (s), 873 (s), 793 (m), 740 (s), 677 (s), 628 (s), 607 /m); **MS (EI 70 eV):** *m/z* (%) = 251 ([M]$^+$, 41), 135 (100), 116 (23), 107 (31), 92 (38), 89 (33), 77 (43), 76 (11), 64 (21), 63 (38), 50 (10); **HRMS (ESI-TOF):** *m/z* = Calcd. for C$_{16}$H$_{13}$N$_1$O$_2$ 252.10191 ([M+H]$^+$), found 252.10176.

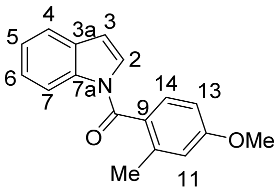
N-(4-Methoxybenzoyl)-indole (47)



The compound was synthesized following the procedure for (**40**) starting from 0.5 mmol (**38**) and 0.5 mmol 2-methoxybromobenzene, giving 94 % (**47**) as a solid. **M.P.:** 137–138°C; **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 8.39 – 8.31 (m, 1H, CH(7)), 7.79 – 7.71 (m, 2H, CH(10 + 14)), 7.61 (ddd, ^{3}J = 7.5 Hz, ^{4}J = 1.5 Hz, ^{4}J = 0.7 Hz, 1H, CH(4)), 7.43 – 7.27 (m, 3H, CH(2 + 5 + 6)), 7.06 – 6.98 (m, 2H, CH(11 + 13)), 6.62 (dd, ^{3}J =

3.8 Hz, ^4J = 0.8 Hz, 1H, CH(3)), 3.91 (s, 3H, OMe) ppm; **^{13}C-NMR (75 MHz, CDCl$_3$):** δ = 168.4 (C=O), 162.8 (C-OMe), 136.2 (C$_{quart}$(7a)), 131.8 (CH(10 + 14)), 130.8 (C$_{quart}$(3a)), 127.9 (CH(4)), 126.7 (C$_{quart}$(9)), 124.8 (CH(2)), 123.8 (CH(5)), 121.0 (CH(6)), 116.3 (CH(7)), 114.0 (CH(11 + 13)), 108.1 (CH(3)), 55.7 (OMe) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3150 (w), 3113 (w), 3052 (w), 3010 (w), 2918 (w), 2843 (w), 1683 (m), 1603 (m), 1573 (m), 1530 (m), 1507 (m), 1448 (m), 1414 (m), 1372 (m), 1329 (s), 1301 (m), 1246 (s), 1205 (m), 1179 (m), 1169 (s), 1154 (m), 1127 (m), 1109 (m), 1065 (m), 1021 (s), 941 (m), 887 (s), 872 (m), 837 (s), 789 (m), 772 (m),751 (s); 731 (s), 704 (m), 661 (m), 629 (m), 606 (s); **MS (EI 70 eV):** *m/z* (%) = 251 ([M]$^+$, 17), 135 (100), 116 (23), 107 (11), 92 (27), 89 (25), 77 (27), 64 (16), 63 (25); **HRMS (EI):** *m/z* = calcd. for $C_{16}H_{13}O_2N_1$ 251.09408, found 251.09452.

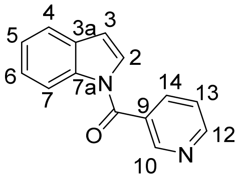
N-(4-Methoxy-2-methylbenzoyl)-indole (48)



The compound was synthesized following the procedure for (**40**) starting from 0.5 mmol (**38**) and 0.5 mmol 4-methoxy-2-methylbromobenzene, giving 98 % (**48**) as viscous liquid. **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 8.33 (dd, ^3J = 8.2 Hz, ^4J = 1.1 Hz, 1H, CH(7)), 7.60 (ddd, ^3J = 7.4 Hz, ^4J = 1.6 Hz, ^4J = 0.7 Hz, 1H, CH(4)), 7.43 – 7.27 (m, 2H, CH(5 + 6)), 7.13 (d, ^3J = 3.8 Hz, 1H, CH(2)), 6.88 – 6.77 (m, 3H, CH(11 + 13 + 14)), 6.59 (dd, ^3J = 3.8 Hz, ^4J = 0.8 Hz, 1H, CH(3)), 3.87 (s, 3H, OMe), 2.36 (s, 3H, CH$_3$) ppm; **^{13}C-NMR (75 MHz, CDCl$_3$):** δ = 169.1 (C=O), 161.3 (C-OMe), 138.9 (CH(14)), 135.8 (C$_{quart}$(7a)), 132.9 (C$_{quart}$(9)), 131.1 (C$_{quart}$(3a)), 130.0 (CH(11)), 127.4 (CH(4)), 125.0 (CH(2)), 124.0 (CH(5)), 121.0 (CH(6)), 116.5 (CH(7)), 113.0 (CH(13)), 111.1 (C$_{quart}$(10)), 108.7 (CH(3)), 55.5 (OMe), 19.9 (CH$_3$) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 2958 (w), 2928 (m), 2837 (w), 1681 (s), 1604 (s), 1571 (m), 1533 (m), 1500 (m), 1471 (m), 1448 (s), 1376 (m), 1330 (s), 1286 (s), 1250 (s), 1205 (s), 1185 (s), 1164 (m), 1150 (m), 1135 (m), 1115 (m), 1085 (m), 1062 (m), 1037 (m), 1016 (m), 936 (m), 928 (m), 883 (m), 852 (m), 816 (m), 770 (m), 759 (s), 747 (s), 724 (m), 658 (m), 618 (m), 600 (m); **MS (EI 70 eV):** *m/ z*(%) = 265 ([M]$^+$, 17), 150 (14), 149 (100), 121 (13), 91 (12);

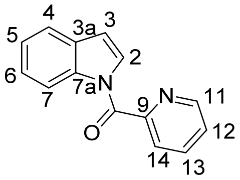
HRMS (ESI-TOF): *m/z* = calcd. for $C_{17}H_{15}N_1O_2$ 266.11756 ([M+H]$^+$), found 266.11752.

(1*H*-Indol-1-yl)-(pyridin-3-yl)-methanone (49)



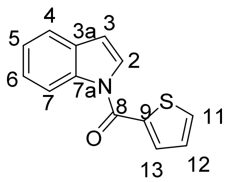
The compound was synthesized following the procedure for (**40**) starting from 0.5 mmol (**38**) and 0.5 mmol 3-bromopyridine, giving 50 % (**49**) as a viscous liquid. **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 9.00 – 8.96 (1H, m, CH(10)), 8.84 (dd, ^3J = 4.9 Hz, ^4J = 1.7 Hz, 1H, CH(12)), 8.41 (d, ^3J = 8.1 Hz, 1H, CH(7)), 8.06 (ddd, ^3J = 7.9 Hz, ^4J = 2.3 Hz, ^4J = 1.7 Hz, 1H, CH(14)), 7.61 (ddd, ^3J = 7.5 Hz, ^4J = 1.5 Hz, ^4J = 0.7 Hz, 1H, CH(4)), 7.49 (ddd, ^3J = 7.9 Hz, ^3J = 4.9 Hz, ^4J = 0.9 Hz, 1H, CH(13)), 7.45 – 7.30 (m, 2H, CH(6 + 5)), 7.22 (d, ^3J = 3.8 Hz, 1H, CH(2)), 6.67 (dd, ^3J = 3.8 Hz, ^4J = 0.8 Hz, 1H, CH(3)) ppm; **^{13}C-NMR (75 MHz, CDCl$_3$):** δ = 166.4 (C=O), 152.5 (C$_{\text{quart}}$(9)), 149.7 (CH(10)), 136.8 (CH(12)), 136.0 (C$_{\text{quart}}$(7a)), 130.9 (C$_{\text{quart}}$(3a)), 130.8 (CH(14)), 126.9 (CH(4)), 125.4 (CH(2)), 124.5 (CH(5)), 123.6 (CH(13)), 121.2 (CH(6)), 116.5 (CH(7)), 109.8 (CH(3)) ppm**; IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3146 (w), 3119 (w), 3049 (w), 2921 (w), 2849 (w), 1674 (m), 1585 (m), 1568 (m), 1538 (m), 1479 (m), 1471 (m), 1450 (m), 1412 (m), 1381 (m), 1347 (s), 1250 (m), 1205 (m), 1192 (m), 1183 (m), 1152 (m), 1113 (m), 1088 (m), 1074 (m), 1024 (m), 1015 (m), 969 (m), 938 (m), 888 (m), 873 (m), 822 (m), 773 (m), 765 (m), 749 (s), 734 (s), 718 (s), 700 (m), 638 (m), 605 (m); **MS (EI 70 eV):** *m/z* (%) = 222 ([M]$^+$, 54), 116 (25), 106 (100), 89 (37), 78 (84), 63 (24), 62 (10), 51 (47), 50 (25), 39 (13); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{14}H_{10}O_1N_2$ ([M+H]$^+$) 222.07876, found 222.07881.

(1*H*-Indol-1-yl)-(pyridin-2-yl)-methanone (50)



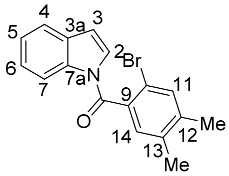
The compound was synthesized following the procedure for (**40**) starting from 0.5 mmol (**38**) and 0.5 mmol 2-bromopyridine, giving 28 % (**50**) as a solid. **M.P.:** 65–67°C, **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 8.75 (ddd, ^3J = 4.8 Hz, ^4J = 1.7 Hz, ^5J = 0.9 Hz, 1H, CH(11)), 8.59 – 8.49 (m, 1H, CH(7)), 8.09 (ddd, ^3J = 7.9 Hz, ^4J = 1.1 Hz, ^5J = 1Hz, 1H, CH(14)), 8.04 – 7.89 (m, 2H, CH(12 + 13)), 7.60 (ddd, ^3J = 7.4 Hz, ^4J =1.6 Hz, ^4J = 0.7 Hz, 1H, CH(4)), 7.52 (ddd, ^3J = 7.6 Hz, ^4J = 4.8 Hz, ^5J = 1.3 Hz, 1H, CH(6)), 7.45 – 7.27 (m, 2H, CH(2 + 5)), 6.64 (dd, ^3J = 3.8 Hz, ^5J = 0.8 Hz, 1H, CH(3)) ppm; **^{13}C-NMR (75 MHz, $CDCl_3$)**: δ = 165.8 (C=O), 152.5 (C_{quart}(9)), 148.7(CH(11)), 137.5 (CH(11)), 136.6 (C_{quart}(7a)), 130.9 (C_{quart}(3a)), 128.6 (CH(4)), 126.3 (CH(12)), 125.9 (CH(14)), 125.1 (CH(2)), 124.3 (CH(5)), 121.0 (CH(6)), 117.0 (CH(7)), 109.3 (CH(3)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3162 (w), 3098 (w), 3061 (w), 3048 (w); 3031 (w); 3016 (w), 3004 (w); 2959 (w); 2924 (w); 1677 (s), 1585 (m), 1569 (m), 1545 (m), 1470 (w), 1450 (s), 1438 (s), 1385 (s), 1358 (s), 1291 (m), 1240 (m); 1197 (s), 1154 (m), 1125 ()m), 1082 (m), 1047 (m), 1017 (m); 995 (m), 888 (m), 871 (m), 870 (m), 765 (m), 748 (s); 732 (s); 719 (s); 695 (s), 673 (m), 638 (m), 620 (s); **MS (EI 70 eV):** *m/z* (%) = 222 ([M]$^+$, 55), 221 (23), 106 (44), 89 (13), 78 (100), 51 (13); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{14}H_{10}N_2O_1$ ([M+H]$^+$) 223.08659, found 223.08626.

(1*H*-Indol-1-yl)-(thiophen-2-yl)-methanone (51)



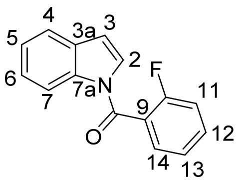
The compound was synthesized following the procedure for (**40**) starting from 0.5 mmol (**38**) and 0.5 mmol 2-bromothiophene, giving 39 % (**51**) as a viscous liquid. **^{1}H-NMR (250 MHz, $CDCl_3$):** δ = 8.41 (d, ^3J = 8.1 Hz, 1H, CH(7)), 7.74 – 7.66 (m, 3H, CH(2 + 11 + 13)), 7.62 (ddd, ^3J = 7.5 Hz, ^4J = 1.5 Hz, ^4J = 0.8 Hz, 1H, CH(4)), 7.45 – 7.27 (m, 2H, CH(5 + 6), 7.20 (dd, ^3J = 4.9 Hz, ^3J = 3.9 Hz, 1H, CH(12)), 6.68 (dd, ^3J = 3.8 Hz, ^4J = 0.8 Hz, 1H, CH(3)) ppm; **^{13}C-NMR (63 MHz, $CDCl_3$):** δ = 161.8 (C=O), 137.3 (C_{quart}(9)), 136.3 (C_{quart}(7a)), 133.46 (CH(13)), 132.78 (CH(11)), 130.8 (C_{quart}(3a)), 127.7 (CH(4)), 127.17 (CH(12)), 125.1 (CH(52)), 124.1(CH(5)), 121.1 (CH(6)), 116.4 (CH(7)), 108.9 (CH(3)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3149 (w), 3103 (w), 2923 (w), 2851 (w), 1660 (s), 1604 (m), 1583 (m), 1533 (m), 1472 (m); 1449 (s), 1412 (s), 1377 (m), 1353 (s), 1325 (s), 1244 (m), 1203 (s), 1175 (m), 1150 (m), 1079 (m), 1059 (m), 1036 (m), 1016 (m), 938 (w), 882 (m), 865 (m), 845 (m), 813 (s), 770 (m), 747 (s), 732 (s), 715 (s), 687 (m), 630 (m); **MS (EI 70 eV):** *m/z* (%) = 227 ([M]$^+$, 32), 111 (100), 39 (10); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{13}H_{9}N_{1}O_{1}S_{1}$ 228.04776 ([M+H]$^+$), found 228.04763.

(2-Bromo-4,5-dimethylphenyl)(1*H*-indol-1-yl)-methanone (53)



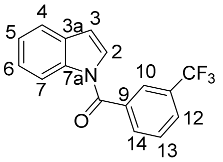
The compound was synthesized following the procedure for (**40**) starting from 0.5 mmol (**38**) and 0.5 mmol 1,2-dibromo-4,5-dimethylbenzene, giving 18 % (**53**) as a solid. **M.P.:** 64–67°C; **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 8.38 (d, ^3J = 8.1 Hz, 1H, CH(7)), 7.65 – 7.50 (m, 3H, CH(4 + 11 + 14)), 7.51 – 7.27 (m, 2H, CH(5 + 6)), 7.01 (d, ^3J = 3.8 Hz, 1H, CH(2)), 6.63 – 6.57 (m, 1H, CH(3)), 2.33 (s, 3H, CH$_3$), 2.27 (s, 3H, CH$_3$) ppm; **^{13}C-NMR (63 MHz, CDCl$_3$):** δ = 167.1 (C=O), 141.3 (C_{quart}(10)), 136.7 (C_{quart}(7a)), 134.5 (C_{quart}(9)), 133.9 (C_{quart}(12)), 130.0 (C_{quart}(3a)), 127.1 (CH(4)), 125.3 (CH(2)), 124.9 (CH(11)), 124.3 (CH(5)), 121.0 (CH(6)), 120.9 (CH(14)), 116.6 (CH(7)), 116.4 (C_{quart}(13)), 109.5 (CH(3)), 19.8 (CH$_3$), 19.40 (CH$_3$) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3368 (w), 3050 (w), 2920 (w), 2850 (w), 1726 (w), 1685 (m), 1600 (m), 1534 (m), 1480 (m), 1471 (m), 1449 (s), 1385 (s), 1364 (m), 1329 (s), 1293 (m), 1252 (m), 1221 (m), 1205 (m), 1148 (m), 1221 (m), 1205 (m), 1148 (m), 1118 (m), 1096 (m), 1073 (m), 1016 (m); 964 (m), 880 (m), 833 (s), 812 (m), 767 (m), 747 (s), 719 (m), 668 (m), 628 (m); **MS (EI 70 eV):** *m/z* (%) = 329 ([M(^{81}Br)]$^+$, 20), 327 ([M(^{79}Br)]$^+$, 20), 213 (98), 211 (100), 104 (22), 103 (16), 77 (10); **HRMS (EI):** *m/z* = calcd. for $C_{17}H_{14}O_{1}N_{1}{}^{78}Br_{1}$: 327.02533, found: 327.02523.

N-(2-Fluorobenzoyl)-indole (54)



The compound was synthesized following the procedure for (**40**) starting from 0.5 mmol (**38**) and 0.5 mmol 2-fluoro-bromobenzene, giving 25 % (**54**) as a viscous liquid.**^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 8.48 (d, ^3J = 8.1 Hz, 1H, CH(7)), 7.64 – 7.52 (m, 3H, CH(4 + 12 + 13), 7.45 – 7.37 (m, 1H, CH(6)), 7.37 – 7.29 (m, 2H, CH(5 + 14)), 7.24 – 7.19 (m, 1H, CH(11)), 7.13 (dd, ^3J = 3.8 Hz, ^6J = 2.5 Hz, 1H, CH(2)), 6.62 (dd, ^3J = 3.8 Hz, ^4J = 0.8 Hz, 1H, CH(3)) ppm; **^{13}C-NMR (75 MHz, CDCl$_3$):** δ = 164.5 (C=O), 159.1 (d, ^1J = 252.0 Hz, (C-F)), 135.8 (C_{quart}(7a)), 133.2 (d, ^3J = 8.1 Hz, CH(12)), 131.1 (C_{quart}(3a)), 130.1 (d, ^3J = 2.7 Hz, CH(14)), 126.9 (d, ^5J = 2.0 Hz, CH(2)), 125.3 (CH(4)), 124.74 (d, ^4J = 3.6 Hz, CH(13)), 124.4 (CH(5)), 123.52 (d, ^2J = 16.0 Hz, C_{quart}(9)), 121.1 (CH(6)), 116.6 (CH(7)), 116.5 (d, ^2J = 21.0 Hz, CH(11)), 109.6 (CH(3)) ppm; **^{19}F-NMR (282 MHz, CDCl$_3$):** δ = -112.72 ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3101 (w), 2917 (w), 1684 (m), 1648 (m), 1613 (m), 1585 (m), 1540 (m), 1490 (m), 1473 (m), 1449 (m), 1379 (m), 1339 (m), 1241 (m), 1204 (m), 1183 (m), 1162 (m), 1150 (m), 1105 (m), 1087 (m), 1067 (m), 1032 (m), 1015 (m), 943 (m), 936 (m), 889 (m), 872 (m), 816 (m), 778 (m), 759 (m), 742 (s), 721 (m), 704 (m), 673 (m), 605 (m); **MS (EI 70 eV):** *m/z* (%) = 239 ([M]$^+$, 34), 123 (100), 95 (28); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{15}H_{10}O_1N_1F_1$ 240.08192 ([M+H]$^+$), found 240.08174.

N-(3-Trifluorobenzoyl)-indole (55)



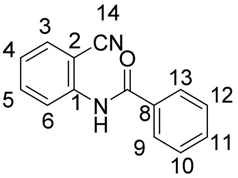
The compound was synthesized following the procedure for (**40**) starting from 0.5 mmol (**38**) and 0.5 mmol 3-trifluoromethylbromobenzene, giving 49 % (**55**) as a solid. **M.P.:** 83–86°C; **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 8.32 (d, ^3J = 8.1 Hz, 1H, CH(7)), 7.94 – 7.92 (m, 1H, CH(11)), 7.86 –7.76 (m, 2H, CH(13 + 14)), 7.63 – 7.56 (m, 1H, CH(4)), 7.53 (ddd, ^3J = 7.5 Hz, ^4J = 1.5 Hz, ^4J = 0.7 Hz, 1H, CH(12)), 7.32 (ddd, ^3J =

8.3 Hz, ^3J = 7.8 Hz, ^4J = 1.4 Hz, 1H, CH(6)), 7.28 – 7.22 (m, 1H, CH(5)), 7.11 (d, ^3J = 3.8 Hz, 1H, CH(2)), 6.57 (dd, ^3J = 3.8 Hz, ^4J = 0.8 Hz, 1H, CH(3)) ppm; **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 167.2 (C=O), 136.1 (C_{quart}(7a)), 135.6 (CH(14)), 132.4 (q, ^4J = 1.4 Hz, (C_{quart}(9)), 131.49 (q, ^2J = 33.1 Hz, C_{quart}(11)), 130.9 (C_{quart}(3a)), 129.4 (CH(13)), 128.45 (q, ^3J = 3.6 Hz, CH(12)), 127.0 (CH(4)), 126.04 (q, ^3J = 3.8 Hz, CH(10)), 125.4 (CH(2)), 124.5 (CH(5)), 121.2 (CH(6)), 120.0 (q, ^1J = 272.7 Hz, CF_3), 116.6 (CH(7)), 109.6 (CH(3)) ppm; **^{19}F-NMR (282 MHz, $CDCl_3$):** δ = -62.81 ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3150 (w), 3125 (w), 3047 (w), 2913 (w), 1679 (m), 1616 (w), 1585 (w), 1538 (w), 1472 (w), 1453 (m), 1382 (m), 1363 (w), 1356 (w), 1318 (m), 1240 (m), 1205 (m), 1180 (m), 1164 (m), 1151 (m), 1130 (m), 1112 (m), 1097 (m), 1069 (m), 1015 (w), 986 (w), 938 (w), 914 (w), 898 (m), 881 (w), 874 (w), 811 (m), 781 (m), 771 (m), 767 (m), 757 (m), 727 (m), 705 (m), 964 (m), 661 (m), 643 (m), 630 (m); **MS (EI 70 eV):** *m/z* (%) = 290 (15), 289 ($[M]^+$, 80), 174 (18), 173 (100), 145 (96), 95 (11), 89 (11); **HRMS (EI):** *m/z* = calcd. for $C_{16}H_{10}O_1N_1F_3$: 289.07090. found mass: 289.07061.

1.1.4. Synthesis of *N*-(*o*-cyanophenyl)-benzamides

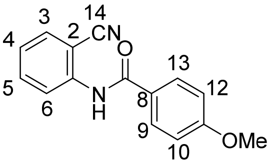
General procedure: 1 mmol 2-aminobenzonitril (118 mg, **57**), 1.2 mmol bromobenzene (126 µl, **39**), 6.7 mg $Pd(OAC)_2$ (3 mol%), 21.5 mg $^nBuPAd_2$ (6 mol%), 1.5 mmol DBU (225 µl), 0.5 mmol $Mo(CO)_6$ (132 mg) and 4 ml DMF were given in an argon flushed pressure tube which was subsequently sealed. The mixture was heated to 130°C under stirring for 16 hours. After cooling to room temperature, the crude mixture was diluted in ethyl acetate and washed with water. The aqueous phase was extracted two times with ethyl acetate. The organic layers were combined, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Column chromatography (hexane/ethyl acetate 4:1) gave 176 mg (79%) *N*-(2-cyanophenyl)benzamide (**58**) as a white solid.

N-(2-Cyanophenyl)-benzonitrile (58)



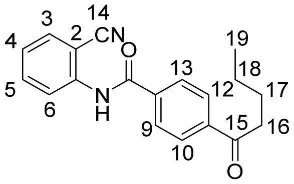
M.P.: 241–243°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 12.55 (s, 1H, NH), 8.23 – 8.13 (m, 3H, CH(7 + 10 + 14), 7.85 (ddd, ^3J = 8.5 Hz, ^3J = 7.0 Hz, ^4J = 1.6 Hz, 1H, CH(5)), 7.77 – 7.71 (m, 1H, CH(12)), 7.62 – 7.49 (m, 4H, CH(4+ 6 + 11 + 13)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 165.7 (C=O(7)), 140.4 (C$_{quart}$(1)), 133.8 (CH(5)), 133.5 (C$_{quart}$(8)), 133.1 (CH(3)), 132.2 (CH(11)), 128.6 (CH(10 + 12)), 127.8 (CH(9 + 13)), 126.8 (CH(6)), 126.4 (CH(4)), 117.0 (C$_{quart}$(14)), 109.4 (C$_{quart}$(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3131 (w), 3059 (m), 2955 (w), 1661 (m), 1599 (m), 1572 (m), 1557 (m), 1510 (m), 1480 (m), 1470 (m), 1451 (m), 1344 (m), 1334 (m), 1287 (m), 1239 (m), 1189 (m), 1143 (m), 1102 (m), 1020 (w), 1020 (w), 941 (m), 862 (m), 820 (m), 794 (m), 766 (m), 692 (m), 675 (m), 618 (m); **MS (EI, 70 eV):** *m/z* (%) = 222 ([M]$^+$, 100), 119 (99), 104 (11), 92 (14), 90 (17), 77 (22), 76 (11), 51 (10); **HRMS (EI):** *m/z* = calcd. for $C_{14}H_{10}O_1N_2$: 222.07876, found: 222.07881.

N-(2-Cyanophenyl)-4-methoxybenzamide (67)



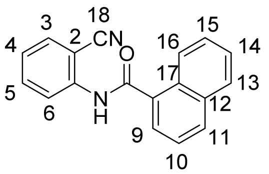
The compound was synthesized following the procedure for (**58**) starting from 0.5 mmol (**57**) and 0.6 mmol 4-methoxy-bromobenzene, giving 36 % (**67**) as a solid, **M.P.:** 170–172°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.45 (s, 1H, NH), 8.03 – 7.96 (m, 2H, CH(9 + 13), 7.86 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, CH(3)), 7.73 (ddd, ^3J = 8.0 Hz, ^3J = 7.5 Hz, ^4J = 1.6 Hz, 1H, CH(5)), 7.61 – 7.52 (m, 1H, CH(6)), 7.41 (ddd, ^3J = 7.6 Hz, ^3J = 7.6 Hz, ^4J = 1.2 Hz, 1H, CH(4)), 7.10 (m, 1H, CH(10 + 12), 3.34 (s, 3H, OMe) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 165.0 (C=O(7)), 162.3 (C$_{quart}$(11)), 140.6 (C$_{quart}$(1)), 133.7 (CH(5)), 133.1 (CH(3)), 129.8 (CH(9 + 13)), 126.8 (CH(6)), 126.1 (CH(4)), 125.59 (C$_{quart}$(8)), 117.1 (C$_{quar}$(14)), 113.81 (CH(10 + 12)), 109.3 (C$_{quart}$(2)), 55.51 (CH_3) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3273 (m), 2923 (w), 2227 (m), 1648 (m), 1604 (m), 1579 (m), 1526 (s), 1507 (s), 1446 (m), 1315 (m), 1302 (m), 1273 (m), 1250 (s), 1176 (s), 1108 (m), 1022 (m), 909 (m), 840 (m), 814 (m), 796 (m), 764 (s), 753 (m), 699 (m), 653 (m), 622 (m); **MS (EI, 70 eV):** *m/z* (%) = 252 ([M]$^+$, 11), 135 (100), 92 (16), 77 (17), 64 (10); **HRMS (EI):** *m/z* = calcd. for $C_{15}H_{12}O_2N_2$ 252.08933, found 252.09008.

