Synthesis of new calcineurin inhibitors via Pd-catalyzed cross-coupling reactions

Dissertation

zur Erlangung des akademischen Grades
doctor rerum naturalium
(Dr. rer. nat.)

im Fach Chemie
eingereicht an der

Mathematisch-Naturwissenschaftlichen Fakultät **I**
der Humboldt-Universität zu Berlin

vorgelegt von
M. Sc.-chem. Lunxiang Yin
geb. am 26.03.1966 in Anhui, V. R. China

Präsident der Humboldt-Universität zu Berlin
Prof. Dr. Jürgen Mlynek

Dekan der Mathematisch-Naturwissenschaftlichen Fäkultät I
Prof. Thomas Buckhout, Ph D

Gutachter: 1. Prof. Dr. Jürgen Liebscher
2. Prof. Dr. Gunter Fischer
3. PD. Dr. Habil. Rainer Mahrwald

Datum der mündlichen Prüfung: 09, 05, 2005

Promotionskommission:

Prof. Dr. Michael W. Linscheid, Institut für Chemie, HU Berlin (vorsitzender)

Prof. Dr. Jürgen Liebscher, Institut für Chemie, HU Berlin
Prof. Dr. Erhard Kemnitz, Institut für Chemie, HU Berlin
PD. Dr. habil. Rainer Mahrwald, Institut für Chemie, HU Berlin
Prof. Dr. Gunter Fischer, (MPG, Halle)

Abstracts

In the present thesis, I tried to vary the central nitrogen-heterocyclic cores, the functionalised side chains and its position of attachment. As a synthetic strategy, palladium-catalyzed coupling reactions were used to introduce side chains and aryl substituents into the central heterocycle. In this way the utility of such reactions to heterocyclic systems, which were neglected so far, could be figured out.

Halogen substituted diaryl heterocycles are important intermediates in the synthesis of general structures. The introduction of the desired side chains by Carbon-Carbon bond formation reactions was achieved by Sonogashira coupling and Heck coupling. Buchwald-Hartwig amination and nucleophilic substitution were used to establish side chains which are connected to the core heterocycle by heteroatom-Carbon bonds. Sonogashira reaction turned out to be the most effective and convenient method to introduce functionalized alkynyl group into the heterocyclic cores.

In the present work, more than 180 compounds were synthesized. Among them, about 130 compounds are new products. 86 of them fit into the general structure.

Keywords: calcineurin-inhibitor, diaryl heterocycles, palladium-catalyzed, cross-coupling, functionalised side chain, inhibiting activity, organic synthesis,

Zusammenfassung

In dieser Dissertation versuche ich, die zentralen Nitrogen-heterocyclischen Kerne, die Seitenketten und deren Position zu variieren. Als synthetische Strategie wurden Palladium-katalysierte Kupplungsreaktionen verwendet, um Seitenketten und Aryl-Substituenten einzuführen.

Halogensubstituierte Diarylheterocyclen sind wichtige Intermediate in der Synthese der allgemeine Strukture. Die Einführung der gewünschten Seitenketten durch Carbon-Carbon und Carbon-Nitrogen-Bindungsknüpfung wurde durch Sonogashira-Kupplung, Heck-Kupplung und Buchwald-Hartwig-Aminierung erzielt. Mit der Sonogashira-Reaktion kann eine funktionalisierte Alkynylgruppe in die heterocyclischen Kerne effektiv und bequem eingeführt werden. Eine anschliessende katalytische Hydrierung der Alkynylgruppe führt zu funktionalisierten Alkyl substituierten Diarylheterocyclen.

In der vorliegenden Arbeit wurden mehr als 180 Substanzen synthetisiert. Unter ihnen sind ungefähr 130 neue Substanzen. 86 von ihnen passen in die allgemeine Strukture.

Schlagwörtern: calcineurine-Inhibitor, Heterocyclen, Palladium-katalysierte, cross-Kuplung, funktionalisierte Seitenketten, inhibitiertung Aktivität, organische Synthese

Die vorliegende Arbeit entstand auf Vorschlag und unter Anleitung von Herrn Prof. Dr. Jürgen Liebscher in der Zeit von Okt. 2001 bis Dez. 2004 am Institut für Organische und Bioorganische Chemie der Humboldt-Universität zu Berlin.

Herrn Prof. Dr. J. Liebscher danke ich für die vielen wertvollen Anregungen und Ratschläge, seine ständige Diskussionsbereitschaft sowie für den großen Freiraum, den er mir bei der Gestaltung und Durchführung dieser Arbeit gewährte.

Weiterhin gilt mein Dank allen, die zum Gelingen dieser Arbeit beigetragen haben:

■ Meinen Kolleginnen und Kollegen (Dr. Hamann, Dr. Leistner, Dr.Pätzel, Frau Brosche, Frau Brauer, Frau Werner, Daniela, Oxala, Christoph, Magda, Wolfgang, etc.) für viele hilfreiche Diskussionen und die gute Zusammenarbeit.

■ Frau A. Thiesis und Herrn W. D. Bloedorn für die stets rasche Anfertigung von NMR-Specktren.
■ Frau U. Kätel und Herrn Dr. U. Hartmann für die Anfertigung der Elementaranalyse.
■ Frau. A. Woyda und Herrn Dr. M. Löwis für die Anfertigung der Massenspektren.
■ Prof. Dr. Fischer (MPG Halle) für viele hilfreiche Diskussion und die Bestimmung der calcineurin-inhibierenden Wirkung unser Substenzen.

■ Meinen chinesischen Freundinnen und Freunden (Lijun, Zhijian, Yanqin, Luxia, Lisong, Zhongyang, Xufei, Xiaojun, etw.) für viele hilfreiche Diskussionen und unsere Freundschaft.

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Abbreviations

Ac	acetyl
AIBN	α, α'-Azobisisobutyronitrile
Ar	aryl or aromatic
Ar	argon
9-BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	t-butyloxycarbonyl
b.p.	boiling point
n-Bu	n-butyl
t-Bu	*tert*-butyl
°C	degrees celsius
Cbz	carbobenzyloxy
CC	column chromatography
4-ClPh (*p*-ClPh)	4-chlorophenyl
d	day
dba	dibenzylideneacetone
DCM	dichloromethane
DMA	N,N-dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
EA	elemental analysis
equiv	equivalent
Et	ethyl
h	hour
HRMS	high resolution mass spectrometry

HMBC	heteronuclear multiple bond coherence
HMPA	hexamethylphosphoric triamide
HMQC	heteronuclear multiple quantum coherence
HOAc	acetic acid
HPLC	high-pressure liquid chromatography
LDA	lithium diisopropylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidine
Me	methyl
m.p.	melting point
MS	mass spectrometry
NBS	N-bromosuccinimide
NDP	no definite product
NIS	N-iodosuccinimide
NMP	1-methyl-2-pyrrolidinone
NOE	the nuclear Oberhauser effect
NPhth	phthalimido (1,3-dioxo-1,3-dihydro-isoindol-2-yl)
Nu	nucleophile
Ph	phenyl
Pr	propyl
i-Pr	iso-propyl
Py	pyridine
R	Alkyl etc.
RT	room temperature
TBAB	tetrabutylammonium bromide
TEA	triethylamine
Tf	Trifluromethyanesulfonyl (triflyl)
THF	Tetrahydrofuran
THP	tetrahydropyran
TLC	thin-layer chromatography
TMS	Tetramethylsilane
o-Tol	*o*-tolyl
Tr	Triphenylmethyl
Ts	p-toluenesulfonyl

Chapter 1: Introduction

1.1 Background of the project

1.1.1 Calcineurin and its physiological roles

Calcineurin (CaN) is a serine/threonine protein phosphatase [1-5], activated by calcium and the calmodulin-calcium complex. CaN was first purified from bovine brain, where it was found in high concentrations in neurons (over 1 % of total protein in brain). CaN is widely distributed in mammalian tissues and plants. There are two kinds of calcineurins: calcineurin A and calcineurin B.

Calcineurin activity [6] is necessary for the synthesis of several cytokine genes through the dephosphorylation of a family of transcription factors known as NF-AT (nuclear factor of activated T cells). By inhibiting calcineurin activity, cyclosporin A (CsA) and FK506 prevent the nuclear translocation of NF-AT secondary to dephosphorylation, thereby suppressing T cell activation.

Calcineurin has numerous physiological roles in budding yeast including recovery from α-factor-induced growth arrest, salt and temperature tolerance, Ca^{2+} homeostasis, and Mn^{2+} tolerance. In addition, calcineurin inhibits the activity of the vacuolar H^{+}/Ca^{2+} exchanger and causes conversion of the K^{+} channel to the high-affinity state.

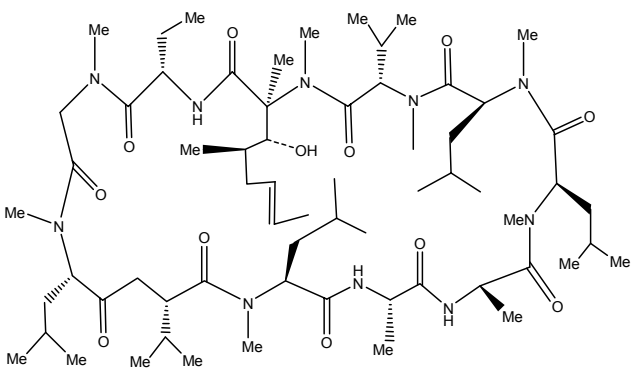
1.1.2 Inhibitors of calcineurin

Calcineurin inhibitors [3, 6-12], which specifically inhibit T-cell activation, are essential for T-cell activation and proliferation. They are very important for the activities of cells, metabolism and the health of humans. In order to cure a series of diseases (heart diseases, skin diseases, etc.) caused by lacking calcineurin inhibitors, many synthetic chemists and medicinal chemists are interested in developing new calcineurin inhibitors.

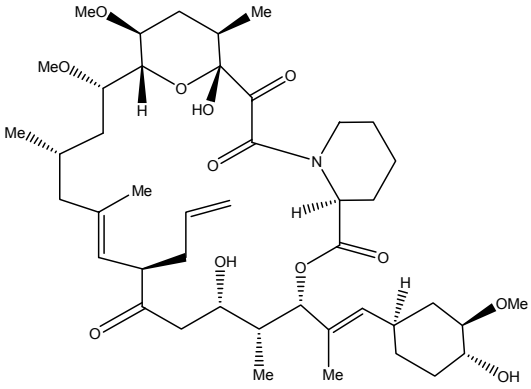
(1) Natural calcineurin inhibitors

A number of natural cyclic peptides have been isolated and demonstrated to be inhibitors of calcineurin and other serine/threonine protein phosphatases. The most potent, specific and well-known inhibitor of calcineurin is the immuno-suppressant drug, cyclosporin A. Other cyclic peptides, for example, microcystin LR, AKAP79 (A-kinase-anchoring-protein 79), and FKBP12, are also useful inhibitors of calcineurin.

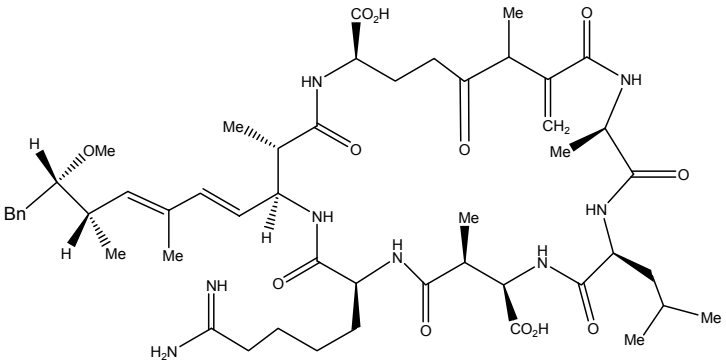
A few non-peptide natural products also have inhibitory activities against calcineurins and other serine/threonine protein phosphatases, such as FK506, okadaic acid, and dibefurin. Some known natural calcineurin inhibitors are shown in **Figure 1.1**.



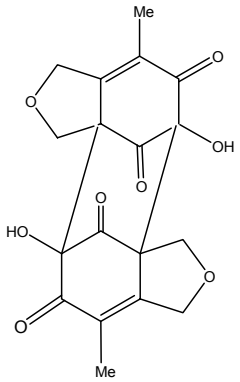
Cyclosporin A



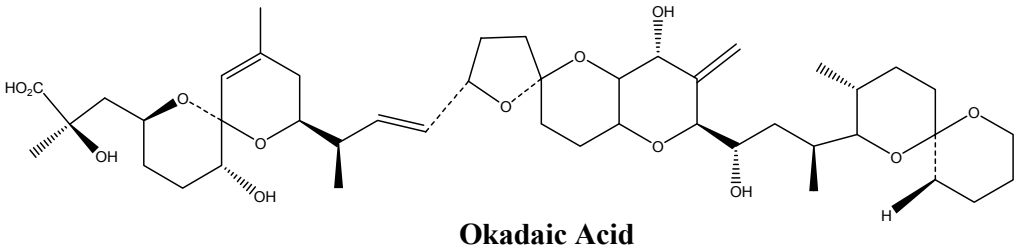
FK506



Microcystin LR



Dibefurin

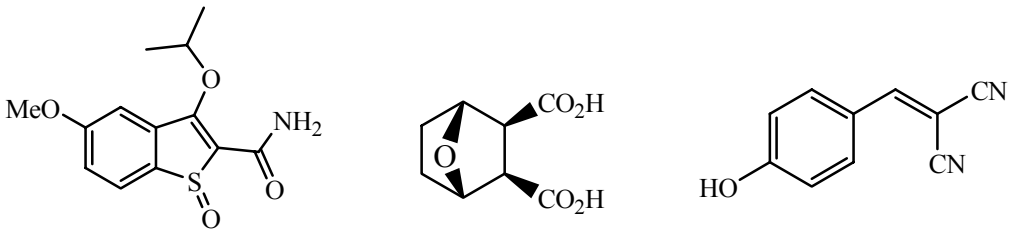


Okadaic Acid

Figure 1.1 Natural product inhibitors of calcineurin

(2) Synthetic calcineurin inhibitors

Several synthetic compounds have been found to be reasonable inhibitors of calcineurin and other phosphatases. They are, *exo*-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid (an endothal derivative), a variety of alkylphosphonic acid derivatives containing an additional thiol or carboxylate group, tyrphostin A8 and PD 144795 (a benzothiophene derivative). Some of the known synthetic inhibitors of calcineurin are shown in **Figure 1.2**.



PD 144795 **Endothal derivative** **Tyrphostin A8**

Figure 1.2 Synthetic inhibitors of calcineurin

(3) Necessity to develop new non-peptidic calcineurine inhibitors

So far, the most important calcineurin inhibitors are from natural origin (natural peptidic calcineurin inhibitors). Peptidic drugs normally cause the problem of easy *in vivo* hydrolysis and short live time. The immunosuppressive currently used results in a number of unwanted side effects, such as neurotoxicity, nephrotoxicity and carcinogenity [1]. The known synthetic calcineurin inhibitors usually have poor inhibiting activities. Therefore, there is a high need to develop better calcineurine inhibitors, in particular to non-peptidic compounds.

1.1.3 Our research background

On the basis of previous work in our group [13-16], we try to develop a series of special calcineurin inhibitors, which have better inhibiting power or higher selectivity than the known calcineurin inhibitors. These inhibitors will represent a guidance structure for new immune suppressive drug with lower side effect.

For this purpose, an assembly of three aromatic systems and an aminoalkyl unbranched chain was developed as the guidance structure (**Figure 1.3**). The polar central heteroaromatic ring is hydrophilic, and always flanked by two typically hydrophobic aromatic rings and a saturated unbranched side chain. The side chain is terminated by a hydrophilic functional group. The results of this thesis will help to refine our structural model of calcineurin-inhibiting heterocycles.

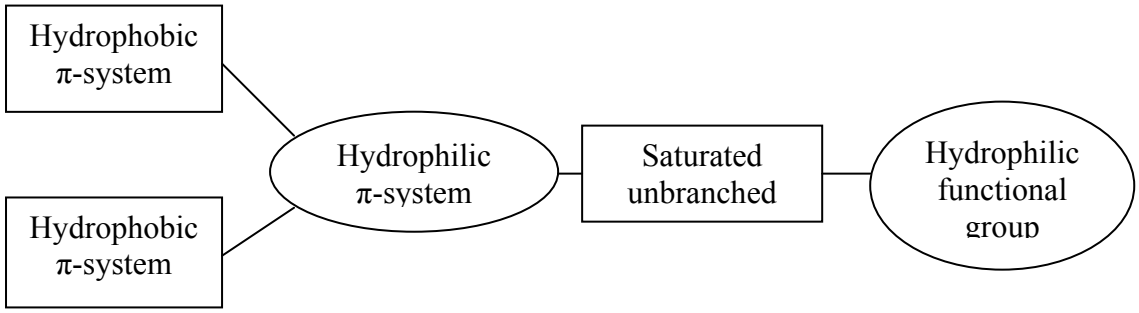
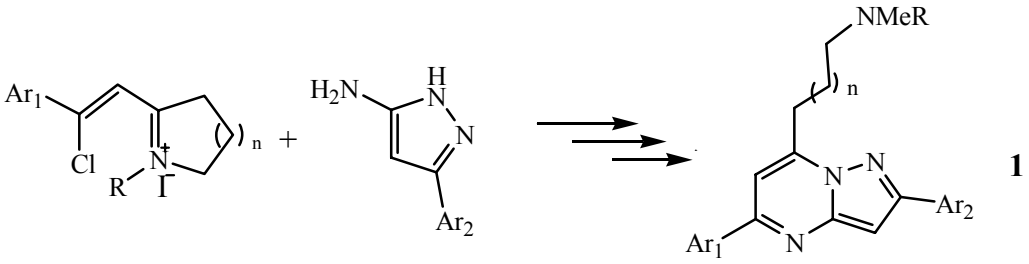


Figure 1.3 The generic structural component of guiding structure

In this guidance structure, the polar hydrophilic π-systems are normally nitrogen containing heterocycles, the two hydrophobic π-systems are unsubstituted or substituted aromatic systems or arylvinyl systems, but not polar heteroaromatic systems. The terminal hydrophilic functional groups are unsubstituted and substituted amino groups, hydroxy group, etc.

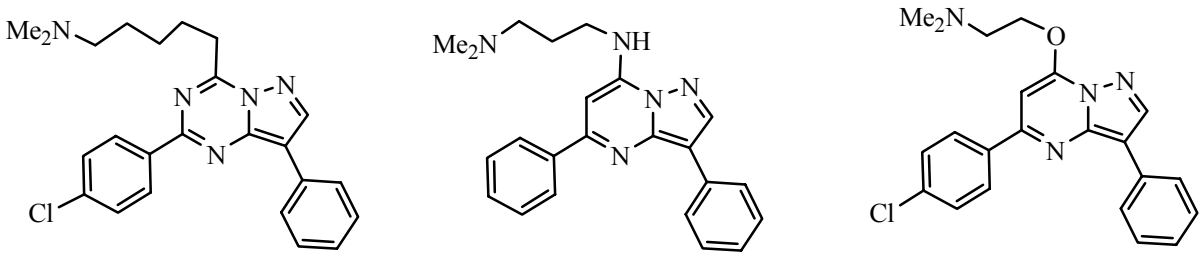
So far, only a few structural types of this kind are known. The ring-chain-transformation-synthesis concept, developed by us [16a] represents an efficient entrance to such structures and provided access to pyrazolo[1,5-a]pyrimidines and other heterocyclic derivatives with aminoalkyl substituents in 7-position. (**Scheme 1.1**)



Scheme 1.1 Synthesis of pyrazolo[1,5-a]pyrimidines by ring-chain-transformation

Some structural examples with high activity of calcineurin inhibitor are successfully synthesized by our group [16], using ring-chain-transformation and other synthetic routes. They are either bicyclic heterocycles (**Figure 1.4**) or monocyclic heterocycles (**Figure 1.5**).

Bicyclic heterocycles:



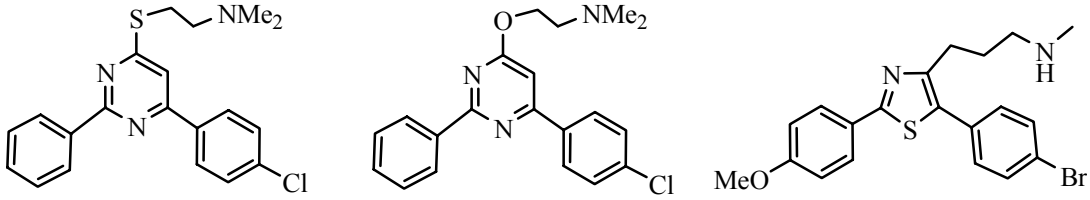
2 Lie-1476
IC_{50} = 1.5 µM

3 Lie-1330
IC_{50} = 7.5 µM

4 Lie1412
IC_{50} = 2.0 µM

Figure 1.4 Potent bicyclic heterocyclic inhibitors

Monocyclic heterocycles:



5 Lie-1396
IC_{50} = 6.0 μM

6 Lie-1393
IC_{50} = 14.0 μM

7 Lie-1427
IC_{50} = 18 μM

Figure 1.5 Potent monocyclic heterocyclic inhibitors

These known examples are limited to pyrazolo[1,5-a]triazines, pyrazolo[1,5-a]pyrimidines, pyrimidines, triazines and thiazoles as the core heterocycles.

1.2 Target molecules and synthetic strategies

1.2.1 Synthetic target molecules

According to the analysis and discussion above, a synthetic target molecular model of non-peptide calcineurin inhibitors are designed as below (**Figure 1.6**). The general structure **8** will be followed up in the present work.

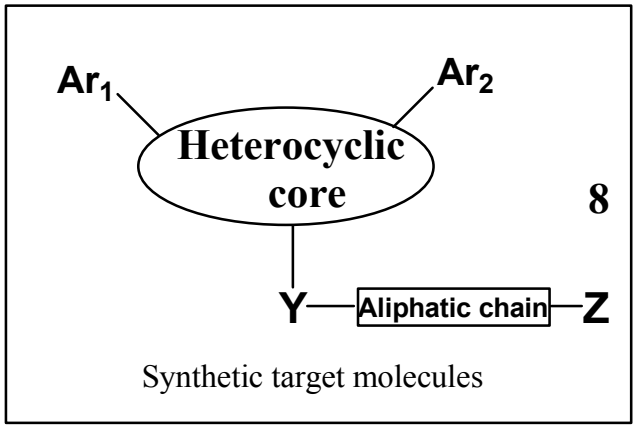


Figure 1.6 Synthetic target molecules

The following variation of structural parameters is envisaged:

Ar_1, Ar_2: phenyl, substituted phenyl, pyridyl, and other aromatic group.

Y: CH_2, CH=CH, C≡C, C=O, CH_2NH, CH(OH), NH, NR, O, S.

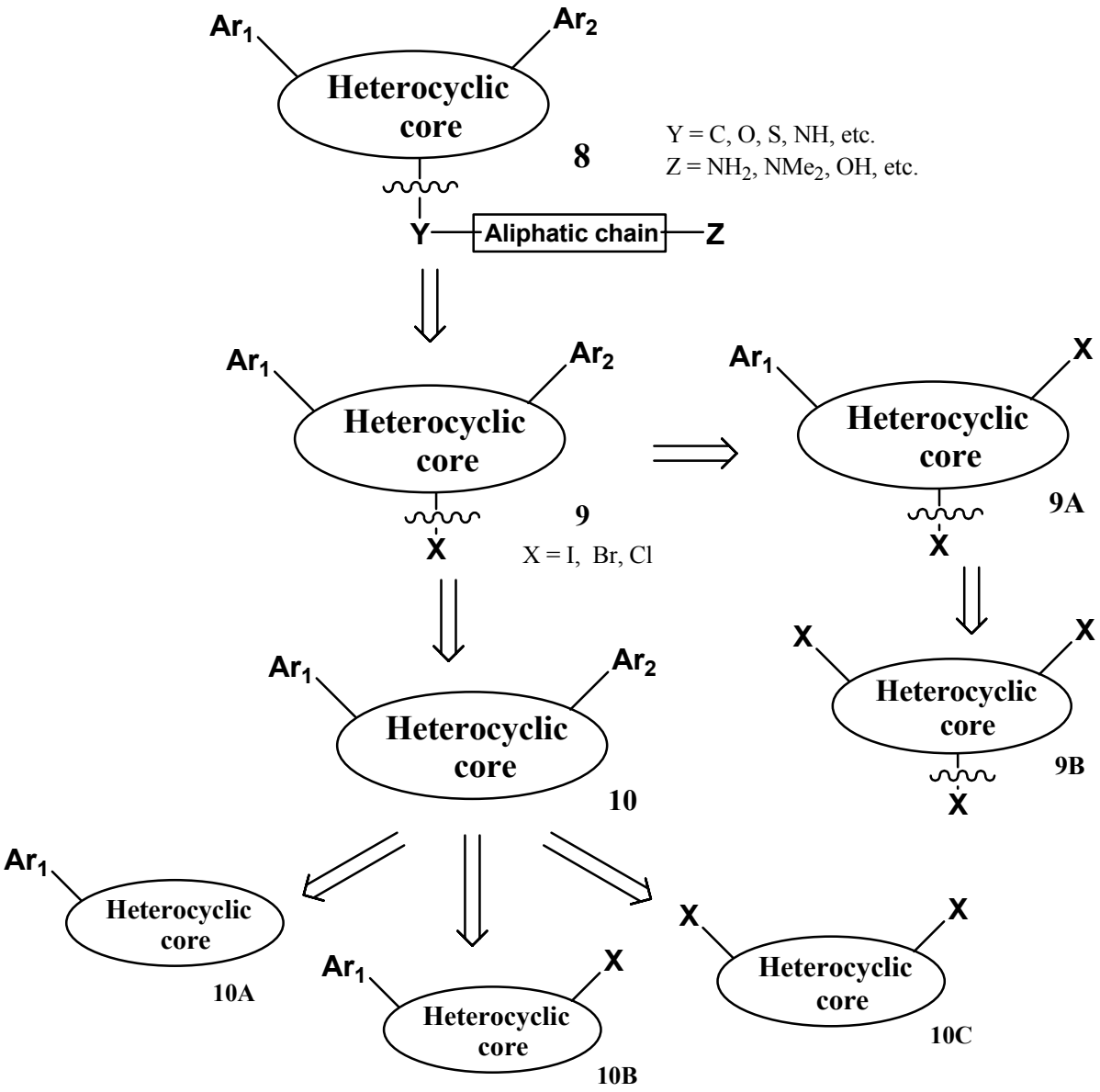
Z: NH_2, NHR, NR_1R_2, OH, OR, CO_2R,CN, $CONH_2$, $CONR_2$, etc.

Aliphatic-chain: unbranched chain (saturated or unsaturated chain) with 2 to 5 carbon atoms.

Heterocyclic cores: mono-, or bicyclic nitrogen-containing heterocycles, such as pyrazolo[1,5-a]pyrimidine, purine, pyrido[2,3-b]pyrazine, imidazo[1,2-a]pyridine, pyrimidine, pyridine, pyrazine, oxazole, pyrazole, imidazole.

1.2.2 Disconnection of target molecules

The desired target molecules can be retrosynthetically disconnected as follow:



Scheme 1.2 Disconnection of target molecules

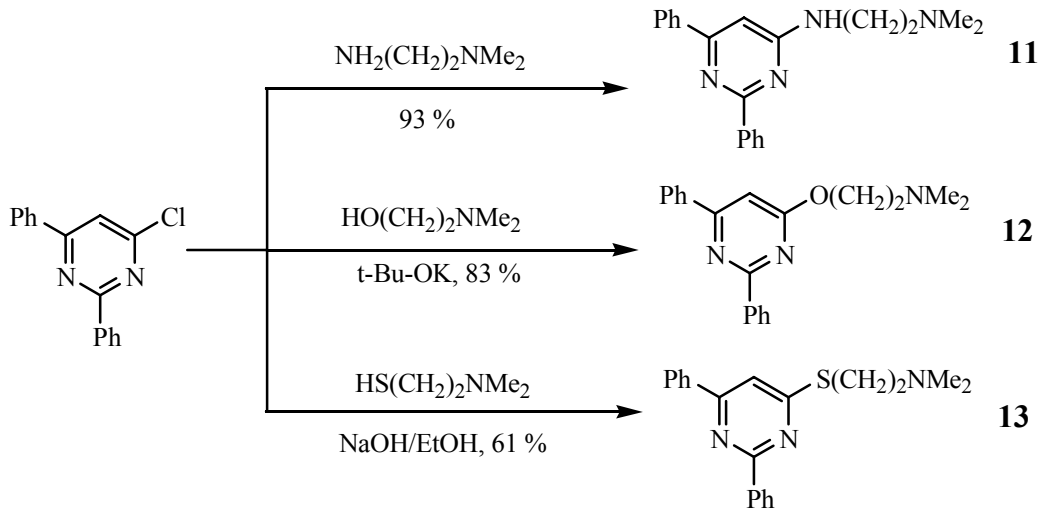
1.2.3 Synthetic strategies for target molecules

The chemo-, regio-, stereoselective formation of new carbon-carbon (carbon-oxygen or carbon-nitrogen) bonds is our major goal.

At first, we synthesized a series of heterocyclic ring cores, and introduced one or more leaving groups X (I, Br, Cl) into the heterocyclic cores, then one or two aryl groups were introduced. In the last and most important step, the side chains were introduced into the heterocycles.

Introducing the ***Y-aliphatic-chain-Z*** chain into diarylheterocycle is the key step of our project. In order to introduce the ***Y-aliphatic-chain-Z*** into the heterocyclic cores**,** there are two main methods. One way is using nucleophlic substitution, and the other one is using Pd-catalyzed cross-coupling reactions.

Classic nucleophilic substitution is used for active electron deficient halo-heterocycles. For example, the nucleophilic substitution of 4-chloro-2,6-diphenylpyrimidine [17] is shown in **Scheme 1.3**:



Scheme 1.3 Introducing branch chains by nucleophilic substitution

The transition metal catalyzed cross-coupling reactions, which were developed starting from the 1970s, are extensively used for the formation of C-C bonds, C-N bonds, C-O bonds and C-P bonds. Among them, the most important are Pd-catalyzed cross-coupling reactions. This is a good way to introduce aryl group as well as aliphatic groups into carbocyclic arenes or heteroarenes.

1.3 Pd-catalyzed cross-coupling of heterocycles

Palladium was discovered by W. H. Wollaston in 1803. It is known for its ability to absorb large amounts of hydrogen gas (up to 900 times of its own volume of H_2 at room temperature), which led to one of its earliest chemical uses, as a hydrogenation catalyst. In the last few decades, palladium compounds have been used as catalyst to develop many new synthetic transformations, such as carbon-carbon and carbon-heteroatom coupling reactions (e.g., by Buchwald-Hartwig, Heck, Suzuki-Miyaura, Kumada, Negishi, Nozaki-Hiyama, Sonogashira, Stille, and Tsuji-Trost) [18-23]. The Pd-catalyzed cross-coupling reactions gained increasing popularity amongst pharmaceutical chemists as they are generally tolerant of a wide-range of functional groups and therefore can be used for the synthesis of complicated molecules.

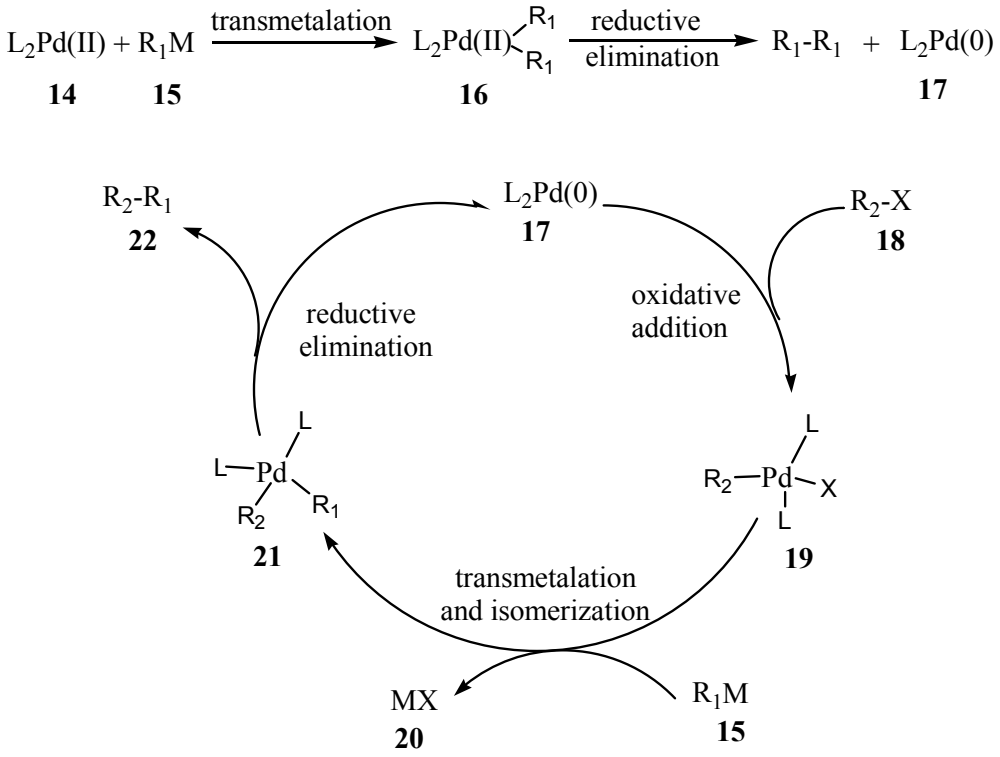
1.3.1. Overview of relevant Pd-catalyzed cross-coupling

1.3.1.1 Cross-coupling reactions with organometallic reagents

Palladium-catalyzed cross-coupling reactions of organohalides (organotriflates, etc.) with organometallic reagents follow a general mechanistic cycle. The $L_2Pd(0)$ **17**, as a 14-electron structure [the active catalyst PdL is 12 electron when $P(o\text{-}tol)_3$ is used as the ligand] is sometimes reduced from a Pd(II) species **14** by an organometallic reagent R_1M **15**. The transmetalation product **16** from **14** and **15** undergoes a reductive elimination step, giving rise to the Pd(0) species **17**, along with the homocoupling product R_1-R_1. This is one of the reasons why the organometallic coupling partners are often used in a slight excess relative to the electrophilic partners. When the Pd(0) catalyst **17** is generated, the catalytic cycle goes through a three-step sequence. (a) Electrophile R_2-X **18** undergoes an oxidative addition step to Pd(0) to afford a 16-electron Pd(II) intermediate **19**. (b) Subsequently, **19** undergoes a transmetalation and isomerisation step with the organometallic reagent R_1M **15** to produce the intermediate **21**. When there is more than one group attached to the metal M, such as with Sn, the order of transmetalation for different substituents is:

alkynyl > vinyl > aryl > allyl ~ benzyl >> alkyl

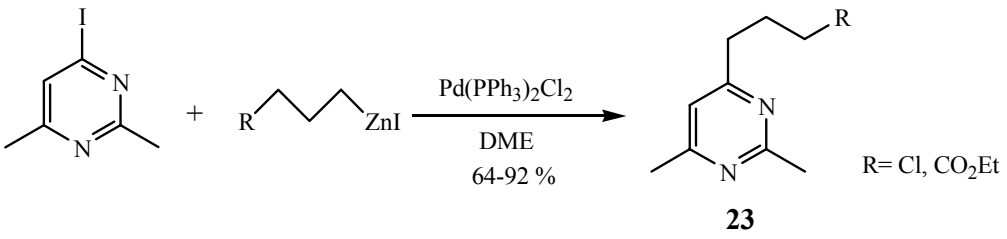
The transmetalation step, often rate-limiting, is the step to which attention should be directed if the reaction goes awry. (c) Finally, with appropriate *syn* geometry, intermediate **21** undergoes a reductive elimination step to produce the coupling product R_2—R_1 **22**, regenerating the palladium (0) catalyst **17** to close the catalytic cycle (**Scheme 1.4**).



Scheme 1.4 Catalytic cycle of coupling reactions of organometallic reagents

(1) Negishi coupling

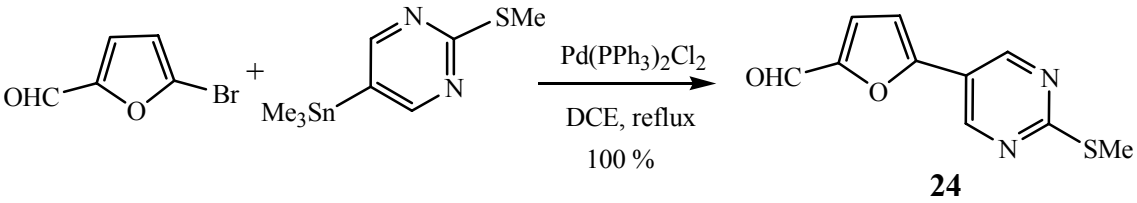
The Negishi reaction is the Pd-catalyzed cross-coupling between organozinc reagents and organohalides (or triflates) [24-26], for an example [27] see **Scheme 1.5**. It is compatible with many functional groups including ketones, esters, amine and nitriles. Organozinc reagents are usually generated and used *in situ* by transmetalation of Grignard or organolithium reagents with $ZnCl_2$. In addition, some organo halides can be oxidatively added to Zn (0) to give the corresponding organozinc reagents. The Negishi coupling is often advantageous over other cross-coupling, because organozinc reagents have a high tolerance of functional groups.



Scheme 1.5 Example of the Negishi coupling reaction

(2) The Stille coupling

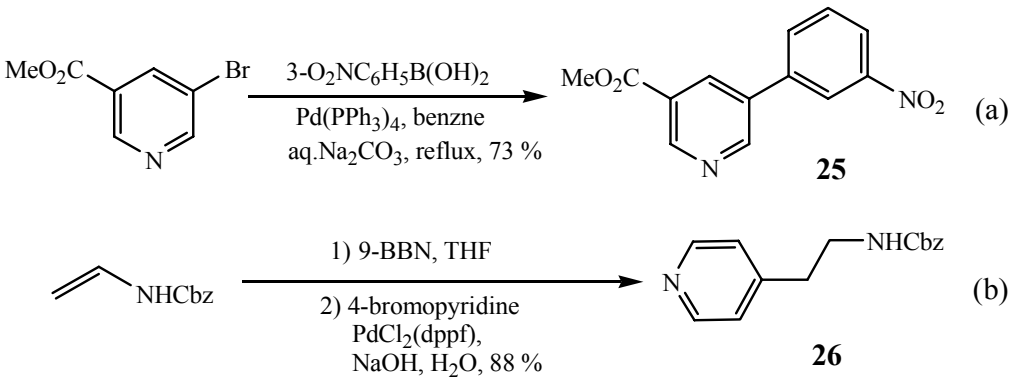
The Stille coupling is the Pd-catalyzed cross-coupling between an organostannane and an electrophile to form a new C-C single bond [28-30], for an example [31] see **Scheme 1.6**. This is regarded as one the most versatile methods in Pd-catalyzed cross-coupling reactions with organometallic reagents for two reasons. First, the organostannanes are readily prepared, purified and stored. Second, the conditions of the Stille reaction tolerate a wide variety of functional groups. In contrast to the Suzuki, Kumada, Heck, and Sonogashira reactions which are run under basic conditions, the Stille reaction can be run under neutral conditions. The pitfall of the Stille reaction is the toxicity of stannanes, making it not suitable for large-scale synthesis or the synthesis of pharmaceutical products.



Scheme 1.6 Examples of the Stille coupling reactions

(3) The Suzuki coupling

The Suzuki reaction is the Pd-catalyzed cross-coupling between organoboron reagents and organohalides (or triflates) [32-34], some examples [35, 36] are shown in **Scheme 1.7** .



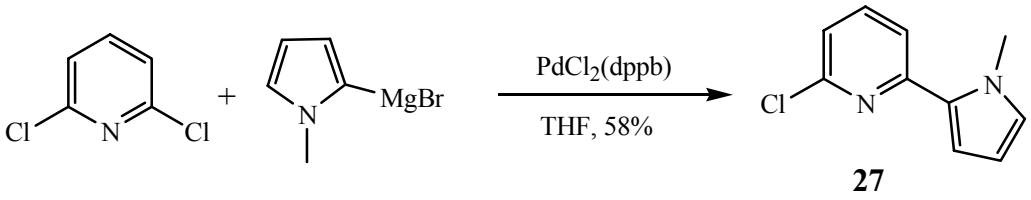
Scheme 1.7 Example of the Suzuki coupling reactions

In comparison to the abundance of heterarylstannanes, heteroarylboron reagents are not as prevalent. There are major reasons why one should consider the Suzuki coupling when designing a Pd-catalyzed reaction in heteroaryl synthesis. First, a growing number of

heteroarylboron reagents are known now. Second, judiciously designing the coupling partners will enable the use of a heteroaryl halide to couple with a known organoboron reagent for the use of certain molecules. Third, there is no toxicity issue involved in organoboron reagents. Therefore, Suzuki reaction is a more attractive choice in carbon-carbon bond formation reactions.

(4). The Kumada coupling

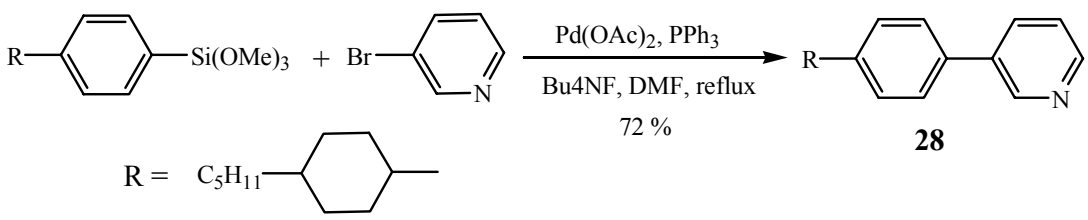
The Kumada coupling represents the Pd-catalyzed cross-copling of a Grignard reagent with an electrophile such as an alkenyl-, aryl-, and heteroaryl halide or triflate [37-39], for an example [40] see **Scheme 1.8**. The advantage of this reaction is that numerous Grignard reagents are commercially available. Those that are not commercially available may be readily prepared from the corresponding halides. Another advantage is that the reaction can often be run at room temperature or lower. A drawback of this method is the intolerance of many functional groups (such as –OH, -NH_2, -C=O, etc.) by the Grignard reagents.