N-(2-Cyanophenyl)-4-pentanoylbenzamide (68)



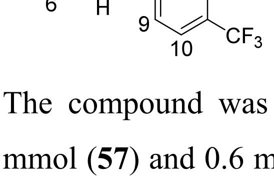
The compound was synthesized following the procedure for (**58**) starting from 0.5 mmol (**57**) and 0.6 mmol 4-pentanoyl-bromobenzene, giving 31 % (**68**) as a solid, **M.P.:** 148–150°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.80 (s, 1H, NH), 8.13 (m, 4H, CH(9 + 10 + 12 + 13))), 7.90 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, CH(3)), 7.85 – 7.70 (m, 1H, CH(5)), 7.60 (dd, ^3J = 8.2 Hz, ^4J = 1.1 Hz, 1H, CH(6)), 7.46 (ddd, ^3J = 7.6 Hz, ^3J = 7.6 Hz, ^4J = 1.2 Hz, 1H, CH(4)), 3.09 (t, ^3J = 7.2 Hz, 2H, CH_2(16)), 1.73 – 1.54 (m, 2H, CH_2(17)), 1.38 (m, 2H, CH_2(18)), 0.92 (t, ^3J = 7.3 Hz, 3H, CH_3(19)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 199.9 (C=O(15)), 164.9 (C=O(7)), 140.0 (C_{quart}(1)), 139.2 (C_{quart}(11)), 137.06 (C_{quart}(8)), 133.8 (CH(5)), 133.1 (CH(3)), 128.1 (CH(9 + 13)), 128.0 (CH(10 + 12)), 126.9 (CH(6)), 126.6 (CH(4)), 116.8 (C_{quart}(14)), 109.4 (C_{quart}(2)), 38.0 (CH_2(16)), 25.8 (CH_2(17)), 21.7 (CH_2(18)), 13.8 (CH_3(19)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3275 (m), 2953 (m), 2869 (w), 2226 (m), 1679 (s), 1653 (s), 1603 (s), 1580 (w),1571 (m), 1517 (m), 1490 (s), 1448 (m), 1439 (m), 1405 (m), 1378 (m), 1346 (m), 1315 (m), 1285 (m), 1260 (m), 1207 (m), 1117 (m), 1017 (m), 979 (m), 917 (m), 861 (m), 848 (m), 839 (m), 788 (w), 766 (m), 755 (s), 726 (m), 687 (m), 643 (m), 624 (m), 609 (m); **MS (EI, 70 eV):** *m/z* (%) = 306 ([M]$^+$, 28), 264 (11), 249 (14), 147 (18), 104 (29), 76 (19); **HRMS (EI):** *m/z* = calcd. for $C_{19}H_{18}O_2N_2$ 306.13628, found 306.13643.

N-(2-Cyanophenyl)-1-naphthamide (69)



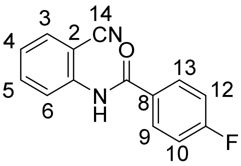
The compound was synthesized following the procedure for (**58**) starting from 0.5 mmol (**57**) and 0.6 mmol 1-bromonaphthalene, giving 82 % (**69**) as a solid, **M.P.:** 159–161°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.88 (s, 1H, NH), 8.40 – 8.32 (m, 1H, CH(16)), 8.12 (dd, ^3J = 8.4 Hz, ^4J = 1.0 Hz, 1H, CH(11)), 8.07 – 8.00 (m, 1H, CH(13)), 7.92 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, CH(9)), 7.87 (dd, ^3J = 7.2 Hz, ^4J = 1.2 Hz, 1H, CH(3)), 7.83 – 7.74 (m, 1H, CH(5)), 7.69 – 7.57 (m, 4H, CH(6 + 10 + 14 + 15)), 7.47 (ddd, ^3J = 7.6 Hz, ^3J = 7.6 Hz, ^4J = 1.2 Hz, 1H, CH(4)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 167.7 (C=O(7)), 140.1 C_{quart}(1)), 134.0 (CH(5)), 133.4 (C_{quart}(8)), 133.3 (CH(3)), 133.3 (C_{quart}(12)), 130.8 (CH(11)), 129.8 (C_{quart}(17)), 128.4 (CH(13)), 127.2 (CH(14)), 126.8 (CH(6)), 126.6 (CH(9)), 126.6 (CH(4)), 126.0 (CH(10)), 125.3 (CH(15)), 125.1 (CH(13)), 117.2 (C_{quart}(18)), 109.3 (C_{quart}(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3139 (w), 3057 (m), 3047 (m), 2976 (w), 2935 (w), 2227 (m), 1926 (w), 1637 (m), 1600 (m), 1513 (m), 1485 (m), 1431 (m), 1306 (m), 1285 (m), 1247 (m), 1197 (m), 1167 (m), 1139 (m), 1103 (w), 955 (m), 926 (m), 910 (m), 874 (m), 810 (m), 777 (s), 764 (m), 754 (s), 729 (m), 659 (m), 634 (m), 604 (m); **MS (EI, 70 eV):** *m/z* (%) = 272 ([M]$^+$, 19), 155 (100), 127 (77), 126 (16); **HRMS (EI):** *m/z* = calcd. for $C_{18}H_{12}O_1N_2$: 272.09441, found 272.09428.

N-(2-Cyanophenyl)-4-trifluoromethylbenzamide (70)



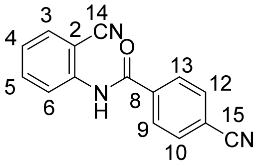
The compound was synthesized following the procedure for (**58**) starting from 0.5 mmol (**57**) and 0.6 mmol 4-trifluoromethyl-bromobenzene, giving 66 % (**69**) as a solid, **M.P.:** 189–191°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.88 (s, 1H, NH), 8.23 – 8.11 (m, 2H, CH(10 + 12)), 8.03 – 7.94 (m, 2H, CH(9 + 13)), 7.91 (ddd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, ^5J = 0.5 Hz, 1H, CH(3)), 7.77 (ddd, ^3J = 8.1 Hz, ^3J = 7.5 Hz, ^4J = 1.6 Hz, 1H, CH(5))), 7.61 (ddd, ^3J = 8.2 Hz, ^4J = 1.2 Hz, ^5J = 0.5 Hz, 1H, CH(6))), 7.47 (ddd, ^3J = 7.6 Hz, ^3J = 7.6 Hz, ^4J = 1.2 Hz, 1H, CH(4)) ppm; **^{13}C-NMR (75 MHz, DMSO-d_6):** δ = 164.6 (C=O(7)), 139.9 (C_{quart}(1)), 137,3 (C_{quart}(8)),133.8 (CH(5)), 133.2 (CH(3)), 131.9 (q, ^3J = 32.0 Hz, CH(11)), 128.7 (CH(9+13)), 126.9 (CH(6)), 126.7 (CH(4)), 125.6 (q, ^4J = 3.9 Hz, CH(10+12)), 123.7 (q, ^1J = 256.1 Hz, CF_3), 116.8 (C_{quart}(14)), 109.4 (C_{quart}(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3257 (m), 2234 (m), 1659 (m), 1604 (m), 1582 (m), 1521 (m), 1507 (m), 1491 (s), 1437 (m), 1408 (m), 1323 (s), 1317 (s), 1287 (m), 1267 (m), 1247 (m), 1157 (m), 1124 (m), 1116 (m), 1105 (s), 1065 (s), 961 (m), 862 (m), 841 (m), 763 (s), 727 (m), 707 (m), 689 (m), 680 (m); 629 (m); 611 (m); **MS (EI, 70 eV):** *m/z* (%) = 290 ([M]$^+$, 23), 173 (100), 145 (58); **HRMS (EI):** *m/z* = calcd. for $C_{15}H_9O_1N_2F_3$ 290.06615, found 290.06628.

N-(2-Cyanophenyl)-4-fluorobenzamide (71)



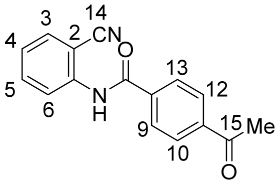
The compound was synthesized following the procedure for (**58**) starting from 0.5 mmol (**57**) and 0.6 mmol 4-fluoro-bromobenzene, giving 40 % (**71**) as a solid, **M.P.:** 185–187°C; **^{1}H-NMR (300 MHz, DMSO-d_6):** δ = 10.66 (s, 1H, NH), 8.12 – 8.04 (m, 2H, CH(10 + 12)), 7.88 (dd, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1H, CH(3)), 7.75 (ddd, ^3J = 8.1 Hz, ^3J = 7.5 Hz, ^4J = 1.6 Hz, 1H, CH(5)), 7.58 (dd, ^3J = 8.2 Hz, ^4J = 1.1 Hz, 1H, CH(6)), 7.48 – 7.37 (m, 3H, CH(4 + 9 + 13)) ppm; **^{13}C-NMR (75 MHz, DMSO-d_6):** δ = 164.6 (C=O(7)), 164.42 (d, ^1J = 249.8 Hz, CF(11))), 140.2 (C_{quart}(1)), 133.8 (CH(5)), 133.1(CH(3)), 130.6 (d, ^3J = 9.3 Hz, CH(9 + 13)), 130.0 (d, ^4J = 3.0 Hz, C_{quart}(8)), 126.9 (CH(6)), 126.5 (CH(4)), 117.0 (C_{quart}(14)), 115.6 (d, ^2J = 21.9 Hz, CH(10 + 12)), 109.4 (C_{quart}(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3255 (w), 3074 (w), 3058 (w), 2224 (w), 1653 (m), 1600 (m), 1578 (m), 1522 (m), 1502 (m), 1484 (m), 1444 (m), 1308 (m), 1287 (m), 1286 (m), 1239 (m), 1223 (m), 1164 (m), 1104 (m), 1036 (m), 1009 (m), 941 (m), 907 (m), 859 (m), 809 (m), 762 (s), 754 (s), 659 (m), 619 (m); **MS (EI, 70 eV):** *m/z* (%) = 240 ([M]$^+$, 18), 123 (100), 95 (48), 75 (21); **HRMS (EI):** *m/z* = calcd. for $C_{14}H_9O_1N_2F_1$ 240.06934, found 240.06962.

N-(2-Cyanophenyl)-4-cyanobenzamide (72)



The compound was synthesized following the procedure for (**58**) starting from 0.5 mmol (**57**) and 0.6 mmol 4-cyano-bromobenzene, giving 61 % (**72**) as a solid, **M.P.:** 228–230°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.89 (s, 1H, NH), 8.15 (d, ^3J = 8.3 Hz, 2H, CH(9 + 13)), 8.07 (d, ^3J = 8.2 Hz, 2H, CH(10 + 12)), 7.91 (dd, ^3J = 7.6 Hz, ^4J = 1.6 Hz, 1H, CH(3)), 7.77 (ddd, ^3J = 7.7 Hz, ^4J = 1.6 Hz, 1H, CH(5)), 7.60 (d, ^3J = 8.1 Hz, 1H, CH(6)), 7.47 (ddd, ^3J = 7.7 Hz, ^4J = 1.3 Hz, 1H, CH(4)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 164.4 (C=O(7)), 139.9 (C$_{quart}$(1)), 137.5 (CH(5)), 133.9 (C$_{quart}$(9)), 133.2 (CH(3)), 132.7 (CH(9 + 13)), 128.6 (CH(10 + 12)), 126.9 (CH(6)), 126.8 (CH(4)), 118.2 (C$_{quart}$(15)), 116.8 (C$_{quart}$(14), 114.4 (C$_{quart}$(12)), 109.4 (C$_{quart}$(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3283 (m), 3059 (w), 2235 (w), 2223 (m), 1651 (m), 1605 (m), 1581 (m), 1533 (m), 1501 (m), 1472 (w), 1311 (m), 1294 (m), 1268 (m), 1242 (m), 1183 (m), 1161 (m), 1125 (m), 1015 (m), 957 (m), 908 (m), 864 (m), 841 (m), 763 (m), 758 (m), 736 (m), 725 (m), 662 (m), 634 (m), 604 (m); **MS (EI, 70 eV):** *m/z* (%) = 247 ([M]$^+$, 25), 130 (100), 102 (51), 75 (14); **HRMS (EI):** *m/z* = calcd. for $C_{15}H_9O_1N_3$: 247.07401, found mass: 247.07433.

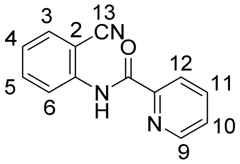
4-Acetyl-*N*-(2-cyanophenyl)-benzamide (73)



The compound was synthesized following the procedure for (**58**) starting from 0.5 mmol (**57**) and 0.6 mmol 4-bromo-acetopheneone, giving 68 % (**73**) as a solid, **M.P.:** 240–242°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.81 (s, 1H, NH), 8.32 (d, ^3J = 8.5 Hz, 2H, (CH(10 + 14)), 8.23 – 8.07 (m, 2H, (CH(11 + 13)), 7.91 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, CH(3)), 7.82 – 7.73 (m, 1H, CH(5))), 7.56 (ddd, ^3J = 8.1 Hz, ^3J = 7.0 Hz, ^4J = 1.3 Hz, 1H, CH(4)), 2.65 (s, 3H, CH$_3$)) ppm; **^{13}C-NMR (75 MHz, DMSO):** δ = 197.7

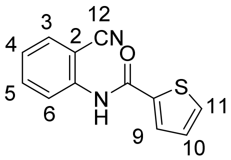
(C=O(15)), 165.0 (C=O(7)), 140.1 (C_{quart}(2)), 137.3 (C_{quart}(15)), 133.9 (CH(5)), 133.2 (CH(3)), 128.5 (CH(10 + 14)), 128.2 (CH(11 + 13)), 126.9 (CH(6)), 126.6 (CH(4)), 116.9 (C_{quart}(14)), 109.4 (C_{quart}(2)), 27.06 (CH_3(16)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3281 (m), 2230 (m), 1685 (m), 1657 (m), 1601 (m), 1580 (m), 1516 (m), 1489 (m), 1439 (m), 1403 (m), 1354 (m), 1313 (m), 1305 (m), 1282 (m), 1257 (m), 1162 (m), 1116 (m), 1014 (m), 956 (m), 945 (m), 913 (m), 870 (m), 860 (m), 913 (m), 870 (m), 860 (m), 836 (m), 767 (m), 751 (m), 969 (m), 621 (m); **MS (EI, 70 eV):** *m/z* (%) =264 ([M]$^+$, 22), 147 (100), 104 (14), 91 (19), 76 (17); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{16}H_{12}N_2O_2$ 265.09715 ([M+H]$^+$), found 265.09739.

N-(2-Cyanophenyl)-picolinamide (74)



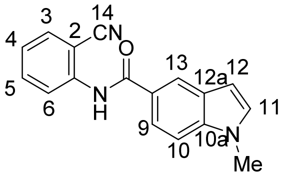
The compound was synthesized following the procedure for (**58**) starting from 0.5 mmol (**57**) and 0.6 mmol 2-bromopyridine, giving 49 % (**74**) as a solid, **M.P.:** 126–128°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.92 (s, 1H, NH), 8.78 (ddd, ^3J = 4.8 Hz, ^4J = 1.7 Hz, ^5J = 0.9 Hz, 1H, (CH(9)), 8.25 – 8.16 (m, 1H, CH(12)), 8.15 – 8.04 (m, 2H, CH(11 + 10))), 7.89 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, CH(3)), 7.84 – 7.68 (m, 2H (CH(5 + 6)), 7.39 (ddd, ^3J = 7.6 Hz, ^3J = 7.6 Hz, ^3J = 1.1 Hz, 1H, CH(4)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 162.5 (C=O(7)), 148.7 (C_{quart}(8)), 148.7(CH(9)) 140.0 (C_{quart}(1)), 138.4 (CH(11)), 134.1 (CH(5)), 133.0 (CH(3)), 127.6 (CH(6)), 125.5 (CH(4)), 123.8 (CH(10)), 122.6 (CH(12)), 116.6 (C_{quart}(13)), 105.9 (C_{quart}(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3329 (m), 3087 (m), 3056 (m), 2225 (m), 1691 (m), 1577 (m), 1512 (s), 1463 (m); 1448 (m), 1428 (m), 1300 (m), 1278 (m), 1232 (m), 1209 (m), 1184 (m), 1162 (m), 1124 (m), 1093 (m), 1084 (m), 1041 (m), 996 (m), 960 (m), 848 (m), 811 (m), 763 (s), 746 (s), 726 (m), 688 (m), 627 (m), 620 (s); **MS (EI, 70 eV):** *m/z* (%) = 223 ([M]$^+$, 69), 106 (30), 90(17), 79 (99), 78 (100), 76 (100), 63 (11), 52 (31), 51 (32), 50 (12); **HRMS (EI):** *m/z* = calcd. for $C_{13}H_9O_1N_3$: 223.07401, found 223.07400.

N-(2-cyanophenyl)-thiophene-2-carboxamide (75)



The compound was synthesized following the procedure for (**58**) starting from 0.5 mmol (**57**) and 0.6 mmol 2-bromo-thiophene, giving 39 % (**75**) as a solid, **M.P.:** 134–136°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.64 (s, 1H, NH), 8.02 (dd, ^3J = 3.8 Hz, ^4J = 1.2 Hz, 1H, CH(9)), 7.92 (dd, ^3J = 5.0 Hz, ^4J = 1.1 Hz, 1H, CH(11)), 7.90 – 7.86 (m, 1H (CH(3)), 7.75 (ddd, ^3J = 8.2 Hz, ^3J = 7.5 Hz, ^4J = 1.6 Hz, 1H, CH(5)), 7.57 (m, 1H, CH(6)), 7.44 (ddd, ^3J = 7.6 Hz, ^3J = 7.6 Hz, ^4J = 1.2 Hz, 1H, (CH(4)), 7.27 (dd, ^3J = 5.0 Hz, ^3J = 3.7 Hz, 1H, CH(10)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 160.1 (C=O(7)), 139.8 (C$_{\text{quart}}$(1)), 138.5 (C$_{\text{quart}}$(8)), 133.8 (CH(5)), 133.2 (CH(3)), 132.5 CH(9)), 129.9 (CH(11)), 128.2 (CH(10)), 126.9 (CH(6)), 126.5 (CH(4)), 116.9 (C$_{\text{quart}}$(12)), 109.3 (C$_{\text{quart}}$(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3281 (m), 3108 (w), 2227 (m), 1646 (m), 1603 (m), 1580 (m), 1527 (m), 1475 (m), 1446 (m), 1414 (m), 1347 (m), 1305 (m), 1270 (m), 1233 (m), 1162 (m), 1112 (m), 1065 (m), 1037 (m), 960 (m), 894 (m), 875 (m), 859 (m), 846 (m), 820 (m), 763 (m), 744 (m), 721 (s), 625 (m); **MS (EI, 70 eV):** *m/z* (%) = 228 ([M$^+$], 23), 111 (100), 39 (20); **HRMS (EI):** *m/z* = calcd. for $C_{12}H_8O_1N_2S_1$ 228.03519, found 228.03500.

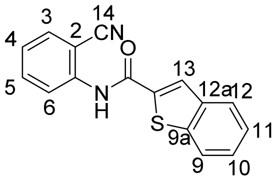
N-(2-Cyanophenyl)-1-methyl-1H-indole-5-carboxamide (76)



The compound was synthesized following the procedure for (**58**) starting from 0.5 mmol (**57**) and 0.6 mmol 5-bromo-*N*-methylindole, giving 61 % (**76**) as a solid, **M.P.:** 162–164°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.47 (s, 1H, NH), 8.31 (d, 1H, ^4J = 1.6 Hz, CH(13)), 7.92 – 7.80 (m, 2H, CH(3 + 10)), 7.74 (ddd, ^3J = 8.1 Hz, ^3J = 7.5 Hz, ^4J = 1.6 Hz, 1H, CH(5)), 7.60 (m, 2H, (CH(6 + 9), 7.47 (d, ^3J = 3.1 Hz, 1H, CH(11)), 7.41 (ddd, ^3J = 7.6 Hz, ^3J = 7.6 Hz, ^4J = 1.2 Hz, 1H, (CH(4)), 6.62 (dd, ^3J = 3.1 Hz, ^4J =

0.8 Hz, 1H, CH(12)), 3.86 (s, 3H, CH$_3$) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 166.4 (C=O(7)), 141.0 (C$_{quart}$(1)), 138.2 (C$_{quart}$(10a)), 133.6 (CH(5)), 133.0 (CH(3)), 131.4 (C$_{quart}$(12a)), 129.3 (C$_{quart}$(8)), 127.3 (CH(11)), 126.6 (CH(6)), 125.8 (CH(4)), 121.1 (CH(10)), 121.0 (CH(13)), 117.1 (CN(14)), 109.5 (CH(9)), 109.0 (C$_{quart}$(2)), 101.7 (CH(12)), 32.67 (CH$_3$) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3255 (m), 3100 (w), 3058 (w), 2922 (w), 2223 (m), 1743 (w), 1652 (m), 1639 (m), 1608 (m), 1603 (m), 1579 (m), 1521 (m), 1515 (m), 1483 (m), 1470 (m), 1448 (m), 1423 (m), 1383 (m), 1366 (m),1343 (m), 1309 (m), 1261 (m), 1240 (m), 1190 (m), 1162 (m), 1117 (m), 1105 (m), 1081 (m), 1038 (m), 1007 (m), 957 (m), 947 (m), 896 (m), 871 (m), 844 (m), 811 (m), 776 (m), 745 (m), 718 (m), 673 (m), 640 (m), 625 (m); **MS (EI, 70 eV):** *m/z* (%) = 275 ([M]$^+$, 21), 159 (11), 158 (100), 130 (28), 103 (13), 77 (15); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{17}H_{13}N_3O_1$ 274.09932 ([M-H]$^-$), found 274.09859.

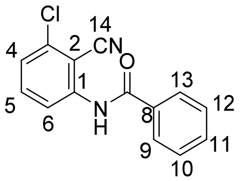
***N*-(2-Cyanophenyl)-benzo[*b*]thiophene-2-carboxamide (77)**



The compound was synthesized following the procedure for (**58**) starting from 0.5 mmol (**58**) and 0.6 mmol 2-bromo-benzo[*b*]thiophene, giving 43 % (**77**) as a solid, **M.P.:** 164–166°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.69 (s, 1H, NH), 8.65 (s, 1H, CH(13)), 8.48 – 8.43 (m, 1H, CH(9)), 8.13 – 8.09 (m, 1H, (CH(12)), 7.90 (ddd, ^3J = 7.7 Hz, ^4J = 1.6 Hz, ^5J = 0.5 Hz, 1H, (CH3)), 7.77 (ddd, ^3J = 8.1 Hz, ^3J = 7.5 Hz, ^4J = 1.6 Hz, 1H, CH(5)), 7.61 (ddd, ^3J = 8.1 Hz, ^4J = 1.2 Hz, ^5J = 0.5 Hz, 1H, CH(6)), 7.51 – 7.44 (m, 3H, (CH(4 + 10 + 11)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 161.9 (C=O(7)),148.2 (C$_{quart}$(8)) 140.0 (C$_{quart}$(1)), 139.5 (C$_{quart}$(9a)), 136.9 (C$_{quart}$12a)), 133.8 (CH(5)), 133.1 (CH(3)), 126.5 (CH(6)), 126.2 (CH(4)), 125.1 (CH(11)), 125.1 (CH(10)), 124.5 (CH(12)), 124.3 (CH(9)), 122.9 (CH(13)), 117.0 (C$_{quart}$(14)), 109.1 (C$_{quart}$(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3240 (m), 3083 (w), 3064 (w), 2229 (m), 1924 (w), 1640 (s), 1603 (m), 1582 (m), 1507 (s), 1487 (s), 1460 (m), 1441 (m), 1424 (m), 1367 (m), 1301 (m), 1272 (m), 1253 (m), 1223 (m), 1162 (m), 1153 (m), 1104 (m), 1065 (m), 1039 (w), 1022 (m), 1016 (m), 908 (m), 869 (m), 812 (m), 765 (s), 785 (s), 741 (m), 727 (m), 713 (m), 701 (m), 653 (m), 622 (m); **MS (EI, 70 eV):** *m/z* (%) = 278

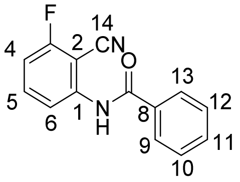
($[M]^+$, 21), 162 (11), 161 (100), 133 (20), 90 (10), 89 (38); **HRMS (EI):** *m/z* = Calcd. for $C_{16}H_{10}O_1N_2S_1$ 278.05084, found 278. 5081.

N-(3-Chloro-2-cyanophenyl)-benzonitrile (78)



The compound was synthesized following the procedure for (**578**) as a solid, **M.P.:** 163–165°C; **^{1}H-NMR (300 MHz, DMSO-d_6):** δ = 10.79 (s, 1H, NH), 8.03 – 7.96 (m, 2H, CH(10 + 14)), 7.77 (dd, ^3J = 8.1 Hz, ^3J = 8.1 Hz, 1H, CH(5)), 7.70 – 7.53 (m, 5H, CH(4 + 6 + 11 + 12 + 13)) ppm; **^{13}C-NMR (75 MHz, DMSO-d_6):** δ = 165.7 (C=O(7)), 142.6 (C_{quart}(1)), 135.6 (C_{quart}(3)), 134.7 (CH(5)), 133.2 (C_{quart}(8)), 132.4 (CH(11)), 128.7 (CH(10 + 12)), 127.9 (CH(9 + 13)), 126.8 (CH(6)), 125.3 (CH(4)), 114.2 (C_{quart}(14)), 109.9 (C_{quart}(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3248 (m), 3071 (w), 2955 (w), 2925 (w), 2229 (m), 1656 (s), 1593 (m), 1571 (m), 1515 (m), 1489 (m), 1454 (m), 1427 (m), 1305 (m), 1264 (m), 1208 (m), 1176 (m), 1116 (m), 1027 (m), 1000 (m), 946 (m), 930 (m), 913 (m), 901 (m), 787 (s), 761 (m), 711 (s), 689 (m), 649 (m), 613 (m); **MS (EI, 70 eV):** *m/z* (%) = 256 ($[M]^+$, 16), 105 (100), 77 (50), 51 (16); **HRMS (EI):** *m/z* = calcd. for $C_{14}H_9O_1N_2{}^{35}Cl_1$ 256.03979, found 256.03978, Calcd. for $C_{14}H_9O_1N_2{}^{37}Cl_1$ 258.03684, found 258.03727.