Scheme 1.8 Example of the Kumada coupling reaction

(5) The Hiyama coupling

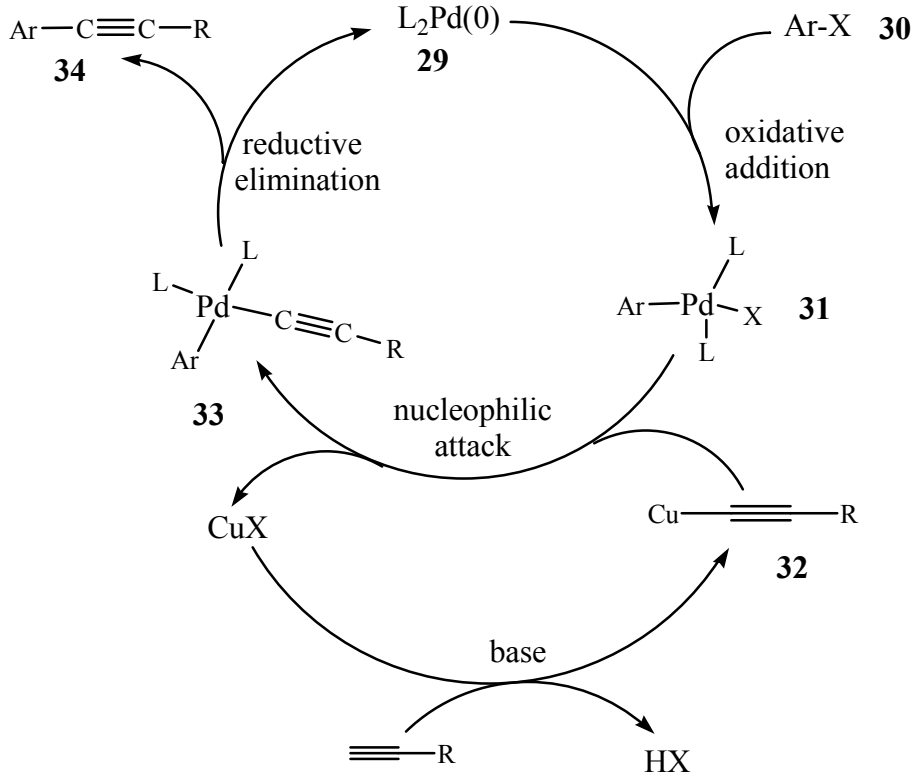
The Hiyama coupling is the Pd-catalyzed cross-copling of an organosilicon reagent (activated by F or alkyloxy) with organohalides (or triflates) [41-42], for an example [43] see **Scheme 1.9**. One of the advantages of the Hiyama coupling is that organosilicon reagents are innocuous. Another advantage is the better tolerance of functional groups in comparison to other strong nucleophilic organometallic reagents.



Scheme 1.9 Example of the Hiyama coupling reaction

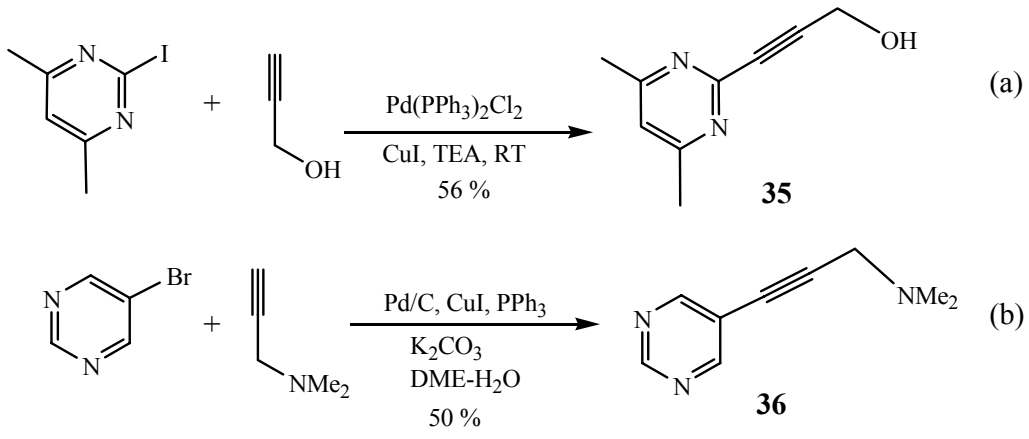
1.3.1.2 The Sonogashira reaction

The Sonogashira reaction is the palladium-catalyzed cross-coupling reaction between terminal alkynes with aryl and vinyl halides in the presence of an aliphatic amine or inorganic base under mild conditions [44-46]. The proposed catalytic cycle is shown in **Scheme 1.10**:



Scheme 1.10 Catalytic cycle of the Sonogashira coupling

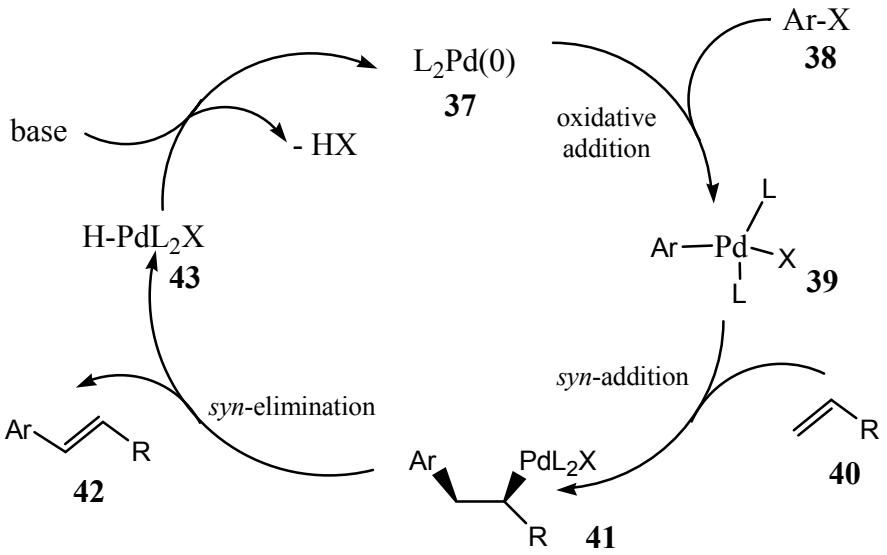
Some examples [47, 48], which are also interesting with respect to this thesis are shown in **Scheme 1.11**:



Scheme 1.11 Examples of the Sonogashira coupling reactions

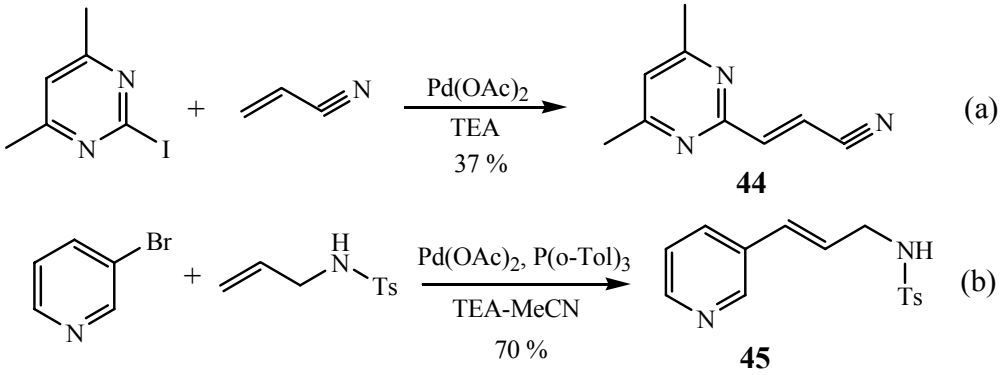
1.3.1.3 The Heck reaction

The Heck reaction is the palladium-catalyzed cross-coupling reaction of organohalides (or triflates) and olefins [49-51]. Nowadays it has become an indispensable tool for organic synthesis. The proposed catalytic cycle is shown in **Scheme 1.10**:



Scheme 1.12 Catalytic cycle of the Heck coupling

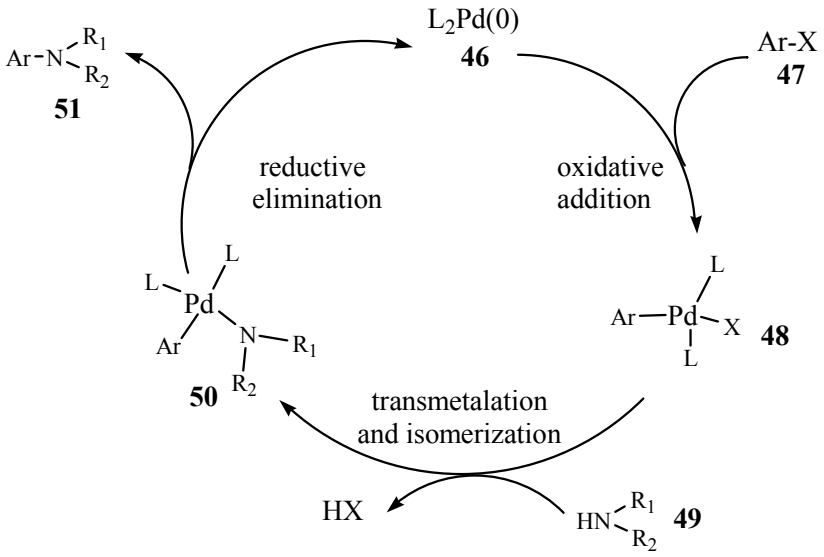
Some useful known examples [52, 53], where side chain with terminal N-atom were introduced are shown in **Scheme 1.11**:



Scheme 1.13 Examples of the Heck coupling reaction

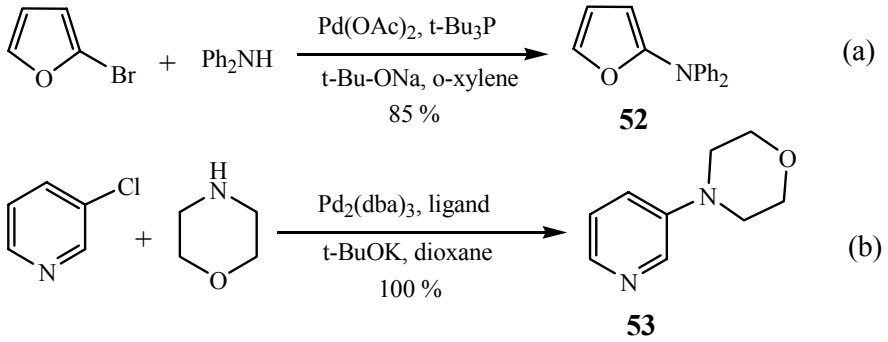
1.3.1.4 The Buchwald-Hartwig C-N bond formation

The direct Pd-catalyzed C-N bond formations of aryl halides with amines were discovered by Buchwald and Hartwig independently in 1995 [54, 55]. $Pd(OAc)_2$ or $Pd_2(dba)_3$ was often chosen as catalyst, and t-Bu_3P, BINAP, or other bulky phosphorous compound was used as ligand. It is an effective way to introduce substituted amino groups into aromatic rings. The proposed catalytic cycle is shown in **Scheme 1.14:**



Scheme 1.14 Catalytic cycle of the Buchwald-Hartwig amination

Some useful examples [56, 57] are shown in **Scheme 1.15**:



Scheme 1.15 Examples of the Buchwald-Hartwig amination

1.3.2 Pd-catalyzed cross-coupling reactions of heterocycles

1.3.2.1 The characteristics and importance of Pd-catalyzed cross-coupling reactions of heterocycles

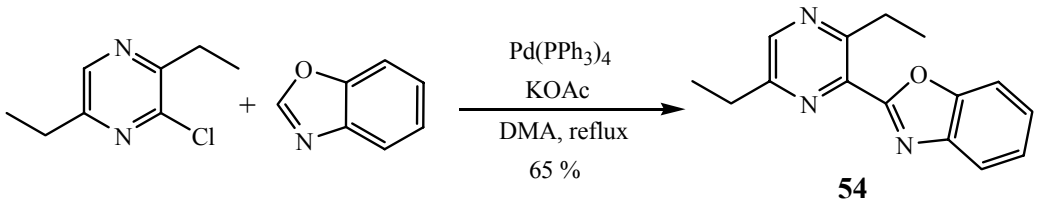
The applications, in which the palladium chemistry is used for the synthesis of heterocycles, have increased exponentially. Several review articles summarize the development of palladium chemistry in the synthesis of heterocyclic products [58-62]. The importance of these reactions is shown below:

(1) A myriad of heterocycles are biologically active and therefore of paramount importance to medicinal and agricultural chemists. Many heterocycle-containing natural products have elicited great interest from both academic and industrial research groups. Today palladium-catalyzed cross-coupling reaction is the common method to the synthesis of a wide range of fine chemicals, pharmaceutical intermediates and active pharmaceutical ingredients.

In addition, palladium-mediated polymerisation of heterocycles is extensively used in material chemistry. Heterocycles are also important as ligands in coordination chemistry of palladium

(2) Palladium chemistry involving heterocycles has its unique characteristics stemming from the heterocycles' inherently structural and electronic properties in comparison with the corresponding carbocyclic aryl compounds.

One example illustrating the striking difference in reactivity between a heteroarene and a carbocyclic arene is called "heteroaryl Heck reaction", which is defined as an intermolecular or intramolecular Heck reaction occurring onto heteroaryl recipient. Intermolecular Heck reaction of carbocyclic arenes as the recipients are rare, whereas heterocycles including thiophenes, furans, thiazoles, oxozoles, imidazoles, pyrroles and indoles, etc. are excellent substrates. For instance, the heteroaryl Heck reaction of 2-chloro-3,6-diethylpyrazine and benzoxazole occurred at the C(2) position of benzoxazole to elaborate the pyrazinylbenzoxazole **54** [63] (**Scheme1.16**).



54

Scheme 1.16 Intermolecular heteroaryl Heck reaction

The second salient feature of heterocycles is the marked activation at position α- and γ- to the heteroatom. For N-containing 6-membered heterocycles, the presence of N-atom polarizes the aromatic ring, thereby activating α and γ positions, making them more prone to nucleophilic attack. The order of S_NAr displacement of heteroaryl halides with EtO^- is:

4-chloropyrimidine	> 2-chloroquinoline	> 2-chloropyridine	>> chlorobenzene
7×10^5	3×10^2	1	

There is certain similarity in the order of the reactivities between S_NAr displacement reactions and oxidative additions in palladium chemistry. Therefore, the ease with which the oxidative addition occurs for these heteroaryl chlorides has a comparable trend. Even α- and γ-chloro-N-heterocycles are sufficiently activated for Pd-catalyzed reactions, whereas chlorobenzene requires sterically hindered, electron-rich phosphine ligands.

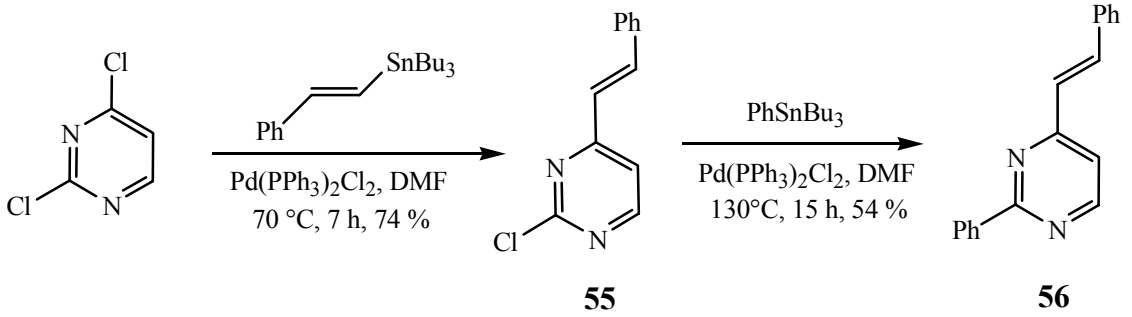
As a consequence of α and γ activation of di- or trihaloheterocycle, Pd-catalyzed chemistry may take place regioselectively at the more activated position. This phenomenon is rarely seen in carbocyclic analogues.

1.3.2.2. Regioselective Pd-catalyzed cross-coupling of heterocycles

Regioselectivity of reactions are very interesting and also very important in organic synthesis, especially in the synthesis of heterocycles. In this way, a functional group can be introduced to the desired position of a substrate. There are a lot of regioselective reactions involving Pd-catalyzed cross-coupling of heterocycles.

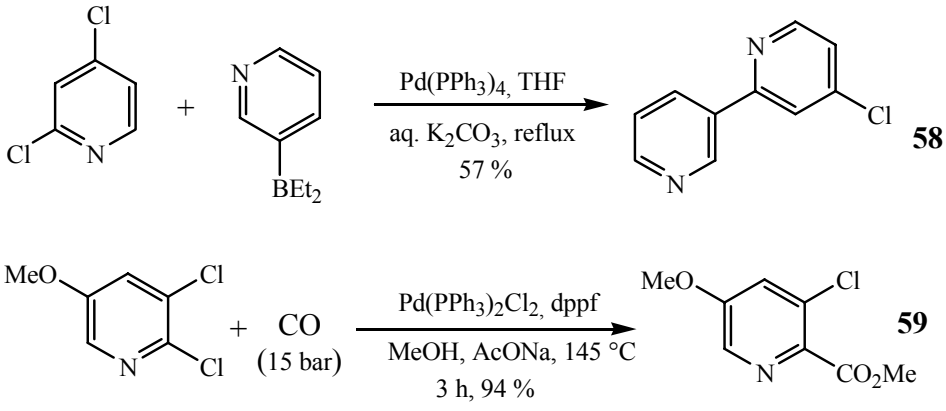
In polyhalo-pyrimidines, the 4-position is more active than 2-position, allowing regiospecific Pd-catalyzed coupling at 4-position. The reaction of 2,4-dichloropyrimidine and styrylstannane first preceeded regiospecifically at C(4), giving rise to **55**, which was

subsequently coupled with phenylstannane at C(2), under more forcing conditions to afford disubstituted pyrimidine **56** [64].



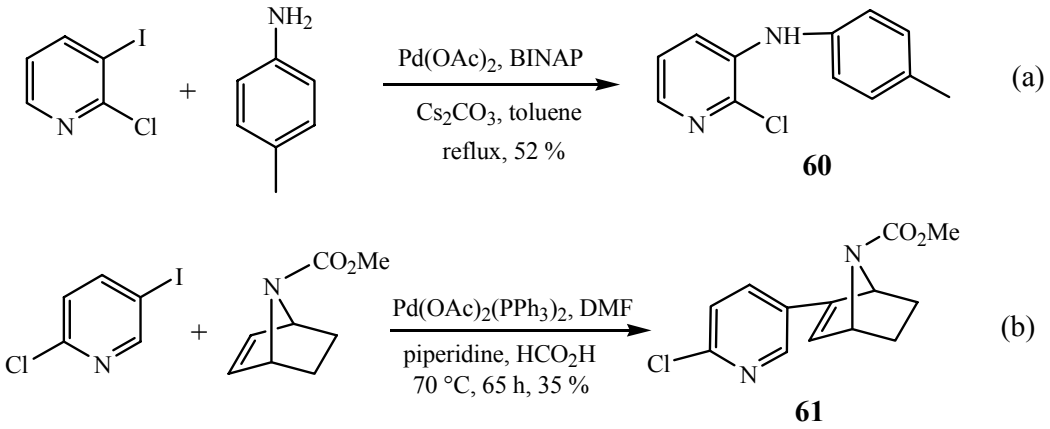
Scheme 1.17 Synthesis of 2,4-disubstituted pyrimidine

In Pd-catalyzed cross-coupling of polyhalopyridines, the 2-position is more active than 4-position and 3-position. For example, the Suzuki reaction of 2,4-dichloropyridine [65] and the carbonylation reaction of 2,3-dichloro-5-methoxypyridine occurred regioselectively at 2-position [66].



Scheme 1.18 Regioselective Pd-catalyzed cross-couplings of polyhalopyridine

The positional preference can be overridden by choosing different leaving groups. Thus, the iodo-substituted position is more active than the chloro-substituted position. When 2-chloro-3-iodopyridine reacts with 4-methylaniline, catalyzed by $Pd(OAc)_2$, the amino group was introduced to 3-position [67]. Similarly, the reaction of 2-chloro-5-iodopyridine with an olefin took place at 5-position [68, 69].



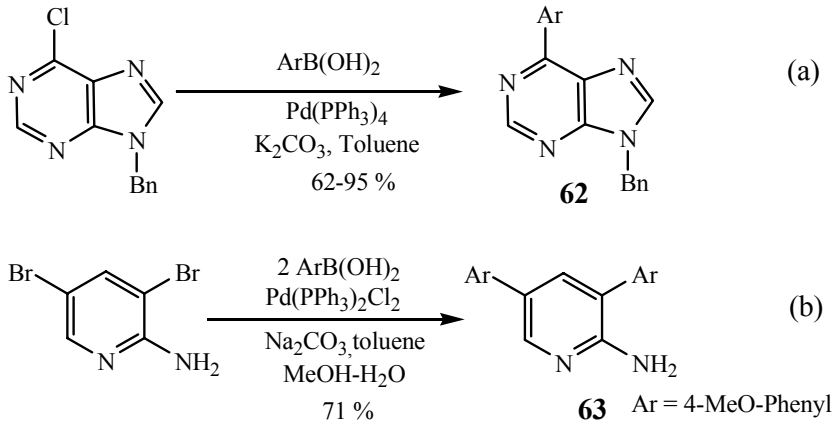
Scheme 1.19 Regioselective Pd-catalyzed cross-coupling of halopyridines

Facing the vast variety of heterocyclic compounds, the aspect of reactivity and regioselectivity of Pd-catalyzed cross-coupling reactions of heterocycles is still a weakly explored and important field of organic synthesis. We tried to employ these reactions in the synthesis of new calcineurin inhibitors with the general structure **8**. Either the aryl groups or the fuctionalized side chains can be introduced into the central heterocycles in this way.

1.3.3 Prospected application of Pd-catalyzed cross-coupling to the synthesis of new calcineurin inhibitors

1.3.3.1 Introducing aryl groups to the heterocycles

There are a lot of ways to introduce aryl groups to the heterocycles, for example, Suzuki coupling, Negishi coupling, Kumada coupling, Hiyama coupling, etc. The most important and most effective reaction is the Suzuki reaction, using aromatic halides cross-coupling with aryl boronic acid. Some examples [70, 71] which are interesting to our project are shown in **Scheme 1.20**:



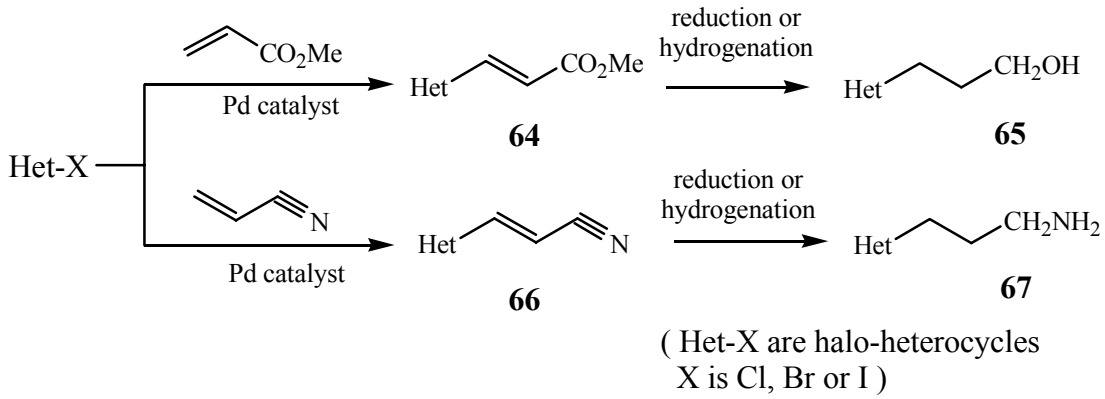
Scheme 1.20 Introducing aryl groups to heterocycles by Suzuki couplings

1.3.3.2 Introducing the functionalized side chains

In the establishment of calcineurin inhibiting assemblages of the general structure **8**, the introduction of the functionalized side chains is often the key step to the target molecules. The application of Pd-catalyzed cross-coupling reactions envisaged for these synthetic transformations is shown by the following protocols. When the side chain contains π-bond, it should be possible to transform it into saturated side chain by reduction or hydrogenation.

(1) Using Heck cross-coupling

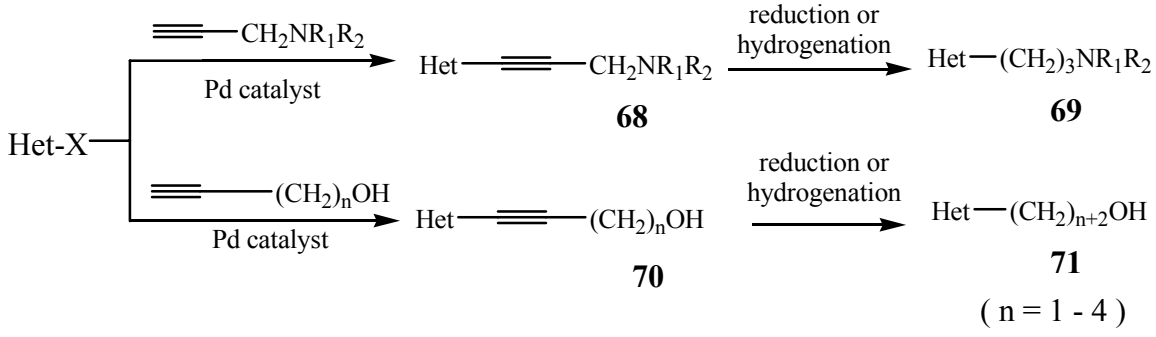
Designed synthetic strategy:



Scheme 1.21 Introducing side chains by the Heck coupling

(2) Using Sonogashira cross-coupling

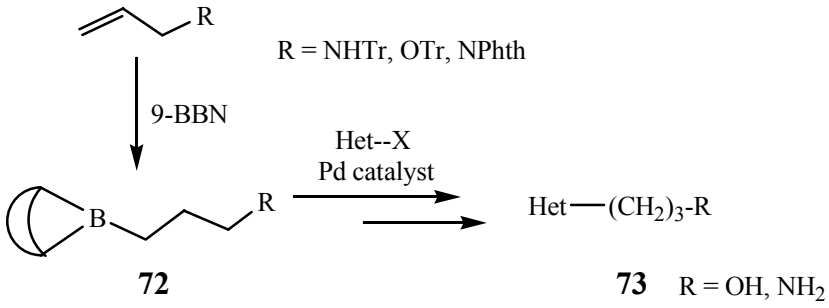
Designed synthetic strategy:



Scheme 1.22 Introducing side chains by the Sonogashira coupling

(3) Using Suzuki cross-coupling

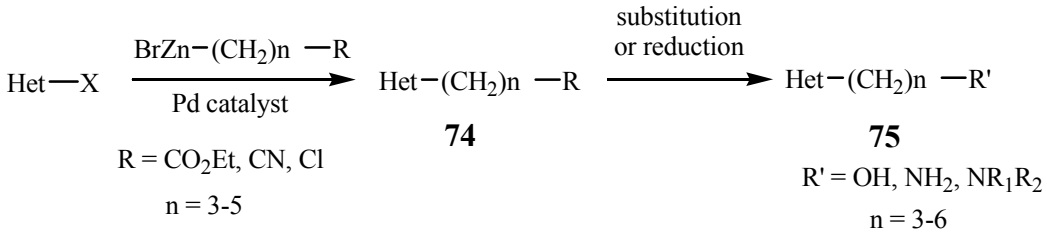
Designed synthetic strategy:



Scheme 1.23 Introducing side chains by the Suzuki coupling

(4) Using Negishi cross-coupling

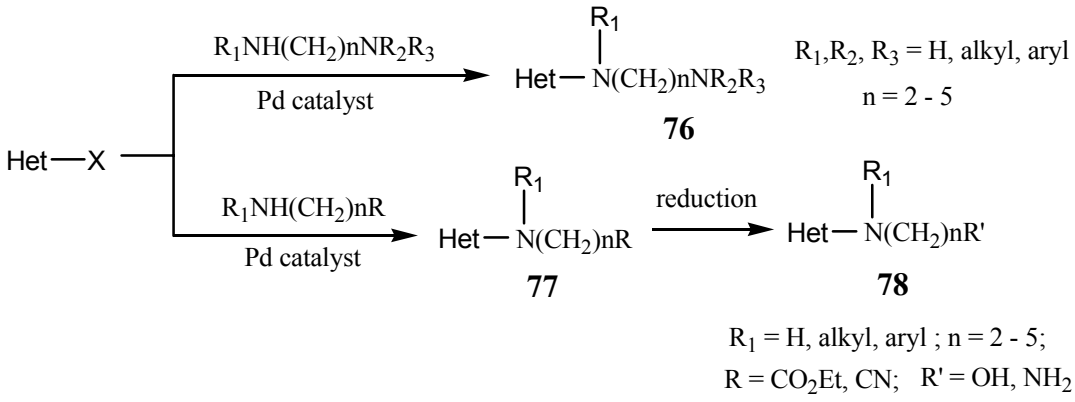
Designed synthetic strategy:



Scheme 1.24 Introducing side chains by the Negishi coupling

(5) Using Buchwald-Hartwig amination

Designed synthetic strategy:

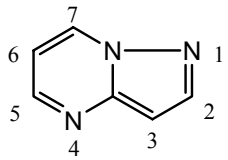


Scheme 1.25 Introducing side chains by the Buchwald-Hartwig amination

Chapter 2: Pyrazolo[1,5-a]pyrimidine derivatives

2.1 Introduction

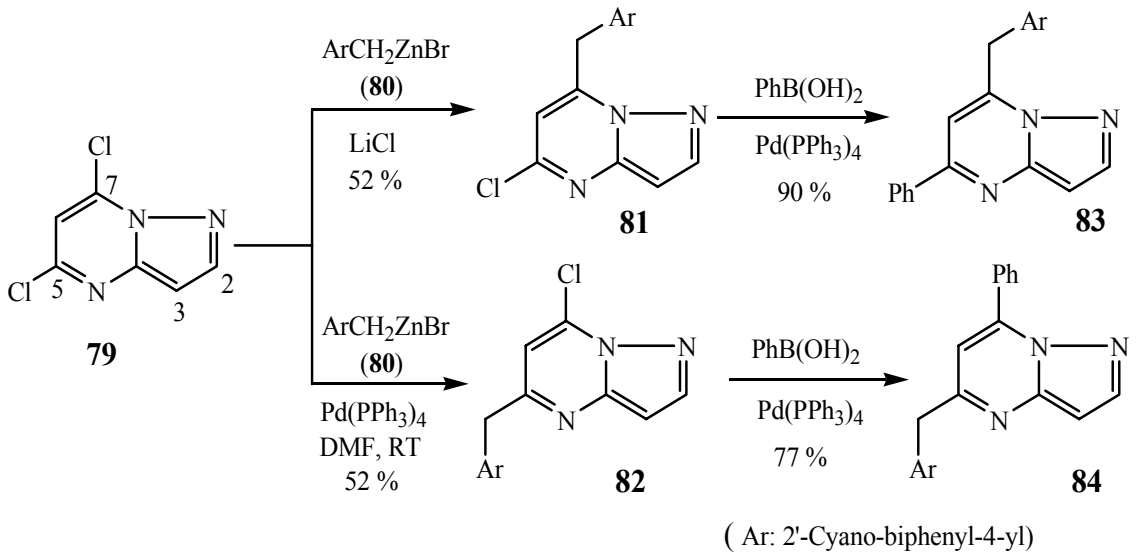
Pyrazolo[1,5-a]pyrimidines are purine analogues and have useful properties as antimetabolites in purine biochemical reactions. Compounds of this class have attracted wide pharmaceutical interest because of antitrypanosomal activity [72], antischistosomal activity [73]. They are used as HMG-CoA reductase inhibitors [74], COX-2-selective inhibitors [75], AMP phosphodiesterase inhibitors [76], KDR kinase inhibitors [77], selective peripheral benzodiazepine receptor ligands [78], and antianxiety agents [79]. These interesting biological properties initiate activities to develop new efficient general procedures for the synthesis of pyrazolo[1,5-a]pyrimidine derivatives.



pyrazolo[1,5-a]pyrimidine

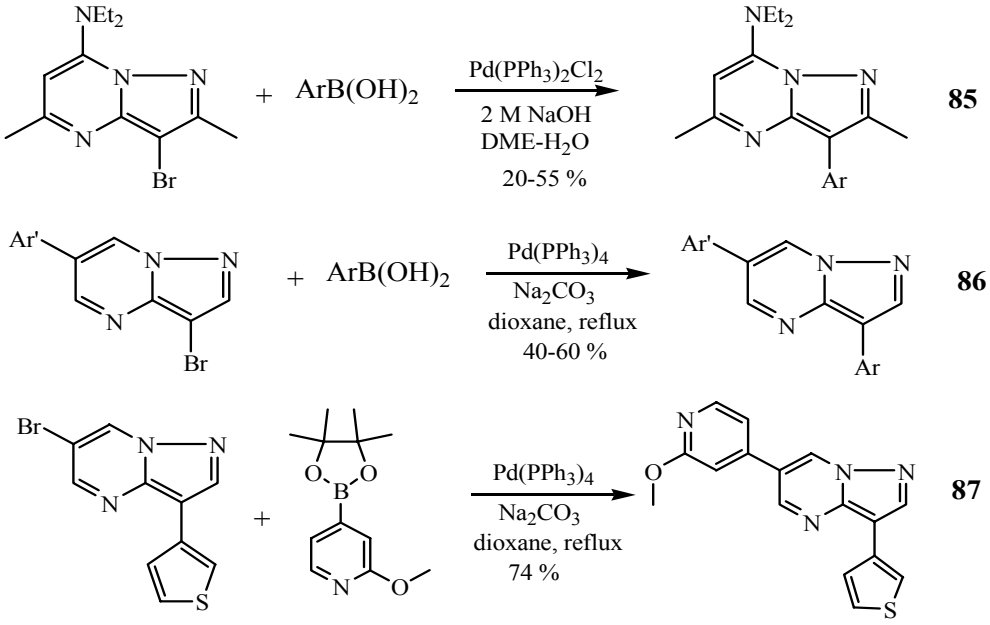
Pyrazolo[1,5-a]pyrimidine is composed of a pyrimidine ring and a pyrazole ring. The pyrimidine part is π-electron deficient, so the nucleophilic displacement takes place more readily. The 7-position is more active than the 5-position. The pyrazole part is π-electron excessive, and can readily undergo electrophilic substitution.

Although cross-coupling reactions have been extensively used in organic synthesis of heterocyclic compounds, to the best of our knowledge, only a few publications are devoted to cross-couplings of pyrazolo[1,5-a]pyrimidines. Shiota and Yamamori [80] reported the regioselective coupling of organzinc reagents **80** with 5,7-dichloropyrazolo[1,5-a]pyrimidine **79**. When the reaction was catalyzed by lithium chloride, the 7-substituted product **81** was obtained, while catalysis by $Pd(PPh_3)_4$ afforded the 5-substituted product **82**. By further $Pd(PPh_3)_4$ catalyzed reaction of **81** or **82** with phenylboronic acid, phenyl groups could be introduced into 5-position or 7-position respectively. (**Scheme 2.1**)



Scheme 2.1 Regioselective cross-coupling reactions of organzinc reagent with 5,7-dichloropyrazolo[1,5-a]pyrimidine

Kumar [81] reported the synthesis of 3-aryl-7-diethylamino-pyrazolo[1,5-a]pyrimidines **85** by Suzuki coupling of 3-bromopyrazolo[1,5-a]pyrimidines. Fraley reported the Suzuki cross-coupling reactions of 3-bromo-6-arylpyrazolo[1,5-a]pyrimidines [82] and 6-bromo-3-aryl-pyrazolo[1,5-a]pyrimidines [76] and obtained products **86** and **87**, respectively.**(Scheme 2.2)**



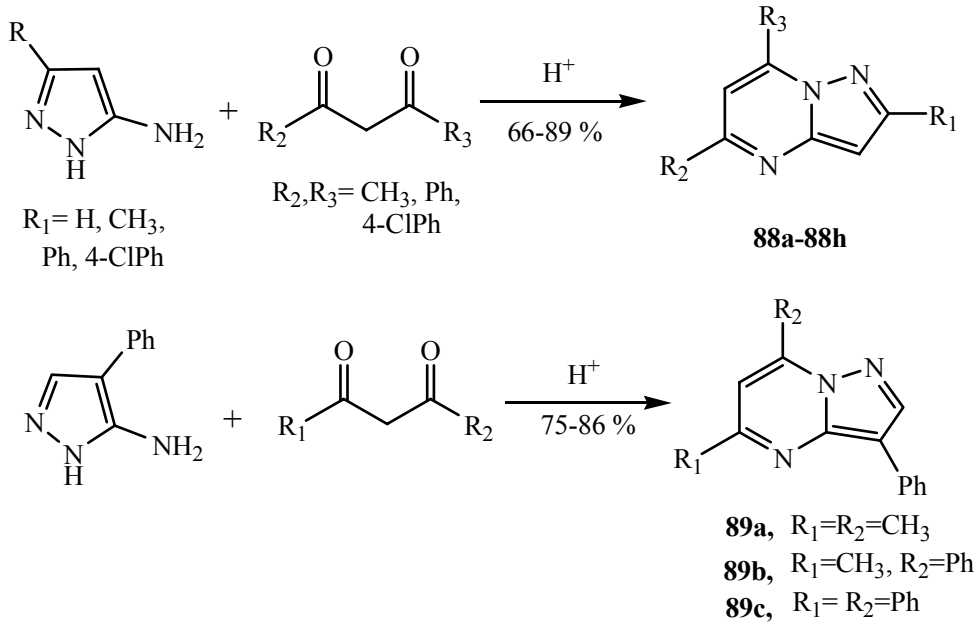
Scheme 2.2 Suzuki corss-coupling of bromopyrazolo[1,5-a]pyrimidines

We envisaged the synthesis of calcineurin-inhibiting compounds with the general structure **8** with the pyrazolo[1,5-a]pyrimidine system as the core heterocycle. They would be synthesized by Pd-catalyzed cross-coupling reactions of halo-pyrazolo[1,5-a]pyrimidines. Routes to the starting materials are described in the following chapters. Since the reactivity of halo-leaving groups in Pd-catalyzed cross-coupling reactions drop in the sequence of I > Br >> Cl, we preferred to start with iodo- or bromo-pyrazolo[1,5-a]pyrimidines, but the chloro-compounds were also included.