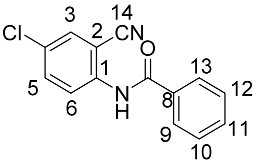
N-(2-Cyano-3-fluorophenyl)-benzonitrile (79)



The compound was synthesized following the procedure for (**58**) starting from 0.5 mmol 2-amino-6-fluoro-benzonitrile and 0.6 mmol (**39**), giving 92 % (**79**) as a solid, **M.P.:** 167–169°C; **^{1}H-NMR (300 MHz, DMSO-d_6):** δ = 10.81 (s, 1H, NH), 8.05 – 7.97 (m, 2H, CH(9 + 13)), 7.81 (ddd, ^3J = 8.4 Hz, ^3J = 8.4 Hz, ^4J = 6.6 Hz, 1H, CH (5)), 7.71 – 7.35 (m, 5H, CH(4 + 6 + 10 + 11 + 12)) ppm; **^{13}C-NMR (75 MHz, DMSO-d_6):** δ =

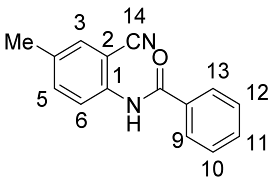
165.7 (C=O(7)), 162.8 (d, ^{1}J = 254.5 Hz, C_{quart}(3))), 142.0 (d, ^{4}J = 2.5 Hz, (C_{quart}(1)), 135.5 (d, ^{3}J = 10.2 Hz, CH(5)), 133.3 (C_{quart}(8)), 132.4 (CH(11)), 128.7 (CH(9 + 13)), 128.0 (CH(10 + 12)), 122.3 (d, ^{4}J = 3.1 Hz, CH(6)), 112.9 (d, ^{2}J = 19.4 Hz, (CH(4)), 112.2 (C_{quart}(14)), 98.38 (d, ^{2}J = 17.2 Hz, (C_{quart}(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3271 (w), 2229 (w), 1659 (s), 1617 (m), 1600 (m), 1580 (m), 1525 (m), 1475 (s), 1447 (m), 1438 (m), 1311 (m), 1273 (m), 1249 (s), 1126 (m), 1074 (m), 1031 (m), 989 (m), 910 (w), 846 (w), 787 (s), 733 (m), 707 (s), 649 (m), 602 (m); **MS (EI, 70 eV):** *m/z* (%) = 240 (14), 108 (12), 105 (100), 77 (60), 51 (21); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{14}H_9N_2F_1O_1$ 239.06261 ([M-H]$^-$), found 239.06329.

N-(4-CHloro-2-Cyanophenyl)-benzonitrile (81)



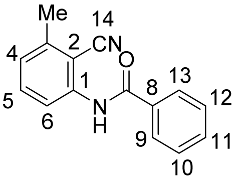
The compound was synthesized following the procedure for (**58**) starting from 0.5 mmol 2-amino-5-CHloro-benzonitrile and 0.6 mmol (**39**), giving 21 % (**81**) as a solid, **M.P.:** 177–179°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.69 (s, 1H, NH), 8.08 (d, ^{4}J = 2.5 Hz, 1H, CH(3)), 8.02 – 7.96 (m, 2H, CH(9 + 13)), 7.83 (dd, ^{3}J = 8.7 Hz, ^{4}J = 2.5 Hz, 1H, CH(5)), 7.69 – 7.53 (m, 4H, CH(6 + 10 + 11 +12)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 165.6 (C=O(7)), 139.5 (C_{quart}(1)), 133.9 (CH(5)), 133.3 (C_{quart}8)), 132.5 (CH(3)), 132.3 (CH(11)), 130.1 (C_{quart}(4)), 128.6 (CH(10 + 12)), 128.3 (CH(6)), 127.9 (CH(9 + 13)), 115.7 (C_{quart}(14)), 110.7 (C_{quart}(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3301 (m), 3180 (w), 3062 (w), 2928 (w), 1670 (m), 1652 (s), 1608 (s); 1579 (m), 1505 (m), 1485 (m), 1476 (m), 1431 (m), 1362 (m), 1294 (m), 1233 (m), 1165 (m), 1124 (m), 1076 (m), 1011 (m), 900 (m), 849 (m), 824 (s), 807 (m), 779 (m), 763 (m), 698 (m), 622 (m), 616 (m); **MS (EI, 70 eV):** *m/z* (%) = 256 ([M]$^+$, 13), 105 (100), 77 (55), 51 (19); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{14}H_9N_2{}^{35}Cl_1O_1$ 255.03306 ([M-H]$^-$), found 255.0334, Calcd. for $C_{14}H_9N_2{}^{37}Cl_1O_1$ 257.03048, found 257.03062.

N-(2-Cyano-4-Methylphenyl)-benzonitrile (82)



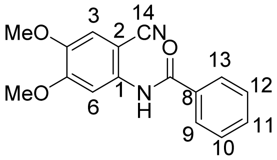
The compound was synthesized following the procedure for (**58**) starting from 0.5 mmol 2-amino-5-methyl-benzonitrile and 0.6 mmol (**39**), giving 42 % (**82**) as a solid, **M.P.:** 204– 206°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.52 (s, 1H, NH), 7.99 (dd, ^3J = 8.3 Hz, ^4J = 1.5 Hz, 2 H, CH(9 + 13)), 7.71 – 7.68 (m, 1H, CH (3)), 7.67 – 7.52 (m, 4H, CH (5 + 10 + 11 + 12), 7.46 (d, ^3J = 8.3 Hz, 1H, CH(6)), 2.36 (s, 3H, CH_3) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 165.7 (C=O(7)), 137.9 C_{quart}(1)), 136.2 (C_{quart}(4)), 134.4 (CH(5)), 133.6 (C_{quart}(8)), 133.0 (CH(3)), 132.1 (CH(11)), 128.6 (CH(10 + 12)), 127.8 (CH(9 + 13)), 126.9 (CH(6)), 117.1 (C_{quart}(14)), 109.3 (C_{quart}(2)), 20.1 (CH_3) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3274 (m), 2952 (w), 2916 (w), 2856 (w), 2228 (m), 1647 (m), 1601 (w), 1588 (w), 1579 (w), 1498 (m), 1485 (m), 1448 (m), 1382 (w), 1314 (w), 1266 (m), 1247 (m), 1176 (m), 1151 (m), 1133 (w), 1102 (w), 1075 (w), 1025 (w), 998 (w), 936 (w), 899 (m), 823 (m), 810 (m), 790 (w), 716 (m), 690 (m), 666 (m), 615 (w); **MS (EI, 70 eV):** *m/z* (%) = 236 ([M$^+$], 26), 105 (100), 77 (67), 51 (20); **HRMS (EI):** *m/z* =calcd. for $C_{15}H_{12}O_1N_2$ 236.09441, found 236.09429.

N-(2-Cyano-3-Methylphenyl)-benzonitrile (83)



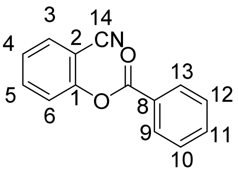
The compound was synthesized following the procedure for (**58**) starting from 0.5 mmol 2-amino-6-methyl-benzonitrile and 0.6 mmol (**39**), giving 64 % (**83**) as a solid, **M.P.:** 152–154°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.56 (s, 1H, NH), 8.02 – 7.97 (m, 2H, CH(9 + 13)), 7.68 – 7.51 (m, 4H, CH(5 + 10 + 11 + 12)), 7.41 (d, ^3J = 8.0 Hz, 1H, CH(4)), 7.34 (d, ^3J = 7.7 Hz, 1H, CH(6)), 2.52 (s, 3H, CH_3) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 165.7(C=O(7)), 142.3 (C_{quart}(3)), 140.7 (C_{quart}(1)), 133.7 (C_{quart}(8)), 133.1 (CH(5)), 132.1 (CH(11)), 128.6 (CH(10 + 12)), 127.8 (CH(9 + 13)), 127.3 (CH(6)), 124.2 (CH(4)), 115.9 (C_{quart}(2)), 110.1 (C_{quart}(14)), 20.2 (CH_3) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3266 (m), 3065 (w), 2925 (w), 2225 (m), 1645 (s), 1599 (m), 1579 (m), 1507 (s), 1488 (m), 1467 (m), 1448 (m), 1440 (m), 1305 (m), 1295 (m), 1266 (m), 1241 (m), 1178 (m), 1072 (m), 1120 (m), 1072 (m), 1026 (m), 1000 (m), 923 (m), 910 (m), 888 (m), 850 (m), 786 (s), 734 (m), 707 (s), 686 (s), 645 (m), 601 (m); **MS (EI, 70 eV):** *m/z* (%) = 236 ($[M]^+$, 28), 105 (100), 77 (65), 51 (20); **HRMS (EI):** *m/z* = calcd. for $C_{15}H_{12}O_1N_2$ 236.09441, found 236.09437.

N-(2-Cyano-4,5-dimethoxyphenyl)-benzonitrile (84)



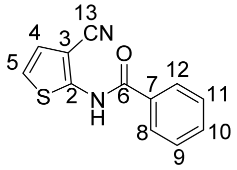
The compound was synthesized following the procedure for (**58**) starting from 0.5 mmol 2-amino-4,5-dimethoxy-benzonitrile and 0.6 mmol (**39**), giving 71 % (**84**) as a solid, **M.P.:** 191–193°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.45 (s, 1H, NH), 8.03 – 7.97 (m, 2H, CH (9 + 13)), 7.67 – 7.40 (m, 3H, CH(10 + 11 + 12)), 7.40 (s, 1H, CH(3)), 7.16 (s, 1H, CH(6)), 3.84 (s, 3H, OMe), 3.83 (s, 3H, OMe) ppm; **^{13}C-NMR (75 MHz, DMSO):** δ = 165.6 (C=O(7)), 152.6 (C_{quart}(5)), 146.8 (C_{quart}(4)), 135.2 (C_{quart}(1)), 133.7 (C_{quart}(8)), 132.0 (CH(11)), 130.3 (CH(10 + 12)), 128.5 (CH(9 + 13)), 127.7 (CH(3)), 114.2(C_{quart}(14)), 110.6 (C_{quart}(2)), 100.6 (CH(6)), 56.11(OMe), 56.0 (OMe) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3290 (m), 3015 (m), 2943 (w), 2834 (w), 2223 (m), 1655 (s), 1609 (m), 1587 (m), 1511 (s), 1487 (m), 1448 (m), 1404 (s), 1350 (m), 1307 (m), 1258 (s), 1222 (s), 1208 (s), 1133 (m), 1089 (m), 1071 (m), 1026 (m), 914 (m), 851 (m), 796 (m), 752 (m); 707 (m), 688 (s), 665 (m), 613 (m); **MS (EI, 70 eV):** *m/z* (%) = 283 (10), 282 ($[M]^+$, 45), 105 (100), 77 (49), 51 (10); **HRMS (EI):** *m/z* = calcd. for $C_{16}H_{14}O_3N_2$ 282. 09989, found 282.09974.

2-Cyanophenylbenzoate (85)



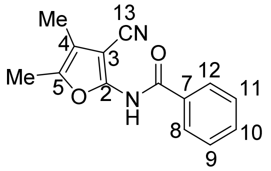
The compound was synthesized following the procedure for (**58**) starting from 0.5 mmol 2-hydroxy-benzonitrile and 0.6 mmol (**39**), giving 54 % (**85**) as a solid, **M.P.:** 104–106°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 8.23 – 8.15 (m, 2H, CH(9 + 13)), 8.01 (ddd, ^3J = 7.8 Hz, ^4J = 1.7 Hz, ^5J = 0.5 Hz, 1H, CH(3)), 7.92 – 7.75 (m, 2H, CH(4 + 5)), 7.72–7.59 (m, 3H, CH(10 +11 + 12)), 7.55 (dd, ^3J = 7.6 Hz, ^4J = 1.1 Hz, 1H, CH(6)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 163.8 (C=O(7)), 152.1 (C$_{quart}$(1)), 135.2 (CH(5)), 134.(CH(3)), 133.6 (CH(11)), 130.1(C$_{quart}$(8)), 129.2 (CH(10 + 12)), 127.8 (CH(9 + 13)), 127.2 (CH(4)), 123.8 (CH(6)), 115.2 (C$_{quart}$(14)), 106.3 (C$_{quart}$(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3042 (w), 2231 (m), 1732 (s), 1600 (m), 1585 (m), 1576 (w), 1494 (m), 1488 (m), 1452 (m), 1446 (m), 1319 (w), 1255 (s), 1226 (s), 1174 (s); 1098 (m), 1077 (m), 1061 (m), 1037 (m), 1023 (m), 1001 (m), 956 (m), 885 (m), 851 (m), 833 (m), 799 (m), 760 (s); 747 (m); 719 (m), 711 (M); 700 (s), 684 (m), 677 (m), 616 (m); **MS (EI, 70 eV):** *m/z* (%) = 223 ([M]$^+$), 1), 105 (100); 77 (52), 51 (21); **HRMS (EI):** *m/z* = calcd. for $C_{14}H_9O_2N_1$ 223.06278, found 223.06293.

N-(3-Cyanothiophen-2-yl)-benzamide (86)



The compound was synthesized following the procedure for (**58**) starting from 0.5 mmol 2-amino-3-cyano-thiophene and 0.6 mmol (**39**), giving 44 % (**86**) as a solid, **M.P.:** 172–174°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 11.89 (s, 1H, NH), 8.01–7.93 (m, 2H, CH(8 + 12)), 7.70 – 7.63 (m, 1H CH(10)), 7.62 – 7.53 (m, 2H, CH(9 + 11)), 7.30 (d, ^3J = 5.8 Hz, 1H, CH(5)), 7.24 (d, ^3J = 5.8 Hz, 1H, CH(4)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 165.4 (C=O(6)), 152.7 (C$_{quart}$(2)), 134.9 (C$_{quart}$(7)); 132.6 (CH(10)), 128.5 (CH (9 + 11)), 128.4 (CH(8 + 12)), 125.4 (CH(4)), 120.2 (CH(5)), 114.8 (C$_{quart}$(13)), 95.4 (C$_{quart}$(3)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3259 (m), 3206 (m), 3104 (m), 3082 (m), 2220 (m), 1672 (m), 1602 (w), 1554 (m), 1503 (m), 1490 (m), 1452 (m), 1374 (m), 1285 (m), 1258 (m), 1201 (m), 1098 (m), 1070 (m), 1026 (m), 988 (m), 964 (m), 925 (m), 876 (m), 818 (m), 790 (m), 719 (m), 701 (m), 688 (m), 679 (m), 632 (m); **MS (EI, 70 eV):** *m/z* (%) = 229 ([M]$^+$, 14), 105 (100), 77 (63), 51 (24); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{12}H_8O_1N_2S_1$ 229.04301 ([M+H]$^+$), found 229.04307

N-(3-Cyano-4,5-dimethylfuran-2-yl)-benzamide (87)

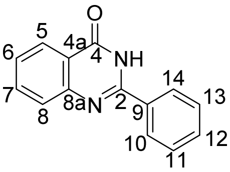


The compound was synthesized following the procedure for (**58**) starting from 0.5 mmol 2-amino-3-cyano-4,5-dimethylfuran and 0.6 mmol (**39**), giving 50 % (**87**) as a solid, **M.P.:** 190–192°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 11.44 (s, 1H, NH), 8.02 – 7.97 (m, 2H, CH(8 + 12)), 7.70 – 7.62 (m, 1H, CH(10)), 7.60 – 7.50 (m, 2H, CH(9 + 11)), 2.22 (s, 3H, CH_3), 2.01 (s, 3H, CH_3) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 164.5 (C=O(6)), 149.3 (C_{quart}(5)), 143.0 (C_{quart}(2)), 132.7 (C_{quart}(7)), 132.2 (CH(10)), 128.7 (CH(9 + 11)), 128.0 (CH(8 + 12)), 115.2(C_{quart}(4)), 113.3 (C_{quart}(13)), 88.1 (C_{quart}(3)), 10.8 (CH_3), 8.4 (CH_3) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3260 (w), 3054 (w); 2917 (w); 2223 (m), 1686 (m), 1672 (m), 1605 (m), 1595 (m), 1536 (m), 1493 (m), 1448 (m), 1387 (m), 1281 (m), 1223 (m), 1162 (m), 1132 (m), 1097 (w), 1073 (w), 1025 (w), 968 (w), 856 (w), 795 (w), 764 (w), 705 (m), 643 (m), 614 (m); **MS (EI, 70 eV):** *m/z* (%) = 240 ([M]$^+$, 10), 105 (100), 77 (42), 51 (12); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{14}H_{12}N_2O_2Na$ 263.07910 ([M+Na]$^+$), found 263.07911.

1.1.5. Synthesis of quinazolin-4(3*H*)-ones

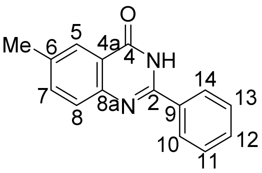
General procedure: To the crude reaction mixture for the synthesis of (**58**) was given 1.8 eq. of urea hydrogen peroxide. The mixture was heated to 100°C under stirring for 7 hours. After cooling, 20 mL water was added to precipitate the crude quinazolinone. The solid was filtered off and washed with hexane/ethyl acetate (4:1). The residue was dissolved in the minimum amount of boiling ethyl acetate and crystallized by the addition of hexane to the hot solution. Filtration gave 170 mg (76 %) 2-phenyl-quinazolinone (**59**) as a white solid.

N-Phenylquinazolin-4(3*H*)-one (59)



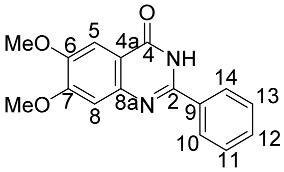
M.P.: 241–243°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 12.55 (s, 1H, NH), 8.23 – 8.13 (m, 3H, CH(7 + 10 + 14), 7.85 (ddd, ^3J = 8.5 Hz, ^3J = 7.0 Hz, ^3J = 1.6 Hz, 1H, CH(5)), 7.77 – 7.71 (m, 1H, CH(12)), 7.62 – 7.49 (m, 4H, CH(6 + 8 + 11 + 13)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 162.3 (C=O(4)), 152.4 (C$_{\text{quart}}$(2)), 148.7 (C$_{\text{quart}}$(8a)), 134.6 (CH(7)), 132.8 (C$_{\text{quart}}$(9)), 131.4 (CH(12)), 128.6 (CH(10 + 14)), 127.8 (CH(11 + 13)), 127.4 CH(6)), 126.6 (CH(7)), 125.8 (CH(5)), 121.0 (C$_{\text{quart}}$(4a)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3300 (w), 3159 (w), 3058 (w), 3033 (w), 1650 (m), 1609 (m), 1507 (w), 1480 (w), 1452 (w), 1437 (m), 1380 (w), 1361 (w), 1328 (w), 1299 (m), 1242 (w), 1148 (m), 1132 (w), 1025 (w), 806 (m), 745 (s), 698 (s), 684 (m), 659 (s), 641 (s), 600 (m); **MS (EI, 70 eV):** *m/z* (%) = 222 ([M]$^+$, 100), 119 (99), 104 (11), 92 (14), 90 (17), 77 (22), 76 (11), 51 (10); **HRMS (EI):** *m/z* = calcd. for $C_{14}H_{10}O_1N_2$ 222.07876, found 222.07881.

6-Methyl-2-phenylquinazolin-4(3*H*)-one (88)



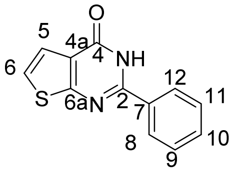
The compound was synthesized following the procedure for (**59**), adding 1.8 eq. UHP to the crude mixture of (**82**), giving 41 % (**88**) as a solid, **M.P.:** 262–264°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 12.47 (s, 1H, NH), 8.20–8.13 (m, 2H, CH(10 + 14)), 7.95 (d, ^4J = 1.9 Hz, 1H, (CH(5)), 7.66 – 7.64 (m, 2H, CH(7 + 8)), 7.59 – 7.50 (m, 3H, CH(11 + 12 + 13)), 2.46 (s, 3H, CH$_3$) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 162.2 (C=O(4)), 151.5 (C$_{\text{quart}}$(2)), 146.8 (C$_{\text{quart}}$(8a)), 136.3 (C$_{\text{quart}}$(6)), 135.90 (C$_{\text{quart}}$(9)), 132.9 (CH(7)), 131.2 (CH(12)), 128.6 (CH(11 + 13)), 127.6 (CH(10 + 14)), 127.4 (CH(5)), 125.3 (CH(8)), 120.7 (C(4a)), 20.9 (CH$_3$) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3158 (w), 3059 (w), 3026 (w), 2916 (w), 2872 (), 1659 (s9; 1622 (m), 1597 (s), 1570 (m), 1505 (m), 1488 (m), 1448 (m), 1352 (m), 1304 (m), 1287 (m), 1239 (m), 1205 (m), 1140 (m), 1082 (m), 969 (m), 946 (m), 902 (m), 875 (m); 829 (s); 776 (m), 696 (s); 666 (m), 617 (m); **MS (EI, 70 eV):** *m/z* (%) = 237 (18), 236 ($[M]^+$, 100), 133 (81), 105 (13), 104 (40), 89 (12), 78 (13), 77 (47), 76 (13), 51 (19); **HRMS (EI):** *m/z* = calcd. for $C_{15}H_{12}O_1N_2$ 236.09441, found 236.09449.

6,7-Dimethoxy-2-phenylquinazolin-4(3*H*)-one (89)



The compound was synthesized following the procedure for (**59**), adding 1.8 eq. UHP to the crude mixture of (**84**), giving 50 % (**89**) as a solid, **M.P.:** 290–292°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 12.42 (s, 1H, NH), 8.23 – 8.11 (m, 2H, CH(10 + 14)), 7.59 – 7.50 (m, 3H, CH(11 + 12 + 13)), 7.49 (s, 1H, CH(5)), 7.22 (s, 1H, CH(8)), 3.94 (s, 3H, OMe), 3.90 (s, 3H, OMe) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 161.6 (C=O(4)), 154.8 (C_{quart}(8a)), 150.8 (C_{quart}(9)), 148.6 (C_{quart}(7)), 144.8 (C_{quart}(6)), 132.8 (C_{quart}(9)), 131.0 (CH(12)), 128.6 (CH(11 + 13)), 127.4 (CH(9 + 14)), 114.0 (C_{quart}(4a)), 108.3 (CH(8)), 104.9 (CH(5)), 56.0 (CH_3), 55.7 (CH_3) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3062 (w), 3044 (w), 2943 (w), 1664 (m), 1615 (m), 1599 (w), 1575 (w), 1494 (m), 1478 (w), 1458 (w); 1435 (m), 1388 (w), 1344 (w), 1305 (w), 1292 (w), 1275 (m), 1244 (w), 1223 (w), 1207 (w), 1173 (w), 1155 (w), 1100 (m), 1033 (w), 998 (m), 947 (m), 865 (w), 849 (m), 826 (w), 784 (w), 769 (w), 759 (w), 705 (w), 689 (m), 676 (w), 654 (w), 638 (w); **MS (EI, 70 eV):** *m/z* (%) = 283 (16), 282 ($[M]^+$, 100), 281 (20), 268 (12), 267 (47), 239 (24), 237 (16), 104 (19), 32 (11); **HRMS (EI):** *m/z* = calcd. for $C_{16}H_{14}O_3N_2$ 282. 09989, found 282.09996

2-Phenylthieno[2,3-d]pyrimidin-4(3*H*)-one (90)

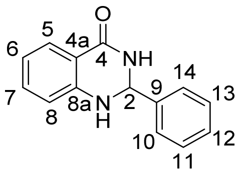


The compound was synthesized following the procedure for (**59**), adding 1.8 eq. UHP to the crude mixture of (**86**), giving 50 % (**90**) as a solid, **M.P.:** 233–235°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 13.44 (s, 1H, NH), 7.93 (m, 2H, CH(5 + 6)), 7.65 (m, 5H, CH(10 + 11 + 12 + 13 + 14)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 167.4 (CH(6)), 162.5 (C=O(4)), 146.2 (C$_{quart}$(2)), 132.7 (C$_{quart}$(7)), 132.1 (CH(10)), 129.3 (CH(8 + 12)), 127.0 (CH(9 + 11)), 123.2 (CH(5)), 116.5 (C$_{quart}$(6a)), 115.7 (C$_{quart}$(4a)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3335 (w), 3172 (w), 2929 (w), 1641 (m), 1544 (m), 1486 (m), 1435 (m), 1398 (m), 1343 (m), 1275 (m), 1184 (m), 1100 (m), 1026 (m); 1000 (m), 960 (m), 860 (m), 797 (m), 688 (s); **MS (EI, 70 eV):** *m/z* (%) = 229 ([M]$^+$, 32), 105 (100), 77 (82), 51 (24), 50 (11); **HRMS (EI):** *m/z* = calcd. for $C_{12}H_8O_1N_2S_1$ 228.03519, found 228.03513.

1.1.6. Synthesis of 2-phenyl-1,2-dihydroquinazolin-4(1*H*)-ones

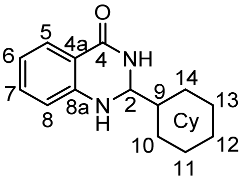
General procedure: A 25 mL pressure tube was charged with 1 mmol (118 mg) 2-aminobenzonitrile (**57**), 1.2 mmol benzaldehyde (122 µL, **107**), 1 mmol K_3PO_4 monohydrate (230 mg) and 5 mL water and subsequently sealed. The mixture was heated under stirring to 100°C for 8 hours. The white precipitate was filtered off under reduced pressure and washed with water. The crude solid was dissolved in the minimum amount of boiling ethyl acetate and recrystallized by the addition of *n*-hexane. Filtering and drying of the white solid gave 162 mg (73 %) 2-phenyl-2,3-dihydro-quinazolin-4(1*H*)-one (**102**).

2-Phenyl-2,3-dihydroquinazolin-4(1*H*)-one (102)



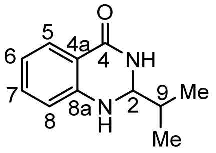
M.P.: 224–226°C; **^{1}H-NMR (250 MHz, DMSO-d$_6$):** δ = 8.28 (s, 1H, NH(3)), 7.61 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, (CH(5)), 7.49 (dd, ^3J = 7.9 Hz, ^4J = 1.9 Hz, 2H, CH(10 + 14)), 7.45–7.29 (m, 3H, CH(11 + 12 + 13)), 7.24 (ddd, ^3J = 8.1 Hz, ^3J = 7.2 Hz, ^4J = 1.6 Hz, 1H, CH(7)), 7.11 (s, 1H, NH(1)), 6.78–6.72 (m, 1H, CH(8)), 6.71–6.63 (m, 1H, CH(6)), 5.75 (dd, ^3J = 1.9 Hz, ^3J = 1.9 Hz, 1H, CH(2)) ppm; **^{13}C-NMR (63 MHz, DMSO-d$_6$):** δ = 163.6 (C=O(4)), 147.8 (C$_{quart}$(8a)), 141.6 (C$_{quart}$(9)), 133.3 (CH(7)), 128.4 (CH(12)), 128.3 (CH(11 + 13)), 127.3 (CH(5)), 126.8 (CH(10 + 14)), 117.1 (CH(6)), 114.9 (C_{quart}(4a)), 114.4 (CH(8)), 66.5 (CH(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3159 (w), 3075 /m), 2957 (w), 1680 (m), 1590 (m), 1540 (m), 1522 (m), 1500 (m), 1461 (m), 1420 (m), 1394 (m), 1291 (m), 1224 (m), 1197 (w), 1172 (m), 1161 (w), 1116 (m), 1101 (w), 1060 (m), 1031 (w), 970 (m), 938 (w), 911 (m), 863 (w), 827 (m), 771 (m), 758 (m), 752 (m), 707 (m), 702 (m), 687 (m), 677 (m), 661 (m), 634 (m); **MS (EI, 70 eV):** *m/z* (%) = 224 ([M]$^+$, 19), 223 (27), 147 (100), 120 (42), 119 (15), 104 (10), 92 (29), 77 (20), 65 (14), 64 (10), 51 (15); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{14}H_{12}N_2O_1$ 225.10224 ([M+H]$^+$), found 225.10259.