2.2 Synthesis of substituted pyrazolo[1,5-a]pyrimidines

2.2.1 Synthesis of pyrazolo[1,5-a]pyrimidines by ring closure

The pyrazolo[1,5-a]pyrimidine skeleton is usually prepared by condensation of 3-amino-pyrazoles or 4-amino-pyrazoles with 1,3-diketones, using hydrochloric acid [83], acetic acid [84], ethanol [85, 86], or ethanol/hydrochloric acid as solvent. We synthesized a series of substituted pyrazolo[1,5-a]pyrimidine derivatives **88a-88h** and **89a-89c** in this way. (**Scheme 2.3** and **Table 2.1**)



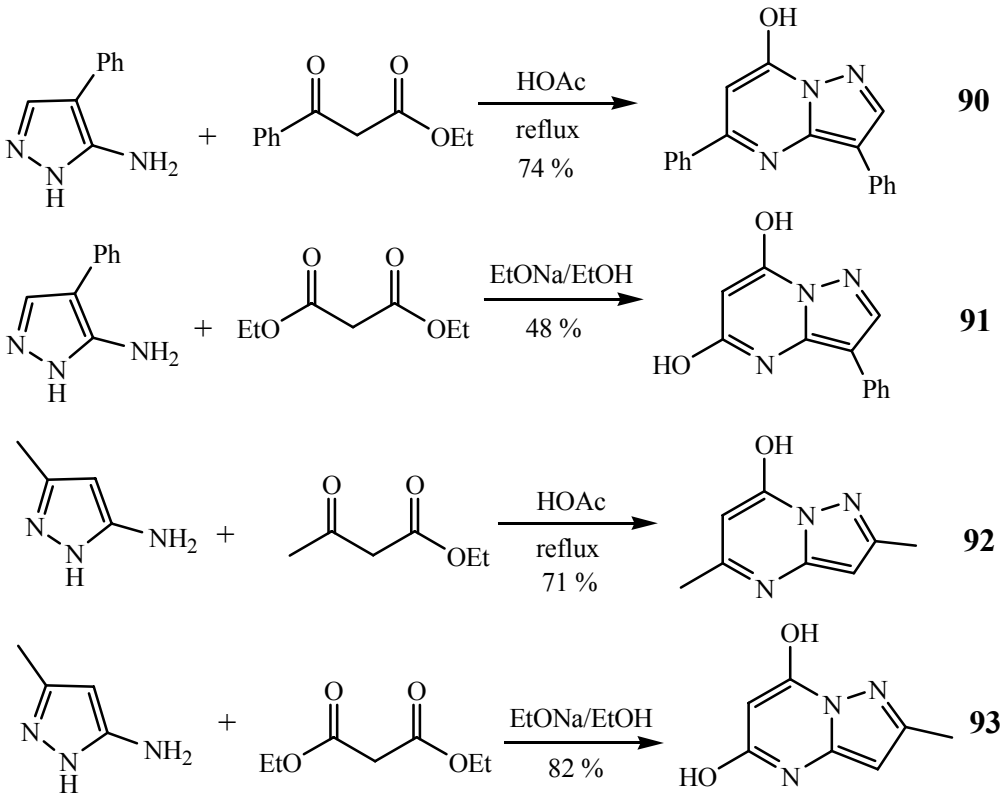
Scheme 2.3 Synthesis of substituted pyrazolo[1,5-a]pyrimidines

Table 2.1 Pyrazolo[1,5-a]pyrimidines **88** and **89**

Product	R_1	R_2	R_3	Yield (%)	Mp (°C)
88a	Ph	Me	Ph	89	185-186 (EtOH)
88b	4-Cl-Ph	Me	Ph	66	156-158 (EtOH)
88c	Me	Ph	Ph	74	113-114 (EtOH/hexane)
88d	Ph	Me	4-Cl-Ph	77	155-117 (EtOH)
88e	Me	Me	Ph	78	81-82 (EtOH)
88f	Me	Me	Me	68	69-70 (hexane/Et_2O)
88g	Ph	Ph	Ph	77	154-155 (EtOH)
88h	H	Ph	Ph	89	85-86 (EtOH)
89a	Me	Me		75	91-2 (EtOH/hexane)
89b	Me	Ph		86	124-5 (EtOHl)
89c	Ph	Ph		86	163-4 (EtOH)

In an analogous manner, mono- or dihydroxy-pyrazolo[1,5-a]pyrimidines *** were synthesized by using β-ketoesters or malonates instead of 1,3-diketones, e.g., 3-amino-4-phenylpyrazole was reacted with ethyl benzoylacetate, using acetic acid as solvent, affording the 2,5-diphenyl-7-hydroxypyrazolo[1,5-a]pyrimidine **90** [73]. 3-Amino-4-phenylpyrazole was reacted with diethyl malonate, using EtONa as base to obtain 3-phenyl-5,7-dihydroxypyrazolo[1,5-a]pyrimidine **91** [87]. 3-Amino-5-methylpyrazole reacted with ethyl acetoacetate and diethyl malonate giving 2,5-dimethyl-7-hydroxy-pyrazolo[1,5-a]pyrimidine **92** [88] and 2-methyl-5,7-dihydroxypyrazolo[1,5-a]pyrimidine **93** [87], respectively. (**Scheme 2.4**)

*** In fact, there are two tautomers in these hydroxypyrazolo[1,5-a]pyrimidines: pyrazolo[1,5-a]pyrimidone and hydroxypyrazolo[1,5-a]pyrimidine, moreover, pyrazolo[1,5-a]pyrimidone is the main structure, we wrote and named these compounds here hydroxypyrazolo[1,5-a]pyrimidines for convenience and simplifying.



Scheme 2.4 Synthesis of hydroxypyrazolo[1,5-a]pyrimidines

2.2.2 Halogen substituted pyrazolo[1,5-a]pyrimidines

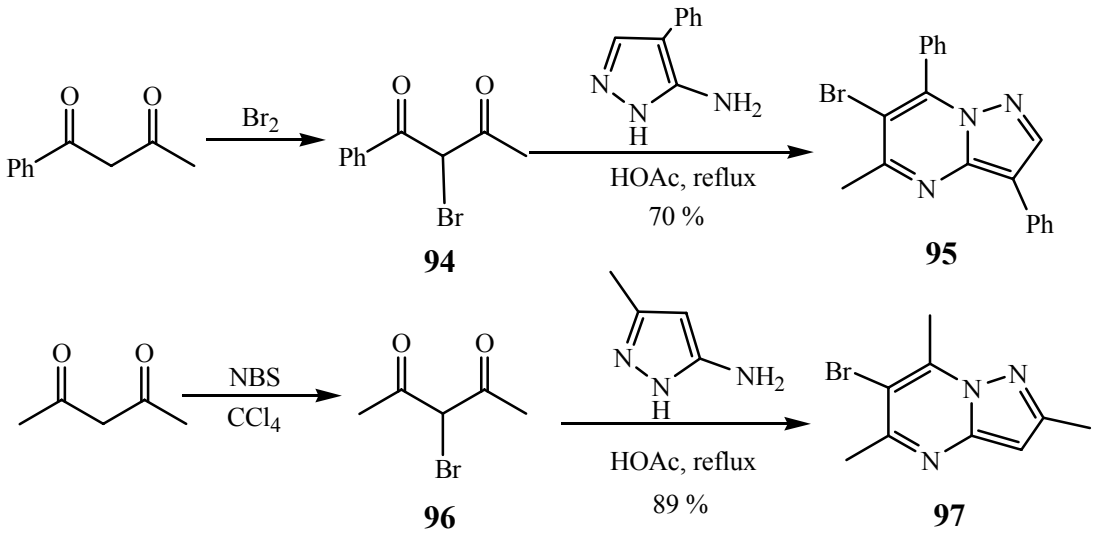
There are three principal ways to prepare halopyrazolo[1,5-a]pyrimidines:

a) cyclisation of halogen-containing open chain precursors.

b) nucleophilic substitution of hydroxyl groups of pyrazolo[1,5-a]pyrimidines by halogen.

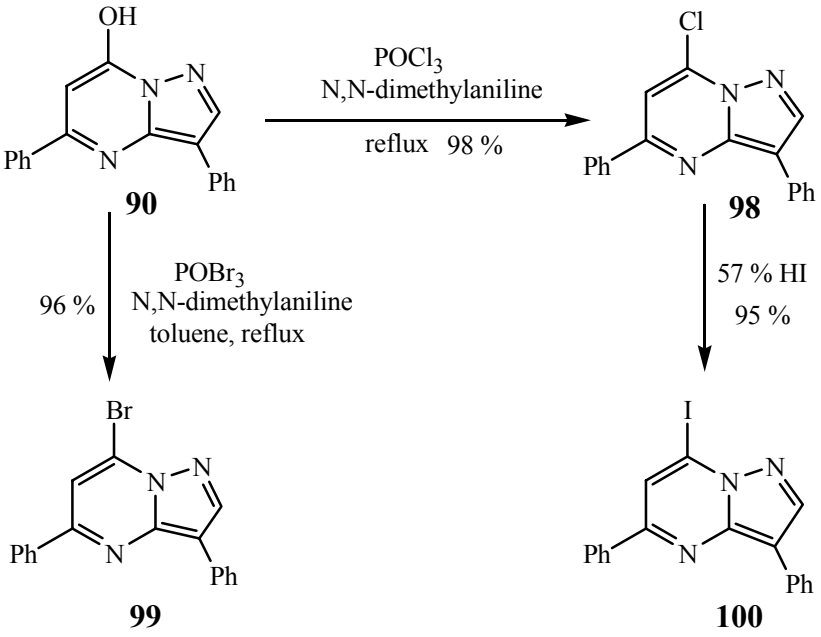
c) electrophilic substitution of H-atoms of pyrazolo[1,5-a]pyrimidines by halogen.

Using bromine or NBS as bromating agent, 1,3-diketones are readily brominated at the active CH_2 position [89, 90]. By further treatment with 3-aminopyrazoles, new 6-bromo-pyrazolo[1,5-a]pyrimidines **95** and **97** could be obtained by ring closure route (a). (**Scheme 2.5**)



Scheme 2.5 Synthesis of 6-bromo-pyrazolo[1,5-a]pyrimidines

Following the S_N-route (b) for halopyrazolo[1,5-a]pyrimidines, 2,5-diphenyl-7-hydroxy-pyrazolo[1,5-a]pyrimidine **90** was refluxed with $POCl_3$ or $POBr_3$, using N, N-dimethylaniline as catalyst. The corresponding 7-Cl [74] and 7-Br substituted pyrazolo[1,5-a]pyrimidine products, **98** and **99,** could be obtained in high yields. 2,5-Diphenyl-7-chloro-pyrazolo[1,5-a]pyrimidine **98** reacted with 57 % hydroiodic acid in a subsequent S_N-reaction providing the corresponding 7-iodopyrazolo[1,5-a]pyrimidine **100**. (**Scheme 2.6**)

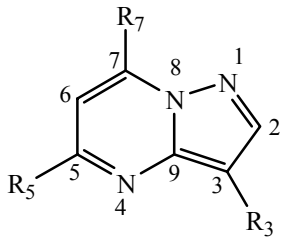


Scheme 2.6 Synthesis of 7-halo-2,5-diphenylpyrazolo[1,5-a]pyrimidines

The structure of the new products **98**, **99**, **100** and **120** (also see page 39), were confirmed by NMR-data. It is worth mentioning that the compound **120** exhibits a strong up field shift of the H-6 signal as compared with its isomer **98**. Furthermore a strong effect of the halo-substituents was observed on the ^{13}C-signal of position C-6, within the series **98**, **99**, and **100**. Some NMR data of these compounds are shown in **Table 2.2**:

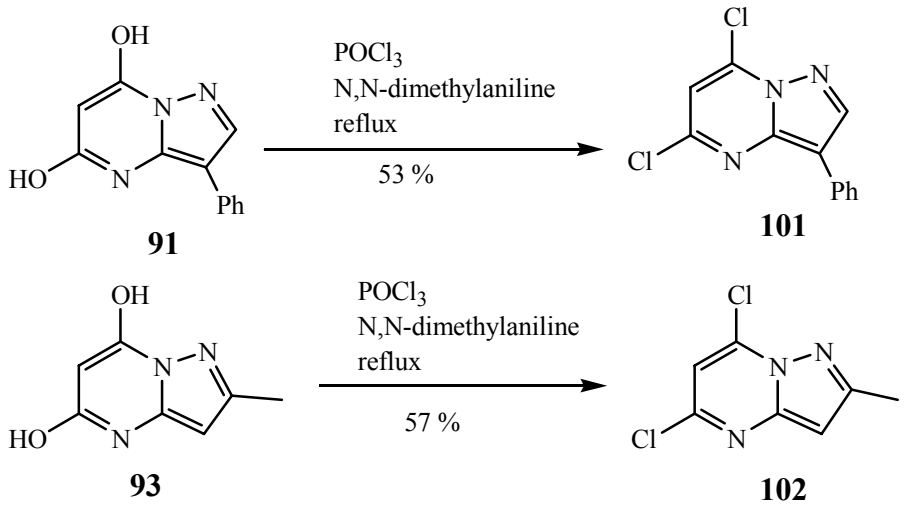
Table 2.2 NMR data of of compounds **98**, **99**, **100** and **120** (δ, ppm)

	120	**98**	**99**	**100**
H-6	6.80	7.49	7.61	7.86
H-2	8.38	8.53	8.52	8.51
Ph-H	7.18-7.96	7.25-8.17	7.25-8.16	7.25-8.12
C-6	108.80	105.58	109.72	117.45
C-7	144.70	139.03	128.99	103.94
C-2	143.40	143.54	143.28	142.60
C-3	110.82	112.31	112.46	112.79
C-4	148.35	145.81	145.30	143.30
C-5	150.70	155.65	155.16	154.47



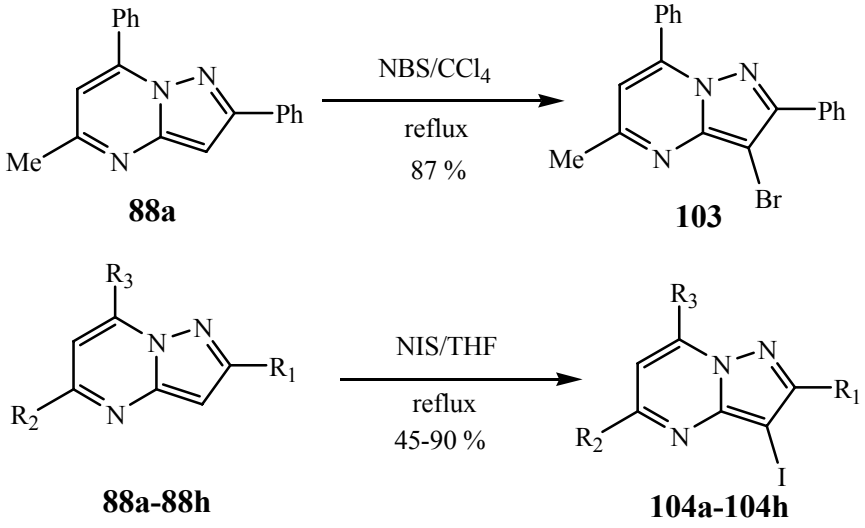
	R_3	R_5	R_7
120	Ph	Cl	Ph
98	Ph	Ph	Cl
99	Ph	Ph	Br
100	Ph	Ph	I

5,7-Dihydroxy-3-phenylpyrazolo[1,5-a]pyrimidine **91** and 5,7-dihydroxy-2-methyl-pyrazolo[1,5-a]pyrimidine **93** could be transformed into the corresponding 5,7-dichloro-pyrazolo[1,5-a]pyrimidines **101** [91] and **102** [92], respectively, by refluxing in $POCl_3$ in the presence of N,N-dimethylaniline. (**Scheme 2.7**)



Scheme 2.7 Synthesis of 5,7-dichloro- pyrazolo[1,5-a]pyrimidines

Following the route (c), i.e. to introduce halogen by electrophilic substitution of H-atoms, substituted pyrazolo[1,5-a]pyrimidine **88a** was treated with NBS, using CCl_4 as solvent under reflux. The substituted 3-bromopyrazolo[1,5-a]pyrimidine **103** was obtained in good yield. **88a-88h** reacted with NIS [93] in THF under reflux providing substituted 3-iodopyrazolo[1,5-a]pyrimidines **104a-104h**. (**Scheme 2.8**, **Table 2.3**)

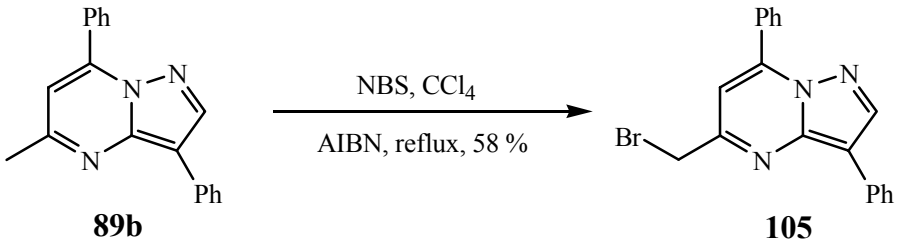


Scheme 2.8 Synthesis of 3-halopyrazolo[1,5-a]pyrimidines

Table 2.3 3-Iodopyrazolo[1,5-a]pyrimidines **104a-104h**

Product	R_1	R_2	R_3	Yield (%)	Mp (°C)
104a	Ph	Me	Ph	70	164-166 (EtOAc)
104b	4-Cl-Ph	Me	Ph	69	166-168 (EtOAc)
104c	Me	Ph	Ph	78	138-140 (EtOAc)
104d	Ph	Me	4-Cl-Ph	83	63-65 (EtOAc)
104e	Me	Me	Ph	63	90-91 (EtOAc)
104f	Me	Me	Me	45	132-133 (EtOAc)
104g	Ph	Ph	Ph	81	202-203 (EtOAc)
104h	H	Ph	Ph	90	160-161 (EtOAc)

We further chose a pyrazolo[1,5-a]pyrimidine compound, where the halo leaving group was found in a alkyl substituent, allowing uncatalyzed nucleophilic substitutions with substituted amines to introduce the functionalized side chain. 5-Methyl-3,7-diphenylpyrazolo[1,5-a]pyrimidine **89b** reacted with NBS in the presence of AIBN using CCl_4 as solvent under reflux. 5-Brromomethyl-3,7-diphenylpyrazolo[1,5-a]pyrimidine **105** was obtained**. (Scheme 2.9)**



89b **105**

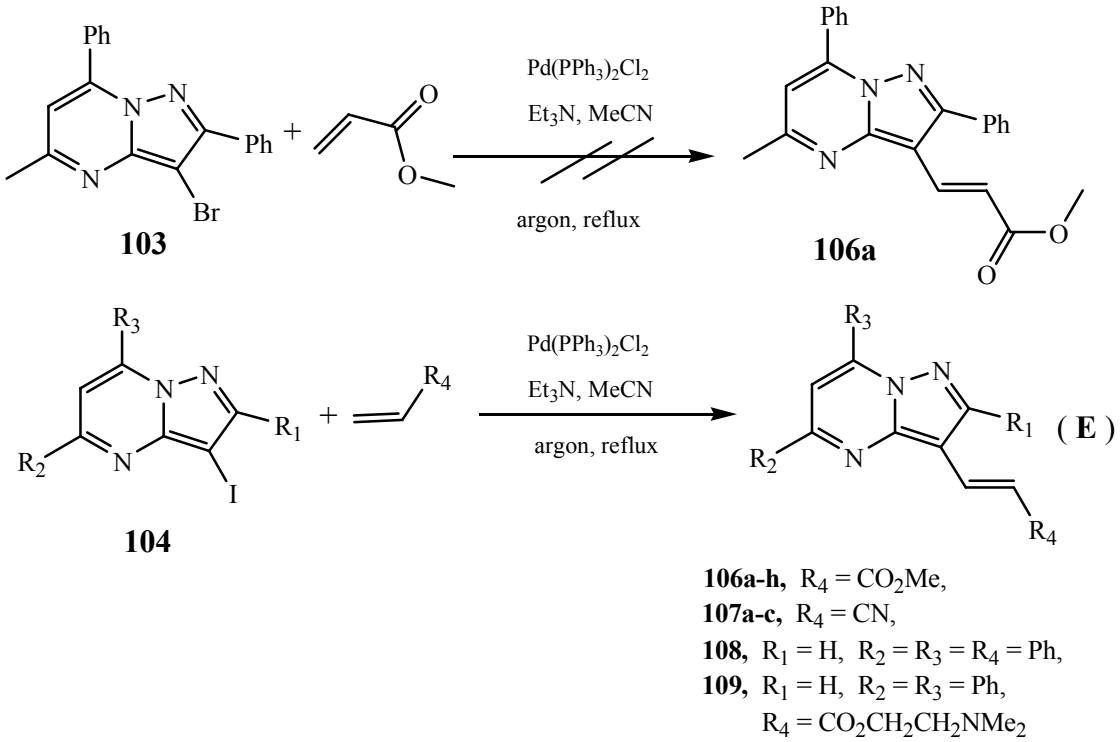
Scheme 2.9 Synthesis of 5-bromomethyl-3,7-diphenylpyrazolo[1,5-a]pyrimidine

2.3 Heck cross-coupling of pyrazolo[1,5-a]pyrimidines

2.3.1 Heck cross-coupling of 3-halopyrazolo[1,5-a]pyrimidines

Heck cross-coupling reaction has shown great versatility in the construction of carbon-aryl bonds [94, 95]. $Pd(PPh_3)_2Cl_2$ [bis(triphenylphosphino)palladium(II) chloride] and $Pd(OAc)_2$ are usually used as catalysts. Therefore, we tried to apply this useful reaction to introduce alkene moieties with a terminal O- or N-containing functional group into pyrazolo[1,5-a]pyrimidines, allowing subsequent reduction to hydroxyl or aminoalkyl side chains.

3-Bromo-5-methyl-2,7-diphenylpyrazolo[1,5-a]pyrimidine **103** was treated with methyl acrylate, using $Pd(PPh_3)_2Cl_2$ as catalyst, triethylamine as base, acetonitrile as solvent under argon. No reaction took place, even at refluxing temperature. But using the same conditions, treatment of the corresponding iodo-compounds **104** with monosubstituted alkenes, such as methyl acrylates, acrylonitrile, or styrene, provided the anticipated coupling products **106-109** in high yields (**Scheme 2.10** and **Table 2.4**). These products possess *E*-configuration, according to ^{1}H-NMR spectra (CH=CH, J = 15-19 Hz).

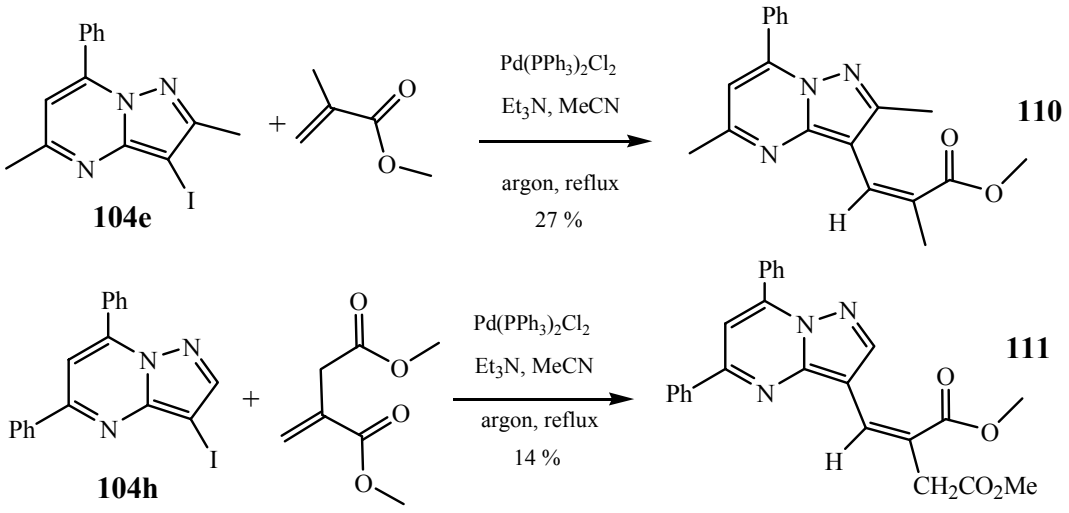


Scheme 2.10 Heck cross-coupling of 3-halopyrazolo[1,5-a]pyrimidines with mono-substituted alkenes

Table 2.4 Pyrazolo[1,5-a]pyrimidines **106-111**

Product	R_1	R_2	R_3	R_4	Yield (%)	Mp (°C)
106a	Ph	Me	Ph	CO_2Me	91	155-156
106b	4-Cl-Ph	Me	Ph	CO_2Me	93	149-151
106c	Me	Ph	Ph	CO_2Me	94	164-165
106d	Ph	Me	4-Cl-Ph	CO_2Me	89	162-164
106e	Me	Me	Ph	CO_2Me	90	194-196
106f	Me	Me	Me	CO_2Me	62	173-175
106g	Ph	Ph	Ph	CO_2Me	90	215-216
106h	H	Ph	Ph	CO_2Me	86	134-135
107a	Ph	Me	Ph	CN	52	206-208
107b	4-Cl-Ph	Me	Ph	CN	43	180-182
107c	Me	Ph	Ph	CN	79	164-165
108	H	Ph	Ph	Ph	36	174-176
109	H	Ph	Ph	CO_2CH_2-CH_2NMe_2	57	glassy material

Using the same conditions, treatment of **104e** or **104h** with di-substituted alkenes such as methyl methylacrylates, or methyl crotonate, gave only low yields of coupling products **110** and **111**, respectively. Remarkably, the *Z*-isomers were formed in these cases, according to NOE spectra, where NOEs were observed between =C-H and =C-CH_3 or =C-CH_2. (**Scheme 2.11**)

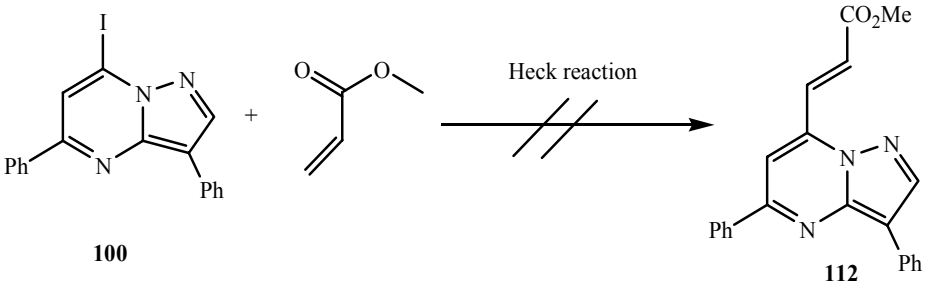


Scheme 2.11 Heck reactions of 3-iodopyrazolo[1,5-a]pyrimidines with di-substituted alkenes

Attempts to use dimethyl maleate or dimethyl fumarate as alkenes in Heck reaction of 3-iodopyrazolo[1,5-a]pyrimidines **104** failed, as did the reaction with acrolein diethyl acetal (3,3-diethyl-1-propene).

2.3.2 Heck cross-coupling of 7-iodopyrazolo[1,5-a]pyrimidine

Attempts to use 7-iodo-3,5-diphenylpyrazolo[1,5-a]pyrimidine to undergo Heck cross-coupling reactions with methyl acrylate, using several kinds of reaction conditions were unsuccessful. Only unchanged starting materials were isolated. (**Scheme 2.12)**



Reaction conditions:

a) $Pd(PPh_3)Cl_2$, Et_3N, CH_3CN, 80°C, 24 h

(b) Pd/C, Et_3N, 80°C, 24 h

(c) $Pd(OAc)_2$, Et_3N, 80°C, 24 h

(d) $Pd(OAc)_2$, P(o-tolyl)$_3$, Et_3N, CH_3CN, 100°C, 24 h

Scheme 2.12 Heck cross-coupling reaction of **100**

It seems that position 7 of the pyrazolo[1,5-a]pyrimidine is not active enough to undergo Heck coupling. However, in Suzuki coupling, it turns out to be possible to act as reactant (see **Scheme 2.17**, page 39).

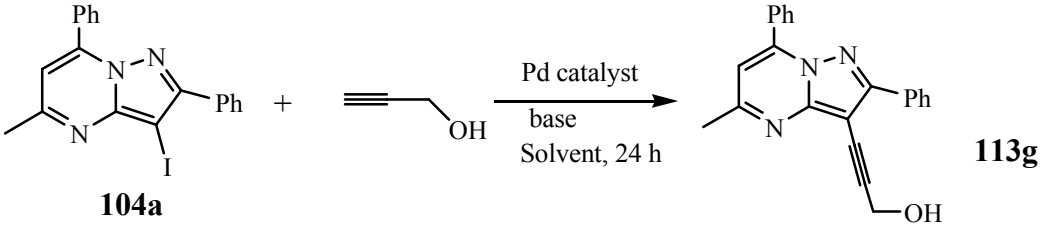
2.4 Sonogashira cross-coupling of halopyrazolo[1,5-a]pyrimidines

2.4.1 Sonogashira cross-coupling of 3-iodopyrazolo[1,5-a]pyrimidines

(a) Pd/C as catalyst

3-Iodo-5-methyl-2,7-diphenylpyrazolo[1,5-a]pyrimidine **104a** was first chosen as staring material in cross-coupling with propargyl alcohol in several kinds of catalytic systems. The homogeneous catalytic systems of $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$, and $Pd(OAc)_2$ were not active enough and failed or provided only low yields of coupling product. But using Pd/C as heterogeneous catalyst, CuI as co-catalyst, PPh_3 as ligand, K_2CO_3 as base in DME/water, it turned out to be more effective. The optimization of reaction conditions are shown in **Table 2.5**.

Table 2.5 Effect of reaction conditions of Sonogashira cross-coupling



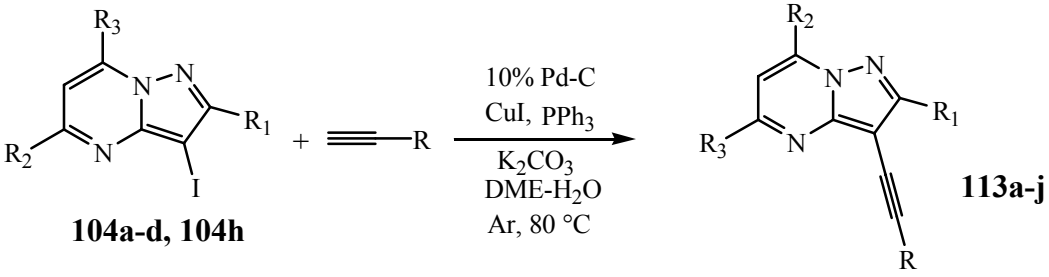
104a **113g**

Entry	Catalyst	Base	Solvent	Temperature	Yield (%)
1	$Pd(PPh_3)_2Cl_2$, CuI	Et_3N	MeCN	RT	9
2	$Pd(PPh_3)_2Cl_2$, CuI	$(i\text{-}Pr)_2NEt$	CH_2Cl_2	RT	14
3	$Pd(OAc)_2$, PPh_3, Bu_4NHSO_4	Et_3N	MeCN-H_2O	RT	27
4	$Pd(PPh_3)_2Cl_2$, CuI	Et_3N	Et_3N-DMF	50°C	50
5	$Pd(PPh_3)_2Cl_2$, CuI	Et_3N	Et_3N	80°C	0
6	$Pd(PPh_3)_2Cl_2$, CuI	Et_3N	DMF-Et_3N	100°C	0
7	$Pd(PPh_3)_4$, CuI,	Et_3N	Et_3N-DMF	50°C	43
8	$Pd(PPh_3)_2Cl_2$, CuI	Et_2NH	Et_2NH	50°C	40
9	10% Pd-C, CuI, PPh_3	K_2CO_3	DME-H_2O	80°C	72

Pd/C is one of the most common heterogeneous palladium catalysts, and many recent reports have demonstrated it is a convenient, inexpensive, reusable, and highly active catalyst [96].

Pd/C catalyst is widely used in Suzuki-Miyaura coupling [97], Heck coupling [98], and Sonogashira coupling [99]. Using Pd/C catalyst in aqueous media, substituted 3-iodo-pyrazolo[1,5-a]pyrimidines **104a-104d, 104h** were successfully coupled with N,N-dimethylpropargyl amine, propargyl alcohol, and 3-butyn-1-ol (see **Table 2.6**).

Table 2.6 Pd/C catalyzed Sonogashira reactions of 3-iodo-pyrazolo[1,5-a]pyrimidines

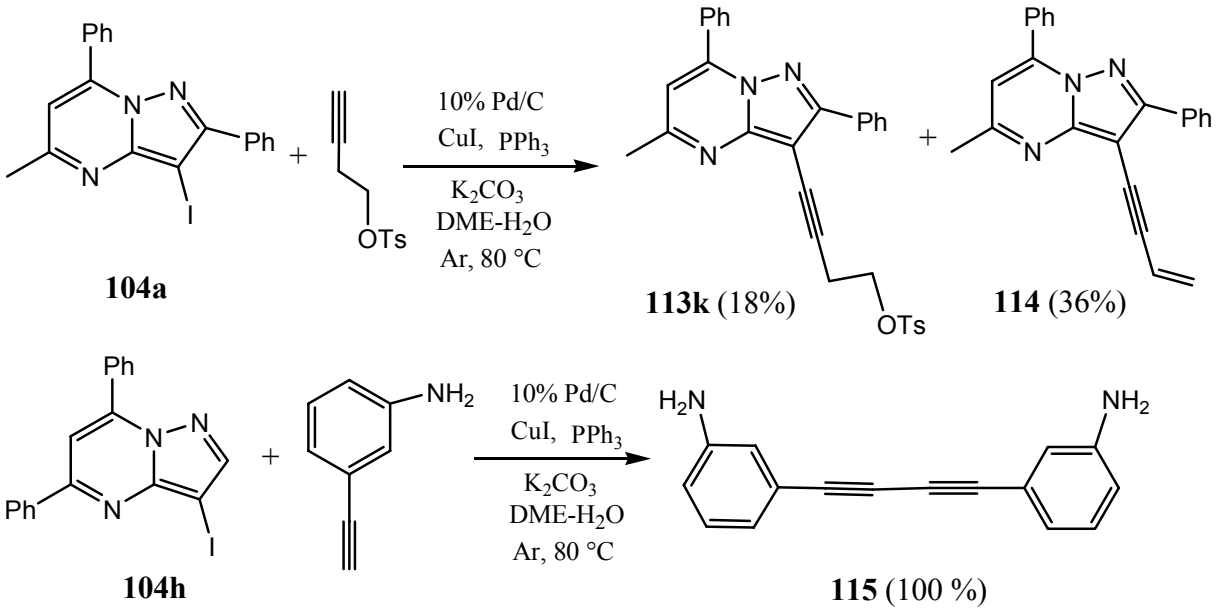


104a-d, 104h **113a-j**

Product	R_1	R_2	R_3	R	Yield (%)
113a	Me	Ph	Ph	CH_2NMe_2	76
113b	H	Ph	Ph	CH_2NMe_2	91
113c	Ph	Me	Ph	CH_2NMe_2	70
113d	*p*-Cl-Ph	Me	Ph	CH_2NMe_2	69
113e	Ph	Me	*p*-Cl-Ph	CH_2NMe_2	54
113f	H	Ph	Ph	CH_2OH	78
113g	Ph	Me	Ph	CH_2OH	72
113h	Ph	Me	Ph	CH_2CH_2OH	71
113i	H	Ph	Ph	CH_2CH_2OH	75
113j	Me	Ph	Ph	CH_2CH_2OH	70

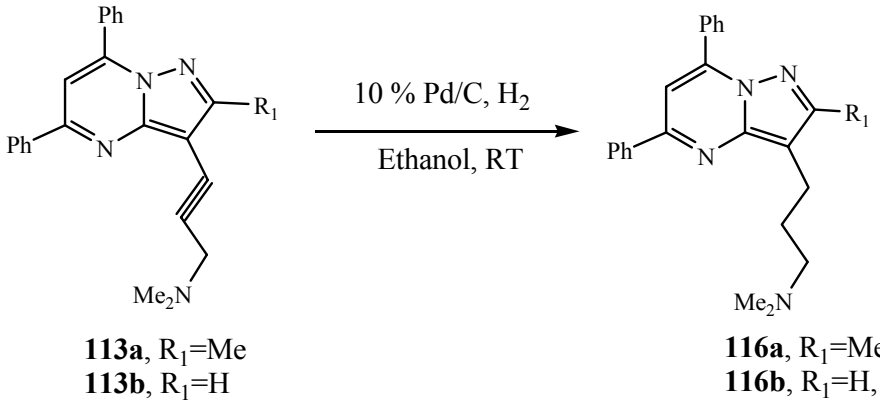
104a reacted with 3-butynyl p-toluenesulphonate to give only 18 % yield of the desired product **113k**. However, 36 % yield of the 3-but-3-en-1-ynyl substituted pyrazolo[1,5-a]-pyrimidine **114** was isolated as major product. Under the same reaction conditions, the reaction of the 3-iodo pyrazolo[1,5-a]pyrimidine **104h** with 3-amino-phenylacetylene, did not result in the desired product, but a homo-coupling (Glaser coupling) product **115** in high yield (**Scheme 2.13**). Obviously, two hydrogen atoms were removed, although there is no definite

dehydrogenating agent in the reaction systems. This unusual result was independently found by Faivlamb [100]. Mechanistic explanation is not on hand yet. When the experiment was repeated under the same conditions without **104h**, the diyne **115** was isolated only 74 %. The result indicated that **104h** accelerated the home-coupling of 3-amino-phenylacetylene.



Scheme 2.13

113a and 113b were hydrogenated with H_2, catalyzed by 10 % Pd/C in ethanol at room temperature and atmosphere pressure. The desired target products **116a, and 116b** were isolated in modest yields (**Scheme 2.14**).

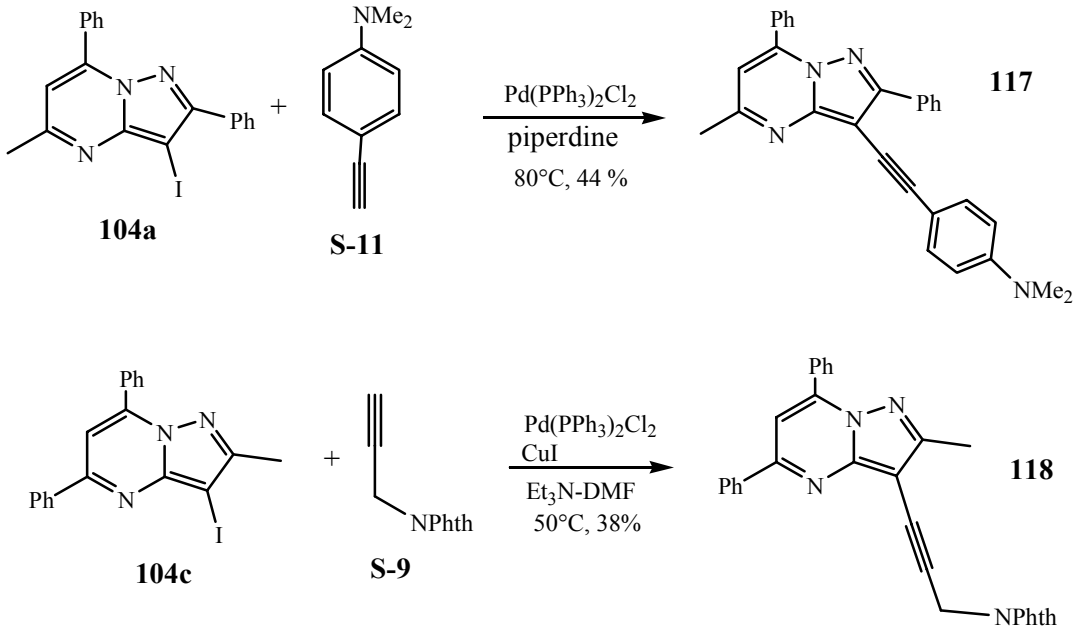


Scheme 2.14 Catalytic hydrogenations of **113a** and **113b**

Attempts to use Pd/C catalyst to undergo cross-coupling of 3-iodo-pyrazolo[1,5-a]pyrimidine **104h** with N-methylpropargylamine, propargylamine or N-propargyl-phthalimide, were unsuccessful. Therefore, other catalytic systems were tested for these cases.

(b) Other conditions for Sonogashira reactions of 3-iodo-pyrazolo[1, 5-a]pyrimidine

3-Iodo-pyrazolo[1,5-a]pyrimidine **104a** reacted with (4-ethynyl-phenyl)-N,N-dimethylamine, using $Pd(PPh_3)_2Cl_2$ as catalyst (no CuI) in a solution of piperdine at 80 °C for 24 h, 44 % of coupling product **117** was isolated. On the other hand, using $Pd(PPh_3)_2Cl_2$ and CuI as catalyst in a solution of Et_3N and DMF at 50°C, it turned out to be suitable for the coupling of 3-iodo-pyrazolo[1, 5-a]pyrimidine **104c** with N-propargyl-phthalamide, 36 % of the coupling product **118** was isolated. (**Scheme 2.15**)

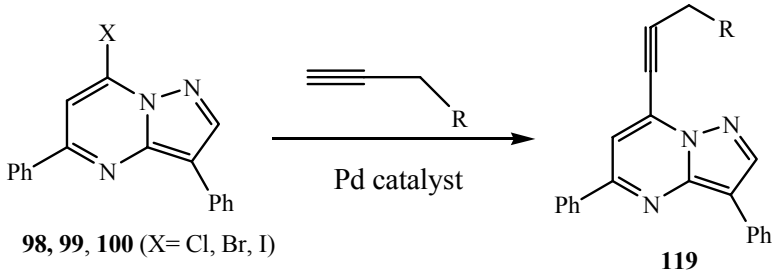


Scheme 2.15

2.4.2 Sonogashira cross-coupling of 7-halopyrazolo[1, 5]pyrimidine

Attempts to use 7-halopyrazolo[1,5-a]pyrimidines in Sonogashira cross-coupling reactions with N,N-dimethylpropargyl amine or propargyl alcohol were unsuccessful, although several kinds of Pd catalysts and reaction conditions were applied. Unfortunately, no definite products could be isolated (**Table 2.7**).