2-Cyclohexyl-2,3-dihydroquinazolin-4(1*H*)-one (108)



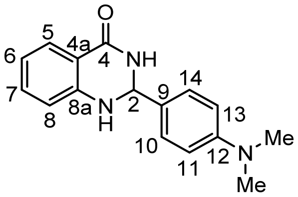
The compound was synthesized following the procedure for (**102**), starting from 1 mmol (**57**) and 1 mmol cyclohexanecarbaldehyde, giving 43 % (**108**) as a solid **M.P.:** 231–233°C; **^{1}H-NMR (400 MHz, DMSO-d$_6$):** δ = 7.87 (s, 1H, NH(3)), 7.55 (dd, ^3J = 7.7 Hz, ^{4}J = 1.6 Hz, 1H, CH(5)), 7.23 – 7.16 (m, 1H, CH(7)), 6.74 (dd, ^3J = 8.2 Hz, ^4J = 1.1 Hz, 1H, CH(8)), 6.60 (ddd, ^3J = 7.4 Hz, ^3J = 7.3 Hz, ^4J = 1.1 Hz, 1H, CH(6)), 6.55 (s, 1H, NH(1)), 4.44 (ddd, ^3J = 4.2 Hz, ^{3}J = 1.9 Hz, ^{3}J = 1.9 Hz, 1H, CH(2)), 1.77– 1.04 (m, 11H, CH_2(Cy)) ppm; **^{13}C-NMR (101 MHz, DMSO-d$_6$):** δ = 163.7 (C=O(4)), 148.3 (C_{quart}(8a)), 133.0 (CH(7)), 127.2 (CH(5)), 116.4 (CH(6)), 114.8 (C_{quart}(4a)), 114.1 (CH(8)), 68.6 (CH(2)), 42.9 (CH_2(Cy)), 27.0 (CH_2(Cy)), 26.7 (CH_2(Cy)), 25.9 (CH_2(Cy)), 25.6 (CH_2(Cy)), 25.6 (CH_2(Cy)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3321 (m), 3193 (m), 3068 (m), 2928 (m), 2850 (m), 2211 (m), 1654 (s), 1605 (s), 1582 (s), 1542 (s), 1491 (s), 1450 (s), 1391 (s), 1313 (s), 1253 (s), 1151 (s), 1086 (s), 1030 (s), 973 (m), 942 (m), 849 (s), 741 (s), 704 (s), 625 (s); **MS (EI, 70 eV):** *m/z* (%) = 230 ([M]$^+$,0.9), 148 (10), 147 (100), 92 (10); **HRMS (EI):** *m/z* = calcd. for $C_{14}H_{18}O_1N_2$ 230.14136, found 230.14067.

2-Isopropyl-2,3-dihydroquinazolin-4(1*H*)-one (110)



The compound was synthesized following the procedure for (**102**), starting from 1 mmol (**57**) and 1 mmol isovaleraldehyde, giving 64 % (**110**) as a solid, **M.P.:** 178–179°C; **^{1}H-NMR (400 MHz, DMSO-d_6):** δ = 7.86 (s, 1H, NH(3)), 7.57 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, CH(5)), 7.20 (ddd, ^3J = 8.5 Hz, ^3J = 7.2 Hz, ^4J =1.7 Hz, 1H, CH(7)), 6.75 (dd, ^3J = 8.2 Hz, ^4J = 1.0 Hz, 1H, CH(8)), 6.62 (ddd, ^3J = 7.5 Hz, ^3J = 7.4 Hz ^4J = 1.1 Hz, 1H, CH(6)), 6.51 (s, 1H, NH(1)), 4.54 – 4.49 (m, 1H, CH(2)), 1.86 (m, 1H, CH(9)), 0.94 (d, ^3J = 6.9 Hz, 3H, CH$_3$), 0.92 (d, ^3J = 6.8 Hz, 3H, CH$_3$) ppm; **^{13}C-NMR (101 MHz, DMSO-d_6):** δ = 163.9 (C=O(4)), 148.5 (C_{quart}(8a)), 133.0 (CH(7)), 127.2 (CH(5)), 116.5 (CH(6)), 114.7 (C_{quart}(4a)), 114.1 (CH(8)), 69.2 (CH(2)), 32.7 (CH(9)), 16.9 (CH$_3$), 16.6 (CH$_3$) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3275 (m), 3184 (m), 3073 (w), 2960 (m), 2929 (w), 2872 (w), 1641 (s), 1608 (s), 1519 (m), 1488 (m), 1450 (m), 1387 (m), 1370 (m), 1331 (m), 1296 (m); 1259 (m), 1199 (m); 1154 (m), 1117 (m), 1100 (m), 1068 (m), 1036 (m), 1017 (m), 866 (m), 804 (m), 780 (m), 751 (s); **MS (EI, 70 eV):** *m/z* (%) = 190 ([M]$^+$, 1), 147 (100), 92 (11), 65 (8); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{11}H_{14}N_2O$ 191.11789 ([M+H]$^+$), found 191.11737.

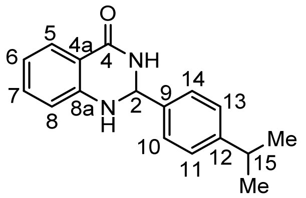
2-(4-(Dimethylamino)phenyl)-2,3-dihydroquinazolin-4(1*H*)-one (95)



The compound was synthesized following the procedure for (**102**), starting from 1 mmol (**57**) and 1 mmol 4-dimethylamino-benzaldehyde, giving 22 % (**95**) as a solid, **M.P.:** 226–227°C; **^{1}H-NMR (400 MHz, DMSO-d_6):** δ = 8.07 (s, 1H, NH(3))), 7.61 (dd, ^3J = 7.7 Hz, ^4J = 1.6 Hz, 1H, (CH(5)), 7.33 – 7.27 (m, 2H, CH(10 + 14)), 7.22 (ddd, ^3J = 7.9 Hz, ^3J = 7.1 Hz, ^4J = 1.6 Hz, 1H CH(7)), 6.91 (s, 1H, NH(1))), 6.75 – 6.69 (m, 3H, CH(8 + 11 + 13)), 6.69 – 6.63 (m, 1H, CH(6)), 5.65 – 5.62 (m, 1H, CH(2)), 3.34 (s, 6H, CH$_3$) ppm; **^{13}C-NMR (101 MHz, DMSO-d_6):** δ = 163.8 (C=O(4)), 150.7 (C_{quart}(9)), 148.2 (C_{quart}(8a)), 133.1 (CH(7)), 128.7 (CH(5)), 127.7 (C_{quart}(12)), 127.3 (CH(10 + 14)), 116.9 (CH(6)), 115.0 (C_{quart}(4a)), 114.4 (CH(8)), 111.9 (CH(11 + 13)), 66.6

(CH(2)), 40.16 (CH_3) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3291 (m), 3188 (m), 3054 (w), 2979 (w), 2889 (w), 2849 (w), 2799 (w), 1666 (m), 1651 (s), 1608 (s), 1506 (m), 1484 (m), 1434 (m), 1383 (m), 1351 (m), 1294 (m), 1236 (m), 1187 (m), 1164 (m), 1151 (m), 1132 (m), 1065 (m), 1033 (m), 1013 (m), 1002 (w); 946 (m), 908 (w), 860 (w); 818 (m), 787 (m), 752 (s); 729 (m), 685 (m), 661 (m), 608 (m); **MS (EI, 70 eV):** *m/z* (%) = 266 ([M-H]$^+$, 18), 265 (100), 264 (45), 146 (21), 145 (18), 119 (18); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{16}H_{17}N_3O$ 268.14444 ([M+H]$^+$), found 268.14429.

2-(4-Isopropylphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (112)

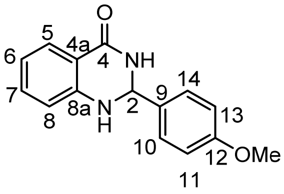


The compound was synthesized following the procedure for (**102**), starting from 1 mmol (**57**) and 1 mmol 4-isopropyl-benzaldehyde, giving 26 % (**112**) as a solid, **M.P.:** 203–204°C; **^{1}H-NMR (400 MHz, DMSO-d$_6$):** δ = 8.21 (s, 1H, NH(3)), 7.61 (dd,^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, CH(5)), 7.46 – 7.37 (m, 2H, CH(10 + 14)), 7.32 – 7.18 (m, 3H, CH(11 + 13 + 7)), 7.05 (s, 1H, NH(1)), 6.79 – 6.70 (m, 1H, CH(8)), 6.71 – 6.63 (m, 1H, CH(6)), 5.76 – 5.67 (m, 1H, CH(2)), 2.88 (m, 1H, CH(15)), 1.19 (d, ^3J = 6.9 Hz, 6H, CH_3) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 163.7 (C=O(7)), 148.8 (C_{quart}(12)), 148.0 (C_{quart}(9)), 139.0 (C_{quart}(8a)), 133.3 (CH(7)), 127.4 (CH(5)), 127.0 (CH(11 + 13)), 126.3 (CH(10 + 14)), 117.1 (CH(6)), 115.0 (C_{quart}(4a)), 114.4 (CH(8)), 66.6 (CH(2)), 33.26 (CH(15)), 23.9 (CH_3) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3292 (m), 3186 (w), 3049 (w), 2953 (w), 2859 (w), 1667 (m), 1653 (s), 1680 (m), 1508 (m), 1486 (m), 1433 (m), 1385 (m), 1328 (m), 1296 (m), 1285 (m), 1152 (m), 1136 (m), 1018 (m), 952 (w), 911 (w), 851 (m), 832 (m), 799 (m), 751 (s), 724 (m), 665 (m), 635 (m), 619 (m); **MS (EI, 70 eV):** *m/z* (%) = 266 ([M]$^+$, 28), 265 (53), 249 (13), 148 (12), 147 (100), 120 (46), 119 (13), 92 (27), 91 (10), 77 (12), 65 (12); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{17}H_{18}N_2O$ 267.14919 ([M+H]$^+$), found 267.14913.

Crystal data and structure refinement for 2-(4-isopropylphenyl)-2,3-dihydro-quinazolin-4(1*H*)-one

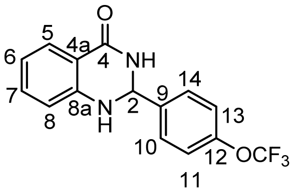
Empirical formula	$C_{17}H_{18}N_2O$	
Formula weight	266.33	
Temperature	150(2) K	
Wavelength	1.54178 Å	
Crystal system	monoclinic	
Space group (H.M.)	$P2_1/c$	
Unit cell dimensions	a = 13.7868(3) Å	α = 90.00°.
	b = 9.5016(2) Å	β = 104.522(1)°.
	c = 10.9971(3) Å	γ = 90.00°.
Volume	1394.56(6) $Å^3$	
Z	4	
Density (calculated)	1.269 Mg/m^3	
Absorption coefficient	0.628 mm^{-1}	
F(000)	568	
Crystal size	0.44 x 0.42 x 0.08 mm^3	
θ range for data collection	3.31 to 63.68°	
Index ranges	$-16 \leq h \leq 14$, $-6 \leq k \leq 11$, $-12 \leq h \leq 12$	
Reflections collected	9161	
Independent reflections	2282 [R(int) = 0.0225]	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.903	
Refinement method	Full-matrix least squares on F^2	
Data / restraints / parameters	2282 / 0 / 191	
Goodness-of-fit on F^2	1.042	
Final R indices [I > 2σ(I)]	R1 = 0.0329, wR2 = 0.0857	
R indices (all data)	R1 = 0.0349, wR2 = 0.0878	

2-(4-Methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (113)



The compound was synthesized following the procedure for (**102**), starting from 1 mmol (**57**) and 1 mmol 4-anisaldehyde, giving 80 % (**113**) as a solid, **M.P.:** 197–198°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 8.21 (s, 1H, NH(3)), 7.62 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, CH(5)), 7.48 – 7.38 (m, 2H, CH(10 + 14)), 7.24 (ddd, 1H, ^3J = 8.1 Hz, ^3J = 7.2 Hz, ^4J = 1.6 Hz, CH(7)), 7.05 (s, 1H, NH(1)), 6.99 – 6.90 (m, 2H, CH(11 + 13)), 6.75 (ddd, ^3J = 8.2 Hz, ^4J = 1.1, ^5J = 0.5 Hz, 1H, CH(8)), 6.68 (ddd, ^3J = 7.7 Hz, ^3J = 7.2 Hz, ^4J = 1.1 Hz, 1H, CH(6)), 5.72 (dd, ^3J = 1.7 Hz, ^3J = 1.7 Hz, 1H, CH(2)), 3.74 (s, 3H, OMe) ppm; **^{13}C-NMR (101 MHz, DMSO-d$_6$):** δ = 163.7 (C=O(4)), 159.4 (C$_{\text{quart}}$(12)), 148.0 (C$_{\text{quart}}$(8a)), 133.5 (CH(7)), 133.3(C$_{\text{quart}}$(9)), 128.2 (CH(10 + 14)), 127.4 (CH(5)), 117.1 (CH(6)), 115.0 (C$_{\text{quart}}$(4a)), 114.4 (CH8)), 113.6 (CH(11 + 13)), 66.3 (CH(2)), 55.2 (OMe) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3296 (m), 3177 (m), 3052 (m), 2989 (m), 2929 (m), 2827 (w), 1665 (m), 1651 (m), 1608 (m), 1589 (m), 1505 (m), 1485 (m), 1467 (m), 1435 (m), 1388 (m), 1322 (m), 1304 (m), 1242 (m), 1166 (m), 1153 (m), 1134 (m), 1109 (m), 1030 (m), 951 (w), 913 (w), 862 (m), 834 (m), 792 (m), 774 (m), 757 (m), 685 (m), 663 (m), 632 (m), 615 (m); **MS (EI, 70 eV):** *m/z* (%) = 254 ([M]$^+$, 50), 253 (100), 252 (16), 147 (70), 134 (13), 120 (75), 119 (31), 92 (49), 91 (17), 77 (16), 65 (21), 64 (20), 63 (17); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{15}H_{14}N_2O_2$ 277.09475 [M+Na]$^+$, found 277.09525.

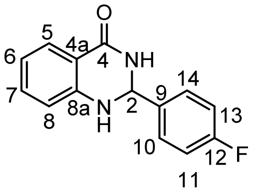
4-(Trifluoromethoxy)phenyl)-2,3-dihydroquinazolin-4(1*H*)-one (114)



The compound was synthesized following the procedure for (**102**), starting from 1 mmol (**57**) and 1 mmol 4-trifluoromethoxy-benzaldehyde, giving 49 % (**114**) as a solid, **M.P.:** 195–196°C; **^{1}H-NMR (400 MHz, DMSO-d$_6$):** δ = 8.44 (s, 1H, NH(3)), 7.77 (d, ^3J = 8.3 Hz, 2H, (CH(11 + 13)), 7.71 (d, ^3J = 8.2 Hz, 2H, CH(10 + 14)), 7.62 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, CH(5)), 7.31 – 7.20 (m, 2H, (CH(7) + NH(1)), 6.76 (dd, ^3J =

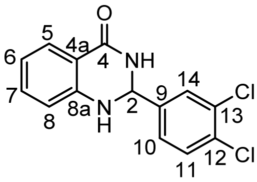
8.2 Hz, ^{4}J = 1.0 Hz, 1H, CH(8)), 6.69 (ddd, ^{3}J = 8.1 Hz, ^{3}J = 7.3 Hz, ^{4}J = 1.1 Hz, 1H, CH(6)), 5.87 (dd, ^{3}J = 2.2 Hz, ^{3}J = 2.2 Hz, 1H, CH(2)) ppm; **^{13}C-NMR (101 MHz, DMSO-d$_6$):** δ = 163.4 (C=O(4)), 147.5 (C_{quart}(8a)), 146.4 (C_{quart}(9)), 133.5 (CH(7)), 128.9 (q, ^{2}J = 31.6 Hz, C_{quart}(12)), 127.7 (CH(10 + 14), 127.4 (CH(5)), 125.31 (q, ^{3}J = 3.7 Hz, CH(11 + 13), 124.16 (q, ^{1}J = 272.2 Hz, CF_3), 117.4 (CH(6)), 114.9 (C_{quart}(4a)), 114.5 (CH(8)), 65.7 (CH(2)) ppm; **^{19}F-NMR (282 MHz, DMSO-d$_6$):** δ = -60.59 (CF_3) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3296 (w), 3176 (w), 3013 (w), 2952 (w), 2831 (w), 1664 (m), 1650 (s); 1609 (m), 1589 (m), 1507 (m), 1484 (m); 1437 (m), 1388 (m), 1322 (m), 1304 (m), 1241 (m); 1166 (m); 1153 (m), 1134 (m); 1109 (m); 1030 (m),951 (w), 914 (w), 834 (m), 802 (m), 792 (m), 774 (m), 758 (s), 685 (m), 663 (m), 632 (m), 615 (m); **MS (EI, 70 eV):** *m/z* (%) = 308 ([M]$^+$, 32), 307 (45), 188 (10), 148 (10), 147 (100), 120 (63), 119 (27), 95 (10), 92 (44), 91 (10), 69 (24), 65 (20), 64 (16), 63 (15); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{15}H_{11}F_3N_2O_2$ 309.08454 ([M+H]$^+$), found 309.08493.

2-(4-Fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (115)



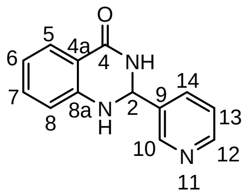
The compound was synthesized following the procedure for (**102**), starting from 1 mmol (**57**) and 1 mmol 4-fluoro-benzaldehyde, giving 37 % (**115**) as a solid, **M.P.:** 202–203°C; **^{1}H-NMR (400 MHz, DMSO-d$_6$):** δ = 8.31 (s, 1H, NH(3)), 7.63 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.6 Hz, 1H, CH(5)), 7.59 – 7.52 (m, 2H, CH(10 + 14)), 7.30 – 7.18 (m, 3H, CH(7 + 11 + 13)), 7.12 (s, 1H, NH(1)), 6.77 (dd, ^{3}J = 8.2 Hz, ^{4}J = 1.0 Hz, 1H, CH(8)), 6.69 (ddd, ^{3}J = 7.5 Hz, ^{3}J = 7.4 Hz, ^{4}J = 1.0 Hz, 1H, CH(6)), 5.79 (dd, ^{3}J = 1.7 Hz, ^{3}J = 1.7 Hz, 1H, CH(2)) ppm**; ^{13}C-NMR (101 MHz, DMSO-d$_6$):** δ = 163.6 (C=O(4)), 162.1 (d, ^{1}J = 244.1 Hz, C_{quart}(12)), 147.8 (C_{quart}(8a)), 137.8 (d, ^{4}J = 2.9 Hz, C_{quart}(9)), 133.4 (CH(7)), 129.1 (d, ^{3}J = 8.3 Hz, CH(10 + 14)), 127.4 (CH(5)), 117.3 (CH(6)), 115.1 (d, ^{2}J = 21.5 Hz, CH(11 + 13)), 115.0 (C_{quart}(4a)), 114.5 (CH(8)), 66.0 (CH(2)) ppm; **^{19}F-NMR (282 MHz, DMSO-d$_6$):** δ = -112.44 – -114.78 (m, CF) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3296 (w), 3174 (w), 3066 (w), 3042 (w), 2935 (w), 1665 (m), 1650 (s); 1601 (s), 1503 (m), 1481 (m), 1437 (m), 1384 (m), 1299 (m), 1226 (m), 1155 (s), 1134 (m), 1097 (m), 1013 (m), 921 (m), 839 (s), 808 (s), 791 (s), 756 (s), 744 (s), 719 (m), 669 (s), 629 (m), 613 (s); **MS (EI, 70 eV):** *m/z* (%) = 242 ($[M]^+$, 32), 241 (45), 148 (10), 147 (100), 122 (11), 120 (76), 119 (23), 95 (12), 92 (40), 65 (17), 64 (11); **HRMS (EI):** Calcd. for $C_{14}H_{11}O_1N_2F_1$ 242.08499, found 242.08414, calcd. for $C_{14}H_{10}O_1N_2F_1$ ($[M-H]^-$) 241.07717, found 241.07699.

2-(3,4-Dichlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (116)



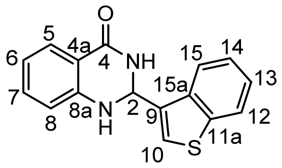
The compound was synthesized following the procedure for (**102**), starting from 1 mmol (**57**) and 1 mmol 3,4-dichloro-benzaldehyde, giving 58 % (**116**) as a solid, **M.P.:** 201–202°C, **^{1}H-NMR (400 MHz, DMSO-d$_6$):** δ = 8.42 (s, 1H, NH(3)), 7.72 (d, ^4J = 2.0 Hz, 1H, CH(14)), 7.66 (d, ^3J = 8.3 Hz, 1H, CH(11)), 7.61 (dd, ^3J = 7.7 Hz, ^4J = 1.6 Hz, 1H, CH(5)), 7.47 (dd, ^3J = 8.3 Hz, ^4J = 2.1 Hz, 1H, CH(10)), 7.29 – 7.22 (m, 2H, NH(1) + CH(7)), 6.79 – 6.74 (m, 1H, CH(8)), 6.72 – 6.65 (m, 1H, CH(6)), 5.80 (dd, ^3J = 2.3 Hz, ^3J = 2.3 Hz, 1H, CH(2)) ppm; **^{13}C-NMR (101 MHz, DMSO-d$_6$):** δ = 163.4 (C=O(4)), 147.3 C_{quart}(8a)), 143.0 (C_{quart}(9)), 133.5 (CH(7)), 130.9 (C_{quart}(13)), 130.8 (C_{quart}(12)), 130.6 (CH(11)), 128.9 (CH(5)), 127.4 (CH(14)), 127.0 (CH(10)), 117.5 (CH(6)), 114.9 (C_{quart}(4a)), 114.5 (CH(8)), 65.0 (CH(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3254 (m), 3170 (m), 3035 (w), 2928 (m), 1647 (s), 1609 (s), 1514 (m), 1491 (m), 1457 (m), 1389 (m), 1334 (m), 1318 (m), 1295 (m), 1248 (m); 1190 (m), 1176 (m); 1150 (m), 1132 (m), 1121 (m); 1030 (m); 1007 (m); 940 (m); 880 (m); 859 (m), 824 (m); 789 (m); 779 (m); 740 (s); 703 (m), 667 (m), 619 (m); **MS (EI, 70 eV):** *m/z* (%) = 294 (10), 293 (12), 292 ($[M]^+$,15), 291 (16), 148 (10), 147 (100), 120 (44), 119 (21), 92 (30), 65 (12). **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{14}H_{10}Cl_2N_2O_1$ 293.02429 ($[M+H]^+$), found 293.02362, Calcd. for $C_{14}H_{10}{}^{37}Cl_2N_2O_1$ 295.02153, found 295.02076.

2-(Pyridin-3-yl)-2,3-dihydroquinazolin-4(1*H*)-one (117)



The compound was synthesized following the procedure for (**102**), starting from 1 mmol (**57**) and 1 mmol pyridine-3-carbaldehyde, giving 64 % (**117**) as a solid, **M.P.:** 223–224°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 8.66 (d, ^{4}J = 2.3 Hz, 1H, CH(10)), 8.55 (dd, ^{3}J = 4.8 Hz, ^{4}J =1.7 Hz, 1H, CH(12)), 8.40 (s, 1H, NH(3)), 7.89 (dd, ^{3}J = 8.0 Hz, ^{4}J = 2.0 Hz, 1H, CH(14)), 7.63 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.6 Hz, 1H, CH(5)), 7.43 (ddd, ^{3}J = 8.0 Hz, ^{3}J = 4.8 Hz, ^{4}J = 0.9 Hz, 1H, CH(13)), 7.27 (ddd, ^{3}J = 8.5 Hz, ^{3}J = 7.2 Hz, ^{4}J = 1.6 Hz, 1H, CH(7)), 7.18 (s, 1H, NH(1)), 6.84 – 6.66 (m, 2H, CH(8 + 6)), 5.85 (dd, ^{3}J = 1.8 Hz, ^{3}J = 1.8 Hz, 1H, CH(2)) ppm; **^{13}C-NMR (101 MHz, DMSO-d$_6$):** δ = 163.6 (C=O(4)), 149.7 (CH(10), 148.4 (CH(12)), 147.7 (C$_{quart}$(8a)), 136.8 CH(14)), 134.7 (C$_{quart}$(9)), 133.6 (CH(7)), 127.4 (CH(5)), 123.6 (CH(13)), 117.6 (CH6)), 115.0 (C$_{quart}$(4a)), 114.6 (CH(4)), 64.7 (CH(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3255 (m), 3159 (w), 3061 (w), 2900 (w), 1653 (m), 1612 (s), 1592 (m), 1583 (m), 1518 (m), 1486 (m), 1444 (m), 1430 (m), 1384 (m), 1354 (m), 1330 (m), 1299 (m), 1260 (m), 1170 (m), 1155 (m), 1132 (m), 1035 (m), 1029 (m), 1006 (w), 955 (w), 877 (w), 846 (m), 820 (w); 782 (m), 752 (s), 713 (s); 689 (m), 658 (m), 625 (m), 604 (m); **MS (EI, 70 eV):** *m/z* (%) = 225 ([M]$^{+}$, 15), 242 (12), 148 (11), 147 (100), 120 (35), 119 (19), 92 (31), 65 (14), 64 (11), 63 (11), 51 (18); **HRMS (EI):** *m/z* **=** calcd. for $C_{13}H_{11}O_1N_3$ 225.08966, found 225.08917.

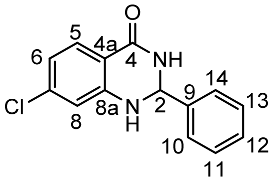
2-(Benzo[*b*]thiophen-3-yl)-2,3-dihydroquinazolin-4(1*H*)-one (118)



The compound was synthesized following the procedure for (**102**), starting from 1 mmol (**57**) and 1 mmol benzo[*b*]thiophene-2-carbaldehyde, giving 28 % (**118**) as a solid, **M.P.:** 220–221°C**; ^{1}H-NMR (400 MHz, DMSO-d$_6$):** δ = 8.35 (s, 1H, NH(3)), 8.21 – 8.14 (m, 1H, CH(12)), 8.05 – 7.96 (m, 1H, CH(15)), 7.77 (s, 1H, CH(10)), 7.67 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.6 Hz, 1H, (CH(5)), 7.46 – 7.36 (m, 2H, CH(13 + 14)), 7.26 (ddd,

^3J = 8.3 Hz, ^3J = 7.2 Hz, ^4J = 1.6 Hz, 1H, (CH(7)), 7.14 (s, 1H, NH(1)), 6.77 (dd, ^3J = 8.2 Hz, ^4J = 1.0 Hz, 1H, CH(8)), 6.76 – 6.70 (m, 1H, CH(6)), 6.20 (dd, ^3J = 1.5 Hz, ^3J = 1.5 Hz 1H, CH(2)) ppm; **^{13}C-NMR (101 MHz, DMSO):** δ = 163.9 (C=O), 148.1 (C_{quart}(8a)), 140.3 (C_{quart}(9), 136.8 (C_{quart}(11a)), 135.4 (C_{quart}(15a)), 133.3 (CH(7)), 127.5 (CH(5)), 126.6 (CH(13)), 124.6 (CH(14)), 124.0 CH(15)), 123.5 (CH(10)), 123.0 (CH(12)), 117.3 CH(6)), 115.1 (C_{quart}(4a)), 114.5 (CH(8)), 62.6 (CH(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3304 (m), 3189 (w), 3119 (w), 3077 (w), 3048 (w), 2919 (w), 1654 (m), 1608 (m), 1566 (w), 1534 (w), 1500 (m), 1481 (m), 1428 (m), 1366 (m), 1318 (w), 1298 (m), 1254 (w), 1178 (w), 1150 (m), 1138 (w), 1127 (m), 1100 (w), 1052 (w), 1031 (w), 1017 (w), 1005 (w), 937 (w), 901 (w), 849 (m), 800 (s), 787 (W), 774 (m), 755 (m), 737 (m), 695 (m), 653 (m), 637 (m); **MS (EI, 70 eV):** *m/z* (%) = 281 (16), 280 ([M]$^+$, 74), 279 100. 160 (16), 147 (51), 134 (17), 120 (94), 119 (20), 92 (39), 89 (20), 95 (15), 63 (10); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{16}H_{12}N_2O_1S_1$ 281.07431 ([M+H]$^+$), found 281.07423.

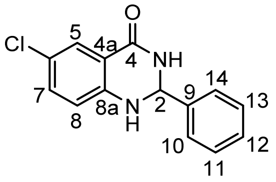
2-Phenyl-7-chloro-2,3-dihydroquinazolin-4(1*H*)-one (121)



The compound was synthesized following the procedure for (**102**), starting from 1 mmol 2-amino-4-chloro-benzonitrile and 1 mmol (**107**), giving 58 % (**121**) as a solid, **M.P.:** 130–133°C; **^{1}H-NMR (300 MHz, DMSO-d_6):** δ = 8.47 (s, 1H, NH(3)), 7.54 (d, ^4J = 2.6 Hz, 1H, CH(8)), 7.50 – 7.45 (m, 2H, CH(10 +14)), 7.44 – 7.34 (m, 3H, CH(11 + 12 + 13)), 7.34 – 7.32 (m, 1H, NH(1)), 7.28 (dd, ^3J = 8.7 Hz, ^4J = 2.7 Hz, 1H, CH(6))), 6.78 (d, ^3J = 8.7 Hz, 1H, CH(5)), 5.78 (dd, ^3J = 1.9 Hz, ^3J = 1.9 Hz, 1H, CH(2)) ppm; **^{13}C-NMR (75 MHz, DMSO-d_6):** δ = 162.4 (C=O(4)), 146.6 (C_{quart}(8a)), 141.2 (C_{quart}(9)), 133.1 (C_{quart}(7)), 128.6 CH(12)), 128.4 (CH(11 + 13)), 126.8 (CH(10 + 14)), 126.4 (CH(5)), 120.7 (CH(6)), 116.4 CH(8)), 116.0 (C_{quart}(4a)), 66.4 (CH(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3455 (w), 3366 (m), 3291 (m), 3165 (w), 3063 (w), 2212 (m), 1653 (m), 1642 (m), 1604 (m), 1560(m), 1477 (m), 1420 (m), 1356 (m), 1322 (m), 1297 (m), 1263 (m), 1135 (m), 1096 (m), 1079 (m), 1009 (m), 912 (m), 863 (m), 838 (m), 817 (m), 783 (m), 768 (m), 752 (m), 692 (m), 650 (m), 616 (m); **MS (EI, 70 eV):** *m/z*

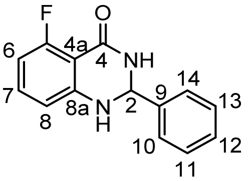
(%) = 259 ($[M]^+$, 10), 258 (20), 257 (27), 183 (37), 182 (14), 181 (100), 156 (18), 155 (11), 154 (46), 153 (15), 126 (26), 104 (17), 90 (10), 77 (27), 63 (18), 51 (19); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{14}H_{11}{}^{35}Cl_1N_2O_1$ 259.06327 ($[M+H]^+$), found 259.06313, calcd. for $C_{14}H_{11}{}^{37}Cl_1N_2O_1$ 261.06069, found 261.06097.

2-Phenyl-6-chloro-2,3-dihydroquinazolin-4(1*H*)-one (122)



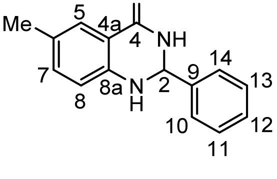
The compound was synthesized following the procedure for (**102**), starting from 1 mmol 2-amino-5-chloro-benzonitrile and 1 mmol (**107**), giving 23 % (**122**) as a solid, **M.P.:** 260–263°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 8.49 (s, 1H, NH(3)), 7.54 (d, ^4J = 2.6 Hz, 1H, CH(5)), 7.50 – 7.45 (m, 2H, CH(10 + 14)), 7.44 – 7.35 (m, 3H, (CH(11 + 12 + 13)), 7.34 (s, 1H, NH(1)), 7.28 (dd, ^3J = 8.7 Hz, ^4J = 2.6 Hz, 1H, CH(7)), 6.78 (d, ^3J = 8.7 Hz, 1H, CH(8)), 5.78 (dd, ^3J = 1.8 Hz, ^3J = 1.8 Hz, 1H, CH(2)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 162.4 (C=O), 146.6 (C_{quart}(8a)), 141.2 (C_{quart}(9)), 133.1 (C_{quart}(6)), 128.6 (CH(12)), 128.4 (CH(11 + 13)), 126.8 (CH (10 + 14)), 126.4 CH(5)), 120.7 (CH(7)), 116.4 (CH(8)), 116.0 (C_{quart}(4a)), 66.4 (CH(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3301 (m), 3180 (w), 3062 (w), 2928 (w), 1670 (m), 1652 (s), 1608 (s); 1579 (m), 1505 (m), 1485 (m), 1476 (m), 1431 (m), 1362 (m), 1294 (m), 1233 (m), 1165 (m), 1124 (m), 1076 (m), 1011 (m), 900 (m), 849 (m), 824 (s), 807 (m), 779 (m), 763 (m), 698 (m), 622 (m), 616 (m); **MS (EI, 70 eV):** *m/z* (%) = 259 (10), 258 ($[M]^+$, 23), 257 (27), 183 (30), 182 (11), 181 (100), 156 (12), 155 (10), 154 (34), 153 (18), 126 (22), 125 (10), 104 (12), 99 (10), 90 (11), 77 (24), 75 (10), 63 (16), 51 (15); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{14}H_{11}{}^{35}Cl_1N_2O_1$ 257.04871 ($[M-H]^-$), found 257.04987, calcd. for $C_{14}H_{11}{}^{37}Cl_1N_2O_1$ 259.04614, found 259.04653.

2-Phenyl-5-fluoro-2,3-dihydroquinazolin-4(1*H*)-one (123)



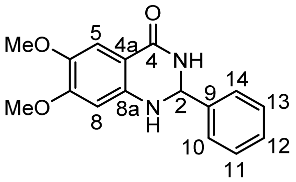
The compound was synthesized following the procedure for (**102**), starting from 1 mmol 2-amino-5-fluoro-benzonitrile and 1 mmol (**107**), giving 41 % (**123**) as a solid, **M.P.:** 217–219°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 8.33 (s, 1H, NH(3)), 7.51 – 7.45 (m, 3H, CH(10 + 14 + NH(1)), 7.44 – 7.34 (m, 3H, CH(11 + 12 + 13)), 7.21 (ddd, ^{3}J = 8.2 Hz, ^{3}J = 8.2 Hz, ^{4}J = 5.8 Hz, 1H, CH(7)), 6.59 (ddd, ^{3}J = 8.2 Hz, ^{4}J = 0.7 Hz, ^{5}J = 0.7 Hz, 1H, CH(8)), 6.39 (ddd, ^{3}J = 11.5 Hz, ^{3}J = 8.1 Hz, ^{4}J = 1.0 Hz, 1H, CH(6)), 5.70 (dd, ^{3}J = 1.9 Hz, ^{3}J = 1.9 Hz, 1H, CH(2)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 162.3 (d, ^{1}J = 256.7 Hz, CF(5)), 160.9 (d, ^{3}J = 2.7 Hz, C=O(4)), 150.2 (d, ^{3}J = 4.0 Hz, $\mathrm{C_{quart}}$(8a)), 141.0 ($\mathrm{C_{quart}}$(9)), 134.1 (d, ^{3}J = 11.5 Hz, (CH(7)), 128.6 (CH(12)), 128.4 (CH(11 + 13)), 126.9 (CH(10 + 14)), 110.5 (d, ^{4}J = 3.4 Hz, CH(8)), 104.5 (d, ^{2}J = 21.3 Hz, CH(6)), 103.83 (d, ^{2}J = 9.3 Hz, $\mathrm{C_{quart}}$(4a)), 66.0 (CH2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3307 (m), 3185 (w), 3062 (w), 1655(s), 1619 (s), 1508 (m), 1474 (m), 1456 (m), 1429 (m), 1379 (m), 1364 (m), 1332 (m), 1294 (m), 1281 (m), 1227 (m), 1174 (m), 1161 (m), 1128 (m), 1069 (m), 1062 (s), 1025 (m), 998 (m), 986 (M), 879 (m), 866 (m), 848 (m), 828 (m), 805 (s), 791 (m), 763 (s), 739 (m), 713 (m), 697 (s), 649 (s), 608 (m); **MS (EI, 70 eV):** *m/z* (%) = 242 ([M]$^+$, 20), 241 (29), 166 (11), 165 (100), 138 (59), 137 (16), 110 (31), 82 (10), 77 (21), 51 (14); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{14}H_{11}F_{1}N_{2}O_{1}$ 243.09282 ([M+H]$^+$), found 243.09302.

2-Phenyl-6-methyl-2,3-dihydroquinazolin-4(1*H*)-one (124)



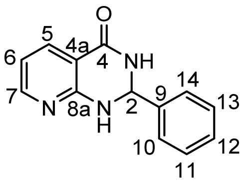
The compound was synthesized following the procedure for (**102**), starting from 1 mmol 2-amino-4-methyl-benzonitrile and 1 mmol (**107**), giving 14 % (**124**) as a solid, **M.P.:** 233–235°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 8.24 (s, 1H, NH(3)), 7.51 – 7.46 (m, 2H, CH(10 + 14)), 7.44 – 7.26 (m, 4H, CH(5 + 11 + 12 + 13)), 7.07 (dd, 1H, ^{3}J = 8.2 Hz, ^{4}J = 1.9 Hz, CH(7)), 6.92 (s, 1H, NH(1)), 6.66 (d, 1H, ^{3}J = 8.2 Hz, CH(8)), 5.70 (dd, 1H, ^3J = 1.9 Hz, ^3J = 1.9 Hz, CH(2)), 2.18 (s, 3H, CH_3) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 163.7 (C=O(4)), 145.7 (C_{quart}(8a)), 141.7 (C_{quart}(9)), 134.1 (C_{quart}(6)), 128.4 (CH(12)), 128.3 (CH(11 + 13)) 127.2 (CH5)), 126.9 (CH(10 + 14)), 125.8 (CH(7)), 115.0 (C_{quart}(4a)), 114.6 (CH(8)), 66.7 (CH(2)), 20.1 (CH_3) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ =3405 (m), 2253 (w), 2128 (w), 1653 (w), 1294 (w), 1153 (w), 1049 (m), 1023 (m), 1000 (m), 823 (m), 761 (m); **MS (EI, 70 eV):** *m/z* (%) = 238 ([M]$^+$, 25), 237 (30), 236 (11), 162 (10), 161 (100), 134 (35), 133 (26), 106 (17), 79 (10), 78 (14), 77 (36), 51 (18); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{15}H_{14}N_2O_1$ 261.09983 ([M+Na]$^+$), found 261.10053.

2-Phenyl-6,7-dimethoxy-2,3-dihydroquinazolin-4(1*H*)-one (126)



The compound was synthesized following the procedure for (**102**), starting from 1 mmol 2-amino-4,5-dimethyl-benzonitrile and 1 mmol (**107**), giving 43 % (**126**) as a solid, **M.P.:** 239–241°C; **^{1}H-NMR (400 MHz, DMSO-d$_6$):** δ = 8.05 (s, 1H, NH(3)), 7.53 – 7.45 (m, 2H, CH(10 + 14)), 7.43 – 7.29 (m, 3H, CH(11 + 12 + 13)), 7.11 (s, 1H, CH(5)), 6.79 (s, 1H, NH(1)), 6.37 (s, 1H, CH(8)), 5.68 (dd, ^3J = 1.9 Hz, ^3J = 1.9 Hz, 1H, CH(2)), 3.72 (s, 3H, OMe), 3.67 (s, 3H, OMe) ppm; **^{13}C-NMR (101 MHz, DMSO-d$_6$):** δ = 163.8 (C=O(4)), 153.9 (C_{quart}(7)), 143.6 (C_{quart}(8a)), 141.7 (C_{quart}(9)), 141.5 (C_{quart}(6)), 128.4 (CH(12)), 128.2 (CH(11 + 13)), 126.8 (CH(10 + 14)), 109.8 (C_{quart}(4a)), 106.6 (CH(5)), 97.9 (CH(8)), 66.9 (CH(2)), 55.8 (OMe)), 55.4(OMe)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = **MS (EI, 70 eV):** *m/z* (%) = 285 (13), 284 ([M]$^+$, 61), 283 (35), 282 (31), 267 (29), 208 (16), 207 (100), 191 (12), 180 (39), 179 (23), 164 (21), 152 (10), 136 (24), 106 (14), 104 (27), 77 (26), 51 (13); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{16}H_{16}N_2O_3$ 285.12337 ([M+H]$^+$), found 285.12395.

2-Phenyl-2,3-dihydropyrido[2,3-d]pyrimidin-4(1*H*)-one (127)

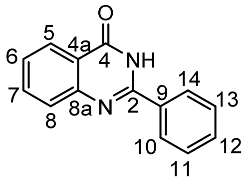


The compound was synthesized following the procedure for (**102**), starting from 1 mmol 2-amino-3-cyanopyridine and 1 mmol (**107**), giving 66 % (**127**) as a solid, **M.P.:** 268–270°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 8.60 (s, 1H, NH(3)), 8.14 (dd, ^3J = 4.9 Hz, ^4J = 2.0 Hz, 1H, CH(7)), 8.01 (s, 1H, NH(1)), 7.90 (dd, ^3J = 7.5, ^{4}J = 2.0 Hz, 1H, CH(5)), 7.62 – 7.14 (m, 5H, CH(10 + 11 + 12 + 13 + 14)), 6.70 (dd, ^3J = 7.5 Hz, ^3J = 4.9 Hz, 1H, CH(6)), 5.83 (dd, ^3J = 2.5 Hz, ^3J = 2.5 Hz, 1H, CH(2)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 162.8 (C=O(4)), 157.5 (C$_{\text{quart}}$(8a)), 152.9 (CH(7)), 142.3 (C$_{\text{quart}}$(9)), 135.7 (CH(5)), 128.4 (CH(12)), 128.3 (CH(11 + 13)), 126.3 (CH(10 + 14)), 113.8CH(6)), 109.5 (C$_{\text{quart}}$(4)), 65.1 (CH(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ =3165 (m), 3106 (m), 3031 (m), 2910 (m), 2850 (m), 1659 (s), 1608 (s), 1591 (m), 1519 (m), 1446 (s); 1407 (m), 1363 (m), 1315 (m), 1276 (m), 1260 (s), 1203 (w), 1134 (m), 1092 (w), 1057 (w), 1027 (w), 1010 (w), 989 (w), 933 (m), 764 (s); 699 (s), 641 (m), 613 (m); **MS (EI, 70 eV):** *m/z* (%) = 225 ([M]$^+$, 14), 224 (26), 148 (100), 121 (27), 93 (28), 77 (17), 51 (14); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{13}H_{11}N_3O_1$ 226.09749 ([M+H]$^+$), found 226.09746.

1.1.7. Synthesis of 2-phenyl-1,2-dihydroquinazolin-4(1*H*)-one

General procedure: To the crude reaction mixture of the synthesis of 2,3-dihydroquinazolinone (**102**), 400 µL TBHP-solution (70 % in H_2O, 4 mmol) was added. The mixture was heated under stirring to 100°C for 6 hours. The conversion was monitored by TLC (hexane/ethylacetate 4:1). After disappearance of dihydroquinazoline on TLC, the formed precipitate was filtered off and recrystallized from boiling ethylactetate by the addition of hexane, giving 134 mg (60 %) 2-phenyl-quinazolinone (**59**).

2-Phenyl-quinazolinone (59)

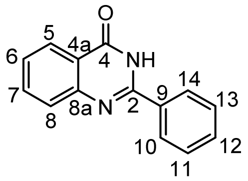


Analytical data was equal to the compound synthesized in **1.1.5.** **^{1}H-NMR (300 MHz, DMSO-d_6):** δ = 12.55 (s, 1H, NH), 8.23 – 8.13 (m, 3H, CH(7 + 10 + 14), 7.85 (ddd, ^{3}J = 8.5 Hz, ^{3}J = 7.0 Hz, ^{4}J = 1.6 Hz, 1H, CH(6), 7.77 – 7.71 (m, 1H, CH(12)), 7.62 – 7.49 (m, 4H, CH(4+ 5 + 11 + 13)) ppm; **^{13}C-NMR (75 MHz, DMSO-d_6):** δ = 162.3 (C=O(4)), 152.4 (C_{quart}(2)), 148.7 (C_{quart}(8a)), 134.6 (CH(7)), 132.8 (C_{quart}(9)), 131.4 (CH(12)), 128.6 (CH(10 + 14)), 127.8 (CH(11 + 13)), 127.4 CH(6)), 126.6 (CH(7)), 125.8 (CH(5)), 121.0 (C_{quart}(4a)) ppm; **MS (EI, 70 eV):** *m/z* (%) = 222 ($[M]^+$, 100), 119 (99), 104 (11), 92 (14), 90 (17), 77 (22), 76 (11), 51 (10).

1.1.8. Synthesis of 2-phenyl-quinazolin-4(3*H*)-ones from alcohols

General procedure: 0.5 mmol anthranilonitrile (59 mg), 0.5 mmol benzylalcohol (62 µl), 200 µL TBHP-solution (70 % in H_2O, 2 mmol), 1 mmol KOH (112 mg) and 2 ml H_2O were given in a glass tube which was subsequently sealed. The mixture was heated to 100°C under stirring for 16 hours. After the reaction time, the precipitate was filtered of and recrystallized from boiling ethylactetate by the addition of hexane, giving 78 mg (35 %) 2-phenyl-quinazolin-4(3*H*)-one (**59**).

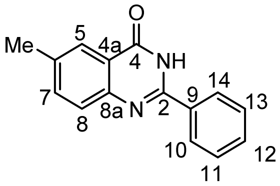
2-Phenyl-quinazolin-4(3*H*)-one (59)



Analytical data was equal to the compound synthesized in **1.1.5.** **^{1}H-NMR (300 MHz, DMSO-d_6):** δ = 12.55 (s, 1H, NH), 8.23 – 8.13 (m, 3H, CH(7 + 10 + 14), 7.85 (ddd, ^{3}J = 8.5 Hz, ^{3}J = 7.0 Hz, ^{3}J = 1.6 Hz, 1H, CH(6)), 7.77 – 7.71 (m, 1H, CH(12)), 7.62 – 7.49 (m, 4H, CH(4+ 5 + 11 + 13)) ppm; **^{13}C-NMR (75 MHz, DMSO-d_6):** δ = 162.3 (C=O(4)), 152.4 (C_{quart}(2)), 148.7 (C_{quart}(8a)), 134.6 (CH(7)), 132.8 (C_{quart}(9)), 131.4

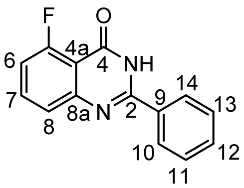
(CH(12)), 128.6 (CH(10 + 14)), 127.8 (CH(11 + 13)), 127.4 CH(6)), 126.6 (CH(7)), 125.8 (CH(5)), 121.0 (C_{quart}(4a)) ppm; **MS (EI, 70 eV):** *m/z* (%) = 222 ($[M]^+$, 100), 119 (99), 104 (11), 92 (14), 90 (17), 77 (22), 76 (11), 51 (10).

6-Methyl-2-phenyl-quinazolin-4(3*H*)-one (88)



The compound was synthesized following the procedure for (**59**), starting from 1 mmol 2-amino-3-cyanopyridine and 1 mmol benzyl alcohol, giving 66 % (**88**) as a solid, **M.P.:** 262–264°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 12.47 (s, 1H, NH), 8.20–8.13 (m, 2H, CH(10 + 14)), 7.97–7.93 (m, 1H, (CH(5)), 7.66 – 7.64 (m, 2H, CH(7 + 8)), 7.59 – 7.50 (m, 3H, CH(11 + 6 + 13)), 2.46 (s, 3H, CH_3) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 162.2 (C=O(4)), 151.5 (C_{quart}(2)), 146.8 (C_{quart}(8a)), 136.3 (C_{quart}(6)), 135.90 (C_{quart}(9)), 132.9 (CH(7)), 131.2 (CH(12)), 128.6 (CH(11 + 13)), 127.6 (CH(10 + 14)), 127.4 (CH(5)), 125.3 (CH(8)), 120.7 (C_{quart}(4a)), 20.9 (CH_3) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3158 (w), 3059 (w), 3026 (w), 2916 (w), 2872 (), 1659 (s9; 1622 (m), 1597 (s), 1570 (m), 1505 (m), 1488 (m), 1448 (m), 1352 (m), 1304 (m), 1287 (m), 1239 (m), 1205 (m), 1140 (m), 1082 (m), 969 (m), 946 (m), 902 (m), 875 (m); 829 (s); 776 (m), 696 (s); 666 (m), 617 (m); **MS (EI, 70 eV):** *m/z* (%) = 237 (18), 236 ($[M]^+$, 100), 133 (81), 105 (13), 104 (40), 89 (12), 78 (13), 77 (47), 76 (13), 51 (19); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{15}H_{12}O_1N_2$ 237.10224 ($[M+H]^+$), found 237.10243.

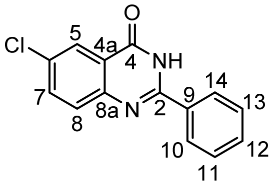
7-Fluoro-2-phenyl-quinazolin-4(3*H*)-one (128)



The compound was synthesized following the procedure for (**59**), starting from 1 mmol 2-amino-3-cyanopyridine and 1 mmol benzyl alcohol, giving 66 % (**128**) as a solid, **M.P.:** 243–245°C; **^{1}H-NMR (250 MHz, DMSO-d$_6$):** δ = 12.53 (s, 1H, NH), 8.16 (dd, ^3J = 8.0 Hz, ^4J = 1.7 Hz, 2H, CH(10 + 14)), 7.80 (ddd, ^3J = 8.2 Hz, ^3J = 8.2 Hz, ^4J = 5.7

Hz, 1H, CH(6)), 7.64 – 7.50 (m, 3H, CH(11 + 12 + 13)), 7.37 – 7.19 (m, 1H, H(7)), 6.58 (d, ^3J = 8.6 Hz, 1H, CH(8)), 6.51 – 6.37 (m, 2H) ppm; **^{13}C-NMR (63 MHz, DMSO-d_6):** δ = 165.2 (C=O), 161.8 (d, ^1J = 272.5 Hz, C-F(5)), 153.4 (C_{quart}(2)), 135.1 (d, ^3J = 11.2 Hz, C_{quart}(8a)), 135.1 (d, ^3J = 11.2 Hz, CH(7)), 133.9 (C_{quart}(9)), 132.0 (d, ^3J = 36.1 Hz, CH(6)), 131.7 (CH(12)), 128.7 (CH(11 + 13)), 127.9 (CH(10 + 14)), 111.1 (d, ^4J = 2.7 Hz CH(8)), 101.18 (d, ^2J = 19.2 Hz, C_{quart}(4a)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3448 (w), 3358 /w), 3054 (m), 2218 (w), 1685 (m), 1676 (m), 1654 (m), 1637 (m), 1618 (m), 1604 (m), 1559 (m), 1555 (m), 1512 (m), 1484 (m), 1469 (m), 1425 (m), 1356 (w), 1319 (m), 1299 (m), 1255 (m), 1238 (m), 1192 (w), 1158 (w), 1139 (m), 1078 (w), 1062 (m), 1050 (w), 1031 (m), 1022 (m), 994 (w), 932 (w), 856 (m), 817 (m), 781 (m), 719 (w), 712 (w), 699 (m), 682 (m), 652 (m), 620 (m); **MS (EI, 70 eV):** *m/z* (%) = 240 (14), 108 (12), 105 (100), 77 (60), 51 (21); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{14}H_9N_2F_1O_1$ 241.07717 ([M+H]$^+$), found 241.07713.

6-Chloro-2-phenyl-quinazolin-4(3*H*)-one (93)

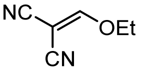


The compound was synthesized following the procedure for (**59**), starting from 1 mmol 2-amino-3-cyanopyridine and 1 mmol benzyl alcohol, giving 66 % (**93**) as a solid, **M.P.:** 296–298°C; **^{1}H-NMR (300 MHz, DMSO-d_6):** δ = 12.70 (s, 1H, NH), 8.18 (dd, ^3J = 7.9 Hz, ^4J = 1.8 Hz, 2H, CH(10 + 14)), 8.08 (d, ^4J = 2.5 Hz, 1H, CH(5)), 7.85 (dd, ^3J = 8.7 Hz, ^4J = 2.5 Hz, 1H, CH(7)), 7.76 (d, ^3J = 8.7 Hz, 1H, CH(8)), 7.63 – 7.50 (m, 3H, CH(11 + 12 + 13)) ppm; **^{13}C-NMR (75 MHz, DMSO-d_6):** δ = 161.7 (C=O), 153.2 (C_{quart}(2)), 147.5 (C_{quart}(8a)), 134.5 (CH(7)), 132.7 (C_{quart}(9)), 131.5 (CH(12)), 130.6 (C_{quart}(6)), 129.6 (CH(5)), 128.6 (CH(10 + 14)), 127.8 (CH(11 + 13)), 124.9 (CH(7)), 122.2 (C_{quart}(4a)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3162 (w), 3101 (w), 3063 (w), 1664 (m), 1649 (m), 1600 (m), 1566 (m), 1507 (w), 1474 (m), 1465 (m), 1407 (w), 1344 (w), 1289 (m), 1228 (w), 1194 (w), 1153 (m), 1119 (m), 1081 (w), 1064 (w), 1029 (w), 1001 (w), 941 (m), 925 (w), 894 (m), 882 (m), 844 (m), 836 (m), 826 (m), 792 (m), 771 (m), 697 (w), 687 (m), 645 (m), 614 (w); **MS (EI, 70 eV):** *m/z* (%) = 258 (34), 257 (17), 256 ([M]$^+$, 96), 155 (32), 153 (100), 126 (11), 125 (10), 124 (12), 104 (16), 77 (26), 75 (11);

HRMS (ESI-TOF): *m/z* = calcd. for $C_{14}H_9O_1N_2{}^{35}Cl_1$ 257.04762 ($[M+H]^+$), found 257.04776.