Table 2.7 Reaction conditions of Sonogashira cross-coupling



98, 99, **100** (X= Cl, Br, I)

119

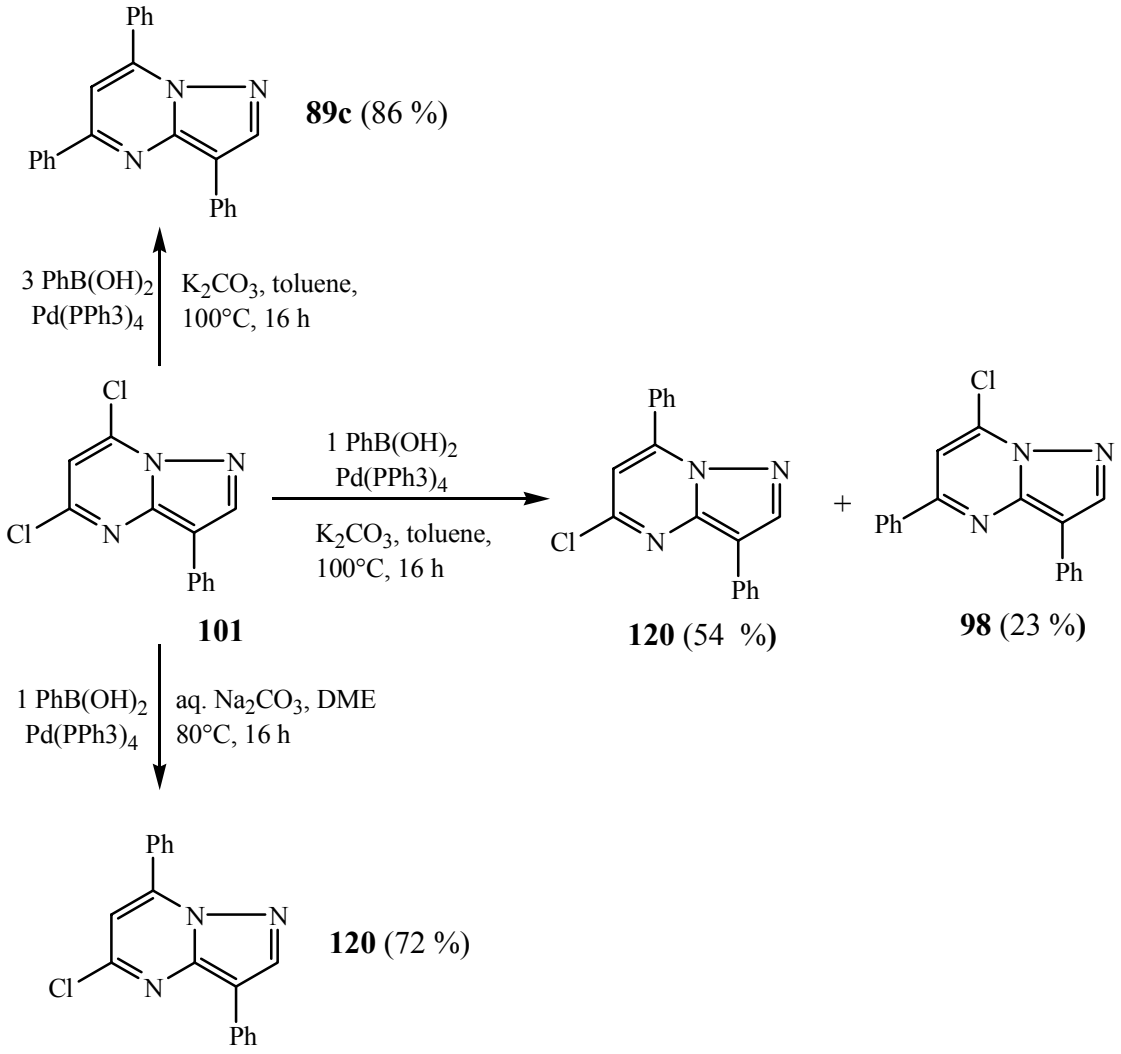
Entry	Reactant, X	R	Reaction conditions	Result
1	**99, Br**	OH	$Pd(PPh_3)_2Cl_2$, CuI, Et_3N, RT, 24 h	NDP*
2	**99, Br**	NMe_2	$Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, 80°C, 24 h	NDP
3	**100, I**	NMe_2	$Pd(PPh_3)_4$, CuI, Et_3N, 50°C ,24 h	NDP
4	**100, I**	NMe_2	10% Pd/C, CuI, PPh_3, K_2CO_3, DME-H_2O, 80°C, 24 h	NDP
5	**100, I**	NMe_2	10% Pd/C, CuI, PPh_3, K_2CO_3, DME-H_2O, 80°C, 24 h	NDP
6	**100, I**	NMe_2	$Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 80°C, 24 h	NDP
7	**100, I**	NMe_2	$Pd(PPh_3)_2Cl_2$, CuI, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, RT, 24 h	NDP
8	**98, Cl**	NMe_2	$Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, 100°C, 24 h	starting material

* NDP: no definite products

2.5 Suzuki cross-coupling of halopyrazolo[1,5-a]pyrimidines

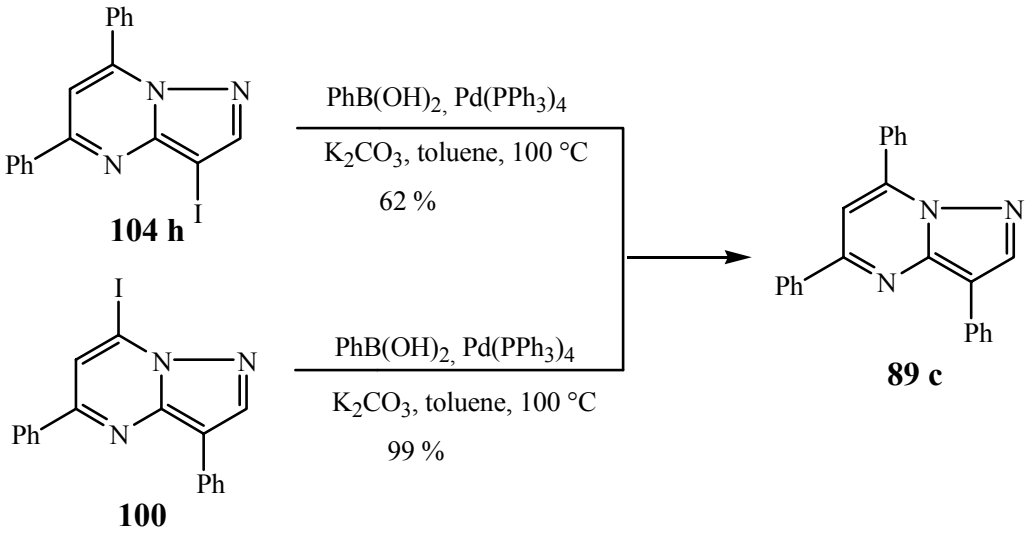
When 5,7-Dichloro-3-phenylpyrazolo[1,5-a]pyrimidine **101** was treated with three equivalents of phenylboronic acid and 1.2 equivalent of potassium carbonate using toluene as solvent and $Pd(PPh_3)_4$ as catalyst, 3,5,7-triphenylpyrazolo-[1,5-a]pyrimidine **89c** was isolated in 86 % yield. (**Scheme 2.16**)

Under the same conditions as above, 5,7-dichloro-3-phenylpyrazolo[1,5-a]pyrimidine **101** was coupled with one equivalent of phenylboronic acid and afforded two isomers **98** and **120** in a ratio of 23:54. The regio-selectivity could be increased by using 2 M aqueous Na_2CO_3 and DME at lower temperature (80 °C) providing **120** in 72% yield. (**Scheme 2.16**)



Scheme 2.16 Suzuki cross-coupling of **101** with phenylboronic acid

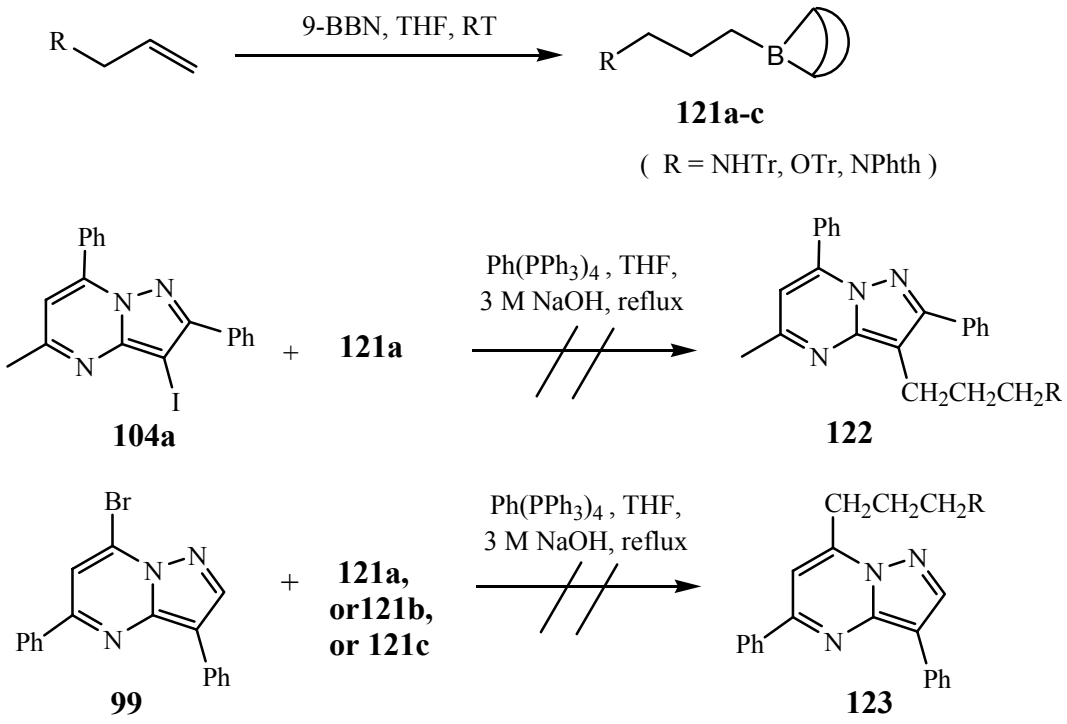
3-Iodo-5,7-diphenylpyrazolo[1,5-a]pyrimidine **104h** and 3-iodo-3,5-diphenylpyrazolo[1,5-a] pyrimidine **100** could be coupled with phenylboronic acid, catalyzed by $Pd(PPh_3)_4$, in the presence of K_2CO_3 in toluene to provide 3,5,7-triphenylpyrazolo[1,5-a]pyrimidine **89c** in 62% and 99%, respectively, after 16 h at 100°C. (**Scheme 2.17**)



Scheme 2.17

It is worth mentioning that the reactant **100** turned out to be an unsuccessful reactant to other Pd-catalyzed cross-coupling reactions, such as Heck coupling reaction and Sonogashira coupling (see **chapter 2.3.2** and **chapter 2.4.2**).

Further attempts to introduce aminopropyl or hydroxypropyl chains into the halopyrazolo-[1,5-a]pyrimidines **104a** or **99** by the help of corresponding 9-BBN derivated borane **121** were performed. Unfortunately, $Pd(PPh_3)_4$ catalysis failed under normal reaction conditions. (**Scheme 2.18**)



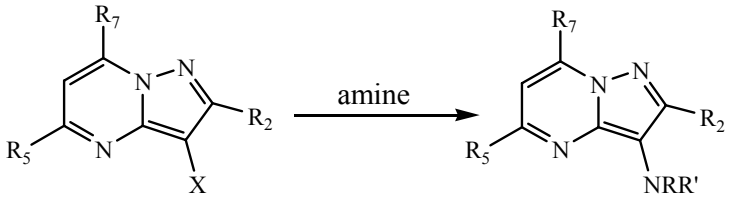
Scheme 2.18

2.6 Attempts to Buchwald-Hartwig amination and Negishi coupling of halopyrazolo[1,5-a]pyrimidines

While 7-chloro or 7-bromopyrazolo[1,5-a]pyrimidine can easily undergo nucleophilic substitution with substituted amines, 3-bromo- or 3-iodopyrazolo[1,5-a]pyrimidine resists uncatalyzed nucleophilic substitution.

Since 3-iodopyrazolo[1,5-a]pyrimidines could successfully be submitted to Suzuki, Heck and Sonagashira cross-coupling reactions, Pd-catalyzed amination (also called Buchwald-Hartwig amination) was advisable. Unfortunately, all attempts for Buchwald-Hartwig amination of 3-halopyrazolo[1,5-a]pyrimidines with several kinds of substituted amines under various reaction conditions were unsuccessful.(**Table 2.8**)

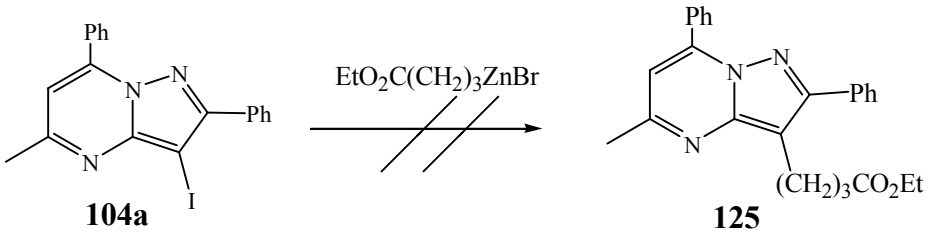
Table 2.8 Reaction conditions of Buchwald-Hartwig amination



103: X=Br, **104**: X=I **124**

Entry	Reactants	Amines	Reaction conditions	Results
1	**103**	$H_2N(CH_2)_3NMe_2$	$PdCl_2$(dppf), dppf, t-BuOK, dioxane 100°C, 4 days	NDP
2	**104a**	$H_2N(CH_2)_3NMe_2$	$Pd_2(dba)_3$, BINAP, t-BuONa, toluene, 100°C, 24 h	NDP
3	**104a**	$H_2N(CH_2)_3NMe_2$	K_2CO_3, glycol, 140°C, 24 h	NDP
4	**104a**	$H_2N(CH_2)_3NMe_2$	Microwave, 180°C, 170W, 20 min	NDP
5	**104a**	$H_2N(CH_2)_3NMe_2$	$Pd_2(dba)_3$, BINAP, t-BuONa, toluene, 80°C, 24 h	NDP
6	**104h**	$H_2N(CH_2)_3NMe_2$	$Pd_2(dba)_3$, BINAP, t-BuONa, toluene, 80°C, 4 days	NDP
7	**104h**	$H_2N(CH_2)_3NMe_2$	$Pd(OAc)_2$, BINAP, t-BuONa, toluene, 100°C, 24 h	NDP
8	**104h**	Morpholine	$Pd(OAc)_2$, BINAP, t-BuONa, toluene, 100°C, 24 h	deiodoproduct
9	**104h**	$NH(n\text{-}Bu)_2$	$Pd(OAc)_2$, $(t\text{-}Bu)_3P$, t-BuONa, toluene, 100°C, 24 h	deiodoproduct 80%

4-Ethoxycarbonyl-butylzincbromide was envisaged to introduce an alkyl chain into halopyrazolo[1,5-a]pyrimidine **104a** or **100**, which could be reduced to a hydroxybutyl group later on. Again, all attempts failed, although several catalysts and different conditions were used. (**Scheme 2.19**)

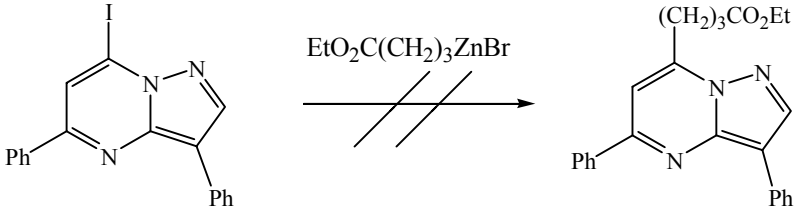


104a **125**

Conditions: **A**. $Ph(PPh_3)_4$, THF, RT, 4 days

B. $Pd(PPh_3)_2Cl_2$, Et_2O, RT, 24 h

C. $Pd(PPh_3)_2Cl_2$, THF, reflux, 20 h



100 **126**

Conditions: **A**. $Ph(PPh_3)_4$,THF, RT, 24 h

B. $Ph(PPh_3)_4$,THF, reflux, 24 h

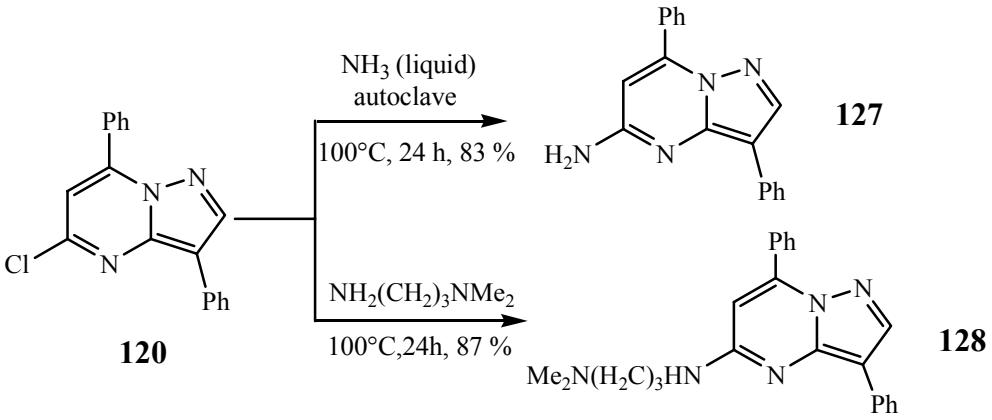
C. DMF, LiCl, 24 h

Scheme 2.19

2.7 Pd-free synthesis of pyrazolo[1,5-a]pyrimidine derivatives

2.7.1 Nucleophilic substitution of halopyrazolo[1,5-a]pyrimidine

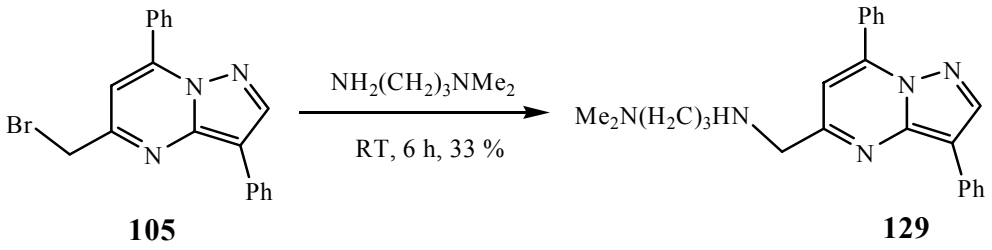
Chloroatoms adjacent to a 6-ring-N-heteroaromatics are prone to uncatalyzed nucleophilic substitutions by amines. Thus, we tried to introduce amino groups into 5-chloro-3,7-diphenylpyrazolo[1,5-a]pyrimidine **120**. The desired products **127** and **128** were obtained in good yields. (**Scheme 2.20**)



Scheme 2.20

The latter product **128** fits well into the pattern of envisaged calcineurin inhibitors **8**, where the side chain is connected to the core heterocycle via a nitrogen atom.

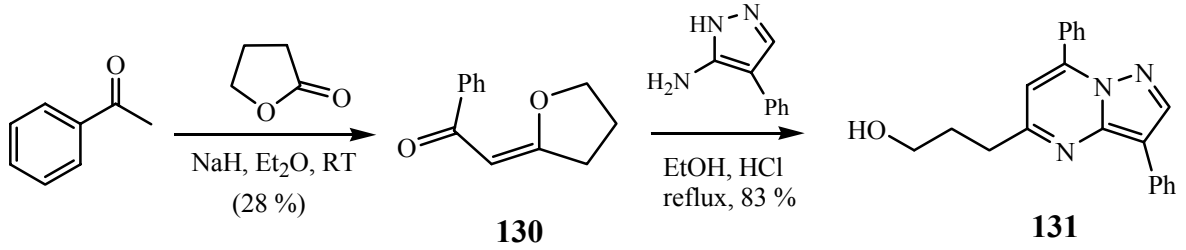
By benzylic-type nucleophilic subsititution at 5-bromomethyl-3,7-diphenylpyrazolo[1,5-a]-pyrimidine **105** a further variation of the side chain was achieved, where a nitrogen atom was in the centre of the alkyl chain.(formation of **129**, **Scheme 2.21**)



Scheme 2.21

2.7.2 Synthesis of pyrazolo[1,5-a]pyrimidine derivatives by ring-chain-transformation

As mentioned before (see **chapter 1.1.3**, page 4), the ring-chain-transformation is an effective tool to synthesize ω-functionalized heterocycles. We tried to apply this type of reaction to synthesize 5-hydroxypropylpyrazolo[1,5-a]pyrimidine **131**. The known 1,3-dicarbonyl precursor **130** [102] was obtained by condensation of acetophone with γ-butyrolactone, and could be ring-chain-transformation with 3-amino-4-phenylpyrazole to the desired product **131** in high yield. (**Scheme 2.22**)



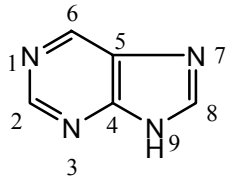
Scheme 2.22

Chapter 3: Purines and other bicyclic heterocycles

3.1 Synthesis of purine derivatives

3.1.1 Properties of purine

Purine derivatives are widely found in nature. They have a lot of biological and pharmaceutical activities. Among them, C-2, N-9 substituted 6-benzylaminopurine derivatives are cyclin-dependent kinase inhibitor [101]. 6-Alkylamino-9-benzyl-9H-purines are a class of anticonvulsant agents [103a]. 9-benzyl-6-dimethylamino-9H-purines have antirhinovirus activity [103b]. 2,6,9-Trisubstituted purines are selective CDK1 inhibitors [104]. 9-Benzylpurines are active against macobacterium tuberculosis [105]. 6-Alkenyl- and 6-alkynylpurines have cytostatic activity [106, 107]. 2-Alkynylpurines have inhibitory activity on platelet aggregation [108] and potent antihypertensive effects [109]. 9-Substituted purines are potent antiparasitic agents [110], high selective sulfotransferase inhibitors [111], and exhibit HIV-1 infectivity [112]. Furthermore, modified purines containing carbon substituents in the 2-, 6-, or 8-position are associated with interesting biological properties.



Purine

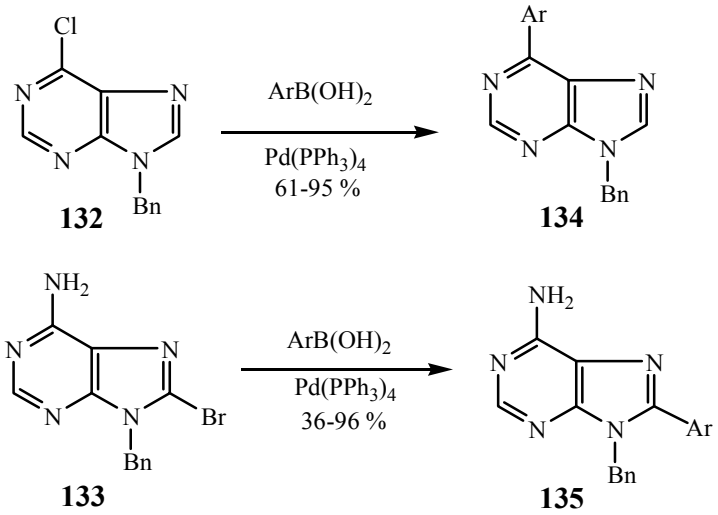
Purine is composed of a pyrimidine ring and an imidazole ring. The pyrimidine part is π-electron-deficient, and then nucleophilic displacement takes place more readily at 6-position than at 2-position. The same is observed in the oxidative addition to Pd(0), even purines with the otherwise weakll reactive chloro leaving group at position 6 can undergo Pd-catalyzed cross-coupling reactions. 8-halo-groups could also be substituted in this way. In our present work, Pd-catalyzed cross-coupling reactions were used to introduce aryl and in particular aminoalkynyl substituent into the purine skeleton in order to establish compounds of the general structure **8** as potential calcineurin inhibitors.

3.1.2 Overview of Pd-catalyzed coupling reactions of halopurines

Using metal-catalyzed coupling reactions of halopurines is the best choice to realize C-C bond formations in different positions. There are many reports about the coupling reactions of organozinc, organotin, organoboronic and Grignard reagents.

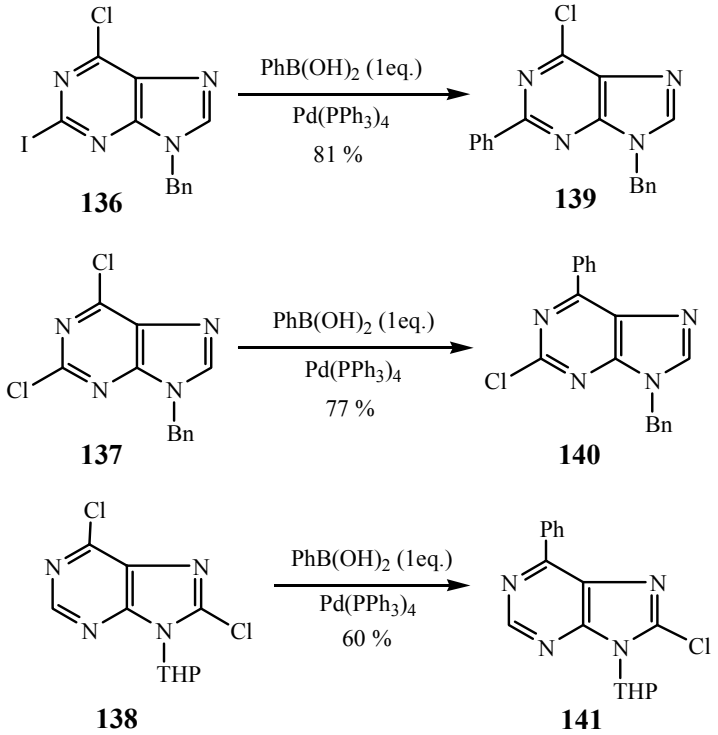
(1) Suzuki coupling

Halopurines can undergo cross-coupling reactions with arylboronic acid, to introduce aryl groups into 2-, 6- or 8-position. When 9-benzyl-6-bromopurine **132** and 6-amino-9-benzyl-8-bromopurine **133** reacted with a series of aryl boronic acid [103], **134** and **135** were obtained. (**Scheme 3**.**1**)



Scheme 3.1

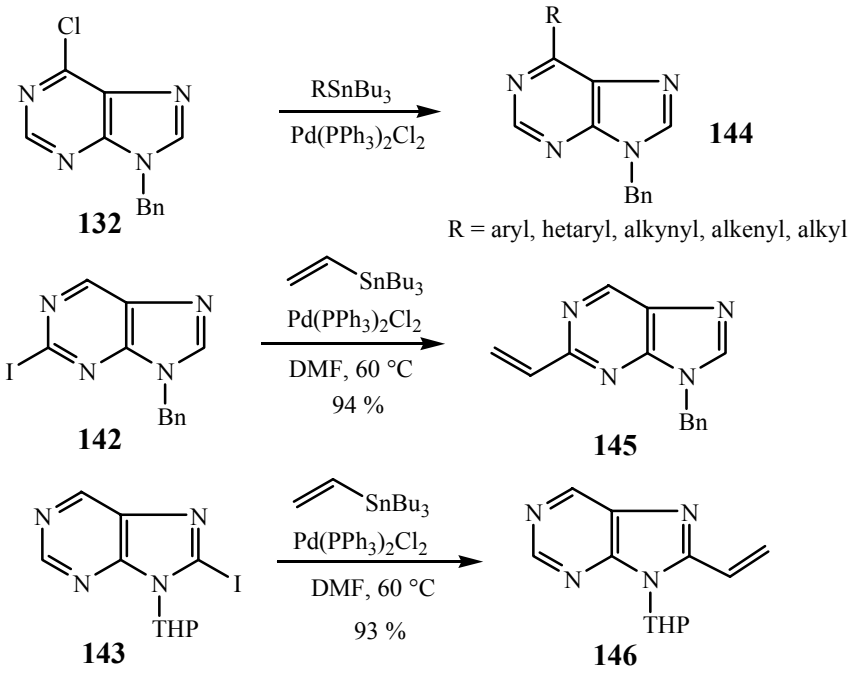
2,6-Dihalopurine **136**, **137** and 6,8-dihalopurine **138** can undergo regioselective Suzuki cross-coupling reactions, when equal equivalents of phenylboronic acid was used [113, 114]. **139**, **140, 141** were obtained in good yields. (**Scheme 3.2**)



Scheme 3.2

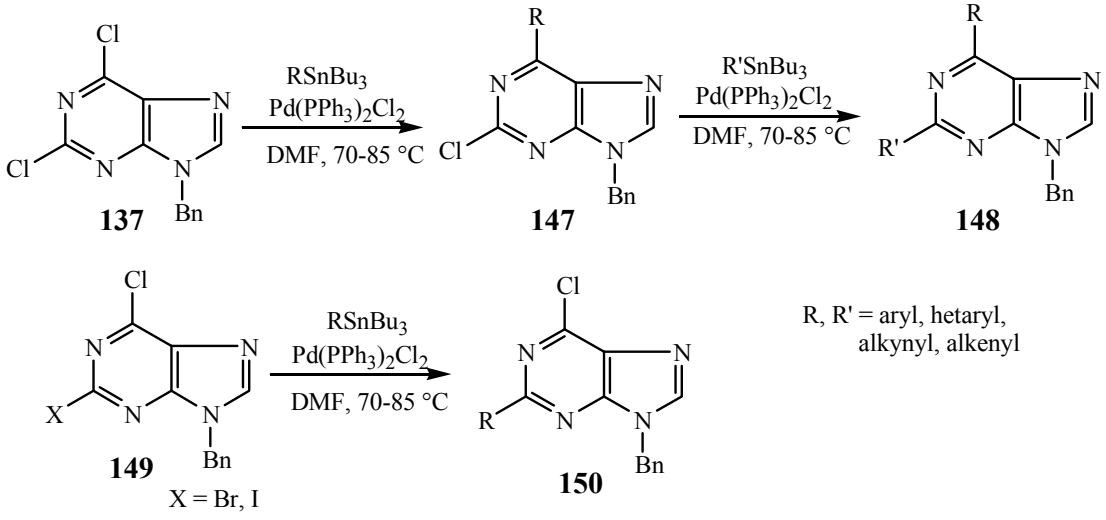
(2) Stille coupling

Halopurines can undergo cross-coupling reactions with organotin reagents. Aryl, alkenyl, alkynyl and alkyl groups were introduced into 2-, 6- or 8-position in this way [115-117], giving access to products **144**, **145**, and **146**. (**Scheme 3.3**)

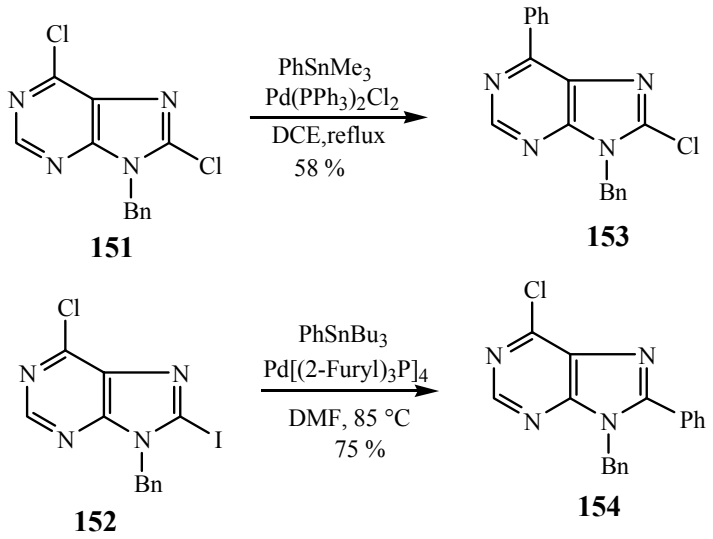


Scheme 3.3

2,6-Dihalopurine and 6,8-dihalopurine can undergo regioselective Stille cross-coupling reactions, when one equivalent of organotin reagent was used [118-120]. (**Scheme 3.4** and **Scheme 3.5**) Again, the regioselectivity depends on either the type of halo-leaving groups or the positions.



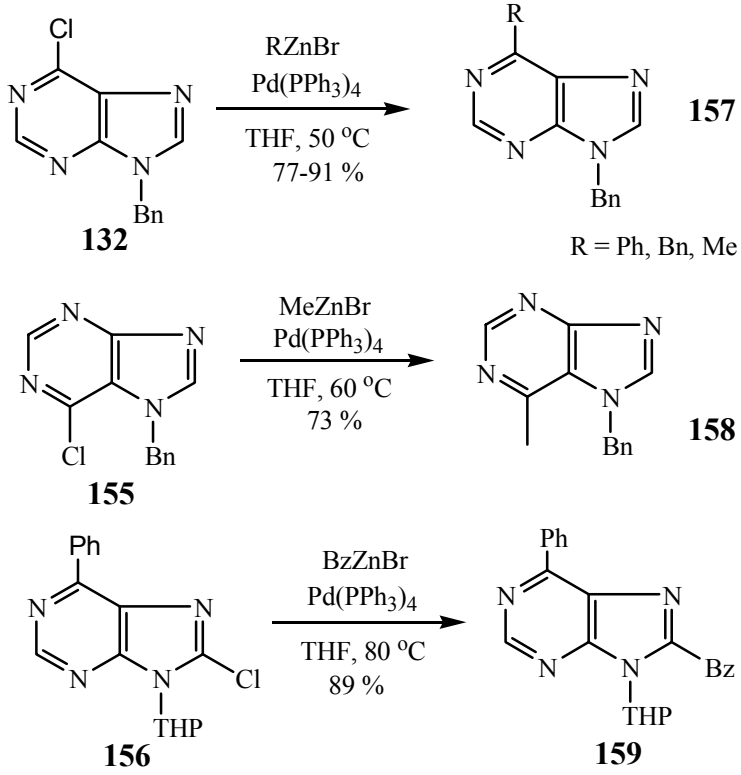
Scheme 3.4



Scheme 3.5

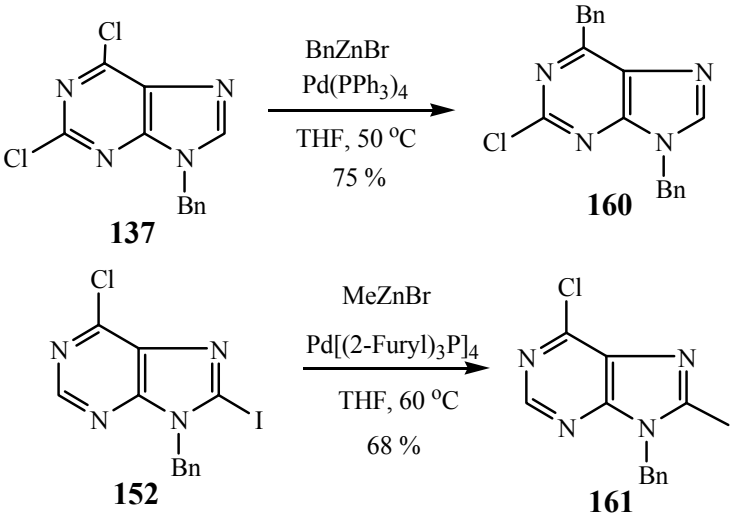
(3) Negishi coupling

9-Benzyl-6-chloropurine and 7-benzyl-6-chloropurine were shown to undergo Negishi cross-coupling reactions with phenyl-, benzyl- and alkylzinc reagents, and introduce phenyl-, benzyl- and alkyl group into the 6-position. 8-Chloro-6-phenyl-9-(tetrahydropyran-2-yl)purine reacted with benzylzinc chloride at 8-position [114, 115]. (**Scheme 3.6**)



Scheme 3.6

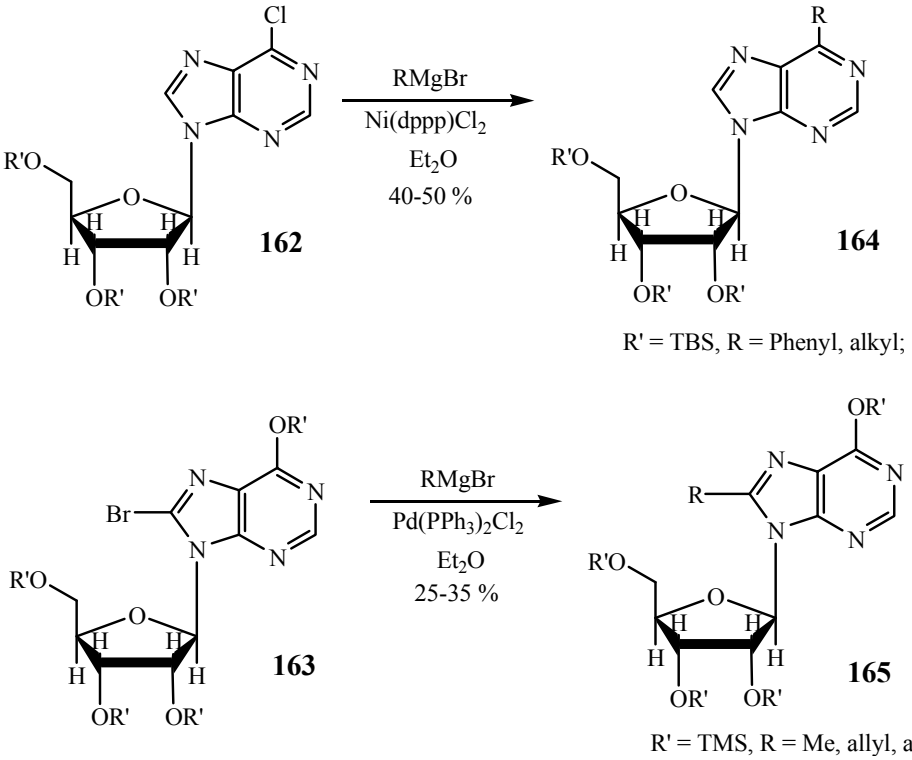
2,6-Dihalopurine and 6,8-dihalopurine can undergo regioselective Negishi cross-coupling reactions, when one equivalent of organozinc reagent was used [116]. (**Scheme 3.7**)



Scheme 3.7

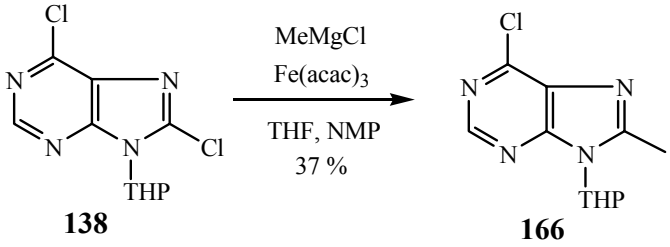
(4) Kumada coupling

Ni- and Pd-catalyzed cross-coupling reactions of halopurines with Grignard reagents were used to introduce aryl or alkyl group into 6- or 8-position [121, 122]. (**Scheme 3.8**)



Scheme 3.8

6,8-Dichloro-9-(tetrahydropyran-2-yl)purine **238** reacted with one equivalent of methyl magnesium chloride by introducing a methyl group into the 8-position rather than into the 6-position. This violates the normal positional reactivity sequence [114]. (**Scheme 3.9**)

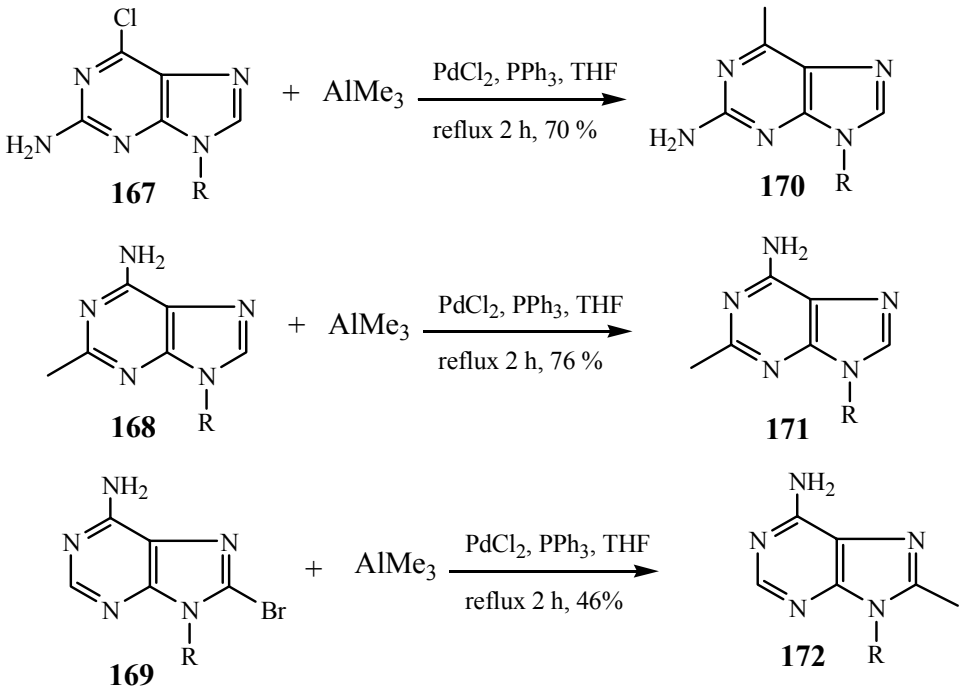


138 **166**

Scheme 3.9

(5) Coupling with alkylaluminium reagents

Halopurines can undergo cross-coupling reactions with trialkylalumiunium by introducing an alkyl group into 2-, 6- or 8-position [123]. (**Scheme 3.10**):



167 **170**

168 **171**

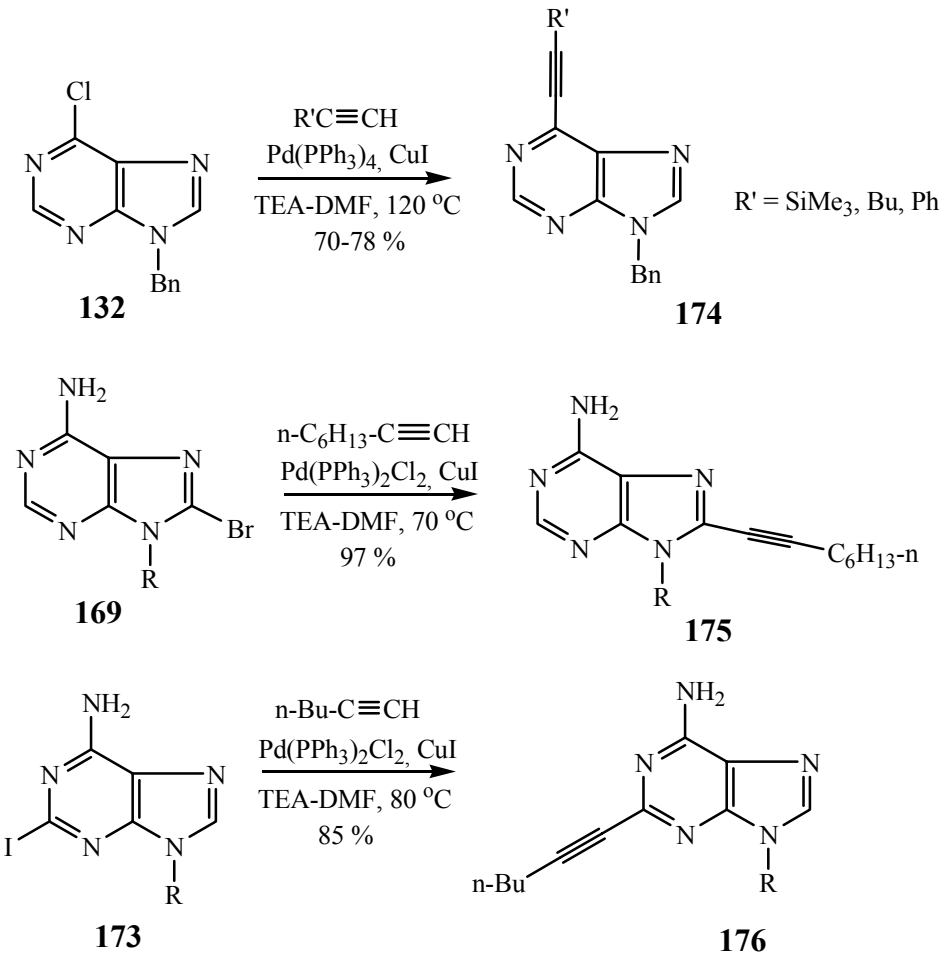
169 **172**

R = 2, 3, 5-Tri-O-acetyl-1-β-D-ribofuranosyl

Scheme 3.10 Pd-catalyzed couplings of halopurines with trimethylaluminium

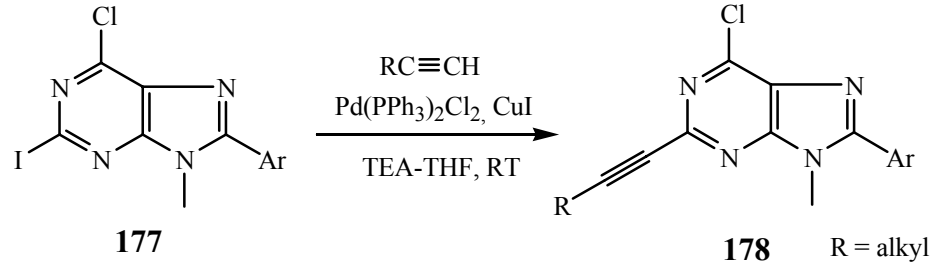
(6) Sonogashira coupling

Alkynyl groups were introduced in into 2-, 6- or 8-position of halopurines by Sonogashira reactions with alkynes [108, 109, and 124]. (**Scheme 3.11**) Generally, high yields of products were obtained.