1.1.9. Synthesis of 2-(ethoxymethylene)-malonitrile (137)

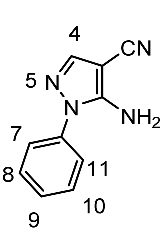
The compound was synthesized following the procedure given in the literature.[i] 3 mmol maolnitrile (200 mg) and 3.3 mmol triethyl orthoformate (550 µl) were dissolved in 10 ml Ac_2O.The solution was refluxed under stirring for 5 hours. The crude mixture was extracted with ethylacetate and washed with water. The compound was recrystallized from EtOH, giving 72 % 2-(ethoxymethylene)-malonitrile (**145**) as a yellow-brown solid. Analytical data was equal to the data given in the literature.



^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.59 (s, 1H, CH), 4.40 (q, ^3J = 7.1 Hz, 2H, CH_2), 1.47 (t, ^3J = 7.1 Hz, 3H, CH_3) ppm.

1.1.10. Synthesis of 2-amino-1-phenyl-pyrazlo-4-carbonitrile (138)

The compound was synthesized following the procedure given in the literature. 0.5 mmol (**137**, 62 mg) and 0.5 mmol phenylhydrazine (49 µ) were dissolved in dry EtOH. The mixture was refluxed for 1hour. The solvent was removed under reduced pressure and the product was purified via column chromatography (EE:Hex:MeOH 4:13:1), giving 86 % 2-amino-1-phenyl-pyrazolo-4-carbonitrile (**138**) as a white solid. Analytical data was equal to the one given in the literature.

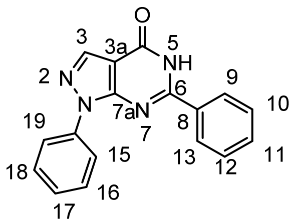


M.P.: 135–137°C; **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 7.62 (s, 1H, CH(4)), 7.59 – 7.39 (m, 5H, CH(7 + 8 + 9 + 10 + 11)), 4.72 (s, 2H, NH_2) ppm; **MS (EI, 70 eV):** *m/z* (%) = 185 (12), 184 ($[M]^+$, 100), 183 (34), 158 (10), 77 (33), 51 (20).

1.1.11. Synthesis of 4*H*-pyrazolo-[3,4-d]-pyrimidine-4[5*H*]-ones

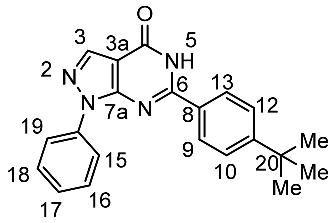
General procedure: 0.5 mmol **138** (92 mg), 0.5 mmol **107** (60 µl), 0.5 mmol K_3PO_4 (56 mg) and 2 ml H_2O were given in a glass tube which was subsequently sealed. The mixture was heated to 100°C under stirring for 16 hours. The precipitate was filtered off and recrystallized from boiling ethylactetate by the addition of hexane, giving 57 % 1,6-diphenyl-1,5-dihydro-4*H*-pyrazolo[3,4-d]pyrimid-in-4-one (**141**) as a white solid.

1,6-Diphenyl-1,5-dihydro-4*H*-pyrazolo[3,4-d]pyrimid-in-4-one (141):



M.P.: 306–308°C; **^{1}H-NMR (300 MHz, DMSO-d_6):** δ = 12.63 (s, 1H, NH), 8.36 (s, 1H, CH(3)), 8.23 – 8.10 (m, 4H, CH(9 + 13 + 15 + 19)), 7.66 – 7.55 (m, 5H, CH(10 + 11 + 12 + 16 + 18)), 7.48 – 7.35 (m, 1H, CH(17)) ppm; **^{13}C-NMR (63 MHz, DMSO-d_6)**: δ = 158.3 (C=O), 156.1 (C_{quart}), 152.3 (C_{quart}), 138.4 (C_{quart}), 136.1 (CH(Ar)), 132.1 (CH(Ar)), 132.0 (C_{quart}), 129.3 (CH(Ar)), 128.8 (CH(Ar)), 128.2 (CH(Ar)), 126.9 (CH(3)), 121.6 (CH(Ar)), 105.9 (C_{quart}) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3166 (m), 3078 (m), 1682 (s), 1590 (m), 1541 (m), 1523 (m), 1500 (m), 1462 (m), 1420 (m), 1393 (m), 1291 (m), 1224 (m), 1197 (m), 1184 (m), 1172 (m), 1161 (m), 1116 (m), 1101 (m), 1060 (m), 1031 (m), 999 (w), 970 (m), 938 (m), 911 (m), 863 (m), 853 (m), 826 (m), 792 (m), 771 (m), 758 (m), 752 (m), 707 (m), 702 (m), 687 (m), 677 (m), 661 (m), 634 (m); **MS (EI, 70 eV):** *m/z* (%)= 289 (20), 288 ($[M]^+$, 100), 287 (10), 185 (16), 104 (14), 77 (32), 51 (12); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{17}H_{12}N_4O_1$ ($[M+H]^+$) 289.10839, found 289.10896.

6-(4-(*tert*-Butyl)phenyl)-1-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-d]pyrimidin-4-one (142):

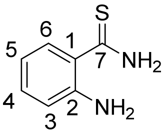


The compound was synthesized following the procedure for (**141**), starting from 0.5 mmol (**138**) and 0.5 mmol 4-*tert*-butyl-benzaldehyde, giving 15 % (**142**) as a solid. **M.P.:** 262–264°C; **^{1}H-NMR (250 MHz, DMSO-d$_6$)**: δ = 12.56 (s, 1H, NH) 8.31 (s, 1H, CH(3)), 8.25 – 8.06 (m, 4H, CH(9 + 13 + 15 + 19)), 7.72 – 7.49 (m, 4H, CH(10 + 12 + 16 + 18)), 7.47 – 7.28 (m, 1H, CH(17)), 1.33 (s, 9H, CH_3) ppm; **^{13}C-NMR (63 MHz, DMSO):** δ = 159.1 (C=O), 156.5 (C_{quart}), 154.6 (C_{quart}), 152.6 (C_{quart}), 138.6 (C_{quart}), 135.9 (CH(Ar)), 129.9 (C_{quart}), 129.2 (CH(Ar)), 127.9 (CH(Ar)), 126.6 (CH(Ar)), 125.5 (CH(Ar)), 121.3 (CH(Ar)), 105.9 (CH(Ar)), 34.7(C_{quart}(20)), 30.8 (CH_3) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3053 (w), 2961 (m), 2867 (w), 1676 (m), 1584 (m), 1547 (m), 1501 (m), 1459 (m), 1423 (m), 1409 (m), 1394 (m), 1365 (m), 1308 (m), 1298 (w), 1287 (w), 1267 (w), 1220 (m), 1175 (w), 1120 (w), 1110 (m), 1056 (w), 1015 (w), 972 (m), 939 (w), 910 (w), 863 (m), 843 (m), 795 (w), 778 (m), 752 (m), 709 (m), 701 (m), 688 (m), 678 (m), 634 (m); **MS (EI, 70 eV):** *m/z* (%) = 345 (12), 344 ([M]$^+$, 62), 330 (23), 329 (100), 301 (11), 144 (10), 77 (18); **HRMS (ESI-TOF):** *m/*z = calcd. for $C_{21}H_{20}N_4O_1$ 345.17099 ([M+H]$^+$), found 345.17134.

1.1.12. Synthesis of 2-aminobenzothioamide

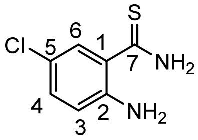
General procedure: 27 mmol 2-aminobenzonitrile (3.18 g, **57**), 27 mmol $MgCl_2$ (2.57 g) and 54 mmol NaHS·H_2O (3.99 g) and 70 ml dry DMF are placed in a roundbottom flask which is subsequently sealed by a needle-pierced septum. The reaction mixture is stirred at 20°C for 72 hours. The conversion is monitored by TLC. After complete conversion, the reaction is quenched with distilled water and the solution is extracted three times with ethyl acetate. The aqueous phase is acidified with 10 ml of 10% HCl and again extracted with ethyl acetate. The combined organic phases are washed with saturated NaCl-solution and dried over Na_2SO_4. The crude product was purified *via* column chromatography (hexane:ethyl acetate 4:1) yielding 3.58 g (88%) 2-aminobenzothioamide (**149**) as yellow solid.

2-Amino-benzothioamide (149)



MP.: 121–122°C; **^{1}H-NMR (300 MHz, DMSO-d_6):** δ = 9.63 (s, 1H, $CSNH_2$), 9.29 (s, 1H, $CSNH_2$), 7.16 (dd, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1H, CH(6)), 7.09 (ddd, ^3J = 8.6 Hz, ^3J = 7.2 Hz, ^4J = 1.6 Hz, 1H, CH(4)), 6.71 (dd, ^3J = 8.2, ^4J = 1.0 Hz, 1H, CH(3)), 6.52 (ddd, ^3J = 7.8 Hz, ^3J= 7.2 Hz, ^4J = 1.2 Hz, 1H, CH(5)), 6.17 (s, 2H, NH_2) ppm; **^{13}C-NMR (63 MHz, DMSO-d_6):** δ = 200.1 (C=S), 147.0 (C_{quart}(2)), 130.6 (CH(4)), 126.9 (CH(6)), 123.6 (C_{quart}(1)), 116.4 (CH(5)), 115.0 (CH(3)) ppm; **MS (EI, 70 eV):** *m/z* (%) = 152 ($[M]^+$, 79), 119 (100), 118 (18), 92 (27), 65 (21); **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3407 (w), 3282 (w), 3054 (w), 1603 (m), 1454 (m), 1408 (m), 1404 (m), 1284 (m), 906 (s), 751 (s), 737 (s); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_7H_8N_2S_1$ 153.04792 ($[M+H]^+$), found 153.04810; **Elemental analysis:** Calcd. for: $C_7H_8N_2S$: C, 55.24; H, 5.30; N, 18.40; S, 21.06. Found: C, 54.81; H, 5.30; N, 18.32; S, 21.16.

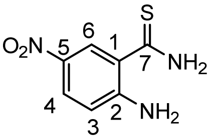
2-Amino-5-chlorobenzothioamide (153):



The compound was synthesized following the procedure for (**149**), starting from 1 mmol 2-amino-5-chloro-benzonitrile, giving 96 % (**153**) as a solid, **MP.:** 143–144°C; **^{1}H-NMR (300 MHz, DMSO-d_6):** δ = 9.78 (s, 1H, $CSNH_2$), 9.44 (s, 1H, $CSNH_2$), 7.16 (d, ^3J = 2,5 Hz, 1H, CH(6)), 7.12 (dd, ^3J = 8,6 Hz, ^4J = 2,5 Hz, 1H, CH(4)), 6.73 (d, ^3J = 8.7 Hz, 1H, CH(3)), 6.22 (s, 2H, NH_2) ppm; **^{13}C-NMR (63 MHz, DMSO-d_6):** δ = 198.7 (C=S), 145.8 (C_{quart}(2)), 130.2 (CH(4)), 126.3 (CH(6)), 124.6 (C_{quart}(5)), 118.4 (C_{quart}(1)), 118.0 (C_{quart}(3)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3411 (w), 3404 (w), 3220 (w), 3021 (w), 1618 (w), 1477 (m), 1431 (m), 1155 (m), 930 (m), 820 (s), 738 (s), 658 (s), 557 (m), 485 (m); **MS (EI, 70 eV):** *m/z* (%) = 188 ($[M]^+$, ^{37}Cl, 30), 186 ($[M]^+$, ^{35}Cl, 56), 155 (23), 154 (39), 153 (100), 152 (80), 125 (24), 118 (23), 90 (23), 63 (21), 61 (20), 52 (18); **HRMS (EI):** *m/z* = Calcd. for $C_7H_7N_2{}^{35}Cl_1S_1$ 186.00130, found 186.00102, calcd.

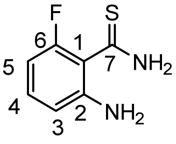
for $C_7H_7N_2{}^{37}Cl_1S_1$ 187.99857, found 187.99858. **Elemental analysis:** Calcd. for: $C_7H_7N_2S_1Cl_1$: C, 54.04; H, 3.78; N, 15.01; S, 17.18. Found: C, 54.68; H, 3.75; N, 14.69; S, 17.43.

2-Amino-5-nitrobenzothioamide (154):



The compound was synthesized following the procedure for (**149**), starting from 1 mmol 2-amino-5-nitro-benzonitrile, giving 80 % (**154**) as a solid, **MP.:** 146–147°C; **^{1}H-NMR (500 MHz, DMSO-d$_6$):** δ = 9.97 (s, 1H, $CSNH_2$), 9.68 (s, 1H, $CSNH_2$), 8.07 (d, ^4J = 2.7 Hz, 1H, CH(6)), 7.98 (dd, ^3J = 9.2 Hz, ^4J = 2.7 Hz, 1H, CH(4)), 7.39 (s, 2H, NH_2), 6.81 (d, ^3J = 9.2, 1H,CH(3)) ppm; **^{13}C-NMR (126 MHz, DMSO-d$_6$):** δ = 197.7 (C=S), 152.6 (C_{quart}(5)), 135.1 (C_{quart}(2)), 126.3 (CH(6)), 124.1 (CH(4)), 122.0 (C_{quart}(1)), 115.6 (CH(3)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3403 (w), 3282 (m), 3159 (m), 2229 (w) 1927 (w), 1646 (m), 1631 (m), 1592 (m), 1568 (m), 1481 (m), 1436 (m), 1300 (s), 1258 (s), 746 (s), 677 (s), 648(s); **MS (EI, 70 eV):** *m/z* (%) = 197 ($[M]^+$, 90), 164 (100), 133 (19), 118 (51), 90 (28), 63 (20), 32 (16); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_7H_7N_3O_2S_1$ 198.03317 ($[M+H]^+$), found 198.03355; **Elemental analysis:** Calcd. for: $C_7H_8N_3O_2S$: C, 42.63; H, 3.58; N, 21.31; S, 16.26. Found: C, 43.09; H, 3.49; N, 20.45; S, 15.39.

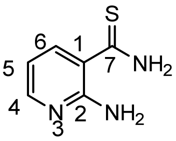
2-Amino-6-fluorobenzothioamide (155):



The compound was synthesized following the procedure for (**149**), starting from 1 mmol 2-amino-6-fluoro-benzonitrile, giving 97 % (**155**) as a solid, **MP.:** 114–115°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.12 (s, 1H, $CSNH_2$), 9.64 (s, 1H, $CSNH_2$), 7.02 (ddd, ^3J = 8.2 Hz, ^3J = 8.2 Hz, ^4J = 6.5 Hz, 1H, CH(4)), 6.52 (dd, ^3J = 8.2 Hz, ^4J = 0.8 Hz, 1H, CH(3)), 6.35 (ddd, ^3J = 10.0 Hz, ^3J = 8.2 Hz, ^4J = 1.0 Hz, 1H, CH(5)), 5.54 (s, 2H, NH_2) ppm; **^{13}C-NMR (63 MHz, DMSO-d$_6$):** δ = 195.2 (d, ^3J = 0.9 Hz, C=S), 157.4

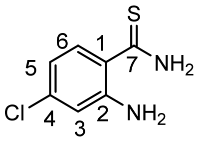
(d, ^1J = 242.7 Hz, C$_{quart}$(6)), 146.9 (d, ^3J = 5.8 Hz, C$_{quart}$(2)), 129.6 (d, ^3J = 10.9 Hz, CH(4)), 115.4 (d, ^2J = 19.0 Hz, C$_{quart}$(1)), 111.3 (d, ^4J = 2.4 Hz, CH(3)), 102.1 (d, ^2J = 22.4 Hz, CH(5)) ppm; **^{19}F-NMR (282 MHz, DMSO-d$_6$):** δ = -116.87 ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3422 (w), 3331 (w), 3257 (w), 3134 (w), 1611 (m), 1462 (m) 1396 (m), 899 (m), 781 (m), 628 (m), 540 (s), 494 (s); **MS (EI, 70 eV):** *m/z* (%) = 170 ([M]$^+$, 100), 137 (96), 136 (17), 117 (29), 109 (16), 90 (26), 83 (18); **HRMS (EI):** *m/z* = calcd. for $C_7H_7N_2F_1S_1$ 170.03085, found 170.03087; **Elemental analysis:** Calcd. for: $C_7H_7N_2SF$: C, 49.40; H, 4.15; N, 16.46; S, 18.84. Found: C, 49.26; H, 3.86; N, 15.95.

2-Aminopyridine-3-carbothioamide (156):



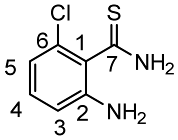
The compound was synthesized following the procedure for (**149**), starting from 1 mmol 2-amino-3-cyano-pyridine, giving 93 % (**156**) as a solid, **MP.:** 128–129°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 9.81 (s, 1H, CSNH$_2$), 9.49 (s, 1H, CSNH$_2$), 8.02 (dd, ^3J = 4.7 Hz, ^4J = 1.7 Hz, 1H, CH(4)), 7.52 (dd, ^3J = 7.6 Hz, ^4J = 1.6 Hz, 1H, CH(6)), 6.83 (s, 2H, NH$_2$), 6.59 (dd, ^3J = 7.6 Hz, ^3J = 4.8 Hz, 1H, CH(5)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 198.9 (C=S), 156.8 (C$_{quart}$(1)), 149.9 (CH(Ar)), 134.8 (CH(Ar)), 118.5 (C$_{quart}$(2)), 111.7 (CH(Ar)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3391 (w), 3265 (w), 3104 (m), 2770 (w), 1614 (m), 1598 (m), 1565 (m), 1465 (m), 1450 (m), 1239 (m), 907 (m), 850 (m), 529 (s), 427 (s); **MS (EI, 70 eV):** *m/z* (%) = 153 ([M]$^+$, 69), 120 (100), 103 (25), 93 (15), 92 (12), 66 (13), 60 (11), 52 (11), 39 (15); **HRMS (EI):** *m/z* = calcd. for $C_6H_7N_3S_1$ 153.03552, found 153.03603; **Elemental analysis:** Calcd. for: $C_7H_7N_3S$: C, 47.10; H, 4.610; N, 27.43; S, 20.93. Found: C, 47.10; H, 4.45; N, 25.05; S, 18.78.

2-Amino-4-chlorobenzothioamide (157):



The compound was synthesized following the procedure for (**149**), starting from 1 mmol 2-amino-4-chloro-benzonitrile, giving 78 % (**157**) as a solid, **MP.:** 142–143°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 9.71 (s, 1H, CSNH$_2$), 9.36 (s, 1H, CSNH$_2$), 7.17 (dd, ^3J = 8.4 Hz, ^4J = 1.3 Hz, 1H, CH(6)), 6.77 (dd, ^4J = 2.2 Hz, ^5J = 1.3 Hz, 1H, (CH(3)), 6.53 (ddd, ^3J = 8.4 Hz, ^4J = 2.2 Hz, ^5J = 1.2 Hz, 1H, (CH(5)) 6.42 (s, 2H, NH$_2$) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 199.0 (C=S), 148.4 (C$_{\text{quart}}$(2)), 135.0 (C$_{\text{quart}}$(4)), 128.8 (CH(6)), 122.3 (C$_{\text{quart}}$(1)), 115.1 (CH(5)), 114.6 (CH(3)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3436 (w), 3419 (w), 3266 (w), 3141 (w), 1621 (m), 1593 (m), 1557 (m), 1435 (m), 1297 (m), 1246 (m), 919 (s), 835 (m), 799 (s), 607 (s), 487 (s), 422 (s); **MS (EI, 70 eV):** *m/z* (%) = 188 ([M]$^+$, ^{37}Cl, 24), 186 ([M]$^+$, ^{35}Cl, 65), 155 (32), 154 (21), 153 (100), 152 (45), 125 (13), 118 (23), 117 (12), 90 (21), 63 (23), 62 (12), 60 (11), 52 (16); **HRMS (EI):** *m/z* = calcd. for $C_7H_7N_2{}^{35}Cl_1S_1$ 186.00130, found 186.00110, calcd. for $C_7H_7N_2{}^{37}Cl_1S_1$ 187.99835, found 187.99858.

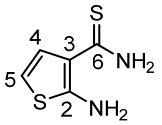
2-Amino-6-chlorobenzothioamide (158):



The compound was synthesized following the procedure for (**149**), starting from 1 mmol 2-amino-6-chloro-benzonitrile, giving 62 % (**158**) as a solid, **MP.:** 111–112°C, **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.15 (s, 1H, CSNH$_2$), 9.68 (s, 1H, CSNH$_2$), 6.98 (dd, ^3J = 8.0 Hz, ^3J = 8.0 Hz, 1H, CH(4)), 6.68 – 6.54 (m, 2H, CH(3 + 5)), 5.18 (s, 2H, NH$_2$) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 198.3 (C=S), 145.3 (C$_{\text{quart}}$(2)), 129.0 (CH(4)), 128.2 (C$_{\text{quart}}$(6)), 126.9 (C$_{\text{quart}}$(1)),116.2 (CH(3)), 13.8 (CH(5)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3427 (w), 3393 (w), 3313 (w), 3085 (w), 1637 (w), 1620 (w), 1595 (m), 1570 (m), 1472 (w), 1447 (m), 1402 (m), 1295 (m), 1202 (w), 1155 (w), 1106 (w), 1047 (w), 964 (w), 88 (m), 878 (m), 775 (s), 746 (m), 719 (m), 654 (m), 608 (s), 580 (s), 540 (s), 502 (s), 453 (s), 430 (s); **MS (EI, 70 eV):** *m/z* (%) = 188 ([M]$^+$, ^{37}Cl, 31), 186 ([M]$^+$, ^{35}Cl, 79), 155 (30), 154 (20), 153 (100), 152 (37), 151 (111), 125 (13), 118 (17), 117 (57), 90 (54), 75 (10), 65 (14), 64 (12), 63 (31), 62 (15), 61 (11), 60 (17), 52 (15), 39

(12); **HRMS (EI):** *m/z* = calcd. for $C_7H_7N_2{}^{35}Cl_1S_1$ 186.00130, found 186.00122, calcd. for $C_7H_7N_2{}^{37}Cl_1S_1$ 187.99835, found 187.99864.

2-Aminothiophene-3-carbothioamide (159):

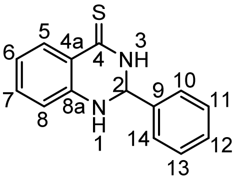


The compound was synthesized following the procedure for (**149**), starting from 1 mmol 2-amino-3-cyano-thiophene, giving 85 % (**159**) as a solid, **MP.:** 118–119°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 8.60 (s, 2H, NH_2), 8.49 (s, 1H, $CSNH_2$), 8.43 (s, 1H, $CSNH_2$), 7.12 (d ^3J = 6.3 Hz, 1H, CH(4)), 6.24 (d, ^3J = 6.0 Hz, 1H, CH(5)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 189.2 ($CSNH_2$(6)), 167.8 (C_{quart}(2), 123.4 (C_{quart}(3), 111.2 (CH(4)), 104.7 (CH(5)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3267 (w), 3165 (w), 1622 (w), 1598 (w), 1559 (m), 1516 (w), 1412 (m), 1386 (m), 1286 (w), 1264 (w), 1082 (w), 911 (w), 869 (w), 830 (s), 776 (m), 724 (w), 643 (s), 588 (s), 554 (s), 483 (s), 446 (s); **MS (EI, 70 eV):** *m/z* (%) = 159 (11), 158 ($[M]^+$, 100), 141 (27), 125 (94), 124 (27), 98 (19), 97 (19), 81 (11), 71 (12), 70 (15), 69 (17), 60 (22), 54 (21), 52 (27), 45 (32), 38 (11), 37 (10), **HRMS (ESI-TOF):** *m/z* = calcd. for $C_5H_6N_2S_2$ 159.00452 ($[M+H]^+$), found 159.00461.

1.1.13. Synthesis of 2-phenyl-1,2-dihydroquinazolin-4(1*H*)-thiones

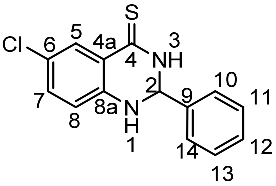
General procedure: A 25 ml glass pressure tube is charged with 1 mmol **158** (152 mg), 1 mmol benzaldehyde (122 µl, **111**) and 2 ml H_2O and the tube is subsequently sealed. The mixture is heated under stirring to 100°C for 24 h. whilst a yellow solid is precipitating. The crude product is filtered off and washed with water. The solid is dissolved in the minimum amount of boiling ethyl acetate and recrystallized by the addition of hexane giving 201 mg (84 %) 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-thione (**172**) as a yellow solid.

2-phenyl-2,3-dihydroquinazolin-4(1*H*)-thione (163)



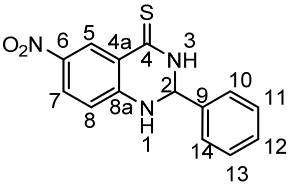
MP.: 174-175°C; **^{1}H-NMR (250 MHz, DMSO-d$_6$):** δ = 10.68–10.45 (m, 1H, NH(3)), 8.05 (d, ^3J = 8.0 Hz, 1H, CH(5)), 7.56 (d, ^3J = 2.0 Hz, 1H, NH(1)), 7.48–7.31 (m, 5H, CH(10 + 11 + 12 + 13 + 14)), 7.26 (ddd, ^3J = 8.4 Hz, ^3J = 7.1 Hz, ^4J = 1.6 Hz, 1H, CH(7), 6.78–6.73 (m, 1H, CH(8)), 6.66 (ddd, ^3J = 8.1 Hz, ^3J = 7.1 Hz, ^4J = 1.1 Hz, 1H, CH(6)), 5.77–5.74 (m, 1H, (CH(2)) ppm; **^{13}C-NMR (63 MHz, DMSO-d$_6$):** δ = 189.2 (C=S(4)), 143.4 (C_{quart}(8a)), 141.0 (C_{quart}(9)), 134.1 (CH(7)), 131.5 (CH(5)), 128.4 (CH(12)), 128.4 (CH(11 + 13)), 126.5 (CH(10 + 14)), 119.5 (C_{quart}(4a)), 117.3 (CH(6)), 114.8 (CH(8)), 65.6 (CH(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3260 (w), 3139 (w), 3029 (w), 2973 (w), 1609 (m), 1524 (m), 1211 (m), 1197 (m), 1149 (m), 1124 (m), 1009 (m), 999 (m), 861 (w), 842 (w), 757 (s), 694 (s), 591 (m); **MS (EI, 70 eV):** *m/z* (%) = 240 ([M]$^+$, 55), 208 (18), 207 (100), 206 (17), 163 (34), 136 (16), 129 (21), 104 (17), 102 (15), 77 (21); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{14}H_{12}N_2S_1$ 241.07940 ([M+H]$^+$), found 241.07888; **Elemental analysis:** Calcd. for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.66; S, 13.34. Found: C, 70.28; H, 5.01; N, 11.22; S, 12.67.