Scheme 3.11

6-Chloro-2-iodopurine can undergo Sonogashira cross-coupling with alkynes regioselectively, and the 2-alkynyl substituted products **178** were obtained [124]. (**Scheme 3.12**)

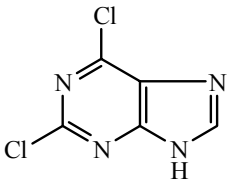


Scheme 3.12

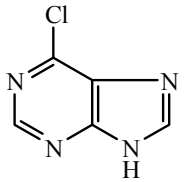
Our strategy of synthesizing potential calcineurin inhibitors of the general structure **8** with purine as central heterocycle, was based on the assembly of halopurines with two aryl substituents, followed by the introduction of a functionalized side chain by Sonogashira coupling or nucleophilic substitution. The aryl groups were either directly connected to the purine rings or separated by a methylene group, i.e. a benzyl group.

3.1.3 Synthesis of aryl-halopurines as starting materials

Synthesis of purine derivatives started with 2,6-dichloropurine **179** and commercially available 6-chloropurine **180**.

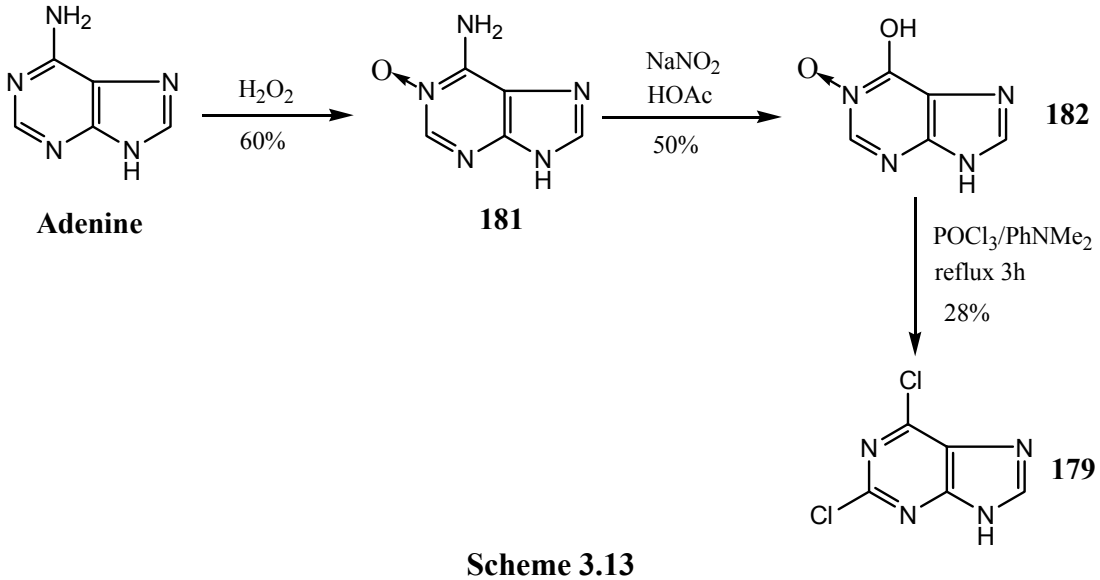


179
2,6-dichloropurine



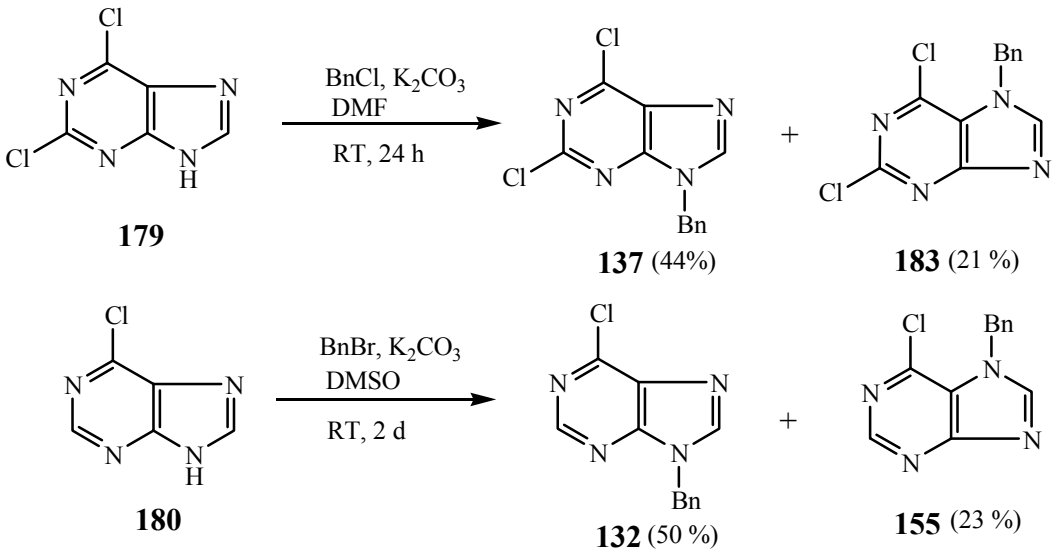
180
6-chloropurine

The former compound was obtained starting from adenine, which was readily oxidized with hydrogen peroxide in aqueous acetic acid to give adenine-1-N-oxide **181**. The hydroxylation of the N-oxide was carried out with sodium nitrite in acetic acid (diazo-hydrolysis) to give hypoxanthine-1-N-oxide **182**. 2,6-Dichloropurine **179** was obtained in low yield by treating **182** with phosphoryl chloride in the presence of catalytic amount of N,N-dimethyl aniline [126]. (**Scheme 3.13**)



Scheme 3.13

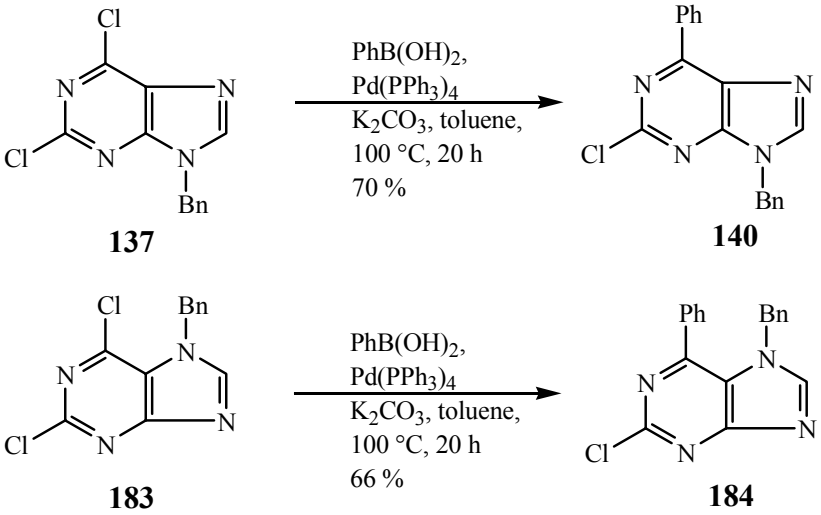
In order to introduce aryl groups into purine skeletons connected by a CH_2- spacer, 2,6-dichloropurine **179** was N-alkylated with benzyl chloride in DMF in the presence of K_2CO_3. The corresponding 9-benzyl r **137** and 7-benzyl isomer **183** were isolated [127] in yields of 44 % and 21 %, respectively. Similarly, 6-chloropurine **180** led to the two isomers **132** and **155** [102] in yields of 50 % and 23 %, respectively, after benzylation. (**Scheme 3.14**)



Scheme 3.14

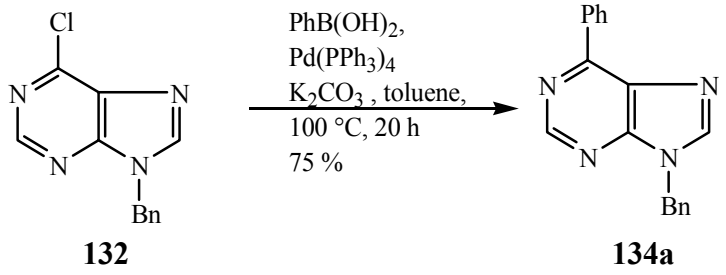
The N-benzylated chloropurines **137**, **183** and **132** were further submitted to Suzuki reactions in order to introduce the second aryl group of the general target structure **8**.

9-Benzyl-2,6-dichloro-purine **137** and 7-benzyl-2,6-dichloro-purine **183** reacted with one equivalent of phenylboronic acid in the presence of $Pd(PPh_3)_4$ and anhydrous K_2CO_3 to give the corresponding 6-phenyl products [113] **140** and **184** in yields of 70 % and 66 %, respectively. (**Scheme 3.15**)



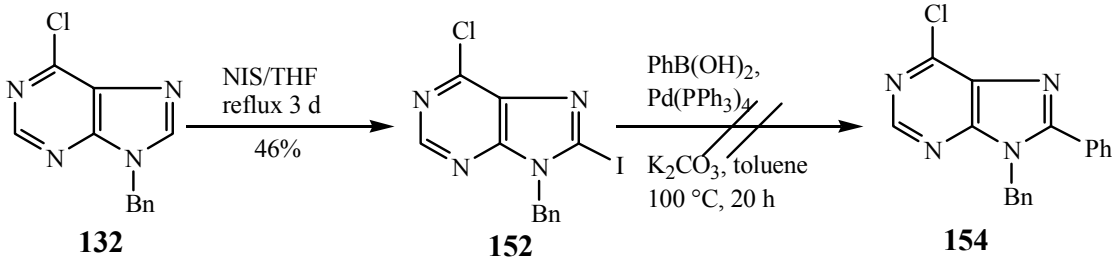
Scheme 3.15

Using the same Suzuki coupling conditions, and starting from 9-benzyl-6-chloro-purine **132**, 9-benzyl-6-phenylpurine **134a** was obtained in 75% yield [70, 113]. (**Scheme3.16**)



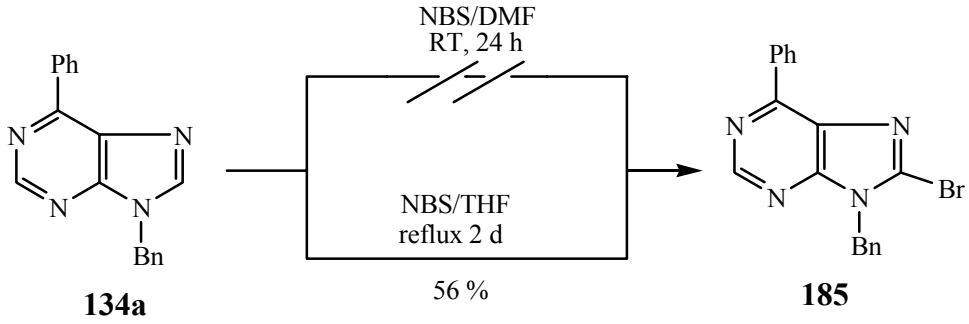
Scheme 3.16

In order to create a second reactive site at the purine skeleton, the chloropurine **132** was iodinated with NIS to give the 9-benzyl-6-chloro-8-iodo-purine **152** in a 46 % yield [120]. Unexpectedly, this product **152** resisted regioselective Suzuki cross-coupling with one equivalent of phenylboronic acid to the envisaged 9-benzyl-6-chloro-8-phenylpurine **154**. (**Scheme 3.17**)



Scheme 3.17

We further introduced a bromo-substituent into the position-8 of the 9-benzyl-6-phenyl-purine **134a** by bromination with NBS. While this reaction failed in DMF at room temperature, refluxing in THF for a long time was appropriate. (**Scheme 3.18**)

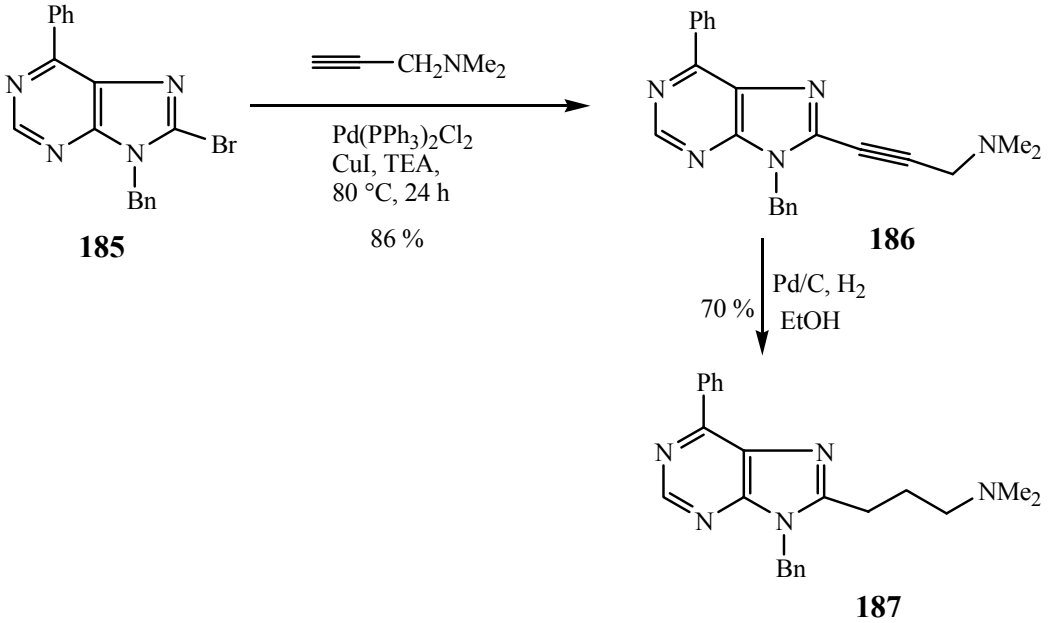


134a **185**

Scheme 3.18

3.1.4 Introduction of functionalized chains into purines

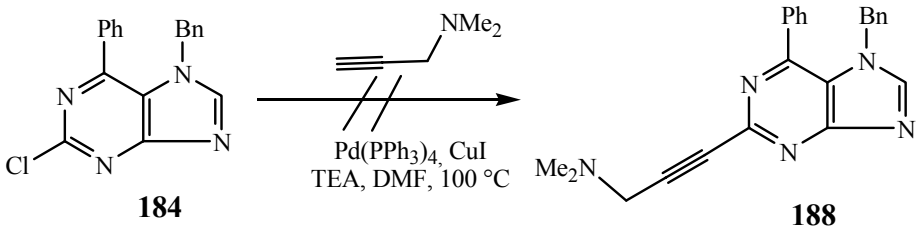
Introduction of a 3-dimethylaminopropyl chain into the 8-bromopurine **185** could be implemented by a two-steps sequence, i.e. first, by Sonogashira coupling of **185** with N,N-dimethyl propargylamine, followed by catalytic hydrogenation. Both steps gave good yields and provided an interesting product **187**. (**Scheme 3.19**) **187** could help to answer the question, whether the separation of one of the two aryl groups from the core heterocycle by a CH_2- spacer in the general structure **8** would effect the calcineurin inhibiting activity.



185 **186** **187**

Scheme 3.19

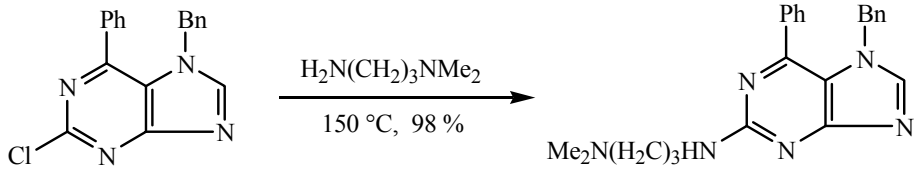
Attempts to introduce the 3-dimethylaminopropynyl chain into the 2-chloropurine **184** failed even under forcing Sonogashira conditions ($Pd(PPh_3)_4$, CuI, TEA, DMF, 100°C, 24 h). (**Scheme 3.20**)



184 **188**

Scheme 3.20

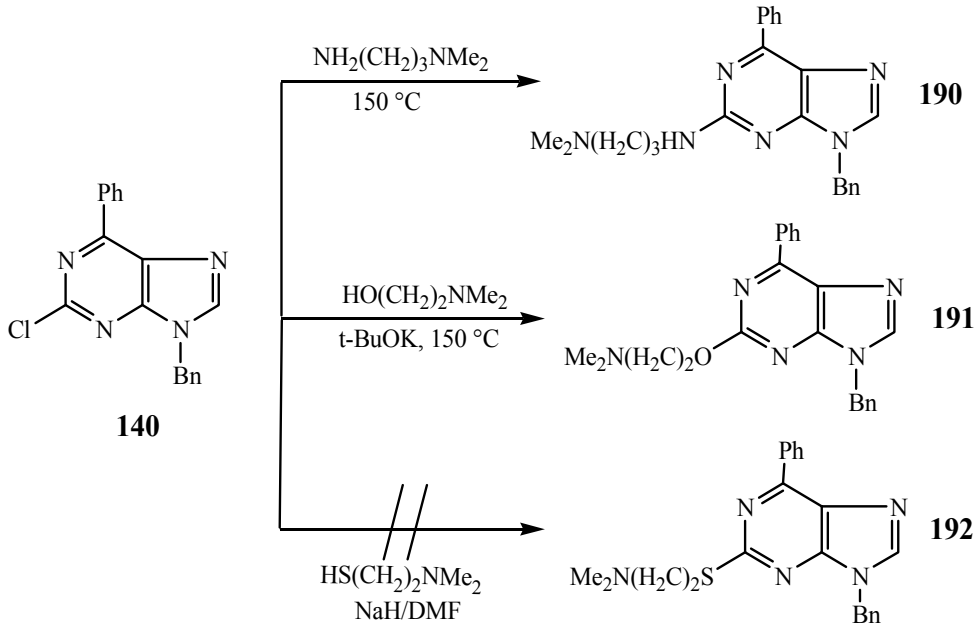
As a structural alternative, a 3-dimethylaminopropylamino group could be readily introduced into the 2-position of the 2-chloropurine **184** by uncatalyzed nucleophilic substitution providing **189** in high yield. (**Scheme 3.21**)



184 **189**

Scheme 3.21

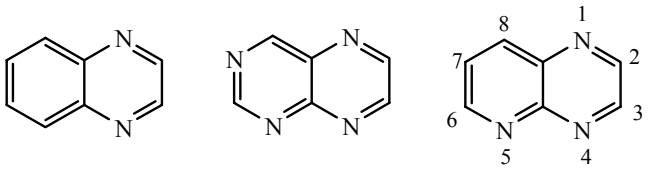
In an analogous way, the 2-(3-dimethylaminopropylamino)-purine **190** and the 2-(2-dimethyl-aminoethoxy)-purine **191** could be obtained starting from the isomeric 2-chloropurine **140** and 3-dimethylaminopropylamine or 2-dimethylaminoethanol, respectively**.** Treatment of **140** with 3-dimethyl-amino-propane-1-thiol, did not lead to the desired product **192**. (**Scheme 3.22**)



Scheme 3.22

3.2 Synthesis of pyrido[2,3-b]pyrazine derivatives

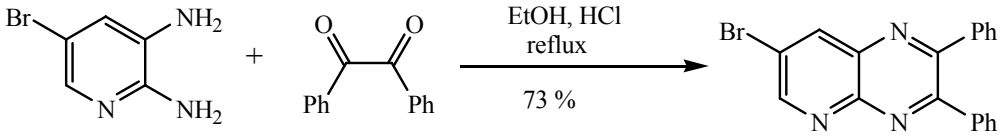
Quinoxaline and pteridine derivatives are very important nitrogen-containing heterocycles and have been widely used as pharmaceuticals. Quinoxaline derivatives have also been used as photoelectrochemical materials. Pyrido[2,3-b]pyrazine (5-azaquinoxaline) derivatives are the analogues of pteridine and quinoxaline, and have potential pharmaceutical activities and other applications [128-130].



quinoxaline pteridine pyrido[2,3-*b*]pyrazine

We chose the pyrido[2,3-b]pyrazine system as core heterocycle in potential calcineurin inhibitors of the general structure **8**.

A starting material **193** with two aryl substituents, suitable for the introduction of the side chains by Pd-catalyzed coupling, was easily on hand. Condensation of 5-bromo-2,3-diaminopyridine with benzil (1,2-diphenyl-ethane-1,2-dione) in refluxing ethanol, in the presence of hydrochloric acid, provided 7-bromo-2, 3-diphenylpyrido[2,3-b]pyrazine **193** in 73 % yield [131, 133]. (**Scheme 3.23**)



193

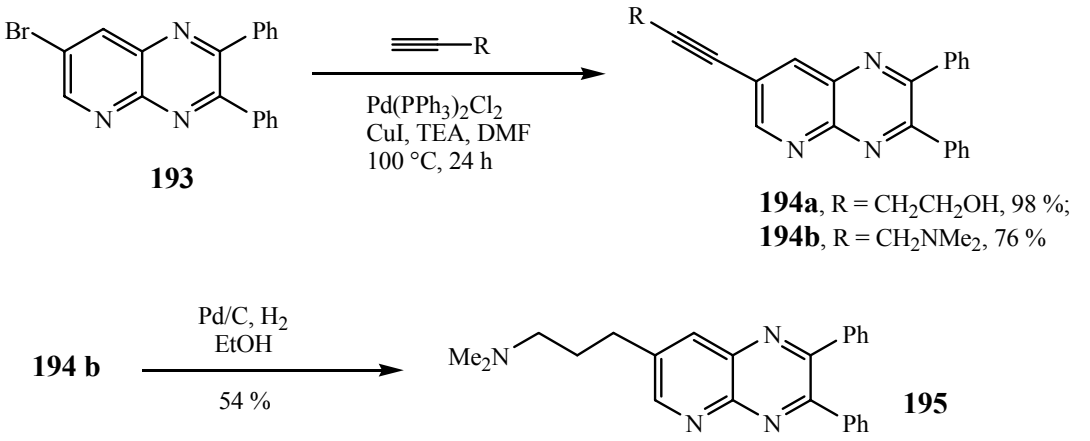
Scheme 3.23

7-Bromo-2,3-diphenylpyrido[2,3-b]pyrazine **193** was used in uncatalyzed nucleophilic substitution before. For instance, Kumari [131] reported the nucleophilic substitution of **193** with secondary amines. A mixture of 7-substituted and 8-substituted products were obtained. Vinot [132] reported the reactions of **193** with organomagnesium reagents. When **193** reacted with phenylmagnesium bromide, 2,3,7-triphenylpyrido[2,3-b]pyrazine was obtained in 28 % yield, while **193** reacted with ethylmagnesium bromide, providing 6-ethyl-4,6-dihydro compound in 55 % by addition reaction. Armoand [133] reported the reduction of pyrido[2,3-b]pyrazine derivatives with $NaBH_4$ to the corresponding 5,6-dihydro compound. To the best of our knowledge, there is no report about the cross-coupling

reaction of pyrido[2,3-b]pyrazine derivatives. Therefore, it is interesting to do some research in this field.

3.2.1 Synthesis of 7-alkynylpyrido[2,3-b]pyrazine and related compounds (Sonogashira cross-coupling reaction)

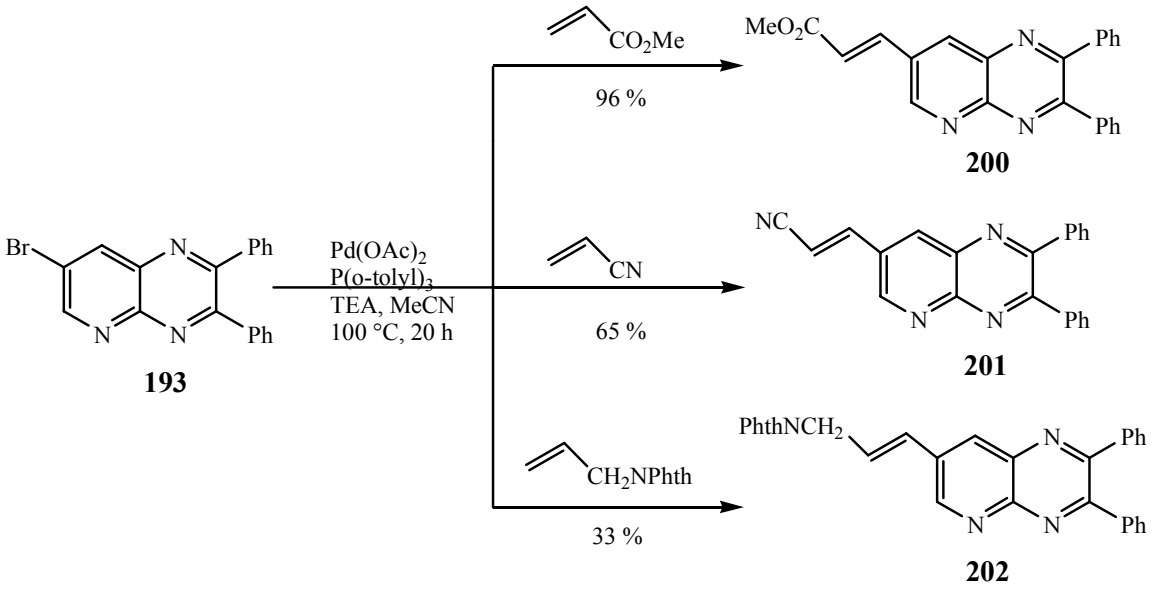
ω-Functionalized side chains could be introduced into 7-bromo-2,3-diphenylpyrido[2,3-b]pyrazine **193** by Sonagashira coupling with 3-butyn-1-ol or N,N-dimethylpropargyl amine, catalyzed by $Pd(PPh_3)_2Cl_2$ and CuI. 4-(2,3-Diphenyl-pyrido[2,3-b]pyrazin-7-yl)-but-3-yn-1-ol **194a**, and [3-(2,3-diphenyl-pyrido[2,3-b]pyrazin-7-yl)-prop-2-ynyl]-dimethyl-amine **194b** were obtained in high yields. Further catalytic hydrogenation of **194b** provided [3-(2,3-diphenyl-pyrido[2,3-b]pyrazin-7-yl)-propyl]-dimethyl-amine **195** in 54 % yield. The aromatic heterocyclic ring was not affected under these reductive conditions. (**Scheme 3.24**)



Scheme 3.24

3.2.2 Synthesis of 7-alkenylpyrido[2,3-b]pyrazine compounds (Heck cross-coupling reaction)

As an alternative to the aforementioned Sonogashira/hydrogenation sequence, the introduction of aminoalkyl or hydroxyalkyl chains into purines was envisaged by Heck coupling followed by reduction. Thus, 7-bromo-2, 3-diphenylpyrido[2,3-b]pyrazine **193** could be coupled with methyl acrylate, acrylonitrile or N-allyl-phthalimide, catalyzed by $Pd(OAc)_2/P(o\text{-}toly)_3$ in MeCN in the presence of TEA at 100 °C. The corresponding trans-alkene products **200**, **201** and **202** were obtained in variable yields depending on the type of alkene. (**Scheme 3. 25**)

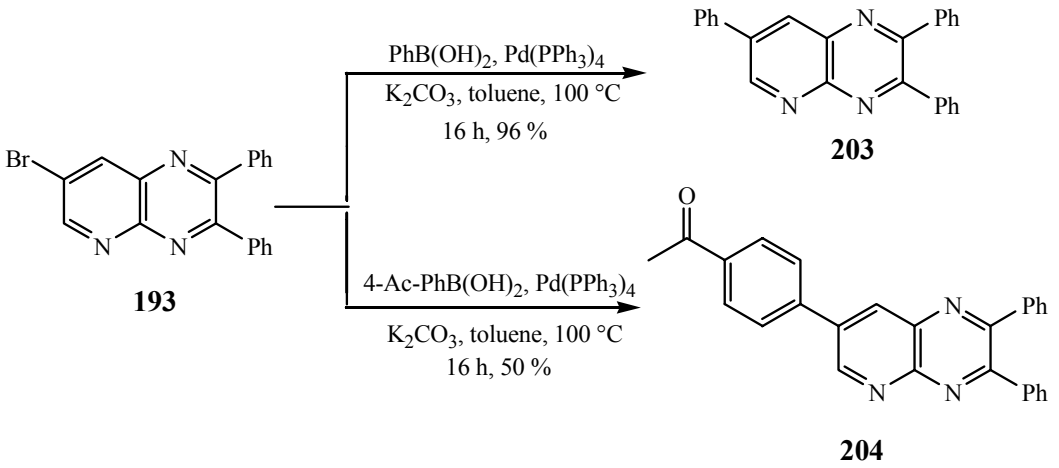


Scheme 3.25

3.2.3 Suzuki cross-coupling of 7-bromo-2, 3-diphenylpyrido[2,3-b]pyrazine

Since the known reaction of 7-bromo-2,3-diphenylpyrido[2,3-b]pyrazine with phenyl magnesium bromide afforded low yield of the corresponding substitution product **203** [133], we checked the suitability of the Suzuki reaction to introduce aryl groups into pyrido[2,3-b]pyrazine series.

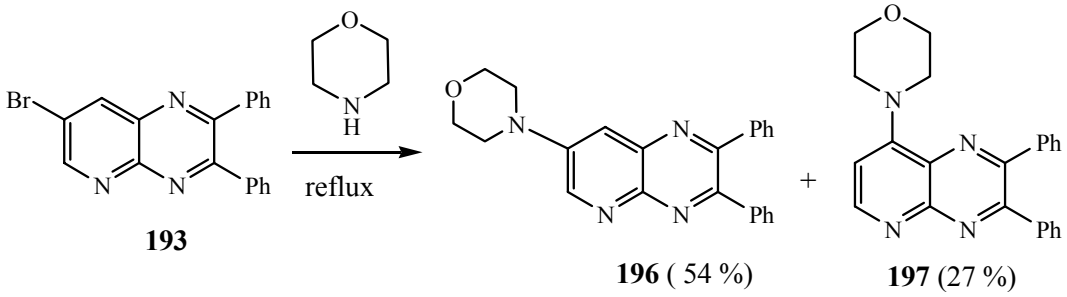
7-Bromo-2, 3-diphenylpyrido[2,3-b]pyrazine **193** reacted with arylboronic acids, in the presence of $Pd(PPh_3)_4$ and K_2CO_3 in toluene, affording 2,3,7-triphenylpyrido[2,3-b]pyrazine **203** and 1-[4-(2,3-diphenyl-pyrido[2,3-b]pyrazin-7-yl)-phenyl]-ethanone **204** in yields of 96% and 50%, respectively. Thus, the Suzuki cross-coupling is much better than the aforementioned uncatalyzed reaction with phenyl Grignard reagent. **(Scheme 3.26)**



Scheme 3.26 Suzuki cross-couplings of
7-bromo-2, 3-diphenylpyrido[2,3-b]pyrazine

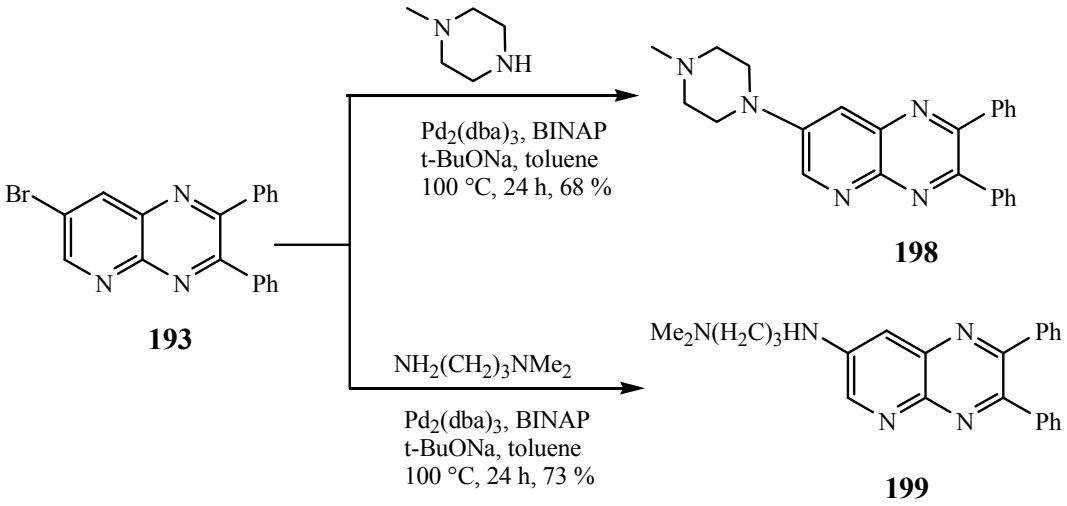
3.2.4 Buchwald-Hartwig amination of 7-bromo-2, 3-diphenylpyrido[2,3-b]pyrazine

Kumuri [131] reported the substitution of 7-bromo-5-azaquinoxaline **193** with secondary amines. In case of morpholine, two isomers of products **196** and **197** were isolated, probably formed via elimination/addition mechanism. (**Scheme 3.27**)



Scheme 3.27

We tried to achieve regioselective introduction of functionalized amines by Pd-catalysis. Using typical reaction conditions of Buchwald-Hartwig amination, 7-bromo-2,3-diphenylpyrido[2,3-b]pyrazine **193** was treated with 1-methyl-piperazine, catalyzed by $Pd_2(dba)_3$ and BINAP. Only one isomeric of amination product 7-(4-methyl-piperazin-1-yl)-2,3-diphenylpyrido[2,3-b] pyrazine **198** was obtained in 68 % yield. Similarly, when N,N-dimethyl-1,3-propan-diamine was used, N'-(2,3-diphenyl-pyrido[2,3-b]pyrazin-7-yl)-N,N-dimethylpropane-1,3-diamine **199** was obtained in 73 % yield. (**Scheme 3.28**)



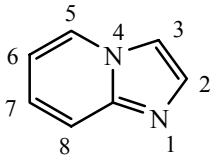
Scheme 3.28

Both products **198** and **199** fit into the general structure **8**, where the side chain is connected to the core heterocycle via a nitrogen bridge. In the former case, the side chain is part of a saturated ring.

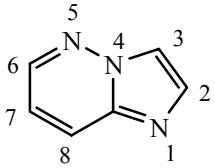
3.3 Synthesis of imidazo[1,2-a]pyridine and imidazo[1,2-b]pyridazine derivatives

3.3.1 Literature survey

Imidazo[1,2-a]pyridine and imidazo[1,2-b]pyridazine derivative are analogues of purine and have potential pharmaceutical and biological activities [134-137].



Imidazo[1,2-*a*]pyridine

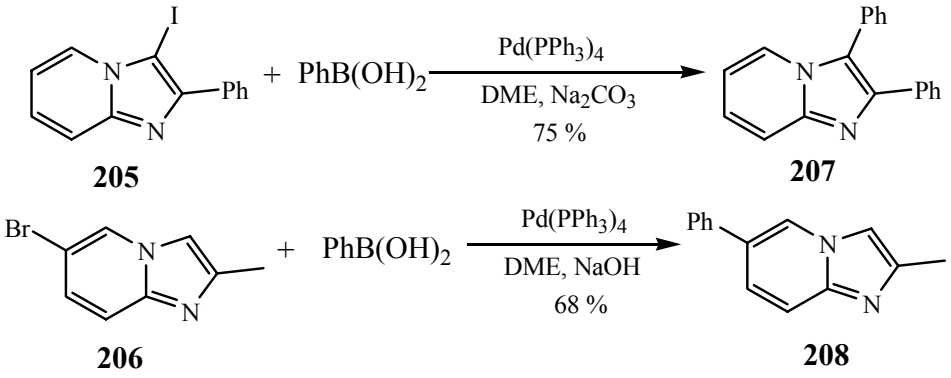


Imidazo[1,2-*b*]pyridazine

Similar to purine, they are composed of a 6-membered N-heterocycle and an imidazole ring. The pyridine (pyrazine) ring is π-electron deficient, and so nucleophilic displacement takes place more readily. The imidazole ring is π-electron excessive and can easily undergo electrophilic substitution.

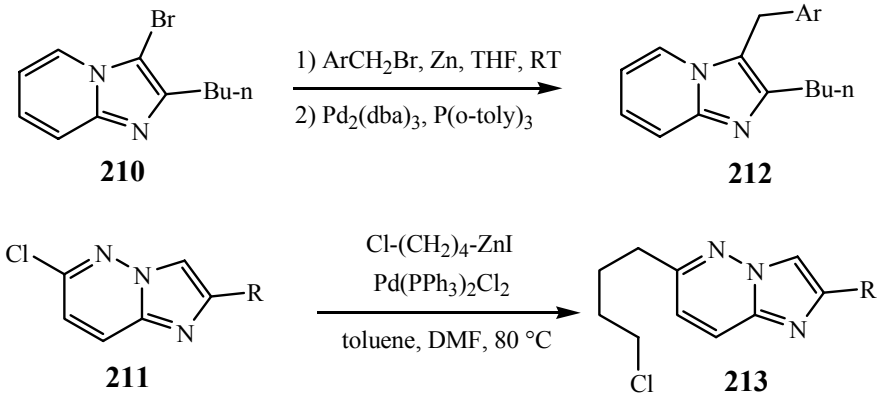
There are some reports about the nucleophilic substitutions at imidazo[1,2-a]pyridines and imidazo[1,2-b]pyridazines, however, only a few cross-coupling reactions are known.