6-Chloro-2-phenyl-2,3-dihydroquinazoline-4(1*H*)-thione (164)



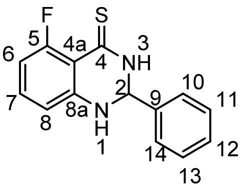
The compound was synthesized following the procedure for (**163**), starting from 1 mmol (**159**) and 1 mmol (**107**), giving 68 % (**164**) as a solid, **MP.:** 174–175°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.74 (d, ^3J = 2.1 Hz, 1H, NH(3)), 8.01 (d, ^4J = 2.5 Hz, 1H, CH(5)), 7.77 (s, 1H, NH(1)), 7.46–7.33 (m, 5H, CH(10 + 11 + 12 + 13 + 14)), 7.30 (dd, ^3J = 8.7 Hz, ^4J = 2.6 Hz, 1H, CH(7)), 6.80 (d, ^3J = 8.7 Hz, 1H, CH(8)), 5.82–5.78 (m, 1H, CH(2)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 187.8 (C=S(4)), 142.1 (C_{quart}(8a)), 140.6 (C_{quart}(9)), 133.7 (CH(7)), 130.1 (CH(5)), 128.6 (CH(12)), 128.5 (CH(11 + 13)), 126.5 (CH(10 + 14)), 120.8 (C_{quart}(4a)), 120.3 (C_{quart}(6)), 117.0 (CH(8)), 65.6 (CH(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3339 (w), 3311 (w), 3132 (w), 2945 (w), 1658 (w), 1611 (m), 1575 (m), 1523 (s), 1363 (m), 1188 (s), 1012 (m), 817 (m), 764 (m), 699 (s), 576 (m); **MS (EI, 70 eV):** *m/z* (%) = 276 ([M]$^+$, 37Cl, 17), 274 ([M]$^+$, 35Cl, 58), 243 (35), 242 (23), 241 (100), 206 (20), 197 (42), 163 (21), 77 (33), 51 (20); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{14}H_{11}N_2Cl_1S_1$ 275.04042 ([M+H]$^+$), found 275.04017.

6-Nitro-2-phenyl-2,3-dihydroquinazoline-4(1*H*)-thione (165)



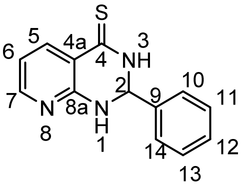
The compound was synthesized following the procedure for (**163**), starting from 1 mmol (**160**) and 1 mmol (**107**), giving 79 % (**165**) as a solid, **MP.:** 230–231°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.97 (d, ^3J = 1.7 Hz, 1H, NH(3)), 8.97 (d, ^4J = 2.7 Hz, 1H, CH(5)), 8.89 (s, 1H, NH(1)), 8.11 (dd, ^3J = 9.1 Hz, ^4J = 2.7 Hz, 1H, CH(7)), 7.46–7.36 (m, 5H, CH(10 + 11 +12 + 13 + 14)), 6.87 (d, ^3J = 9.1 Hz, 1H,CH(8)), 6.05–6.01 (m, 1H, CH(2)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 187.2 (C=S(4)), 147.8 (C$_{quart}$(8a)), 140.5 (C$_{quart}$(9)), 137.5 (C$_{quart}$(6)), 129.1 (CH(5)), 129.0 (CH(7)), 128.8 (CH(11 + 13)), 128.2 (CH(12)), 126.3 (CH(10 + 14)), 116.8 (C$_{quart}$(4a)), 115.1 (CH(8)), 65.8 (CH(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3372 (w), 3294 (w), 3146 (w), 3086 (w), 2973 (w), 1615 (m), 1589 (m), 1537 (m), 1453 (m), 1317 (s), 1193 (m), 1094 (s), 825 (m), 745 (m), 698 (s), 440 (m), **MS (EI, 70 eV):** *m/z* (%) = 285 ([M]$^+$, 36), 253 (100), 252 (80), 220 (87), 206 (26), 57 (20), 44 (39); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{14}H_{11}N_3O_2S_1$ 286.06447 ([M+H]$^+$), found 286.06441.

5-Fluoro-2-phenyl-2,3-dihydroquinazoline-4(1*H*)-thione (166)



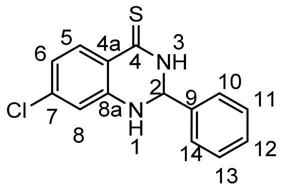
The compound was synthesized following the procedure for (**163**), starting from 1 mmol (**161**) and 1 mmol (**107**), giving 88 % (**166**) as a solid, **MP.:** 178–179 C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.49 (d, ^3J = 3.6 Hz, 1H, NH(3)), 7.91 (s, 1H, NH(1)), 7.44–7.30 (m, 5H, CH(10 + 11 + 12 + 13 + 14)), 7.27–7.18 (m, 1H, CH(7)), 6.66 (d, ${}^{3}J$ = 8.3 Hz, 1H, CH(8)), 6.42 (ddd, ${}^{3}J$ = 11.8 Hz, ${}^{3}J$ = 8.1 Hz, ^{4}J = 0.9 Hz, 1H, CH(6)), 5.67–5.62 (m, 1H, CH(2)) ppm; **^{13}C-NMR (63 MHz, DMSO-d$_6$):** δ = 184.4 (d, ${}^{3}J$ = 4.5 Hz, C=S(4)), 162.7 (d, ${}^{1}J$ = 258.9 Hz, C$_{\text{quart}}$(5)), 146.1 (d, ${}^{3}J$ = 2.1 Hz, C$_{\text{quart}}$(8a)), 139.9 (C$_{\text{quart}}$(9)), 134.2(d, ${}^{3}J$ = 11.8 Hz, CH(7)), 128.5 (CH(12)), 128.4 (CH(11 + 13)), 126.6 (CH(10 + 14)), 111.1 (d, ^{4}J = 3.7 Hz, CH(8)), 110.4 (d, ${}^{2}J$ = 7.1 Hz, C$_{\text{quart}}$(4a)), 105.4 (d, ${}^{2}J$ = 22.5 Hz, CH(6)), 64.8 (CH(2)) ppm; **^{19}F-NMR (282 MHz, DMSO-d$_6$):** δ = -107.37 ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3263 (w), 3127 (w), 3033 (w), 2979 (w), 2929 (w), 1618 (m), 1523 (s), 1192 (s), 1056 (m), 987 (m), 794 (m), 747 (m), 696 (s), 595 (m), 453 (s); **MS (EI, 70 eV):** *m/z* (%) = 258 ([M]$^+$, 31), 226 (23), 225 (100), 224 (59), 223 (50), 181 (16), 147 (19), 122 (20), 104 (19), 77 (42), 51 (16); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{14}H_{11}N_2F_1S_1$ 259.06997 ([M+H]$^+$), found 259.07012.

2-Phenyl-2,3-dihydropyrido[2,3-d]pyrimidine-4(1*H*)-thione (167)



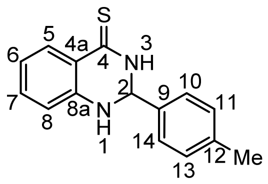
The compound was synthesized following the procedure for (**163**), starting from 1 mmol (**162**) and 1 mmol (**107**), giving 73 % (**167**) as a solid, **MP.:** 249–250°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.79 (s, 1H, NH(3)), 8.36 (s, 1H, NH(1)), 8.30 (d, ^{3}J = 7.2 Hz, 1H, CH(5)), 8.19 (d, ${}^{3}J$ = 2.7 Hz, 1H, CH(7)), 7.45–7.25 (m, 5H, CH(10 + 11 + 12 + 13 + 14)), 6.75–6.68 (m, 1H, CH(6)), 5.87 (m, 1H, CH(2)) ppm; **^{13}C-NMR (63 MHz, DMSO-d$_6$):** δ = 188.7 (C=S(4)), 154.0 (CH(7)), 153.0 (C$_{\text{quart}}$(8a)), 141.3 (C$_{\text{quart}}$(9)), 139.6 (CH(5)), 128.6 (CH(10 + 12)), 128.5 (CH(11)), 126.0 (CH(11 + 13)), 114.2 (CH(6)), 113.7 (C$_{\text{quart}}$(4a)), 65.6 (CH(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3141 (w), 2963 (w), 2845 (w), 1606 (m), 1532 (m), 1440 (w), 1365 (w), 1247 (m), 1218 (m), 1114 (m), 1001 (m), 765 (s), 699 (s), 496 (s), 428 (m); **MS (EI, 70 eV):** *m/z* (%) = 241 ([M]$^+$, 100), 242 (13), 208 (37), 164 (53), 137 (13), 105 (11), 103 (14); **HRMS (EI):** *m/z* = calcd. for $C_{13}H_{11}N_3S_1$ 241.06682, found 241.06630.

7-Chloro-2-phenyl-2,3-dihydroquinazoline-4(1*H*)-thione (168)



The compound was synthesized following the procedure for (**163**), starting from 1 mmol (**149**) and 1 mmol (**107**), giving 57 % (**168**) as a solid, **MP.:** 94–96°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.71 – 10.65 (m, 1H, NH(3)), 8.05 (d, ^3J = 8.6 Hz, 1H, (CH(5)), 7.47 – 7.30 (m, 5H, CH(10 + 11 + 12 + 13 + 14)), 6.81 (d, ^4J = 2.1 Hz, 1H, CH(8)), 6.69 (dd, ^3J = 8.6 Hz, ^4J = 2.1 Hz, 1H, CH(6)), 5.82 (dd, ^3J = 3.6 Hz, ^3J = 1.7 Hz, 1H, CH(2)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 188.2 (C=S(4)), 144.2 (C$_{\text{quart}}$(8a)), 140.7 (C$_{\text{quart}}$(9)), 138.8 (C$_{\text{quart}}$(7)), 133.5 (CH(5)), 128.7 (CH(12)), 128.5 (CH(11 + 13)), 126.5 (CH(10 + 14)), 118.1 (C$_{\text{quart}}$(4a)), 117.4 (CH(6)), 113.8 (CH(8)), 65.6 (CH(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3134 (w), 1669 (w), 1601 (s), 1568 (m), 1506 (m), 1339 (w), 1289 (w), 1194 (s), 1129 (m), 1080 (s), 1000 (m), 899 (m), 806 (m), 761 (m), 693 (s), 456 (m), 418 (m); **MS (EI, 70 eV):** *m/z* (%) = 276 ($[M]^{+}$ ^{37}Cl, 20), 275 (14), 274 ($[M]^{+}$ ^{35}Cl, 78), 273 (16), 256 (13), 243 (31), 242 (28), 241 (100), 240 (25), 239 (57), 206 (19), 197 (28), 170 (10), 163 (11), 153 (16), 138 (10), 104 (10), 77 (17); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{14}H_{11}N_2Cl_1S_1$ 275.04042 ($[M+H]^{+}$), found 275.04017.

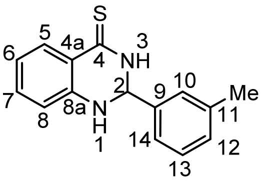
2-(4-Methylphenyl)-2,3-dihydroquinazoline-4(1*H*)-thione (171)



The compound was synthesized following the procedure for (**163**), starting from 1 mmol (**149**) and 1 mmol 4-methyl-benzaldehyde, giving 93 % (**171**) as a solid, **MP.:** 234–235°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.50 (d, ^3J = 2.3 Hz, 1H, NH(3)), 8.04 (dd, ^3J = 8.0 Hz, ^4J = 1.4 Hz, 1H, CH(5)), 7.51 (s, 1H, NH(1)), 7.31 (d, ^3J = 8.1 Hz, 1H, CH(10 + 14)), 7.25 (ddd, ^3J = 8.4 Hz, ^3J = 7.2 Hz, ^4J = 1.6 Hz, 1H, CH(7)), 7.17 (d, ^3J = 8.0 Hz, 2H, CH(11 + 13)), 6.74 (dd, ^3J = 8.2 Hz, ^4J = 0.7 Hz, 1H, CH(8)), 6.65 (ddd, ^3J = 8.1 Hz, ^3J = 7.2 Hz, ^4J = 1.1 Hz, 1H, CH(6)), 5.74–5.67 (m, 1H, CH(2)), 2.27 (s, 3H, CH$_3$) ppm; **^{13}C-NMR (126 MHz, DMSO-d$_6$):** δ = 189.1 (C=S(4)), 143.4

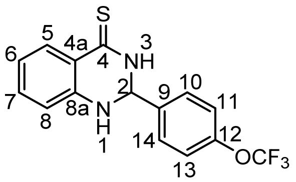
(C_{quart}(8a)), 138.0 (C_{quart}(9)), 137.7 (C_{quart}(12)), 134.0 (CH(7)), 131.4 (CH(5)), 128.9 (CH(11 + 13)), 126.4 (CH(10 + 14)), 119.5 (C_{quart}(4a)), 117.3 (CH(6)), 114.8 (CH(8)), 65.4 (CH(2)), 20.7 (CH3(15)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3270 (m), 3144 (m), 3029 (w), 2974 (w), 2911 (w), 2842 (w), 16.12 (m), 1529 (s), 1209 (s), 1198 (s), 1147 (s), 1007 (m), 817 (s), 586 (s); 493 (s); **MS (EI, 70 eV):** *m/z* (%) = 254 ([M]$^+$, 63), 253 (19), 221 (100), 219 (38), 206 (17), 163 (28), 136 (30), 129 (24), 102 (17), 77 (17), 44 (17), 32 (22); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{15}H_{14}N_2S_1$ 254.08722 ([M+H]$^+$), found 254.08698.

2-(3-Methylphenyl)-2,3-dihydroquinazoline-4(1*H*)-thione (172)



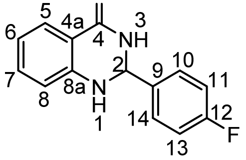
The compound was synthesized following the procedure for (**163**), starting from 1 mmol (**149**) and 1 mmol 3-methyl-benzaldehyde, giving 82 % (**172**) as a solid, **MP.:** 191–192°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.49 (s, 1H, NH(3)), 8.05 (d, ^3J = 7.8 Hz, 1H, CH(5)), 7.52 (s, 1H, NH(1)), 7.31–7.11 (m, 5H, CH(7 + 10 + 12 + 13 + 14)), 6.75 (d, ^3J = 8.1 Hz, 1H, CH(8)), 6.66 (m, 1H, CH(6)), 5.71 (s, 1H, CH(2)), 2.29 (s, 3H, CH_3(15)) ppm; **^{13}C-NMR (63 MHz, DMSO-d$_6$):** δ = 189.2 (C=S(4)), 143.5 (C_{quart}(8a)), 140.9 (C_{quart}(9)), 137.5 (C_{quart}(11)), 134.1 (CH(7)), 131.5 (CH(5)), 129.1 (CH(12)), 128.3 (CH(13)), 127.2 (CH(14)), 123.7 (CH(10)), 119.5 (C_{quart}(4a)), 117.3 (CH(6)), 114.8 (CH(8)), 65.7 (CH(2)), 21.1 (CH3(15)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3262 (w), 3130 (w), 3019 (w), 2968 (w), 2917 (w), 1608 (m), 1583 (m), 1523 (m), 1482 (m), 1205 (s), 1146 (m), 1121 (m), 1033 (m), 998 (m), 762 (s), 697 (s); **MS (EI, 70 eV):** *m/z* (%) = 254 ([M]$^+$, 63), 253 (20), 222 (24), 221 (100), 219 (29), 206 (24), 163 (51), 136 (19), 129 (27), 118 (16), 102 (19), 91 (20), 77 (17), 65 (15); **HRMS (EI):** *m/z* = calcd. for $C_{15}H_{14}N_2S_1$ 254.08722, found 254.08700.

2-(4-Trifluoromethoxy)phenyl-2,3-dihydroquinazoline-4(1*H*)-thione (173)



The compound was synthesized following the procedure for (**163**), starting from 1 mmol (**149**) and 1 mmol 4-trifluormethoxy-benzaldehde, giving 74 % (**173**) as a solid, **MP.:** 161–162°C; **^{1}H-NMR (250 MHz, DMSO-d6):** δ = 10.65–10.55 (m, 1H, NH(3)), 8.06 (dd, ^{3}J = 8.0 Hz, ^4J = 1.4 Hz, 1H, CH(5)), 7.63–7.57 (m, 2H, (CH(11 + 13)), 7.57–7.54 (m, 1H, NH(1)), 7.45–7.36 (m, 2H, CH(10 + 14)), 7.28 (ddd, ^3J = 8.5 Hz, ^3J = 7.2 Hz, ^4J = 1.6 Hz, 1H, CH(7)), 6.82–6.73 (m, 1H, CH(8)), 6.68 (ddd, ^3J = 8.1 Hz, ^3J = 7.2 Hz, ^4J= 1.1 Hz, 1H, CH(6)), 5.96–5.61 (m, 1H, CH(2)) ppm; **^{13}C-NMR (63 MHz, DMSO-d$_6$):** δ = 189.3 (C=S(4)), 148.3 (C_{quart}(12)), 143.2 (C_{quart}(8a)), 140.2 (C_{quart}(9), 134.2 (CH(7)), 131.5 (CH(5)), 128.7 (CH(11 + 13)), 121.1 (CH(10+14), 120.0 (q, ^1J = 256.4 Hz, (OCF_3)), 119.5 (C_{quart}(4a)), 117.6 (CH(6)), 114.9 (CH(8)), 64.9 (CH(2)) ppm; **^{19}F-NMR (282 MHz, DMSO-d$_6$):** δ = -56.43 ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3253 (w), 3136 (w), 2974 (w), 2146 (w), 2075 (w), 2019 (w), 1611 (m), 1526 (m), 1505 (m), 1378 (w), 1253 (m), 1210 (s), 1130 (s), 1014 (m), 764 (s), 522 (m), 493 (s); **MS (EI, 70 eV):** *m/z* (%) = 324 ([M]$^+$, 56), 292 (22), 291 (100), 289 (18), 163 (25), 136 (16), 69 (27); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{15}H_{11}O_1N_2F_3S_1$ 324.05387 ([M+H]$^+$), found 324.05320.

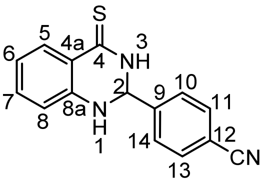
2-(4-Fluorophenyl)-2,3-dihydroquinazoline-4(1*H*)-thione (174)



The compound was synthesized following the procedure for (**163**), starting from 1 mmol (**149**) and 1 mmol 4-fluoro-benzaldehyde, giving 75 % (**174**) as a solid, **MP.:** 176–177°C; **^{1}H-NMR (250 MHz, DMSO-d6):** δ = 10.54 (d, ^3J = 2.2 Hz, 1H, NH(3)), 8.06 (dd, ^3J = 8.0 Hz, ^4J = 1.4 Hz, 1H, CH(5)), 7.54 (s, 1H, NH(1)), 7.53–7.43 (m, 2H, CH(11 + 13)), 7.35–7.16 (m, 3H, CH(7 + 10 + 14), 6.76 (dd, ^3J = 8.3 Hz, ^4J = 1.1 Hz, 1H, CH(8)), 6.67 (ddd, ^3J = 8.1 Hz, ^3J = 7.1 Hz, ^4J = 1.1 Hz, 1H, CH(6)), 5.79–5.76 (m, 1H, CH(2)) ppm; **^{13}C-NMR (63 MHz, DMSO-d$_6$):** δ = 189.3 (C=S(4)), 162.1 (d, ^1J =

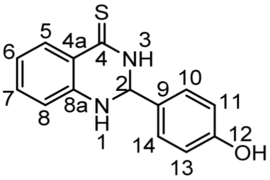
244.5 Hz, (C_{quart}(12)), 143.3 (C_{quart}(8a)), 137.1 (d, ^4J =3.0 Hz (C_{quart}(9)), 134.2 (CH(7)), 131.5 (CH(5)), 128.8 (d, ^3J = 8.5 Hz (CH(10 + 14)), 119.5 (C_{quart}(4a)), 117.5 (CH(6)), 115.2 (d, ^2J = 21.6 Hz, (CH(11 + 13)), 114.9 (CH(8)), 65.1 (CH(2)) ppm; **^{19}F-NMR (282 MHz, DMSO-d$_6$):** δ = -113.08 –-113.47 (m) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3255 (w), 3148 (w), 3026 (w), 2968 (w), 2842 (w), 1607 (m), 1508 (s), 1210 (m), 1199 (m), 1150 (s), 1009 (m), 995 (m), 833 (m), 764 (s), 588 (m), 500 (s); **MS (EI, 70 eV):** *m/z* (%) = 258 ([M]$^+$, 48), 226 (19), 225 (100), 224 (19), 163 (19), 129 (17), 102 (15); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{14}H_{11}N_2F_1S_1$ 258.06215 ([M+H]$^+$), found 258.06171.

2-(4-Cyanophenyl)-2,3-dihydroquinazoline-4(1*H*)-thione (175)



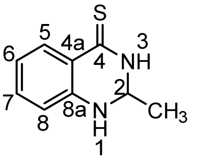
The compound was synthesized following the procedure for (**163**), starting from 1 mmol (**149**) and 1 mmol 4-cyano-benzaldehyde, giving 80 % (**175**) as a solid, **MP.:** 230–231°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.68 (d, ^3J = 2.6 Hz, 1H, NH(3)), 8.04 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, CH(5)), 7.90–7.85 (m, 2H, CH(10 + 14)), 7.71 (s, 1H, NH(1)), 7.64–7.57 (m, 2H, CH(11 + 13)), 7.28 (ddd, ^3J = 8.5 Hz, ^3J = 7.2 Hz, ^4J = 1.6 Hz, 1H, CH(7)), 6.78 (d, ^3J = 7.4 Hz, 1H, CH(8)), 6.71–6.65 (m, 1H, CH(8)), 5.89–5.85 (m, 1H, CH(2)) ppm; **^{13}C-NMR (63 MHz, DMSO-d$_6$):** δ = 189.3 (C=S(4)), 146.4 (C_{quart}(8a)), 142.8 (C_{quart}(9)), 134.4 (CH(7)), 132.5 (CH(11 + 13)), 131.5 (CH(5)), 127.4 (CH(10 + 14)), 119.5 (C_{quart}(4a)), 118.6 (C(CN)), 117.7 (CH(6)), 114.8 (CH(8)), 111.2 (C_{quart}(12)), 64.6 (CH(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3319 (w), 3043 (w), 2833 (w), 2226 (w), 1609 (m), 1582 (m), 1524 (m), 1485 (m), 1208 (s), 1199 (s), 1150 (m), 1132 (m), 1019 (m), 833 (m), 757 (s), 590 (m), 526 (s); **MS (EI, 70 eV):** *m/z* (%) = 265 ([M]$^+$, 40), 233 (15), 332 (100), 231 (18), 230 (25), 163 (15); **HRMS (EI):** *m/z* = calcd. for $C_{15}H_{11}N_3S_1$ 265.06682, found 265.06625.

2-(4-Hydroxyphenyl)-2,3-dihydroquinazoline-4(1*H*)-thione (176)



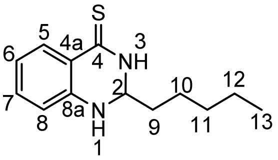
The compound was synthesized following the procedure for (**163**), starting from 1 mmol (**149**) and 1 mmol 4-hydroxy-benzaldehyde, giving 75 % (**176**) as a solid, **M.P.:** 214–216°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.36 (d, ^3J = 2.9 Hz, 1H, NH(3)), 9.52 (s, 1H, OH), 8.05 (dd, ^3J = 8.0 Hz, ^4J = 1.6 Hz, 1H, CH(5)), 7.41 – 7.36 (m, 1H, NH(2)), 7.30 – 7.20 (m, 3H, CH(7 + 10 + 14), 6.75 – 6.69 (m, 3H, CH(8 + 11 + 13), 6.65 (ddd, ^3J = 8.1 Hz, ^3J = 7.1 Hz, ^4J =1.1 Hz, 1H, CH(6)), 5.63 (dd, ^3J = 3.3 Hz, ^3J = 1.7 Hz, 1H, CH(2)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 189.1 (C=S(4)), 157.7 (C$_{\text{quart}}$(10)), 143.7 (C$_{\text{quart}}$(8)), 134.0 (CH(7)), 131.5 (CH(5)), 131.0 (C$_{\text{quart}}$(9)), 128.0 (CH(11 + 13)), 119.4 (C$_{\text{quart}}$(4a)), 117.2 (CH(6)), 115.0 (CH(10 + 14)), 114.7 (CH(8)), 65.8 (CH(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3149 (m), 1608 (m), 1575 (w), 1530 (m), 1511 (s), 1480 (m), 1365 (m), 1297 (w), 1242 (m), 1196 (s), 1168 (s), 1154 (s), 1125 (s), 1015 (m), 999 (s), 829 (s), 760 (s). 750 (s), 706 (s), 526 (s), 501 (s), 466 (s); **MS (EI, 70 eV):** *m/z* (%) = 256 ([M]$^+$, 37), 255 (10), 254 (16), 224 (15), 223 (81), 222 (100), 221 (50), 195 (17), 129 (10), 119 (13); **HRMS (EI):** *m/z* = calcd. for $C_{14}H_{12}O_1N_2S_1$ 256.06649, found 256.06662.

2-Methyl-2,3-dihydroquinazoline-4(1*H*)-thione (177)



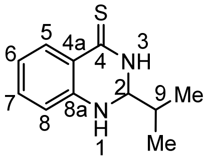
The compound was synthesized following the procedure for (**163**), starting from 1 mmol (**149**) and 1 mmol ethanal, giving 57 % (**177**) as a solid, **M.P.:** 150 – 152°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.19 – 10.01 (s, 1H, NH(3)), 8.04 (dd, ^3J = 8.3 Hz, ^4J=1.6 Hz, 1H, CH(5)), 7.26 (ddd, ^3J = 8.1 Hz, ^3J = 7.2 Hz, ^4J = 1.6 Hz, 1H, CH(7)), 6.92 (s, 1H, NH(1)), 6.75 – 6.62 (m, 2H, CH(6 + 8)), 4.81 – 4.67 (m, 1H, CH(2)), 1.37 (d, ^3J = 5.8 Hz, 3H, CH_3) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 189.8 (C=S(4)), 144.8 (C$_{\text{quart}}$(8a), 133.8(CH(7)), 131.5 (CH5)), 120.0 (C$_{\text{quart}}$(4a)), 117.5 (CH(6)), 114.7 (CH(8)), 61.1 (CH(2)), 20.2 (CH_3) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3162 (w), 2974 (w), 1609 (m), 1578 (m), 1531 (s), 1471 (m), 1383 (m), 1346 (m), 1248 (w), 1213 (S), 1140 (m), 1102 (m), 1067 (m), 994 (s), 850 (w), 753 (s), 718 (m), 692 (m), 584 (m), 521 (s), 454 (s), 436 (s); **MS (EI, 70 eV):** *m/z* (%) = 178 ($[M]^+$, 74), 177 (10), 164 (10), 163 (100), 146 (13), 145 (56), 136 (21), 135 (12), 129 (16), 118 (12), 109 (12), 108 (18), 104 (20), 77 (16); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_9H_{10}N_2S_1$ 177.04851 ($[M-H]^-$), found 177.04851.

2-Pentyl-2,3-dihydroquinazoline-4(1*H*)-thione (178)



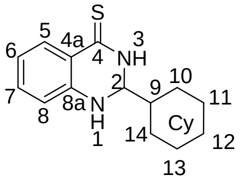
The compound was synthesized following the procedure for (**163**), starting from 1 mmol (**149**) and 1 mmol *n*-hexanal, giving 85 % (**178**) as a solid, **M.P.:** 138–139°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.12 (d, ^3J = 2.5 Hz, 1H, NH(3)), 8.03 (dd, ^3J = 8.0 Hz, ^4J = 1.6 Hz, 1H, CH(5)), 7.25 (ddd, ^3J = 8.5 Hz, ^3J = 7.1 Hz, ^4J = 1.6 Hz, 1H, CH(7)), 6.90 (s, 1H, NH(1)), 6.73 (dd, ^3J = 8.3 Hz, ^4J = 1.1 Hz, 1H, CH(8)), 6.66 (ddd, ^3J = 8.1 Hz, ^3J = 7.1 Hz, ^4J = 1.1 Hz, 1H, CH(6)), 4.62 (tdd, ^3J = 5.4 Hz, ^3J = 2.5 Hz, ^3J = 1.2 Hz, 1H, CH(9)), 1.68 (td, ^3J = 8.2 Hz, ^4J = 5.0 Hz, 2H, CH(10)), 1.49 – 1.20 (m, 6H, CH_2(11 + 12 + 13), 0.87 (m, 3H, CH_3(14)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 189.4 (C=S(4), 144.4 (C_{quart}(8a)), 133.8 (CH(7)), 131.5 (CH(5)), 119.7 (C_{quart}(4a)), 117.1 (CH(6)), 114.7 (CH(8)), 64.4 (CH(2)), 33.6 (CH_2(10), 31.0 (CH_2(11)), 22.9 (CH_2(12)), 22.0 (CH_2(13)), 13.9 (CH_3(14)) ppm. **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3288 (w), 3172 (m), 2923 (m), 2854 (w), 1615 (s), 1579 (s), 1526 (s), 1478 (s), 1446 (m), 1378 (m), 1350 (w), 1310 (w), 1238 (w), 1207 (s), 1148 (s), 1139 (s), 1114 (w), 1026 (w), 994 (S), 856 (w), 769 (s), 747 (s), 647 (w), 525 (m), 514 (m), 452 (m), 418 (m); **MS (EI, 70 eV):** *m/z* (%) = 235 (20), 234 ($[M]^+$, 84), 233 (15), 232 (12), 201 (10), 189 (16), 177 (14), 176 (54), 165 (48), 164 (83), 163 (100), 162 (16), 146 (12), 145 (34), 144 (13), 136 (40), 132 (19), 131 (10), 129 (49), 118 (11), 109 (12), 108 (10), 104 (17), 102 (17), 77 (15); **HRMS (EI):** *m/z* = calcd. for $C_{13}H_{18}N_2S_1$ 234.11852, found 234.11812.

2-(Isopropyl)-2,3-dihydroquinazoline-4(1*H*)-thione (179)



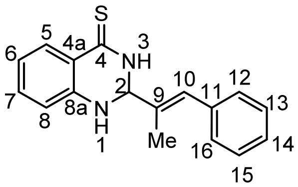
The compound was synthesized following the procedure for (**163**), starting from 1 mmol (**149**) and 1 mmol *iso*-valeraldehyde, giving 82 % (**179**) as a solid, **MP.:** 185–186°C; **^{1}H-NMR (300 MHz, DMSO-d_6):** δ = 10.09 (s, 1H, NH(3)), 8.03 (dd, ^3J = 8.0 Hz, ^4J = 1.6 Hz, 1H, CH(5)), 7.24 (ddd, ^3J = 8.4 Hz, ^3J = 7.1 Hz, ^4J = 1.6 Hz, 1H, CH(7)), 6.92 (s, 1H, NH(1)), 6.75 (dd, ^3J = 8.2 Hz, ^4J = 1.1 Hz, 1H, CH(8)), 6.62 (ddd, ^3J = 8.1 Hz, ^3J = 7.1 Hz, ^4J = 1.2 Hz, 1H, CH(6)), 4.41–4.37 (m, 1H, CH(2)), 2.03–1.90 (m, 1H, CH(9)), 0.93 (d, ^3J = 6.9 Hz, 3H, CH_3), 0.89 (d, ^3J = 6.8 Hz, 3H, CH_3) ppm; **^{13}C-NMR (63 MHz, DMSO-d_6):** δ = 189.3 (C=S(4)), 4.2 (C_{quart}(8a)), 133.9 (CH(7)), 131.5 (CH(5)), 119.5 (C_{quart}(4a)), 116.8 (CH(6)), 114.5 (CH(8)), 69.2 (CH(2)), 32.17 (CH(9)), 17.08 (CH_3(Me)), 16.66 (CH_3(Me)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3279 (m), 3139 (m), 3057 (w), 2997 (w), 2955 (m), 2909 (w), 2865 (w), 1612 (m), 1535 (m), 1474 (m), 1279 (m), 1216 (s), 1146 (s), 981 (m), 766 (s), 749 (s), 689 (m), 435 (s); **GC/MS (EI, 70 eV):** *m/z* (%) = 206 ([M]$^+$, 6), 164 (10), 163 (100), 136 (6), 129 (12), 108 (5), 41 (6); **HRMS (EI):** *m/z* = calcd. for $C_{11}H_{14}N_2S_1$ 206.08722, found 206.08683.

2-(Cyclohexyl)-2,3-dihydroquinazoline-4(1*H*)-thione (180)



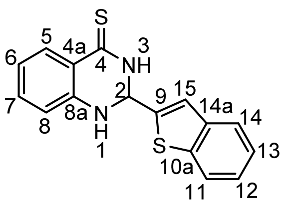
The compound was synthesized following the procedure for (**163**), starting from 1 mmol (**149**) and 1 mmol cyclohexane-carbaldehyde, giving 84 % (**180**) as a solid, **MP.:** 182–183°C; **^{1}H-NMR (300 MHz, DMSO-d_6):** δ = 10.11 (s, 1H, NH(3)), 8.02 (dd, ^3J = 8.0 Hz, ^4J = 1.3 Hz, 1H, CH(5)), 7.23 (ddd, ^3J = 8.4 Hz, ^3J = 7.1 Hz, ^4J = 1.5 Hz, 1H, CH(7)), 6.97 (s, 1H, NH(1)), 6.74 (dd, ^3J = 8.2 Hz, ^3J = 0.8 Hz, 1H, CH(8)), 6.61 (ddd, ^3J = 8.1 Hz, ^3J = 5.8 Hz, ^4J = 1.1 Hz, 1H, CH(6)), 4.36 (s, 1H, CH(2)), 1.79–0.99 (m, 11H, CH_2(Cy)) ppm; **^{13}C-NMR (63 MHz, DMSO-d_6):** δ = 189.0 (C=S(4)), 144.0 (C_{quart}(8a)), 133.9 (CH(7)), 131.5 (CH(5)), 119.5 (C_{quart}(4a)), 116.7 (CH(6)), 114.5 (CH(8)), 68.38 (CH(2)), 42.0 (CH_2(Cy)), 27.0 (CH_2(Cy)), 26.8 (CH_2(Cy)), 25.8 (CH_2(Cy)), 25.4 (CH_2(Cy)), 25.3 (CH(Cy)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3338 (w), 3150 (w), 3041 (w), 2992 (w), 2927 (m), 2848 (w), 1610 (m), 1576 27 (m), 1536 (s), 1213 (s), 1148 (m), 1162 (m), 1003 (m), 989 (m), 956 (m), 761 (s), 743 (s), 530 (s), 524 (s); **MS (EI, 70 eV):** *m/z* (%) = 246 ($[M]^+$, 16), 189 (10), 164 (19), 163 (100), 129 (10); **HRMS (EI):** *m/z* = Calcd. for $C_{14}H_{18}N_2S_1$ 246.11852, found 246.11846.

(*E*)-2-(1-Phenylprop-1-en-2-yl)-2,3-dihydroquinazoline-4(1H)-thione (181)



The compound was synthesized following the procedure for (**163**), starting from 1 mmol (**149**) and 1 mmol 2-methyl-cinnamylaldehyde, giving 71 % (**181**) as a solid, **MP.:** 198–199°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 10.27 (s, 1H, NH(3)), 8.07 (d, ^3J = 6.9 Hz, 1H, CH(5)), 7.42–7.21 (m, 7H, NH(1), CH(7+ 12 + 13 + 14 + 15 + 16)), 6.75 (d, ^3J = 8.1 Hz, 1H, CH(8)), 6.69–6.62 (m, 1H, CH(6)), 6.59 (s, 1H, CH(10)), 5.27 (s, 1H, CH(2)), 1.91 (s, 3H, CH_3(17)) ppm; **^{13}C-NMR (63 MHz, DMSO-d$_6$):** δ = 189.7 (C=S(4)), 144.1 (C_{quart}(8a)), 136.3 (C_{quart}(11)), 135.6 (C_{quart}(9)), 134.0 (CH(7)), 131.5 (CH(5)), 128.9 (CH(13 + 15)), 128.5 (CH(14)), 128.3 (CH(12 + 16)), 127.1 (CH(10)), 119.0 (C_{quart}(4a)), 117.1 (CH(6)), 114.5 (CH(8)), 70.8 (CH(2)), 13.5 (CH3(17)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3317 (w), 3130 (w), 2977 (w), 1608 (m), 1573 (m), 1518 (m), 1208 (s), 1155 (m), 1126 (m), 993 (m), 756 (s), 699 (s), 516 (s), 443 (s), 427 (m); **MS (EI, 70 eV):** *m/z* (%) = 280 ($[M]^+$, 55), 279 (53), 278 (23), 277 (33), 263 (23), 247 (100), 246 (33), 245 (86), 232 (26), 231 (28), 163 (92), 129 (23), 115 (23); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{17}H_{16}N_2S_1$ 281.11070 ($[M+H]^+$), found 281.11077.

2-(Benzo[*b*]thiophen-2-yl)-2,3-dihydroquinazoline-4(1*H*)-thione (182)



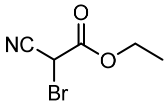
The compound was synthesized following the procedure for (**163**), starting from 1 mmol (**149**) and 1 mmol benzo[*b*]thiophene-carbaldehyde, giving 71 % (**182**) as a solid,

M.P.: 253–255°C; **^{1}H-NMR (300 MHz, DMSO-d$_6$)**: δ = 10.57 (s, 1H, NH(3)), 8.20 – 8.14 (m, 1H, CH(12)), 8.11 (dd, ^3J = 8.0 Hz, ^4J = 1.4 Hz, 1H, CH(15)), 8.04 – 7.99 (m, 1H, CH(5)), 7.66 (s, 1H, CH(10)), 7.55 (s, 1H, NH(1)), 7.49 – 7.37 (m, 2H, CH(13 + 14)), 7.29 (m, 1H, CH(7)), 6.80 – 6.66 (m, 2H, (CH(6 + 8)), 6.18 (m, 1H, CH(2)) ppm; **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 189.7 (C=S(4)), 143.7 (C$_{\text{quart}}$(8a)), 140.3 (C$_{\text{quart}}$(9), 136.6 (C$_{\text{quart}}$(11a)), 134.5(C$_{\text{quart}}$(15a)), 134.1 (CH(7)), 131.6 (CH(5)), 126.9 (CH(13)), 124.7 (CH(14)), 124.2 (CH(15)), 123.1 (CH(10)), 123.1 (CH(12)), 119.7 (C$_{\text{quart}}$(4a)), 117.6 (CH(6)), 114.9 (CH(8)), 62.0 (CH(2)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3274 (w), 3105 (w), 2960 (w), 1607 (w), 1579 (m), 1521 (m), 1460 (m), 1425 (m), 1343 (m), 1240 (m), 1208 (s), 1146 (m), 1125 (m), 1002 (S), 936 (m), 848 (m), 754 (s), 733 (S), 600 (s), 522 (s), 453 (S), 424 (s); **MS (EI, 70 eV):** *m/z* (%) = 297 (10), 296 ([M]$^+$, 54), 264 (21), 263 (100), 262 (36), 261 (28), 178 (10), 129 (11), 44 (11); **HRMS (EI):** *m/z* = calcd. for $C_{16}H_{12}N_2S_2$ 296.04364, found 296.04315.

1.1.14. Synthesis of 2-bromo-ethyl-cyanoactetate

94 mmol ethylcyanoacetate (10 ml) are dissolved in 5 ml CCl_4.The mixture is heated to 65°C and 103 mmol bromine (5.3 ml) dissolved in 10 ml CCl_4 are added dropwise over a period of 2 hours. Afterwards, the mixture is refluxed for 4 hours. The mixture is cooled to room temperature, washed with saturated $Na_2S_2O_3$-solution and water. The aqueous layer is extracted with EtOAc and the organic layers are combined. The solvent was removed under reduced pressure and the crude mixture was distilled at 57°C/0.8 mbar. NMR-analysis showed the presence of 30 % unbrominated ethyl-cyanoacetate, which could not be removed by multiple destillation. NMR-data of the 2-bromo-ethyl-cyanoacetate was similar to the one given in the literature.[ii] The mixture was used without further purification.

2-Bromo-ethyl-cyanoacetate (183)

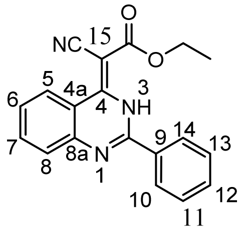


^{1}H-NMR (300 MHz, CDCl3): δ = 4.83 (s, 1H, CHBr), 4.34 (q, ^3J = 7.1 Hz, 1H, CH_2), 1.35 (t, ^3J = 7.2 Hz, 3H, CH_3) ppm.

1.1.15. Synthesis of ethyl-(*Z*)-2-cyano-2-(2-phenylquinazolin-4(3*H*)-ylidene)-acetate

0.4 mmol **163** (100 mg) are dissolved in 2 ml dry EtOH. The crude mixture **183** in 1 ml dry EtOH is added dropwise to the solution at room temperature in a period of 3 hours. After complete addtion, the mixture is stirred at room temperature for 24 hours whilst the solution turns to a redish colour and a dark yellow solid precipitates. The miture is dissolved in EtOAc and washed with water. Column CHromatography (Hex/EtOAc 3:2) gave 41 % ethyl-(*Z*)-2-cyano-2-(2-phenylquinazolin-4(3*H*)-ylidene)-acetate **193** as a dark yellow solid.

Ethyl-(*Z*)-2-cyano-2-(2-phenylquinazolin-4(3*H*)-ylidene)-acetate (184)

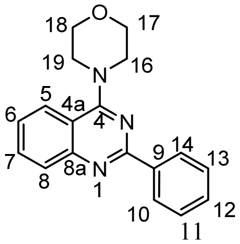


M.P.: 171–172°C; **^{1}H-NMR (250 MHz, DMSO-d6):** δ = 14.63 (s, 1H, NH(3)), 9.06 (dd, ^3J = 8.5 Hz, ^4J = 1.0 Hz, 1H, CH(8)), 8.11–8.04 (m, 2H, CH(5 + 6)), 7.93 (ddd, ^3J = 8.3 Hz, ^3J = 7.1 Hz, ^4J = 1.3 Hz, 1H, CH(7)), 7.82–7.57 (m, 5H, CH(10 + 11 +12 + 13 + 14 + 15)), 4.30 (q, ^3J = 7.1 Hz, 2H, CH_2(17)), 1.32 (t, ^3J = 7.1 Hz, 3H, CH_3(18)) ppm; **^{13}C-NMR (63 MHz, DMSO-d6):** δ = 169.8 (C=O(16)), 155.4 (C_{quart}(15)), 148.2 (C_{quart}(8a)), 147.4 (C_{quart}(9)), 135.7 (CH(7)), 132.3 (CH(5)), 131.3 (C_{quart}(4a)), 129.4 (CH(11 + 13)), 129.0 (CH(12)), 127.6 (CH(6)), 126.4 (CH(10 + 14)), 125.4 (CH(8)), 119.2 (CN) 117.1 (C_{quart}(4)), 66.8 (C_{quart}(2)), 61.4 (CH_2(17)), 14.2 (CH_3(18)); **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3128 (w), 2987 (w), 2913 (w), 2209 (m), 1644 (m), 1589 (m), 1465 (m), 1278 (s), 1258 (s), 1143 (s), 1021 (m), 760 (s), 689 (s), 651 (m); **MS (EI, 70 eV):** *m/z* (%) = 318 (31), 317 ([M]$^+$, 100), 272 (34), 271 (85), 246 (20), 245 (57), 244 (13), 243 (13), 220 (13), 205 (70), 149 (18), 99 (53), 77 (12), 57 (22), 55 (10. 44 (14), 43 (15), 41 (10); **HRMS (EI):** *m/z* = calcd. for $C_{19}H_{15}O_2N$ 317.11588, found 317.11571.

1.1.16. Synthesis of *N*-alkyl-2-phenylquinazolin-4-amines

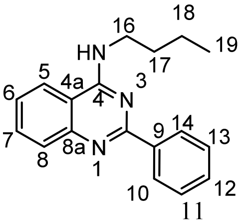
General procedure: 0.4 mmol **163** (100 mg), are dissolved in 3.7 mmol morpholine. 1.3 mmol H_2O_2 (30 %, 0.3 µl) are added dropwise at room temperature. After complete addition, the precipitate is filtered of, and the aqueous layer is extracted with EtOAc. The organic phase is washed with $Na_2S_2O_3$ and the solvent is removed under reduced pressure. Column chromatography gave 30 % 4-(2-Phenylquinazolin-4-yl)morpholine **190** as a solid.

4-(2-Phenylquinazolin-4-yl)morpholine (190)



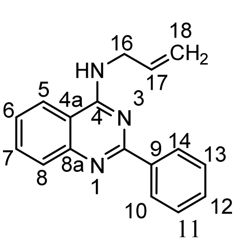
M.P.: 98–99°C; **^{1}H-NMR (400 MHz, CDCl3):** **δ** = 8.56 (dd, ^3J = 7.9 Hz, ^4J = 1.8 Hz, 2H, CH(10 + 14)), 8.02 (dd, ^3J = 8.5 Hz, ^4J = 1.3 Hz, 1H, CH(8)), 7.91 – 7.85 (m, 1H, CH(5)), 7.74 (ddd, ^3J = 8.4 Hz, ^3J = 6.9 Hz, ^4J = 1.4 Hz, 1H, CH(7)), 7.53–7.46 (m, 3H, CH(11 + 12 + 13)), 7.42 (ddd, ^3J = 8.2 Hz, ^3J = 6.9 Hz, ^4J = 1.2 Hz, 1H, CH(6)), 3.93-3.87 (m, 8H, CH_2(16 + 17 + 18 + 19)) ppm; **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 165.0 (C_{quart}(2)), 159.5 (C_{quart}(8a)), 152.8 (C_{quart}(4)), 138.5 (C_{quart}(9)), 132.7 (CH(7)), 130.4 (CH(12)), 129.3 (CH(8)), 128.5 (CH(11 + 13)), 128.5 (CH(10 + 14)), 125.2 (CH(6)), 124.7 (CH(5)), 115.4 (C_{quart}(4a)), 66.9 (CH_2(17 + 18)), 50.5 (CH_2(16 + 19)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3053 (w), 2982 (m), 2844 (m), 2211 (w), 1609 (m), 1559 (m), 1536 (s), 1498 (s), 1430 (s), 1349 (s), 1267 (s), 1252 (s), 1112 (s), 1065 (m), 1019 (s), 950 (s), 855 (m), 764 (s), 707 (s), 684 (s); **MS: (EI, 70 eV):** *m/z* (%) = 291 ([M]$^+$, 47), 290 (48), 260 (26), 246 (23), 234 (52), 233 (55), 207 (14), 206 (59), 205 (100), 104 (17), 103 (52), 102 (53), 86 (11), 77 (40), 76 (33), 75 (21), 56 (19), 51 (18), 29 (11); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{18}H_{17}N_3O$ 292.14444 ([M+H]$^+$), found 292.14492.

***N*-(*n*-Butyl)-2-phenylquinazolin-4-amine (191)**



The compound was synthesized following the procedure for (**190**), starting from 0.4 mmol (**172**) and 3.7 mmol *n*-butylamine, giving 96 % (**191)** as a solid, **M.P.:** 96–97°C; **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 8.58 (dd, ^3J = 7.5 Hz, ^4J = 2.1 Hz, 2H, CH (10 + 14)), 7.94 (dd, ^3J = 8.7 Hz, ^4J = 1.2 Hz, 1H, CH(8)), 7.73–7.67 (m, 2H, CH(5 + 7), 7.53–7.46 (m, 3H, CH(11 + 12 + 13)), 7.39 (ddd, ^3J = 8.1 Hz, ^3J = 7.0 Hz, ^4J = 1.2 Hz, 1H, CH(6)), 5.85 (s, 1H, NH), 3.80 (td, ^3J = 7.1 Hz, 3J = 5.5 Hz, 2H, CH$_2$(16)), 1.77 (m, 2H, CH$_2$(17)), 1.51 (m, 2H, CH$_2$(18)), 1.01 (t, ^3J = 7.3 Hz, 3H, CH$_3$) ppm; **^{13}C-NMR** (75 MHz, CDCl$_3$): δ = 160.6 (C$_{\text{quart}}$(2)), 159.7 (C$_{\text{quart}}$(8a)), 150.2 (C$_{\text{quart}}$(4)), 138.9 (C$_{\text{quart}}$(9)), 132.6 (CH(7)), 130.2 (CH(12)), 128.7 (CH(8)), 128.5 (CH(11 + 13)), 128.4 (CH(10 + 14)), 125.5 (CH(6)), 120.6 (CH(5)), 113.7 (C$_{\text{quart}}$(4a)), 41.2 (CH$_2$(16)), 31.6 (CH$_2$(17)), 20.4 (CH$_2$(18)), 14.1 (CH$_3$(19)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3340 (w), 3062 (w), 2954 (m), 2932 (m), 2865 (m), 1619 (w), 1567 (m), 1526 (m), 1458 (m), 1424 (m), 1364 (m), 1322 (m), 1258 (m), 1146 (m), 1091 (m), 1030 (m), 928 (m), 806 (m), 764 (s), 707 (s), 604 (m); **MS: (EI, 70 eV):** *m/z* (%) = 277 ([M]+, 32), 248 (45), 235 (29), 234 (25), 222 (22), 221 (100), 220 (14), 206 (31), 205 (94), 118 (14), 104 (19), 103 (26), 102 (32), 77 (44), 76 (23), 75 (12), 51 (15), 41 (30), 39 (14), 29 (21); **HRMS (ESI-TOF):** *m/z* = calcd. for $C_{18}H_{19}N_3$ 278.16517 ([M+H]$^+$), found 278.16527.

N-Allyl-2-phenylquinazolin-4-amine (192)



The compound was synthesized following the procedure for (**190**), starting from 0.4 mmol (**172**) and 3.7 mmol allylamine, giving 30 % (**192**) as a solid, **M.P.:** 114–115°C; **^{1}H-NMR (300 MHz, CDCl3):** δ = 8.58 (dd, ^3J = 7.7 Hz, ^4J = 2.1 Hz, 2H, CH(10 + 14)), 7.96 (dd, ^3J = 8.8 Hz, ^4J = 1.2 Hz, 1H, CH(8)), 7.76–7.69 (m, 2H, CH(5 + 7)), 7.52 – 7.45 (m, 3H, CH(11 + 12 + 13)), 7.41 (ddd, ^3J = 8.1 Hz, ^3J = 7.0 Hz, ^4J = 1.3 Hz, 1H, CH(6)), 6.11 (ddt, $^3J_{trans}$ = 17.1 Hz, $^3J_{cis}$ = 10.2 Hz, ^3J = 5.8 Hz, 1H, CH(17)), 5.89 (s, 1H, NH), 5.37 (dqdt, $^{3}J_{trans}$ = 17.1 Hz, ^{4}J = 1.6 Hz, 1H, CH$_2$(18)), 5.24 (dqdt, $^{3}J_{cis}$ = 10.2 Hz, ^{4}J = 1.4 Hz, 1H, CH$_2$(18), 4.45 (ttdt, ^{3}J = 5.7 Hz, ^{4}J = 1.5 Hz, 1H, CH$_2$(16)) ppm; **^{13}C-NMR (63 MHz, CDCl3):** δ = 160.5 (C$_{quart}$(2)), 159.5 (C$_{quart}$(8a)), 150.3 (C$_{quart}$(4)), 138.8 (C$_{quart}$(9)), 134.5 (CH(17)), 132.7 (CH(7)), 130.3 (CH(12)), 128.8 (CH(8)), 128.6 (CH(11 + 13)), 128.4 (CH(10 + 14)), 125.6 (CH(6)), 120.7 (CH(5)), 117.2 (CH$_2$(18)), 113.7 (C$_{quart}$(4a)), 43.9 (CH$_2$(16)) ppm; **IR (ATR, cm^{-1}):** $\tilde{\nu}$ = 3305 (w), 3067 (w), 2923 (w), 2850 (w), 1618 (w), 1561 (m), 1529 (m), 1436 (m), 1375 (m), 1323 (m), 1187 (m), 1068 (m), 997 (m), 926 (m), 767 (m), 707 (m), 576 (m), 542 (m), 433 (m); **MS (EI, 70 eV):** *m/z* (%) = 261 ([M]+, 54), 260 (100), 247 (14), 246 (74), 233 (18), 206 (19), 205 (39), 130 (18), 104 (20), 103 (26), 102 (18), 77 (24), 76 (15); **HRMS (ESI-TOF):** *m/z* = calcd. for C$_{17}$H$_{15}$N$_3$ 262.13387 ([M+H]$^+$), found 262.13406; **Elemental analysis:** Calcd. for C$_{17}$H$_{15}$N$_3$: C, 78.13; H, 5.79; N, 16.08; found: C, 78.18, H, 5.61, N, 15.67.

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