Thus, 3-iodoimidazo[1,2-a]pyridine derivative **205** [138] and 6-bromoimidazo[1,2-a]-pyridine derivative **206** [139] underwent Suzuki cross-coupling reactions with phenylboronic acid to give **207** and **208**. (**Scheme 3.29**)



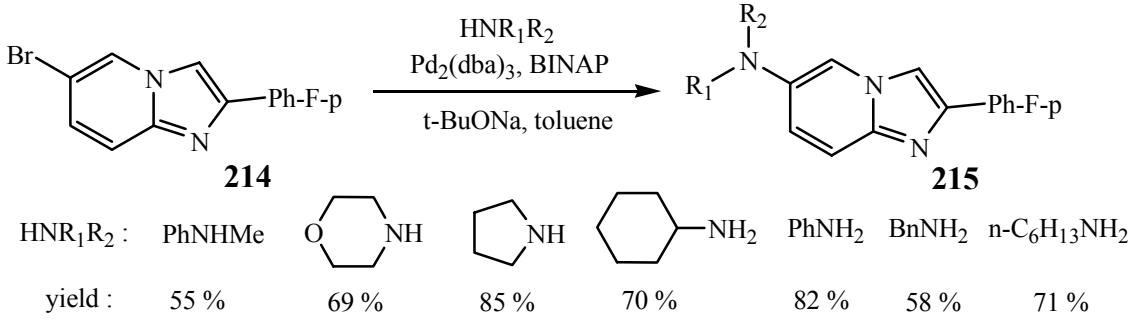
Scheme 3.29

3-Bromo-2-n-butylimidazo[1,2-a]pyridine **210** was coupled in a Negishi reaction with aryl methylzinc bromide to give **212**, catalyzed by $Pd_2(dba)_3$/P(o-toyl)$_3$ [140]. Similarly, 6-chloro-2-substituted imidazo[1,2-b]pyridazine **211** was transformed into **213** with 4-chloro-1-butylzinc iodide under $Pd(PPh_3)_2Cl_2$ catalysis [136]. (**Scheme 3.30**)



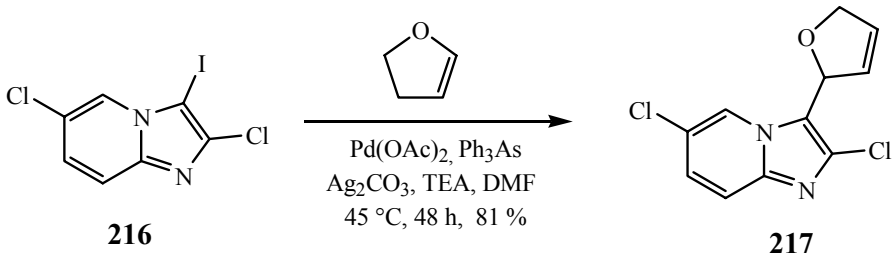
Scheme 3.30

Furthermore, 6-bromoimidazo[1,2-a]pyridine **214** underwent Buchwald-Hartwig aminations with secondary or primary amines in the presence of $Pd_2(dba)_3$ and BINAP [141], providing a series of substituted 6-aminoimidazo[1,2-a]pyridines **215**. (**Scheme 3.31**)



Scheme 3.31

Gudmundson [142] reported the Heck coupling of 3-iodoimidazo[1,2-a]pyridines such as **216** with dihydrofuran in the presence of $Pd(OAc)_2$-$PhAs_3$-Ag_2CO_3 systems. (**Scheme 3.32**)

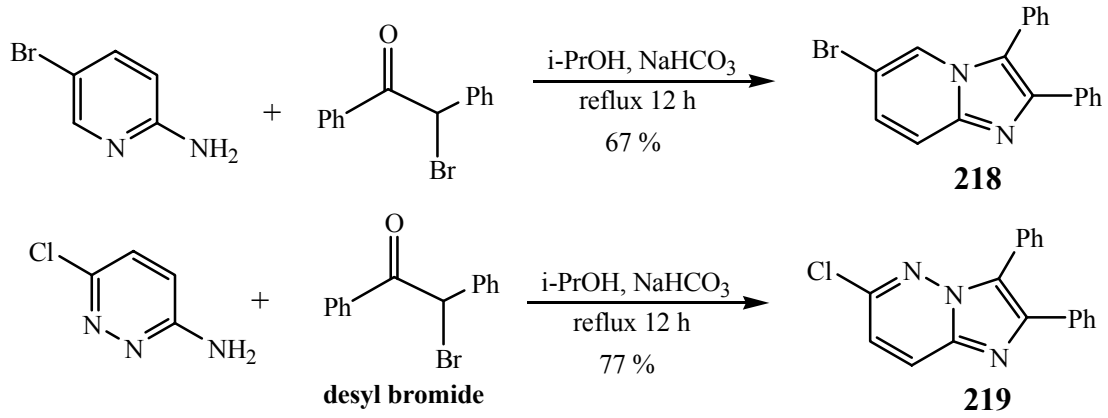


Scheme 3.32

3.3.2 Preparation of starting materials

6-Bromo-2, 3-diphenylimidazo[1,2-a]pyridine **218** and 6-chloro-2,3-diphenylimidazo[1,2-b]pyridazine **219** were chosen as starting materials. These compounds possess purine analogous heterocycles with two peripheral phenyl groups. In order to achieve compounds of the general structure **8**, the ω-functionalized side chains were introduced by Pd-catalyzed cross-couplings.

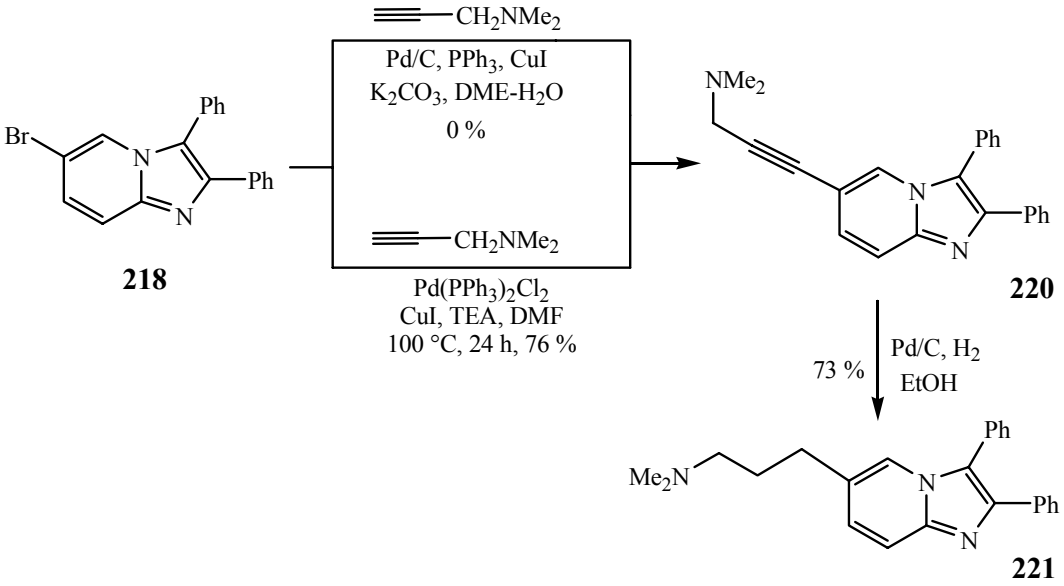
These two heterocycles **218** and **219** were prepared by condensation of 2-aminopyridine or 3-aminopyridazine with desyl bromide in a one-step procedure [143]. (**Scheme 3.33**)



Scheme 3.33

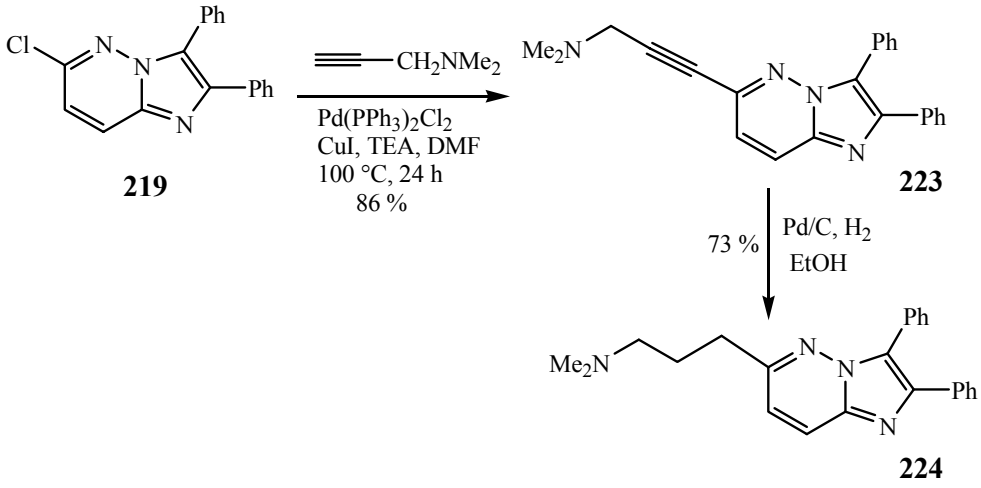
3.3.3 Pd-catalyzed introduction of functionalized side chains

Further following up our strategies to introduce aminoalkyl groups into heterocycles by the sequence Sonogashira coupling/hydrogenation, we tried to submit the imidazo[1,2-a]pyridine **218** and imidazo[1,2-b]pyridazine **219** to this synthetic methodology.
6-Bromo-2,3-diphenylimidadazo[1,2-a]pyridine **218** reacted with N,N-dimethylpropargyl amine to give [3-(2,3-diphenyl-imidazo[1,2-a]pyrimidin-6-yl)-prop-2-ynyl]-dimethyl-amine **220** in 76% yield, using $Pd(PPh_3)_2Cl_2$/CuI catalysis. When the reaction was catalyzed by Pd/C, PPh_3 and CuI, the desired product could not be observed. Further catalytic hydrogenation of **220** led to the [3-(2,3-diphenyl-imidazo[1,2-a]pyrimidin-6-yl)-propyl]-dimethyl-amine **221** in 73 % yield. (**Scheme 3.34**)



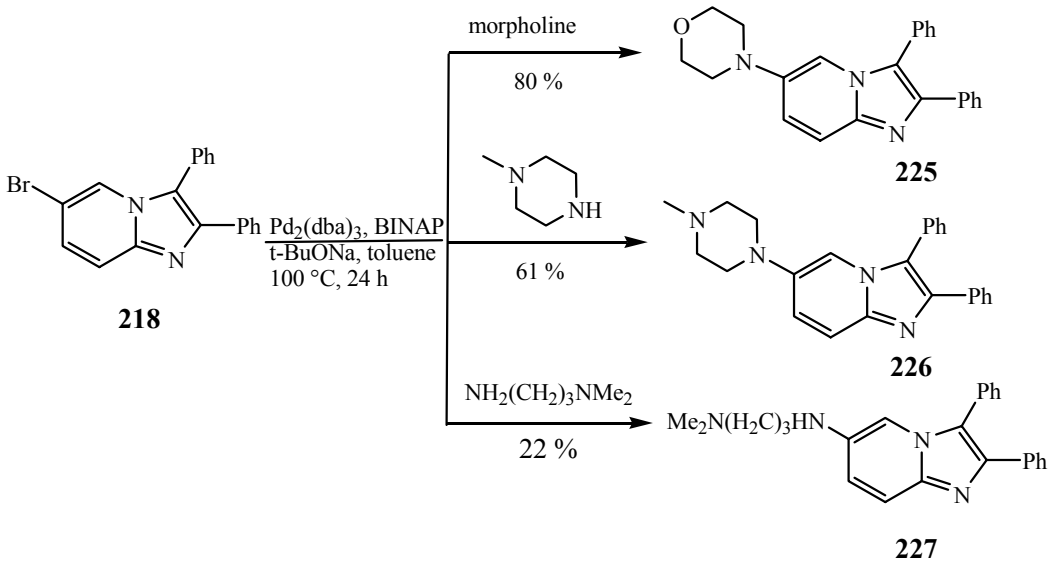
Scheme 3.34

The same sequence could be applied to 6-chloro-2,3-diphenylimidazo[1,2-b]pyridazine **219**, giving access to the [3-(2,3-diphenyl-imidazo[1,2-a]pyrimidin-6-yl)-propyl]-dimethyl-amine **224** in high yield via [3-(2,3-diphenyl-imidazo[1,2-a]pyrimidin-6-yl)-prop-2-ynyl]-dimethyl-amine **223**. (**Scheme 3.35**)



Scheme 3.35

Using the catalytic system $Pd_2(dba)_3$/BINAP, 6-bromo-2,3-diphenylimidazo[1,2-a]pyridine **218** could react with morpholine, 1-methyl-piperazine or N,N-dimethyl-1,3-propan-diamine to give 6-morpholin-4-yl-2,3-diphenylimidazo[1,2-a]pyridine **225**, 6-(4-methyl-piperazin-1-yl)-2,3-diphenylimidazo[1,2-a]pyridine **226**, and N'-(2,3-diphenyl-imidazo[1,2-a]pyridin-6-yl)-N,N-dimethyl-propane-1,3-diamine **227** (**Scheme 3.36**). Unfortunately, the most interesting product **227**, which fits best into the general structure **8**, gave only lower yield.



Scheme 3.36

Chapter 4: Pyrimidines and other monocyclic heterocycles

4.1 Synthesis of pyrimidine derivatives

Pyrimidine-containing molecules are of paramount importance in nucleic acid chemistry. Their derivatives including uracil, cytosine, adenine and guanine, are fundamental building blocks for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Pyrimidine derivatives exist extensively in nature. They have biological and pharmaceutical activities. N-3-substituted pyrimidinones are potent AT1 selective angiotensin II receptor antagonists [144]. Pyrimidine amide derivatives are novel antiallergic agents [145]. S-alkylated derivatives are potent antiviral agents [146]. 6-Alkylaminoderivatives are inhibitors of bacillus subtilis DNA polymerase III [147]. Aziridino derivatives are new cytotoxic agents with tumour-inhibitory activity [148]. Arylamino derivatives of pyrimidines are potential anti-cytomegalovirus agents [149], 2- or 4-(4-methylpiperazino)pyrimidines are 5-HT2A receptor antagonists [150].

Due to the electronegativity of the two nitrogen atoms, pyrimidine is a π-electron-deficient heterocycle. Therefore, nucleophilic displacements of nucleofugal leaving groups take place readily. This trend also translates to palladium chemistry. 4-Chloropyrimidine oxidatively adds to Pd(0) more readily than 2-chloropyrimidine.

We tried to assemble calcineurin inhibiting products of the general structure **8** with pyrimidine as core heterocycle via Pd-catalyzed coupling reactions.

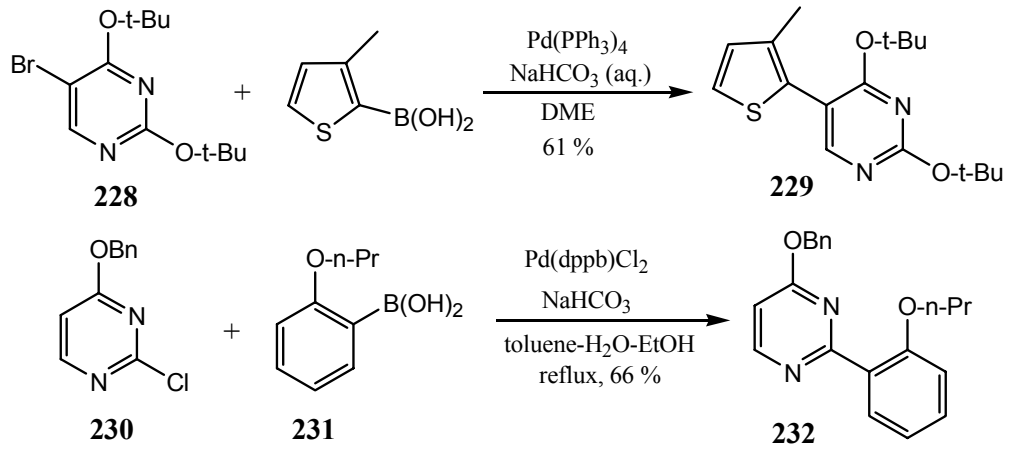
4.1.1 Overview of Pd-catalyzed coupling reactions of halopyrimidines

4.1.1.1 Pd-catalyzed cross-coupling reactions of monohalopyrimidines

Halogenated pyrimidines can undergo a series of Pd-catalyzed cross-coupling reactions, for example, Suzuki reactions, Sonogashira reaction, Stille reactions, Negishi reactions, Heck reactions:

(1) Suzuki reactions

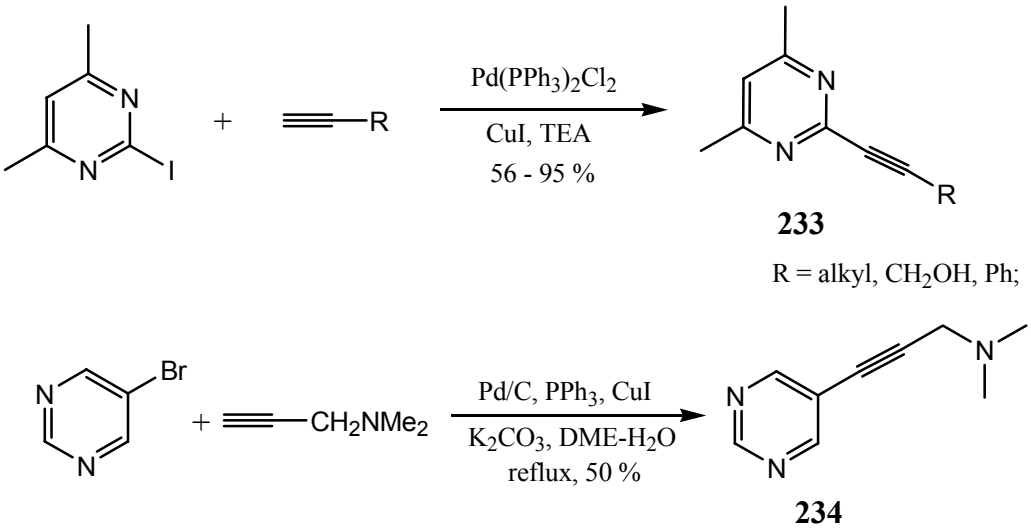
5-Bromo-2,4-di-tert-butoxypyrimidine **228** was coupled with 3-methyl-thiophene-2-boronic acid, and 5-substituted pyrimidine **229** was obtained [151]. Coupling of the 2-chloropyrimidine **230** with the arylboronic acid **231** afforded 2-arylpyrimidine **232** [152]. (**Scheme 4.1**)



Scheme 4.1

(2) Sonogashira reactions

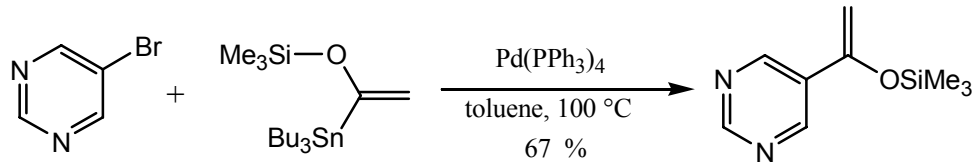
2-Iodo-4,6-dimethylpyrimidine was coupled with a series of terminal alkynes, providing alkynylpyrimidines **233** in good to excellent yields [153]. The Sonogashira coupling of 5-bromopyrimidine with N,N-dimethylpropargylamine gave the aminoalkyne **234** [154]. (**Scheme 4.2)**



Scheme 4. 2

(3) Stille reactions

5-Bromopyrimidine was coupled with 1-(trimethylsilyloxy)vinyltin to give 5-(1-trimethyl-silanyloxy-vinyl)-pyrimidine **235** in 67 % yield [155]. (**Scheme 4.3)**

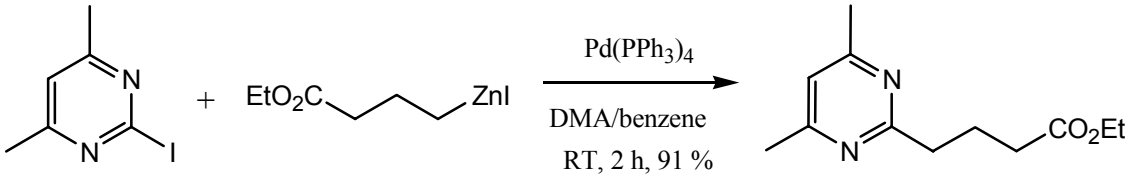


235

Scheme 4.3

(4) Negishi reactions

2-Iodo-4,6-dimethylpyrimidine was coupled with 3-ethoxycarbonylpropylzinc iodide at room temperature, catalyzed by $Pd(PPh_3)_4$, to give 4-(4,6-dimethyl-pyrimidin-2-yl)-butyric acid ethyl ester **236** in 91 % yield [156]. (**Scheme 4.4**)

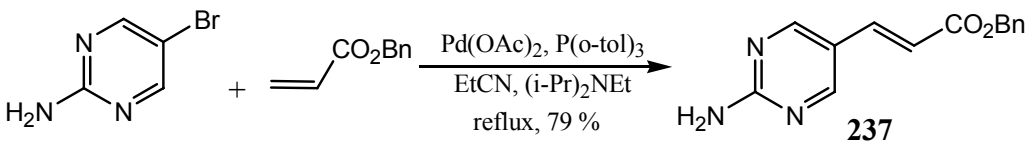


236

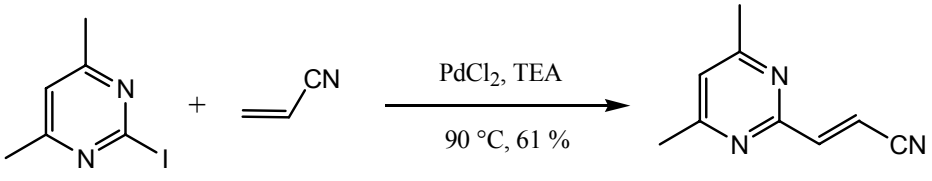
Scheme 4.4

(5) Heck reactions

2-Amino-5-bromo-pyrimidine was coupled with benzyl acrylate in 79 % yield [157], catalyzed by $Pd(OAc)_2/P(o\text{-}tolyl)_3$. 4,6-Dimethylpyrimidine-2-acrynitrile **238** was obtained in 61 % yield [158] by $PdCl_2$-catalyzed reaction of 2-iodo-4,6-dimethylpyrimidine with acrylonitrile. (**Scheme 4.5**)



237



238

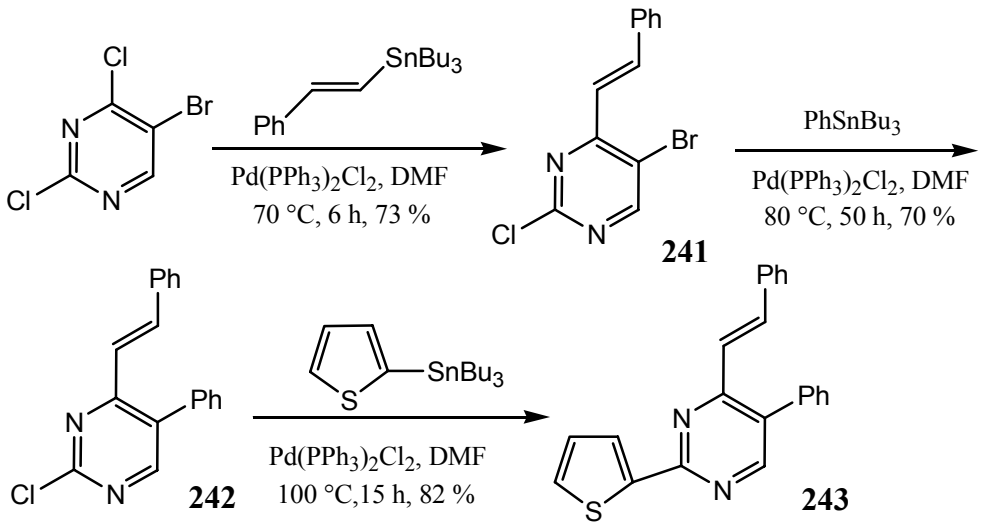
Scheme 4.5

4.1.1.2 Regioselective Pd-catalyzed couplings of polyhalopyrimidines

When more than one halo-substituent exist in a pyrimidine ring, the regioselectivity of cross-coupling has to be considered. If the halo-substituents are the same, the 4-position is in general more active than the 2-position in Pd-catalyzed cross-coupling reactions. But iodo-substituted positions are more active than chloro-substituted positions.

(1) Stille reaction:

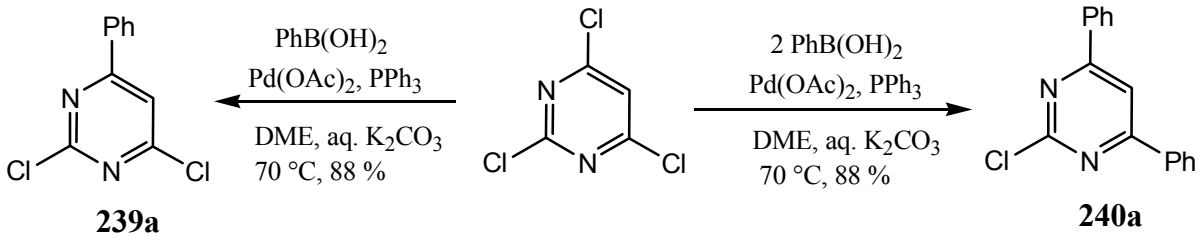
The positional reactivity of 5-bromo-2,4-dichloropyrimidine in Stille reactions is**:** 4-Cl > 5-Br > 2-Cl. Three different substituents could be introduced by stepwise Stille couplings to afford product **243** [159]. (**Scheme 4**.**6**)



Scheme 4.6

(2) Suzuki reaction:

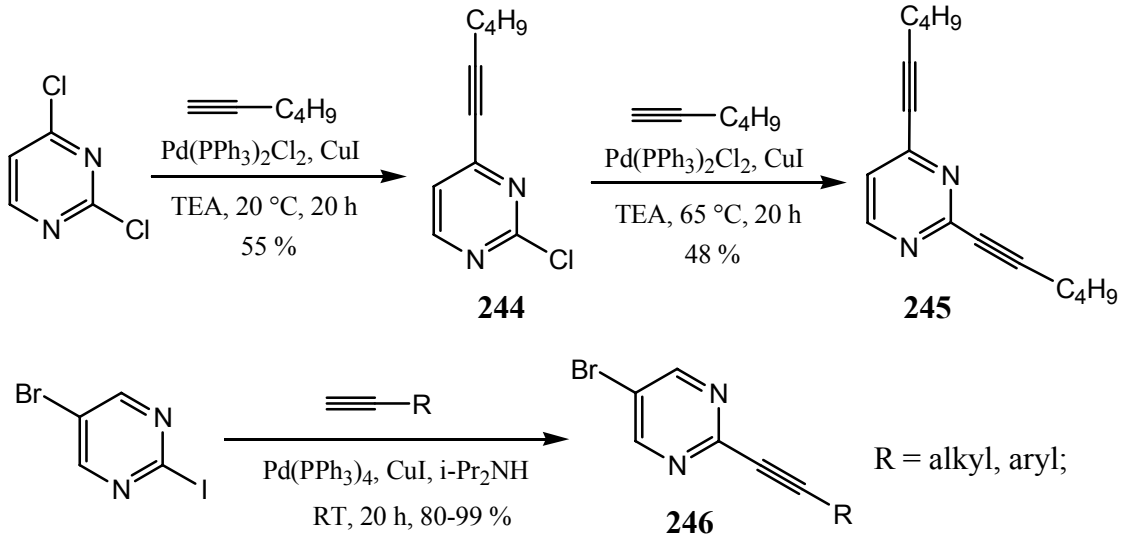
Reaction of 2,4,6-trichloropyrimidine with one equivalent of phenylboronic acid in the presence of $Pd(OAc)_2/PPh_3$ gave rise to the formation of 2,4-dichloro-6-phenylpyrimidine **239** with complete regioselectivity in high yield. Accordingly, 2,4,6-trichloropyrimidine formed 2-chloro-4,6-diphenylpyrimidine **240,** with two equivalents of phenylboronic acid, under the same conditions [160]. (**Scheme 4**.**7**)



Scheme 4.7

(3) Sonogashira reactions

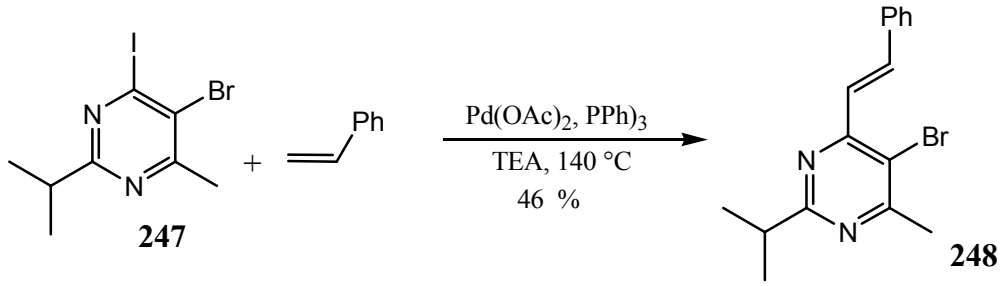
2,4-dichloropyrimidine reacted with one equivalent of 1-hexyne at room temperature, catalyzed by $Pd(PPh_3)_2Cl_2$ and CuI, to give the 2-chloro-4-alkynylpyrimidine **244**. Subsequent coupling of **244** with 1-hexyne at 65 °C, afforded 2,4-dialkynylprimidine **245** [161]. The iodo atom of 5-bromo-2-iodopyrimidine was selectively substituted by terminal alkynes under typical Sonogashira conditions, affording 5-bromo-2-alkynylpyrimidines **246** [162]. (**Scheme 4.8**)



Scheme 4.8

(4) Heck reaction

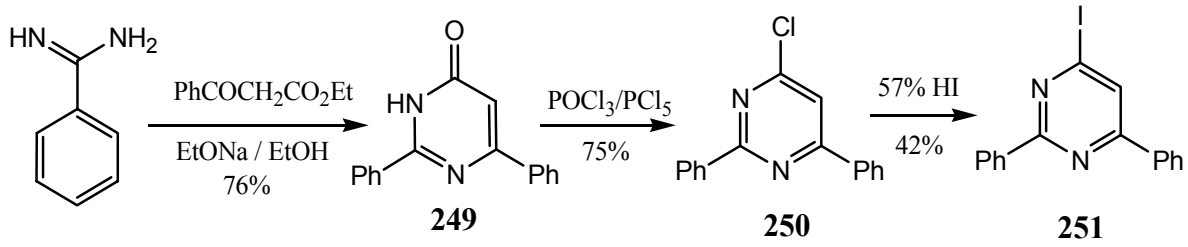
In 5-bromo-4-iodo-2-isopropyl-6-methylpyrimidine **247**, a selective substitution of the iodo atom was observed in Heck reaction, leading to the 4-styrylpyrimidine **248** [163]. (**Scheme 4.9**)



Scheme 4.9

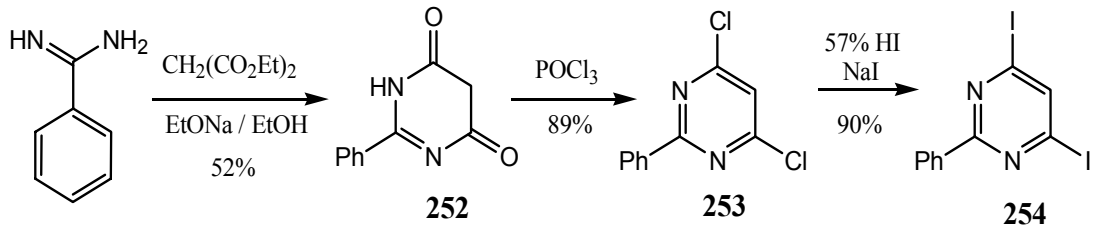
4.1.2 Synthesis of aryl substituted halopyrimidines

The halopyrimidines used in our investigations of Pd-catalyzed cross-couplings were obtained via corresponding pyrimidinones. Following a well-established pyrimidine synthesis, 2,6-diphenylpyrimidin-4-one **249** was obtained from benamidine and ethyl benzoylacetate [164]. **249** was further refluxed with $POCl_3$ and PCl_5 to give 75 % of 4-chloro-2,6-diphenylpyrimidine **250** [165]. After chloro-iodo exchange with HI 4-iodo-2,6-diphenylpyrimidine **251** was obtained in 42 % yield [165]. (**Scheme 4.10**)



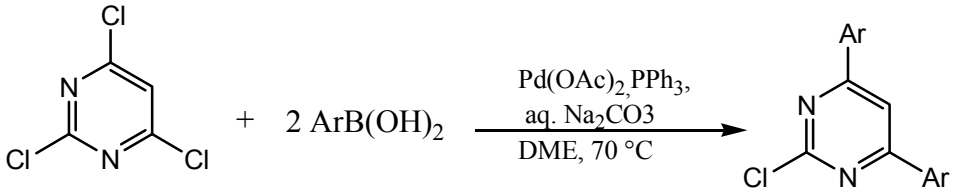
Scheme 4.10

Similarily, 4,6-dichloro-2-phenylpyrimidine **253** and 4,6-diiodo-2-phenylpyrimidine **254** were obtained in a straight forward way, starting from benzamidine and diethyl malonate [166]. (**Scheme 4.11**)



Scheme 4.11

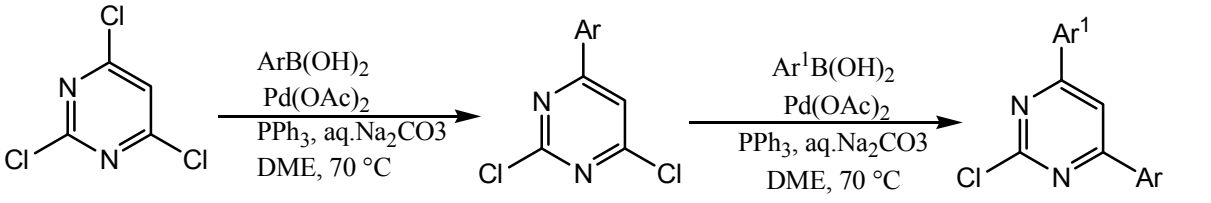
2-Chloro-4,6-diarylpyrimidines **240** were synthesized in high yields by Suzuki coupling of 2,4,6-trichloropyrimidine with 2 equivalents of arylboronic acid [160]. (**Scheme 4.12**)



240a, Ar = Ph, 70 %;
240b, Ar = 4-Cl-Ph, 82 %

Scheme 4.12

Using the same conditions, 2-chloropyrimidine **255** with different aryl substituents at position 4 and 6 was prepared by stepwise Suzuki reactions of 2,4,6-trichloropyrimidine. (**Scheme 4.13**)



239a, Ar = Ph, 81 %
239b, Ar = 4-Cl-Ph, 78 %

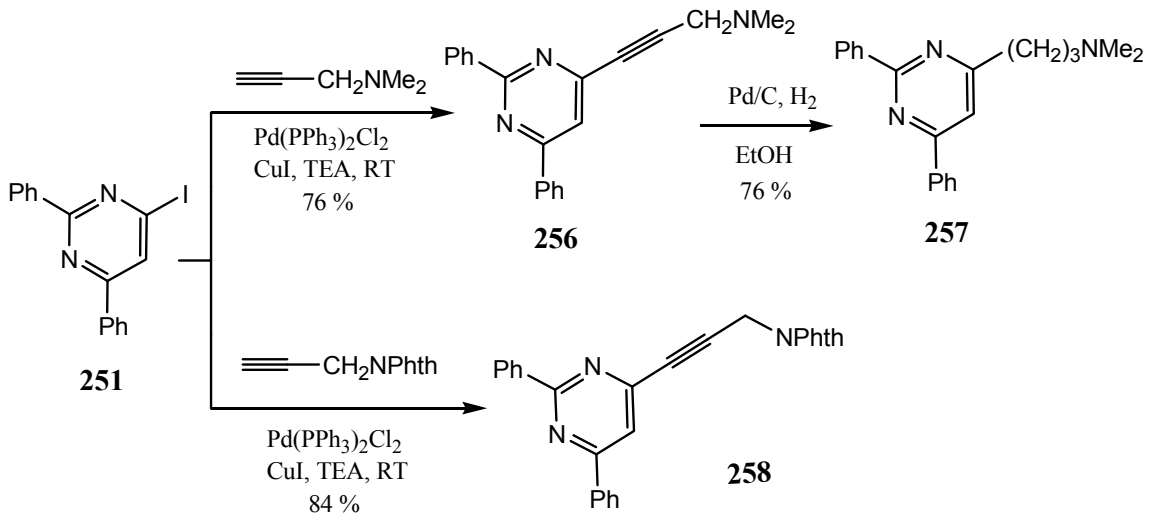
255, Ar = Ph ,
Ar^1 = 4-Cl-Ph

Scheme 4.13

4.1.3 Introduction of side chains into pyrimidines

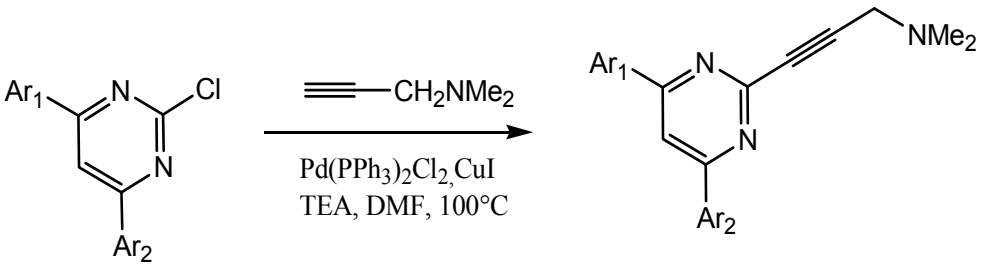
4.1.3.1 Sonogashira cross-coupling of halopyrimidines

In order to introduce teminal heteroatom functionalized chains into pyrimidines, diaryl-halopyrimidines were coupled with propargyl amine. Thus, 4-iodo-2,6-diphenylpyrimidine **251** was treated with N,N-dimethylpropargyl amine, catalyzed by $Pd(PPh_3)_2Cl_2$ and CuI, providing [3-(2,6-diphenyl-pyrimidin-4-yl)-prop-2-ynyl]-dimethyl-amine **256** in 76 % yield. **256** was further hydrogenated in the presence of Pd/C to give [3-(2,6-diphenyl-pyrimidin-4-yl)-propyl]-dimethyl-amine **257** in 76 % yield. Analogously, the phthalimidopropynyl pyrimidine **258** was obtained in high yield. (**Scheme 4.14**)



Scheme 4.14

More forcing conditions were necessary for Sonogashira reactions of 2-chloro-4,6-diaryl-substituted pyrimidines **240** or **255.** After heating at 100 °C for 24 h, the [3-(4,6-diaryl-pyrimidin-4-yl)-prop-2-ynyl]-dimethylamines **259a-259c** were obtained. KOAc turned out to be advantageous over triethylamine. (**Scheme 4.15**)



240 or 255 **259a-259c**

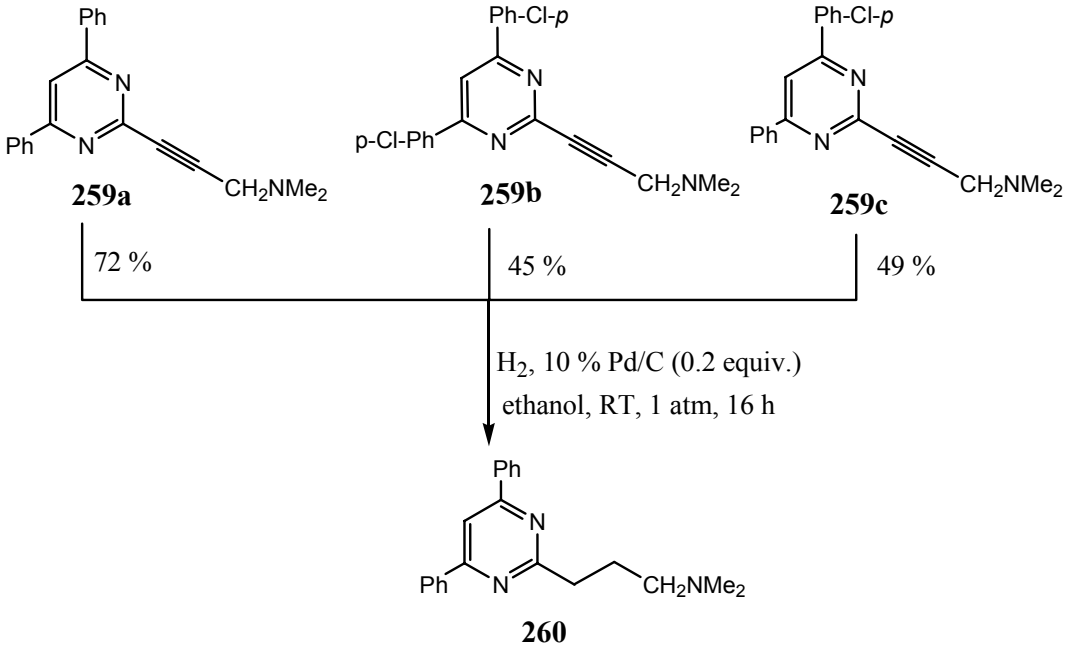
259a, $Ar_1 = Ar_2 =$ Ph, yield 38 %
(using KOAc as base, yield 70 %

259b, $Ar_1 = Ar_2 =$ p-ClPh, yield 51 %
259c, $Ar_1 =$ Ph, $Ar_2 =$ p-ClPh, yield 51 %

Scheme 4.15

The C-C triple bonds of **259a-259c** could be further hydrogenated in the presence of 10 % Pd/C (0.2 equiv.). In the case of the chlorophenyl substituted pyrimidines **259b-259c**, the chloro substituent was lost during the reduction of the triplet bond [167], i.e. the desired

target molecules with chloro substituted phenyl groups could not obtained by this route. (**Scheme 4.16**)



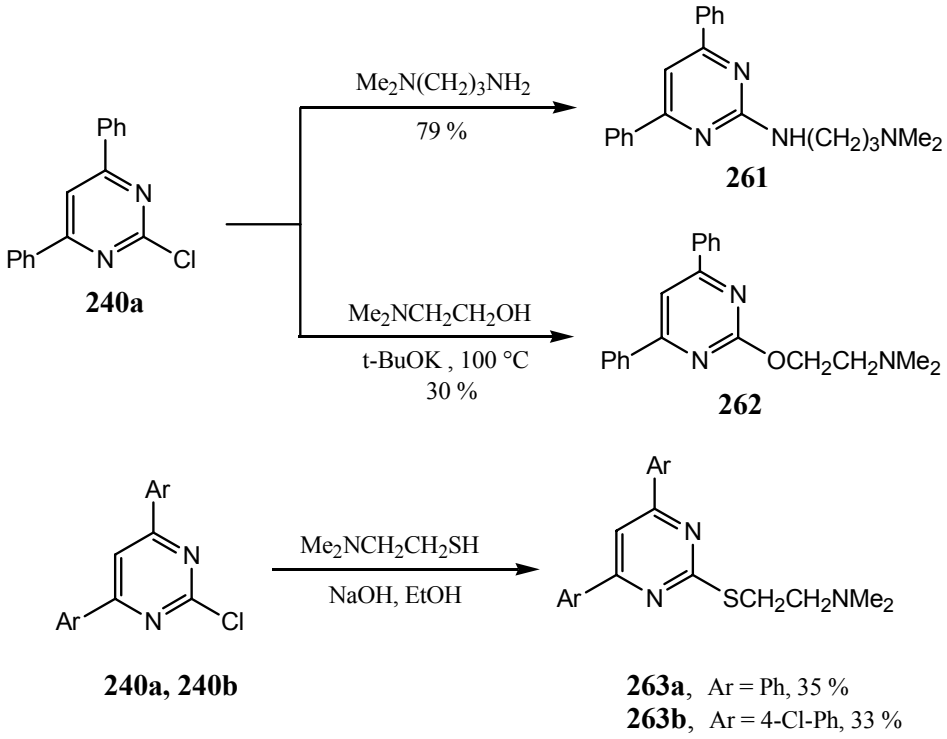
Scheme 4.16

4.1.3.2 Nucleophilic substitution of halopyrimidines

In potential calcineurin inhibiting compounds fitting into the general structure **8** the side chain can also be connected to the core heterocycle via a heteroatom. Such compounds can either be obtained by nucleophilic substitution or by Pd-catalyzed coupling.

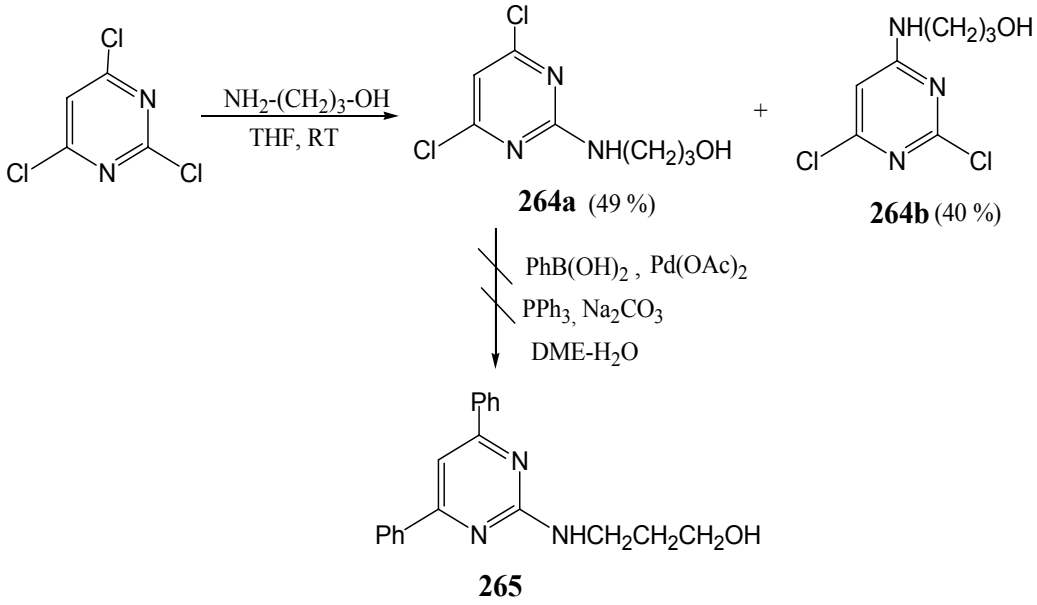
N,N-dimethyl-1,3-propanediamine, 2-dimethylaminoethanol, and 2-dimethylamino-ethanethiol, were applied in uncatalyzed nucleophilic substitution with 2-chloro-4,6-diarylpyrimidine **240**.

While high yield of N'-(4,6-diphenyl-pyrimidin-2-yl)-N,N-dimethyl-propane-1,3-diamine **261** was achieved. N'-(4,6-diphenyl-pyrimidin-2-yl)-N,N-dimethyl-propane-1,3-diamine **262** and [2-(4,6-diaryl-pyrimidin-2-yl-sulfanyl)-ethyl]-dimethyl-amine **263** were formed in low yield (about 30 %). Probably, competing oxidation of the 2-dimethylaminoethanethiol to the corresponding disulfide or substitution of chloride by tert-butoxide, respectively, could be responsible for the low yields. (**Scheme 4.17**)



Scheme 4.17

Reaction of 2,4,6-trichloropyrimidine [168] with two equivalents of propanolamine afforded two isomers **264a** and **264b** in a ratio of 40:49. Subsequent attempts to submit **264a** to a twofold Suzuki reaction to give **265** were unsuccessful. (**Scheme 4.18**) Therefore, the reversed sequence, i. e. first Suzuki coupling and then introduction of the side chain seems to be advantageous.



Scheme 4.18

4.2 Synthesis of pyridine derivatives

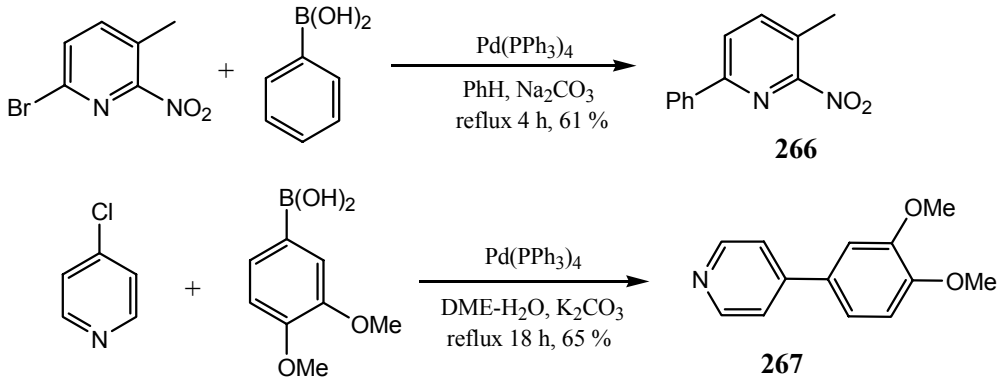
Many pyridine-containing molecules are important because of their biological and pharmacological properties. They have found applications as precursors of pharmacological compounds [169], in the synthesis of liquid crystals [170] or polymers [171], as well as ligands [172] for a lot of transition metal complexes.

Pyridine is a π-electron-deficient heterocycle. Due to the electronegativity of the nitrogen atom, the corresponding α and γ position of pyridine bear partial positive charge, making them prone to nucleophilic attacks. A similar trend occurs in the context of Pd-catalyzed coupling reactions.

4.2.1 Overview of Pd-catalyzed coupling reactions of halopyridines

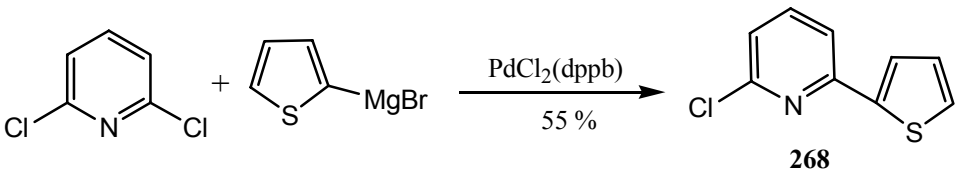
Halogenated pyridines underwent a series of Pd-catalyzed cross-coupling reactions, for example, Suzuki reactions, Sonogashira reaction, Stille reactions, Negishi reactions, Heck reactions, Buchwald-Hartwig amination, etc. Iodide, bromide and chloride could be used as suitable leaving groups. If two halogen atoms are found in the pyridine ring, it is possible to substitutite one and keep the other. (e.g. formation of **268**)

(1) Suzuki reactions [173, 174]



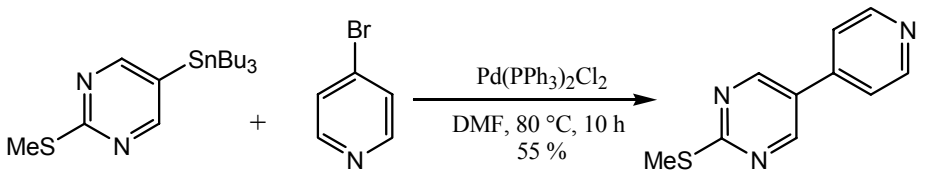
Scheme 4.19

(2) Kumada reactions [175]



Scheme 4.20

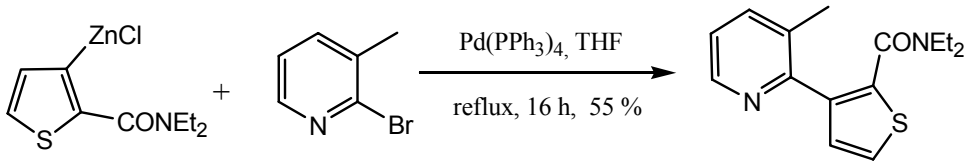
(3) Stille reactions [176]



269

Scheme 4.21

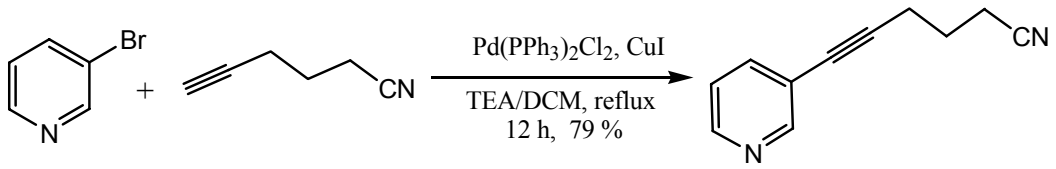
(4) Negishi reactions [173]



270

Scheme 4.22

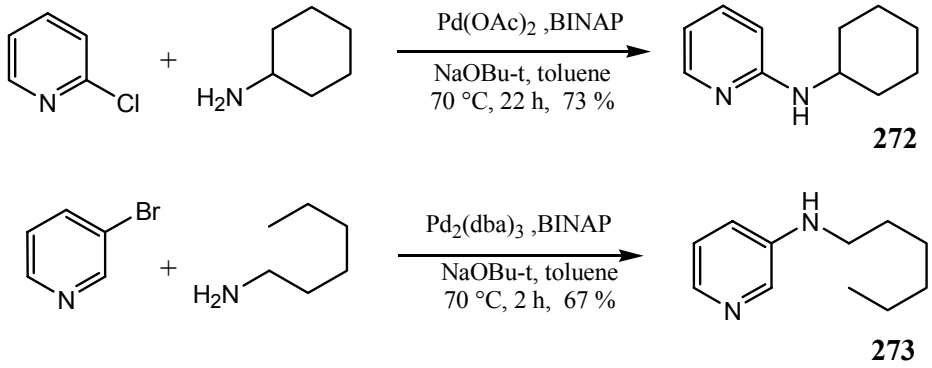
(5) Sonogashira reactions [177]



271

Scheme 4.23

(6) Buchwald-Hartwig aminations [178]

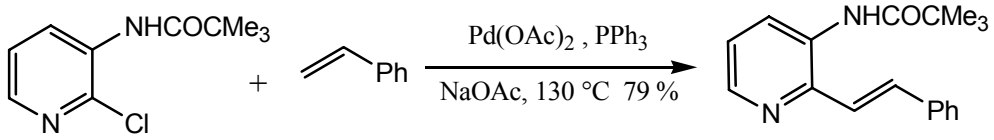


272

273

Scheme 4.24

(7) Heck reactions [179]

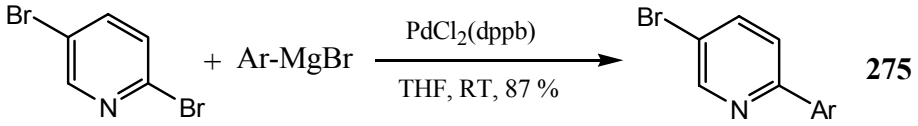


274

Scheme 4 25

Mono couplings are regioselective if two or more different halogen atoms are attached in the pyridine ring (I > Br > Cl) or equal halogen atoms are found at different positions (2-position > 4-position > 3-position).

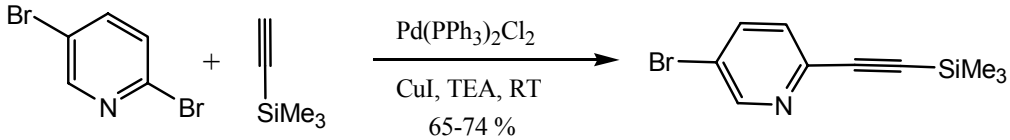
(1) Kumada reactions [180]



275

Scheme 4.26

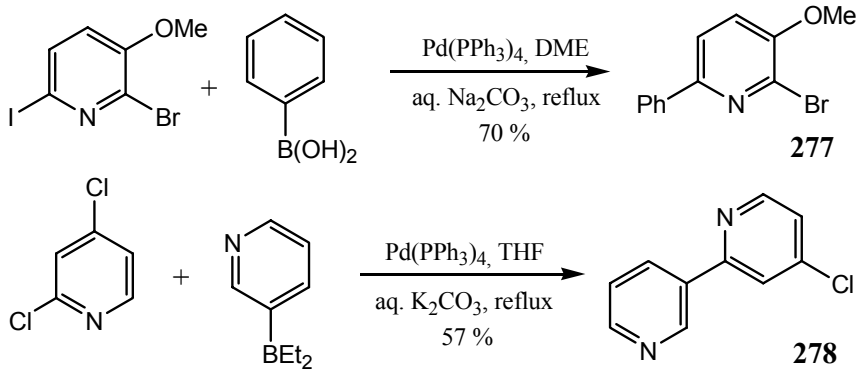
(2) Sonogashira reactions [181, 182]



276

Scheme 4.27

(3) Suzuki reactions [183, 184]

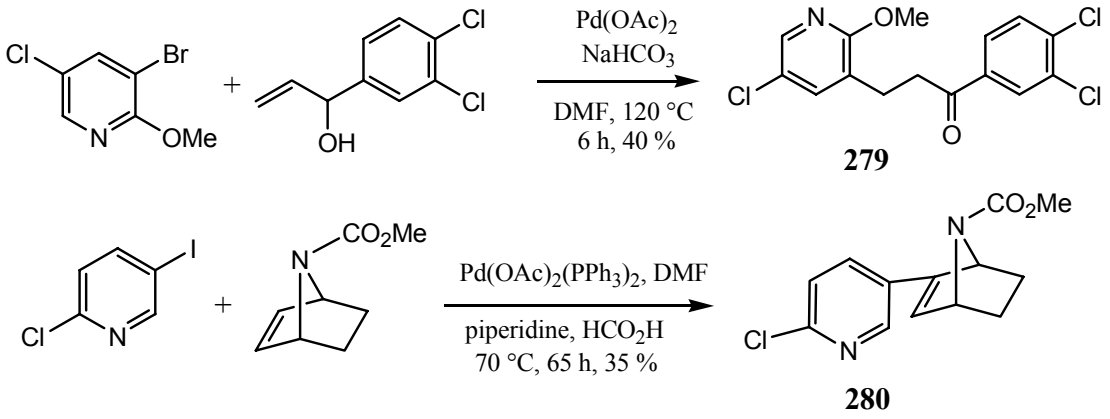


277

278

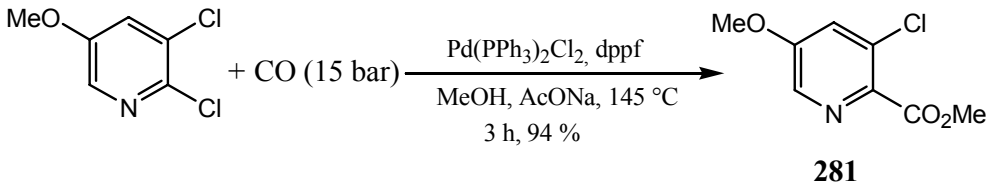
Scheme 4.28

(4) Heck reactions [185, 186]



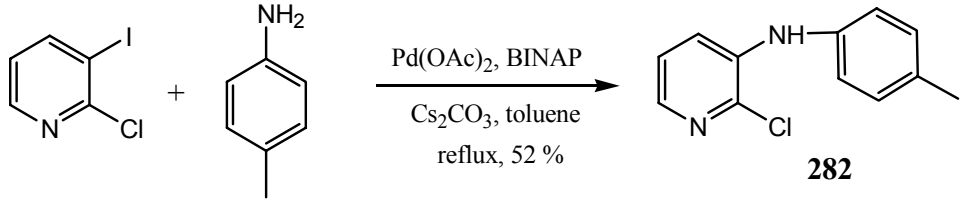
Scheme 4.29

(5) The carbonylation reactions [187]



Scheme 4.30

(6) Buchwald-Hartwig amination [188]



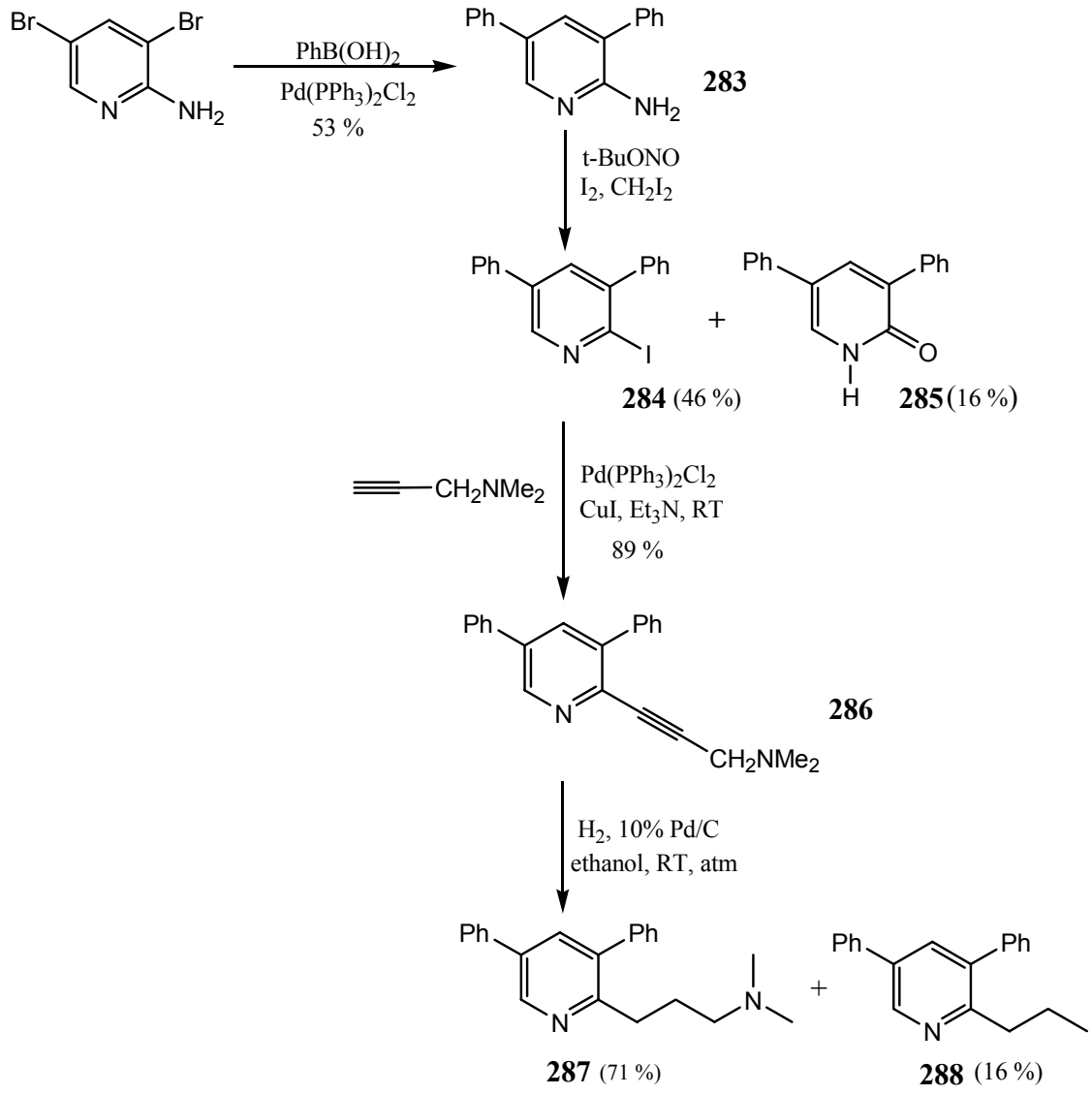
Scheme 4.31

4.2.2 Introduction of dimethylaminopropyl chain into pyridine

We synthesized the dimethylaminopropyl pyridine **287** as a novel representative of calcineurin inhibitors of the general structure **8**, starting from 2-amino-3,5-dibromopyridine and demonstrating the versatility of Pd-catalyzed cross-coupling reactions to introduce all three important peripheral groups into the central pyridine ring.

2-Amino-3,5-dibromopyridine was first treated with phenylboronic acid to give 2-amino-3,5-diphenylpyridine **283** under Suzuki conditions [71]. Then **283** was transformed into the 2-iodo-3,5-diphenylpyridine **284**, while some pyridinone **285** was formed as by product. (**Scheme 4.32**)

2-Iodo-3,5-diphenylpyridine **284** was submitted to Sonogashira coupling with N,N-dimethylpropargylamine in the presence of $Pd(PPh_3)_2Cl_2$, CuI and TEA, affording high yield of the alkynylated pyridine product **286**. Final catalytic hydrogenation of **286** (using 10 % Pd/C as catalyst, at room temperature under atmosphere pressure) gave 3,5-diphenyl-2-(3-dimethylaminopropyl) pyridine **287** as desired target product in 71 % yield. (**Scheme 4.32**) Interestingly, the deaminated 2-propylpyridine **288** was isolated as by-product in 16 % yield. Similarly reductive deamination was reported in literature [189].



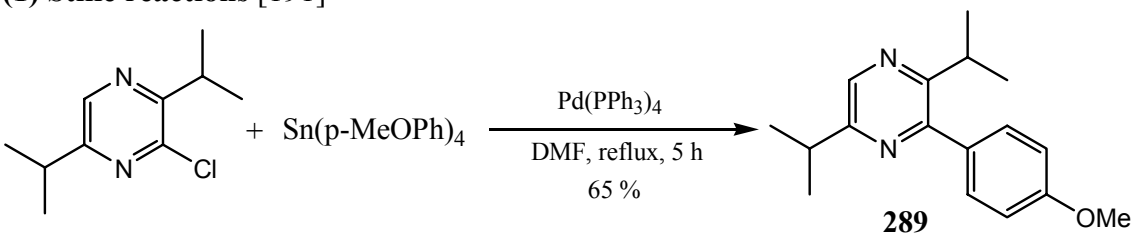
Scheme 4.32 Synthesis of 3,5-diphenyl-2-(3-dimethylaminopropyl) pyridine

4.3 Synthesis of pyrazine derivatives

Minuscule quantities of naturally occurring pyrazines have been found in some foodstuffs and are largely responsible for their flavor and aroma. Pyrazine derivatives have potent pharmaceutical activities [190].

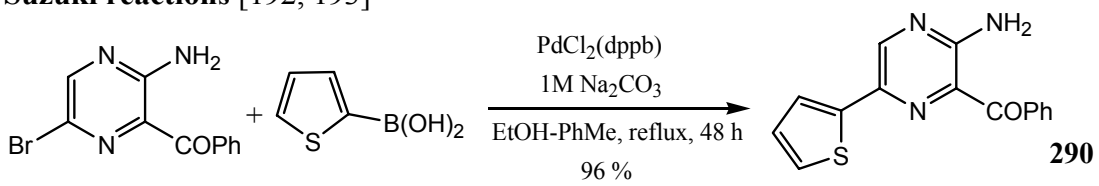
Pyrazine is an electron-deficient, 6π-electron heteroaromatic compound. The inductive effects of the nitrogen atoms induce a partially positive charge on the carbon atoms. As a consequence, oxidative addition of chloropyrazine takes place more readily than with chlorobenzene, and chloropyrazines undergo a wide range of palladium-catalyzed carbon-carbon bond formation reactions:

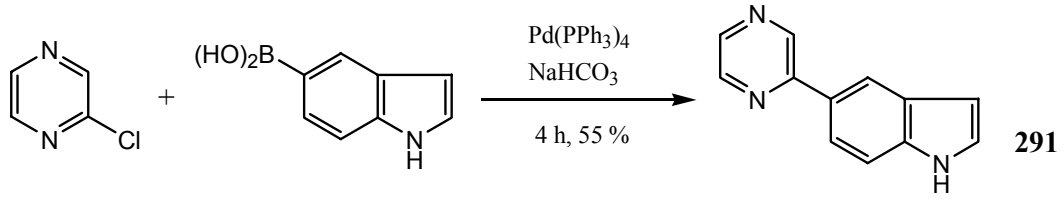
(1) Stille reactions [191]



Scheme 4.33

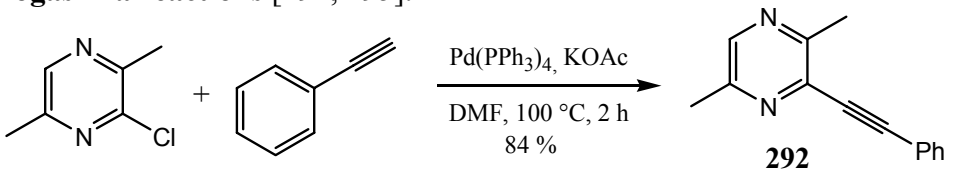
(2) Suzuki reactions [192, 193]

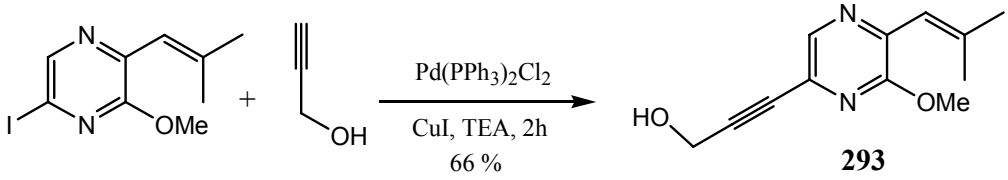




Scheme 4.34

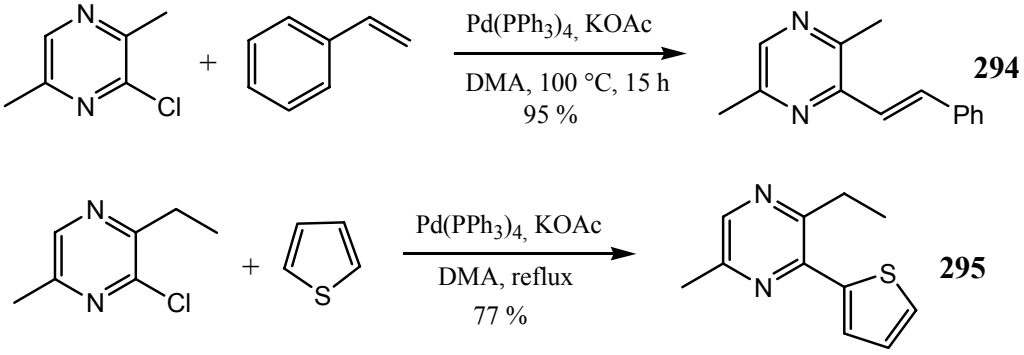
(3) Sonogashira reactions [194, 195].





Scheme 4.35

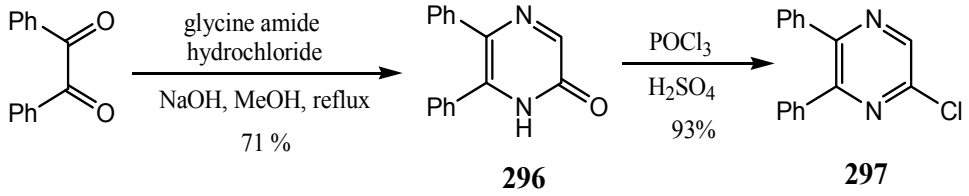
(4) Heck reactions [196, 197]



Scheme 4.36

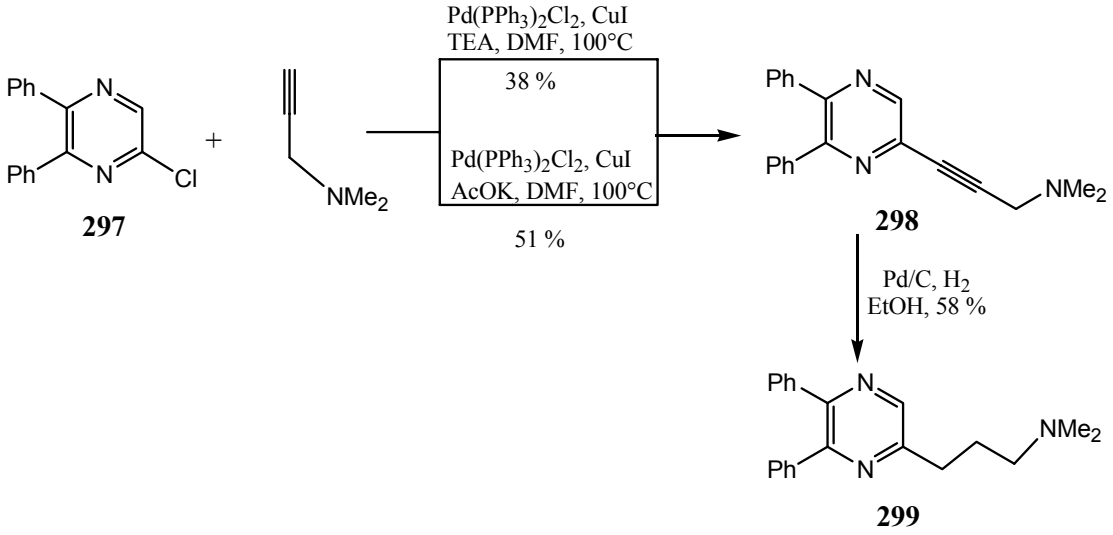
According to the general structure **8**, we aimed to pyrazines substituted by two aryl groups and one dimethylaminopropyl group.

5-Chloro-2,3-diphenylpyrazine **297**, as suitable starting material for the Pd-catalyzed introduction of the aminoalkyl group, was known and can easily be synthesized in high yield [198] starting from benzil and glycine amide in two steps.(**Scheme 4.37**)



Scheme 4.37

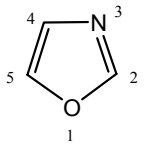
Only modest yield of **298** was achieved in the Sonogashira coupling of 5-chloro-2,3-diphenylpyrazine **297** with N,N-dimethylpropargylamine in TEA and DMF. In the case of the analogous Sonogashira coupling of 2-chloropyrimidine **240a** (see **chapter 4.1.3**), the application of potassium acetate was advantageous over TEA. In the case of **298**, it also led to an increase in the yield from 38 % to 51%. Pd-catalyzed hydrogenation of **298** provided the desired [3-(5,6-diphenyl-pyrazin-2-yl)-propyl]-dimethyl-amine **299** in 58 % yield. (**Scheme 4.38**)



Scheme 4.38

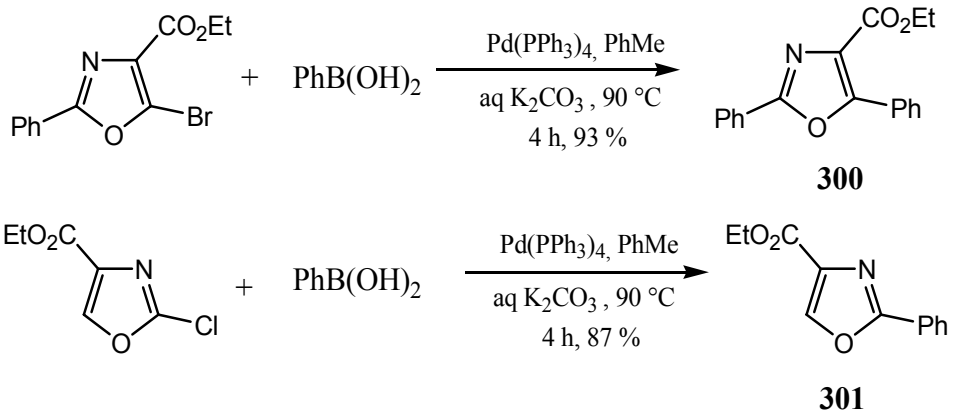
4.4 Synthesis of oxazole derivatives

In the last decade, several oxazole-containing natural products have been isolated and found to be biologically active. Much synthetic effort has been expended in their total synthesis.



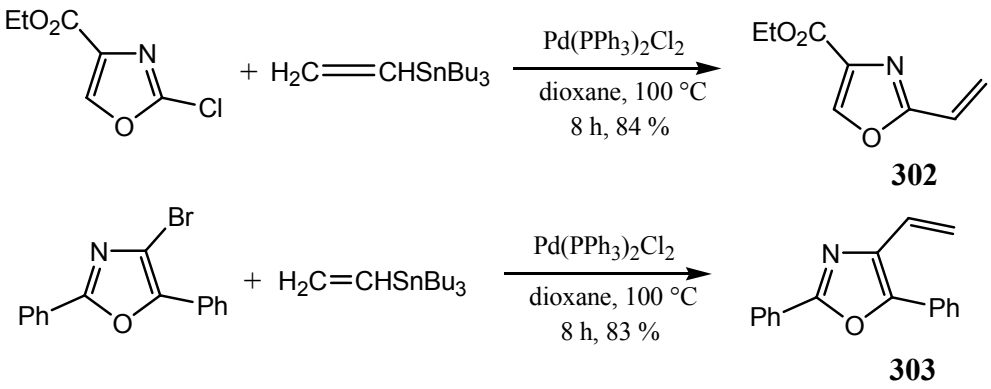
Oxazole is a π-electron-excessive heterocycle. The electronegative nitrogen atom attracts electrons so that C(2) is partially positive and therefore susceptible to nucleophilic attack. In the other side, electrophilic substitution of oxazoles takes place at the electron-rich position C(5) preferentially. More relevant to palladium chemistry, 2-halooxazoles are prone to oxidative addition to Pd(0). Even 2-chlorooxazoles are viable substrates for Pd-catalyzed reactions. Some examples of known Pd-catalyzed coupling reactions are shown in **Scheme 4.39-Scheme 4.43**:

(1) Suzuki reactions [199]



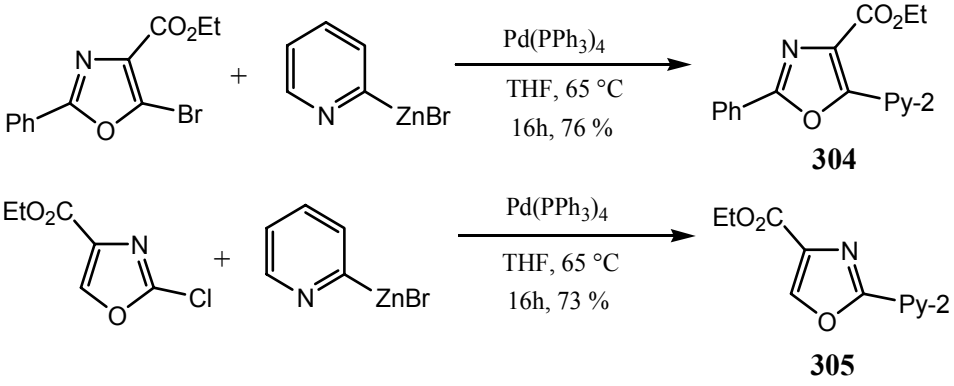
Scheme 4.39

(2) Stille reactions [199]



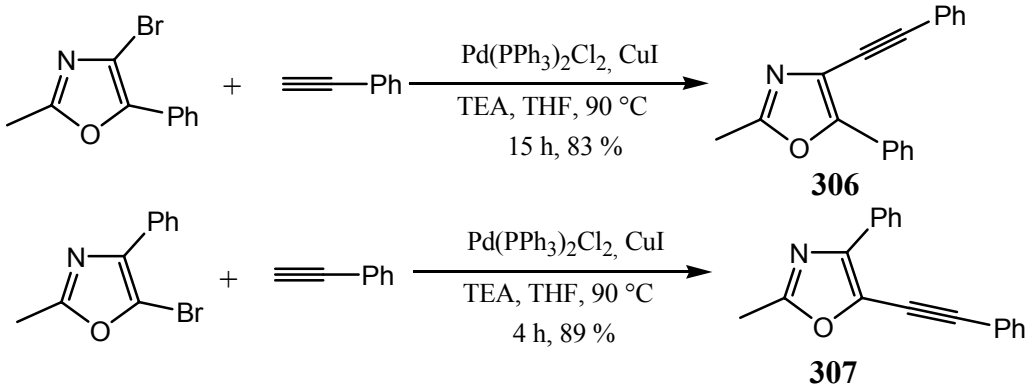
Scheme 4.40

(3) Negishi reactions [199]



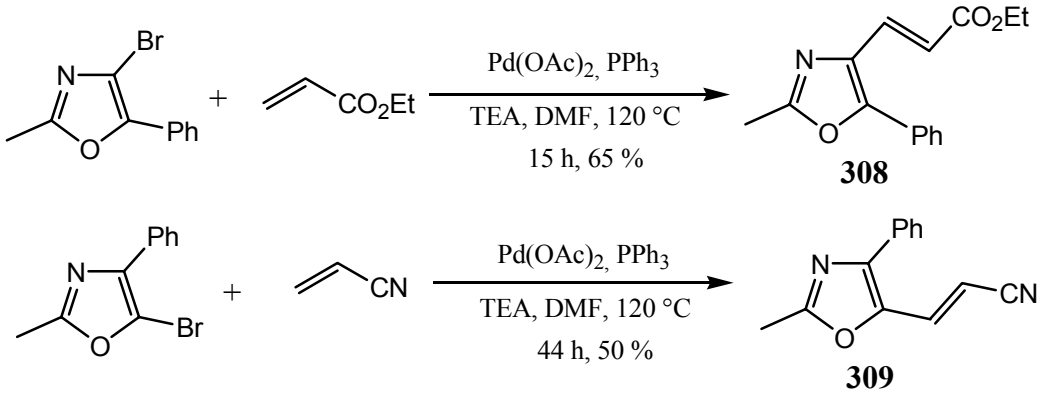
Scheme 4.41

(4) Sonogashira reactions [200]



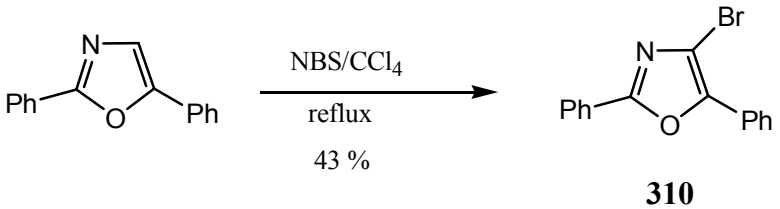
Scheme 4.42

(5) Heck reactions [200]



Scheme 4.43

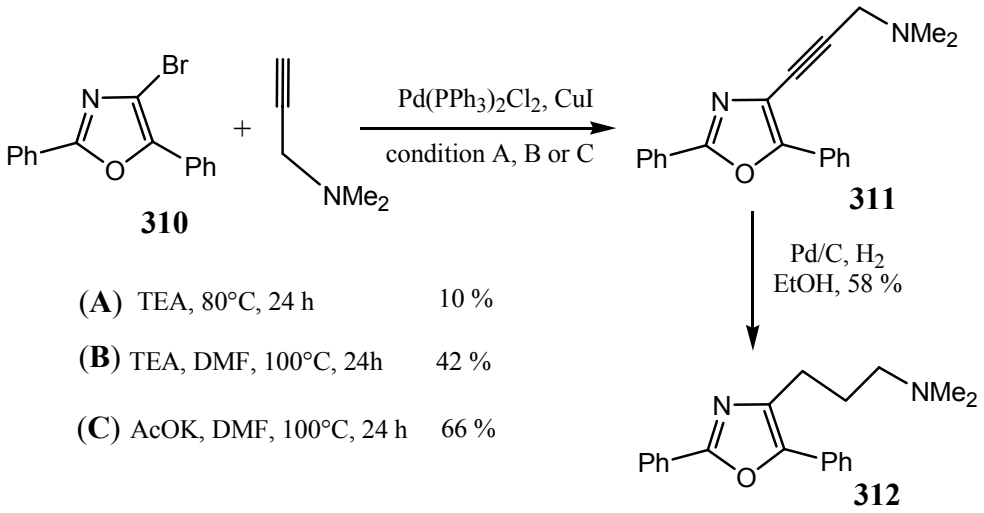
4-Bromo-2,5-diphenyloxazole **310** was readily available [201] by bromination of 2,5-diphenyloxazole. (**Scheme 4.45**)



Scheme 4.44

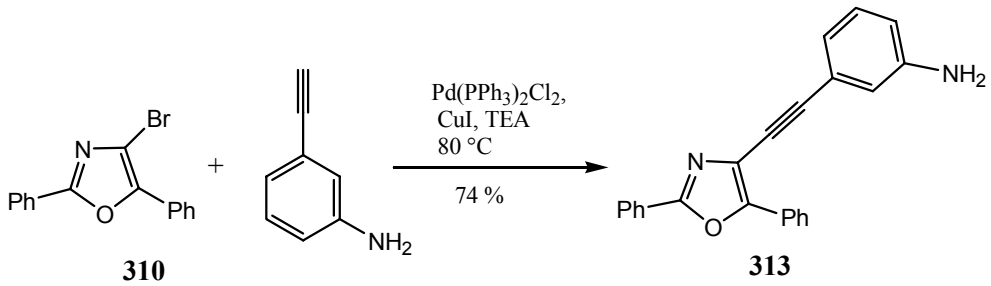
We used 4-bromo-2,5-diphenyloxazole **310**, as reactant to introduce an aminopropyl chain by Sonogashira coupling with N,N-dimethylpropargylamine. Optimized conditions [$Pd(Ph_3)_2Cl_2$, CuI, AcOK, DMF, 100 °C] provided the coupling product **311** in 66 % yield. **311**was further hydrogenated, using H_2 and Pd/C, to give [3-(2,5-diphenyl-oxazol-4-yl)-

propyl]-dimethyl-amine **312** in 58 % yield. **312** was a further new example of potential calcineurin inhibiting compound of the general structure **8**. (**Scheme 4.45**)



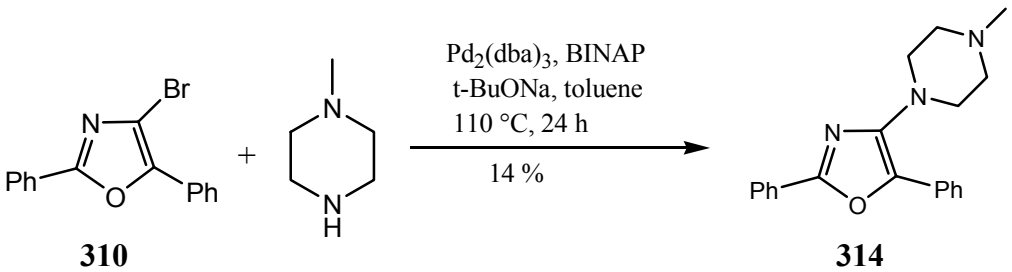
Scheme 4.45

The aminophenylethynyloxazole **313** represents a further variation of the general structure **8**. The side chain amino group is attached to an aromatic ring rather than to a sp^3 carbon atom. This product was obtained by Sonogashira coupling of **310** with 3-aminophenylethyne. (**Scheme 4.46**)



Scheme 4.46

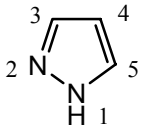
Buchwald-Hartwig amination of 4-bromo-2,5-diphenyloxazole **310** with N-methyl-piperazine furnished low yield of an oxazole **314**, which is related to the general structure **8**. The side chain amino group is part of a saturated ring. (**Scheme 4.47)**



Scheme 4.47

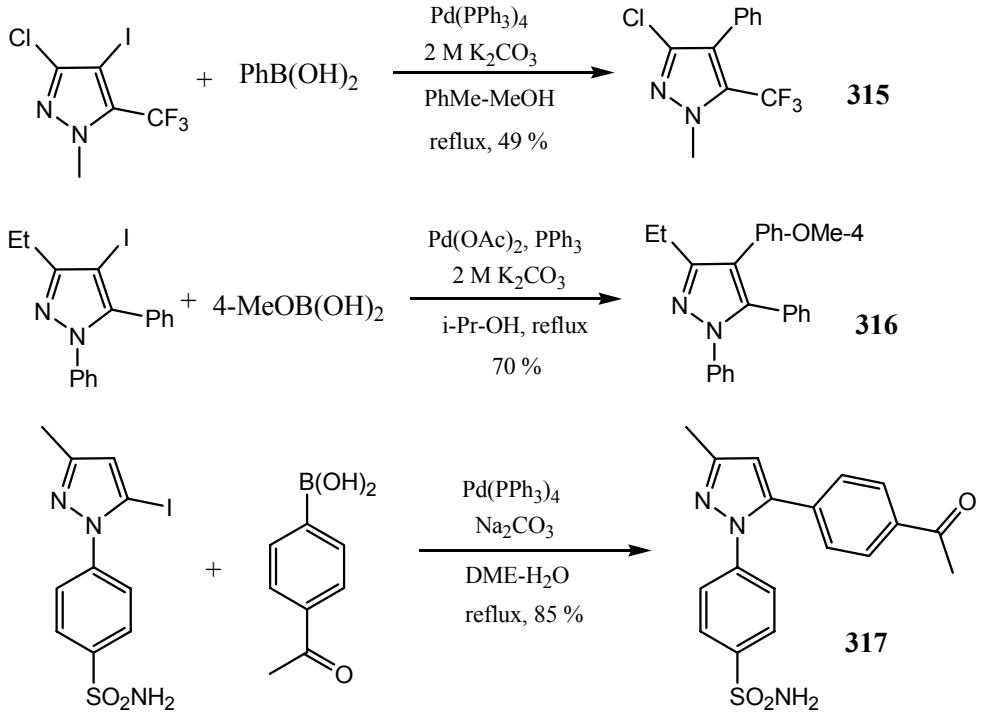
4.5 Synthesis of pyrazole derivatives

Aryl pyrazoles possess widespread occurrence as substructures in a large variety of compounds with important biological and pharmacological properties. Among them, 1,5-diphenylpyrazoles are novel non-nucleoside HIV reverse transcriptase inhibitors [202] and cyclooxygenase-2 inhibitors [203]. 1,3,5-Trisubstituted pyrazoles are inhibitors of cholesterol [204]. Moreover, some substituted pyrazole compounds are potent inhibitors of p38 MAP kinase [205] and estrogen receptors [206].



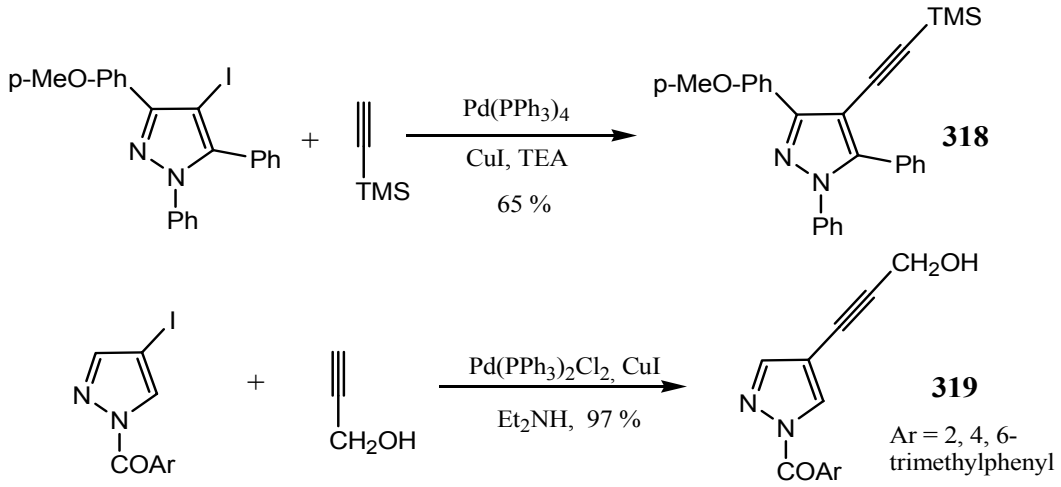
Pyrazole is a π-electron-excessive heterocycle. The electronegativity of the nitrogen atom attracts electrons so that C(3) and C(5) are partially electropositive and therefore susceptible to nucleophilic attack. On the other side, electrophilic substitution of oxazoles takes place at the electron-rich position C(4) preferentially. Several Pd-catalyzed coupling reactions of halopyrazoles have been reported:

(1) Suzuki reactions [206-208]



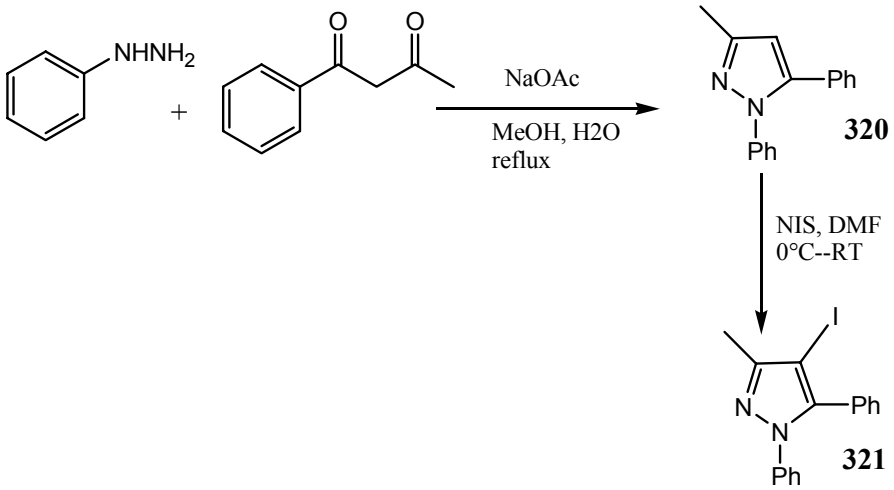
Scheme 4.48

(2) Sonogashira reactions [209, 210]



Scheme 4.49

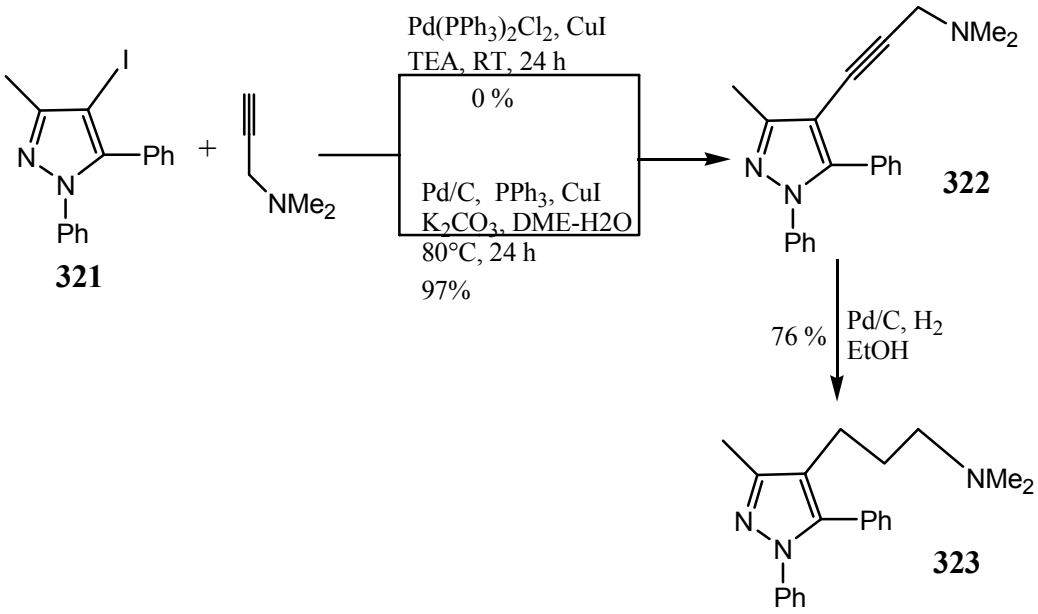
Starting from phenylhydrazine and benzoylacetone [202] and iodination [204] of the intermediate **320**, 4-iodo-3-methyl-1,5-diphenylpyrazole **321** was obtained.(**Scheme 4.50**) With its two phenyl groups at the pyrazole ring, compound **321** just needs an additional aminoalkyl group to fit into the potential calcineurin inhibiting structure **8**.



Scheme 4.50

According to our experienced strategy for the introduction of a dimethylaminopropyl chain by Sonogashira coupling with N,N-dimethylpropargyl amine, followed by catalytic hydrogenation, the envisaged target **323** was afforded in high yield. Remarkably, catalysis

with $Pd(PPh_3)_2Cl_2$ and CuI completely failed, while Pd/C, PPh_3 and CuI provided quantitative Sonogashira coupling.(**Scheme 4.51**)



Scheme 4.51

4.6 Synthesis imidazole derivatives

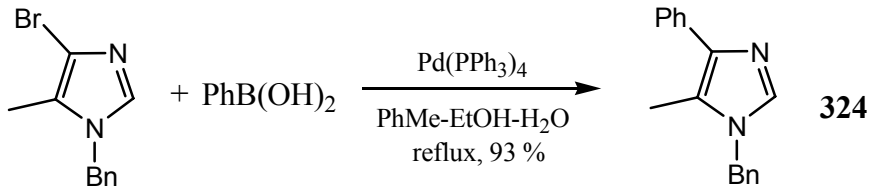
The imidazole ring is present in a number of biologically important molecules as exemplified by the amino acid histidine. It can serve as a general base (*pKa* = 7.1) or a ligand for various metals in biological systems. Furthermore, the chemistry of imidazole is prevalent in protein and DNA biomolecules in the form of histidine or adinine/guanine, respectively.

Aryl substituted imidazoles exist extensively in nature. They have important biological and pharmaceutical activities. For example, substituted 4,5-diaryl-2-thio-imidazoles are potent inhibitors of cholesterol acyltransferase [211], 1,2-diarylimidazoles are new series of COX-2 selective inhibitors [212]; aryl-heteroaryl-imidazoles are potent inhibitors of the MAP kinase p38 [213] and highly active, selective histamine H_1-receptor agonists [214].

Imidazole is a π-electron-excessive heterocycle. Electrophilic substitution normally occurs at C(4) or C(5), whereas nucleophilic substitution takes place at C(2).

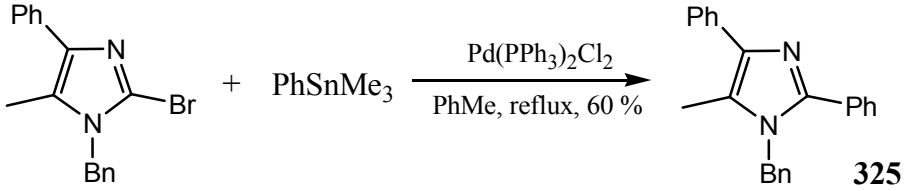
In Pd-catalyzed coupling reactions, a halo leaving group can be found in any C-position of imidazoles. Several known examples are shown below:

(1) Suzuki reaction [215]



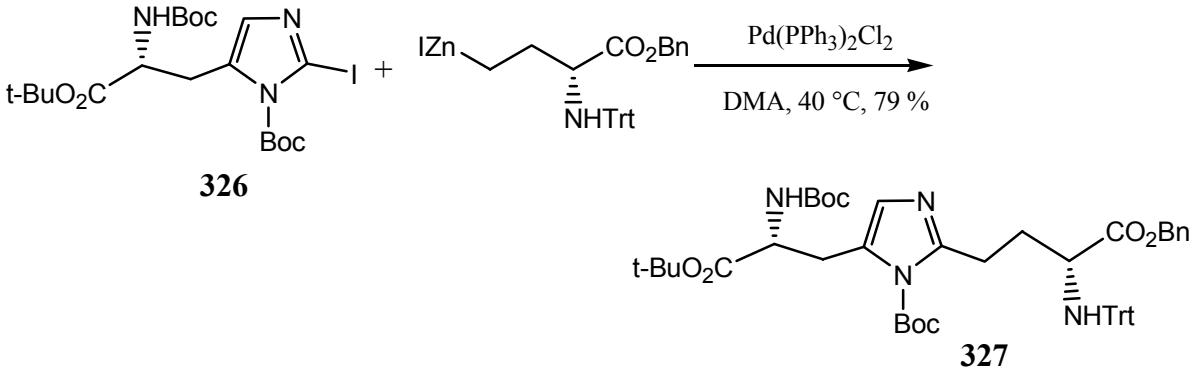
Scheme 4.52

(2) Stille reactions [215]



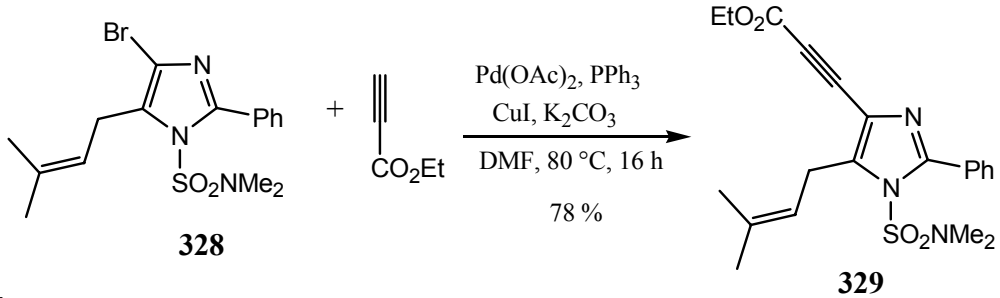
Scheme 4.53

(3) Negishi reactions [216]



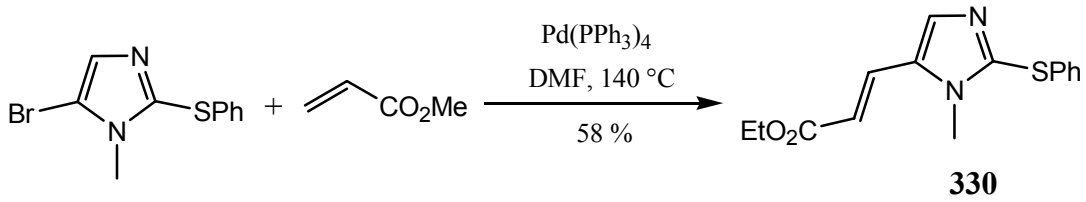
Scheme 4.54

(3) Sonogashira reactions [217]



Scheme 4.55

(4) Heck reaction [218]

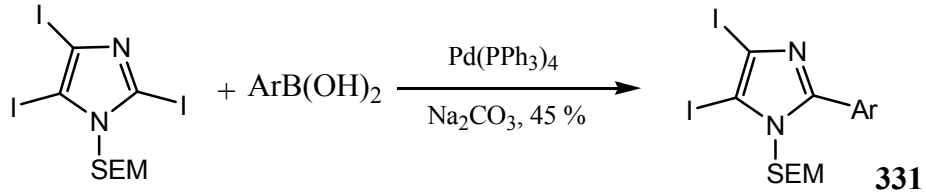


330

Scheme 4.56

As expected in Pd-catalyzed cross-coupling of polyhaloimidazoles, the 2-position is more active than the 4-position and the 5-position.

(1) Suzuki reaction [219]

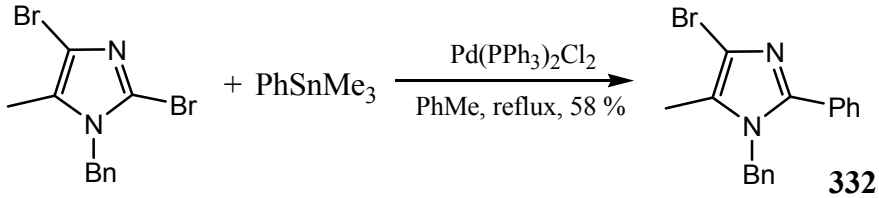


331

Ar = 1-TBS-indole-3-yl

Scheme 4.57

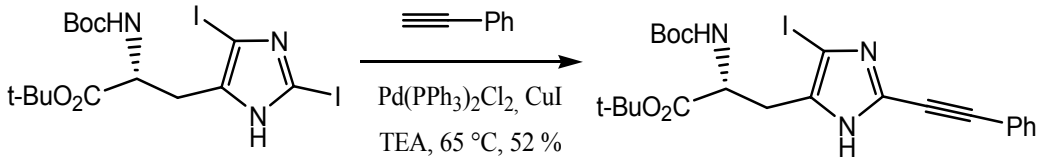
(2) Stille reaction [215]



332

Scheme 4.58

(3) Sonagashira reaction [220]

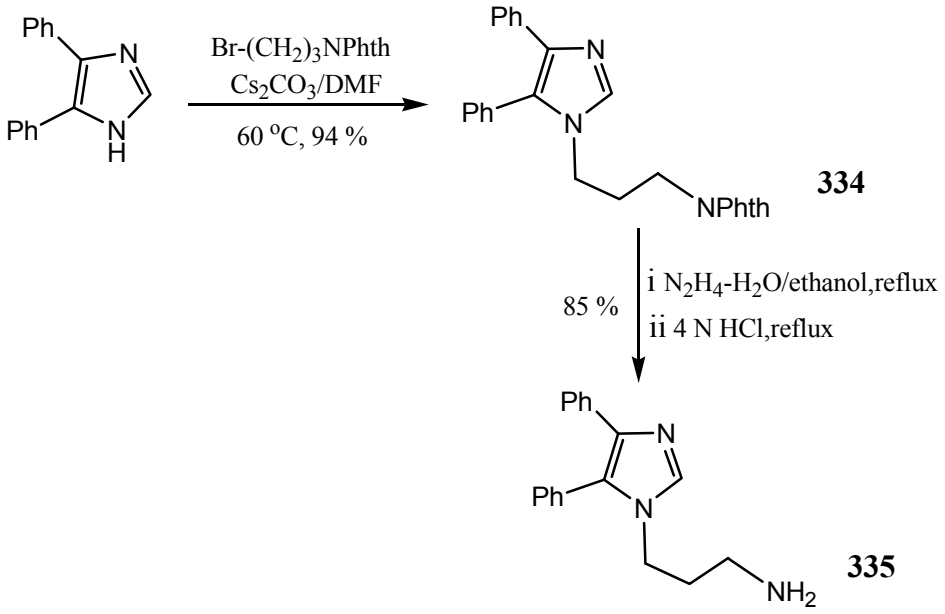


333

Scheme 4.59

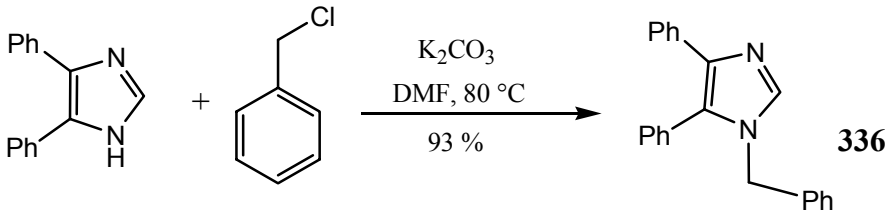
4,5-Diphenylimidazole was chosen as starting material and a series of imidazole derivatives were prepared to achieve potential calcineurin inhibiting compounds, which fitted into the general structure **8**.

The 1-(3-aminopropyl)-imidazole **335**, where the side chain is not attached to a carbon atom but to a nitrogen atom, was synthesized in a Pd-free reaction. Alkylation of 4,5-diphenylimidazole with N-3-bromopropylphthalimide, and final deprotection of the phthalimido product **334** gave 3-(4,5-diphenyl-imidazol-1-yl)-propylamine **335** in 85 % yield. (**Scheme 4.60**)



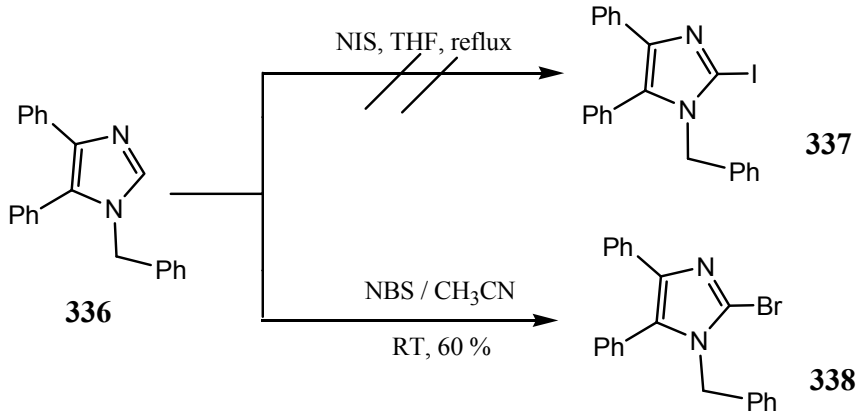
Scheme 4.60

We further tried to introduce an aminoalkyl chain into position 2 of the imidazole ring. 4,5-diphenylimidazole was first N-protected by benzylation [221], thus adding a third aryl group to the core heterocycle. (**Scheme 4.61**)



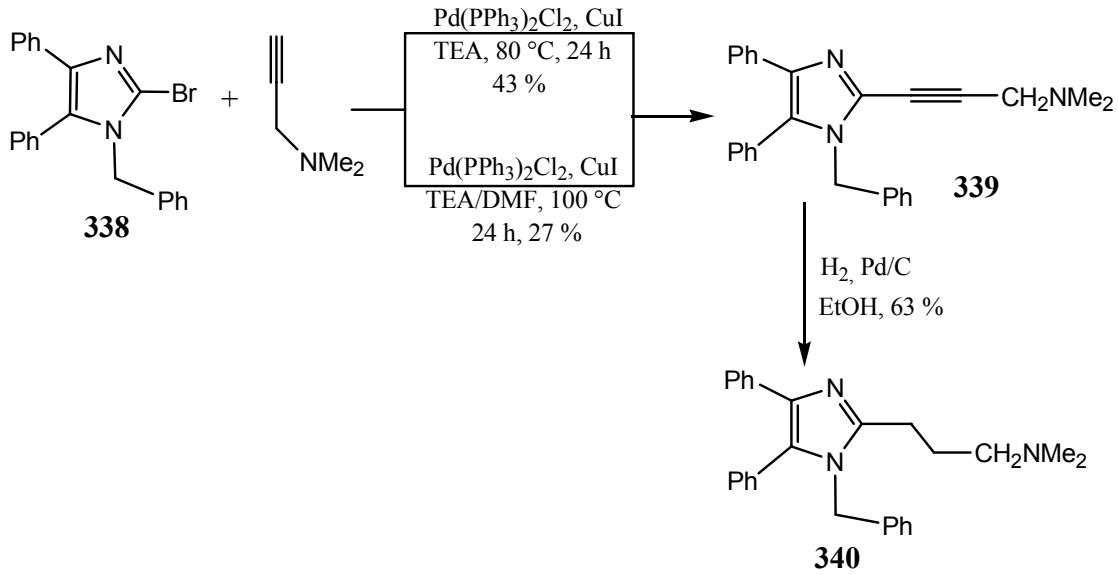
Scheme 4.61

Halogenation of 1-benzyl-4,5-diphenyl-imidazole **336** with NBS was successful, but failed with NIS in THF. (**Scheme 4.62**)



Scheme 4.62

Sonogashira coupling of 1-benzyl-2-bromo-4,5-diphenylimidazole **338** with N,N-dimethyl-propargylamine in the presence of $Pd(PPh_3)_2Cl_2$/CuI gave low yield in DMF. However, when TEA was used as solvent, the coupling product **339** could be obtained in 43 %. **339** was further hydrogenated with hydrogen, catalyzed by 10 % Pd/C, providing [3-(1-benzyl-4,5-diphenyl-imidazol-2-yl)-propyl]-dimethyl-amine **340** in 63 % yield. (**Scheme 4.63**)



Scheme 4.63

Chapter 5: Activities of calcineurin inhibitors

5.1 Measurement of calcineurin inhibitory activity

The enzyme inhibitory effect of a compound is usually characterized by the IC_{50} value, the smaller the IC_{50} value, the higher is the inhibitory activity. For example the known good calcineurin inhibitors, cyclosporin A, microcystin IR and FK506, exhibit IC_{50} values of 0.5 μM, 0.2 μM and 0.2 μM, respectively.

Inhibiting activities of the new compounds synthesized by us are determined up to a value of 20 μM. If the inhibiting activity of a compound is lower (i.e. the inhibitor is weak), the remaining activity of calcineurin is recorded at a concentration of the inhibitor of 20 μM, e.g. "**60 % activity at 20 μM**" means at 20 μM concentration of inhibitor, 60 % of calcineurin protein is still active. Again, the smaller the value, the higher is the activity. If the compound does not show inhibition at a concentration of 20 μM, it is termed "**not active**".

In pharmacology and biochemistry, in order to determine the efficacy of a drug or inhibitor, the following terms are commonly used.

EC_{50}: Clinical efficacy of a drug (Concentration required) to produce 50% of the maximum effect (may be inhibitory or stimulatory effect). This term is used usually with pharmaceuticals.

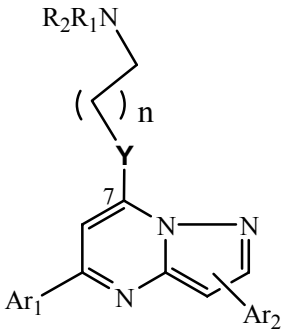
ED_{50}: Medium effective dose (as opposed to concentration) at which 50 % of individuals exhibit the specified quantitative effect.

IC_{50}: Concentration required producing 50 % inhibition.

K_i: Inhibitor concentration at which 50% inhibition is observed. It is calculated using Michaelis-Menten kinetics.

5.2 Calcineurin inhibitory activity of target molecules

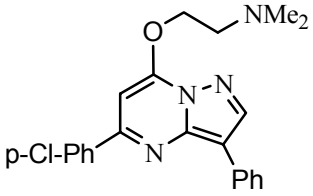
Parallel to the synthesis of new calcineurin inhibiting compounds presented in this thesis, other synthetic efforts in our group [16b] concentrated on pyrazolo[1,5-a]pyrimidine **341**, with a side chain at the position 7. (**Figure 5.1**)



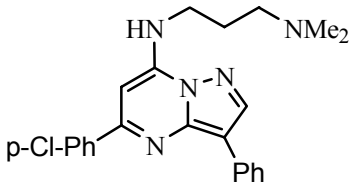
341

Figure 5.1

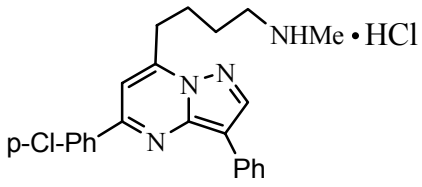
The best inhibiting activities of these pyrazolo[1,5-a]pyrimidines were achieved with compounds **4**, **342** and **343**. (**Figure 5.2**)



4
IC_{50} = 2.0 μM



342
IC_{50} = 3.0 μM



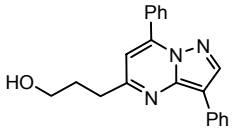
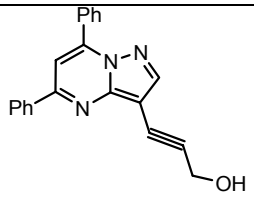
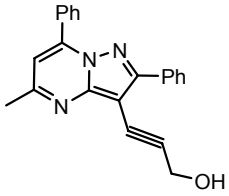
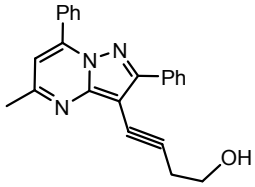
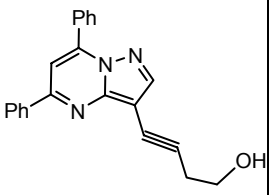
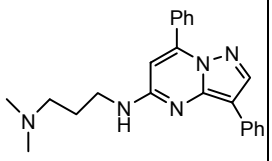
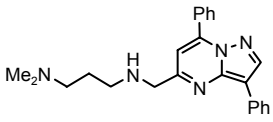
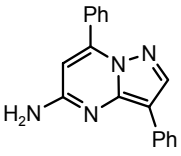
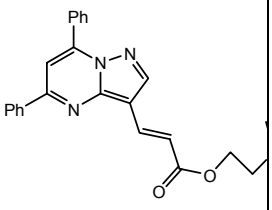
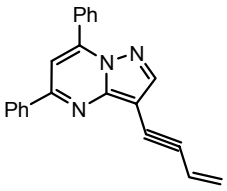
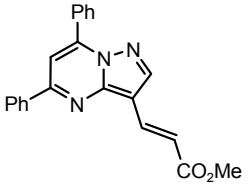
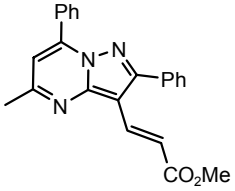
343
IC_{50} = 4.5 μM

Figure 5.2

Calcineurin inhibitory activities of pyrazolo[1,5-a]pyrimidine compounds, synthsized by us, are listed in **Table 5.1**.

Our synthetic strategy allowed to synthesize pyrazolo[1,5-a]pyrimidines, where the ω-functionalized saturated side chain is attached to other positions than in **341**, i.e. position 5 or position 3. This positional change is tolerated to a certain extent (see **Table 5.1** compounds **128**, **129**, **116a**, **116b**), if an aminoalkylamino chain is found in position 5 (see compound **128**). On the other hand, 3-aminoalkyl substituted pyrazolo[1,5-a]pyrimidines show almost no activity (see **Table 5.1** compounds **116a** and **116b).** However**,** the aminopropynyl precursors **113a**, **113 b**, **113c** and **113d** exhibit an unexpectedly high activity. This indicates that the side chain of the general structure **8** can also be unsaturated. Comparison of compounds **113d** and **113e** reveal a massive effect of the aryl substitutent on the inhibition strength. If the terminal group in the side chain is not basic like in the phthalimide compound **118** or in the nitrile (compound **107a**), the activity gets lost as found in other investigation performed in our group [16b].

Table 5.1 Derivatives of pyrazolo[1,5-a]pyrimidine

Structure	Name	Activity	Structure	Name	Activity
	**131** Yl-133	77 % activity at 20 µM		**113f** Yl-215	28 % activity at 20 µM
	**113g** Yl-298	77 % activity at 20 µM		**113k** Yl-293	81 % activity at 20 µM
	**113i** Yl-354	91 % activity at 20 µM			
	**128** Yl-193	IC_{50} =18.5 µm		**129** Yl-217	51 % activity at 20 µm
	**127** Yl-308	not active			
	**109** Yl-245	67% activity at 20 µM		**114** Yl-286	78 % activity at 20 µM
	**106h** Yl-208	not active		**106a** Yl-42	not active

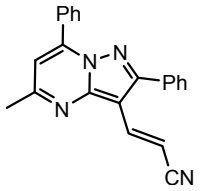
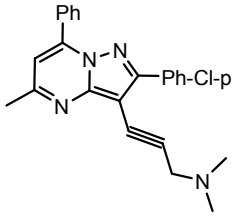
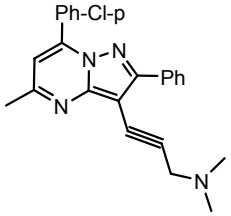
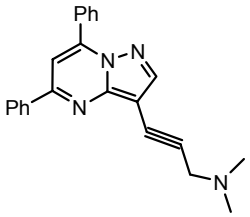
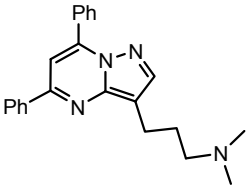
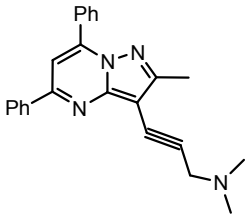
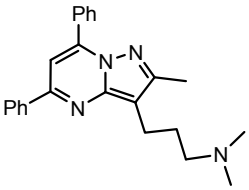
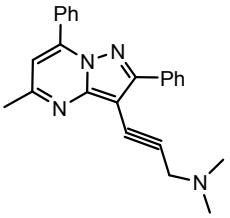
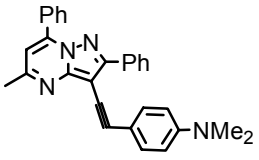
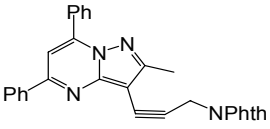
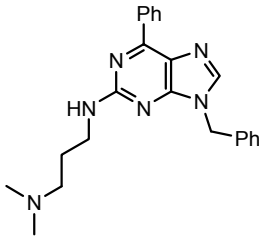
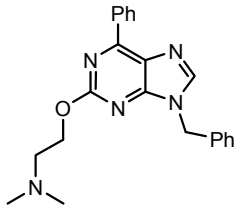
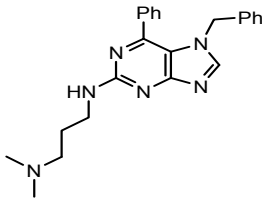
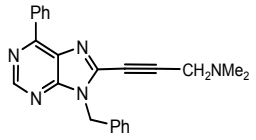
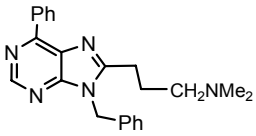
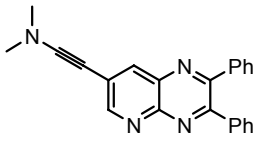
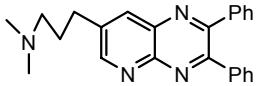
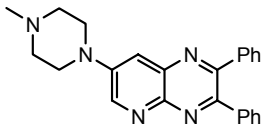
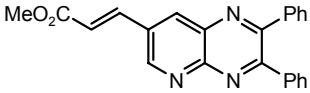
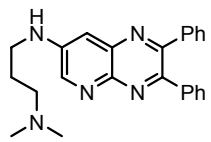
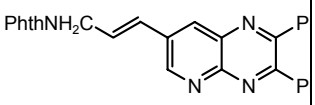
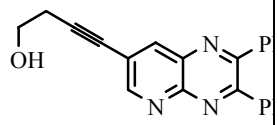
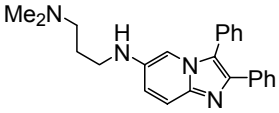
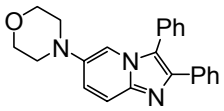
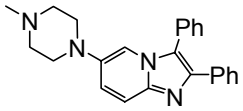
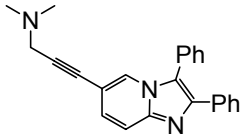
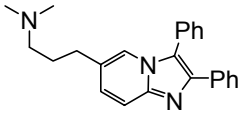
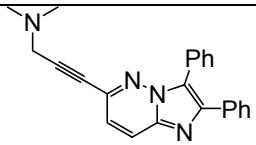
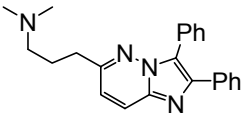
	**107a** Yl-43	not active			
	**113d** Yl-209	IC_{50} = 8.5 μM		**113e** Yl-261	53 % activity at 20 μM
	**113b** Yl-197	IC_{50} = 11.2 μM		**116b** Yl-266	not active
	**113a** Yl-199	IC_{50} = 13.2 μM		**116a** Yl-328	84 % activity at 20 μM
	**113c** Yl-190	IC_{50} = 12.0 μM			
	**117** Yl-282	not active		**118** Yl-352	94 % activity at 20 μM

Table 5.2 shows the results of calcineurin inhibition tests of compounds fitting into the general structure **8**, where the central cores are other N-containing bicyclic heterocycles.

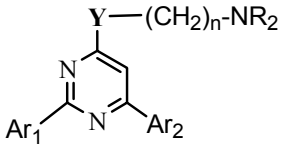
Unexpectedly, none of the examples reached activities of pyrazolo[1,5-a]pyrimidines. This fact demonstrates that the central heterocycle of the structural model **8** plays a crucial role.

Table 5.2 Derivatives of other bicyclic heterocycle

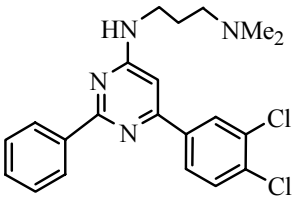
Structure	Name	Activity	Structure	Name	Activity
	**189** Yl-185	84% activity at 20 µM		Yl-202	**190** not active
	**192** Yl-201	not active			
	**186** Yl-368	95 % activity at 20 µM		**187** Yl-376	87 % activity at 20 µM
	**194b** Yl-238	90 % activity at 20 µM		**195** Yl-350	53 % activity at 20 µM
	**198** Yl-247	not active		**200** Yl-354	not active
	**199** Yl-258	70 % activity at 20 µM		**202** Yl-260	74 % activity at 20 µM

	**194a** Yl-377	78 % activity at 20 μM		**227** Yl-252	72 % activity at 20 μM
	**225** Yl-237	81 % activity at 20 μM		**226** Yl-240	not active
	**220** Yl-242	not active		**221** Yl-331	57 % active at 20 μM
	**223** Yl-279	94 % activity at 20 μM		**224** Yl-324	67 % activity at 20 μM

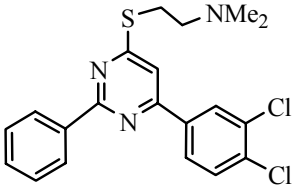
Parallel work in our group has led to pyrimidines **344**, which exhibit high calcineurin inhibiting activities and remarkably low toxicity. (**Figure 5.3**)



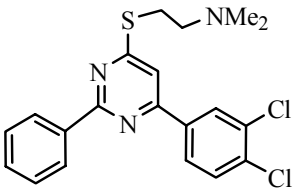
344



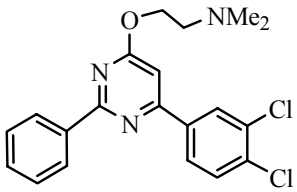
345
IC_{50} = 1.2 μM



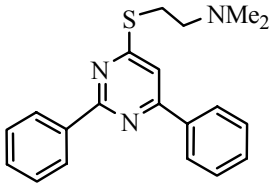
346
IC_{50} = 1.5 μM



347
IC_{50} = 2.7 μM



348
IC_{50} = 3.0 μM

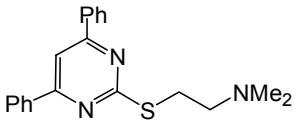
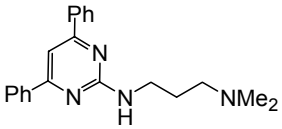
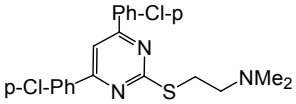
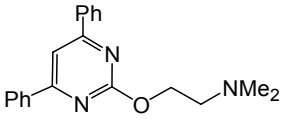
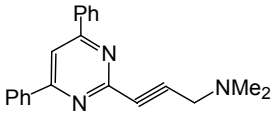
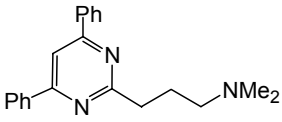
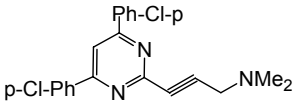
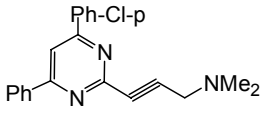
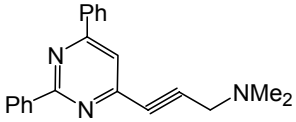
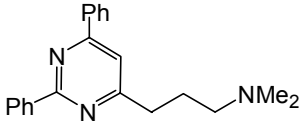
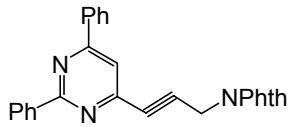


349
IC_{50} = 18.0 μM

Figure 5.3

Calcineurin inhibitory activities of pyrimidine compounds, synthesized by us, are listed in **Table 5.3**.

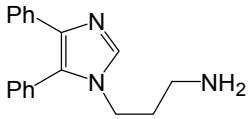
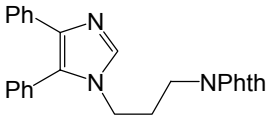
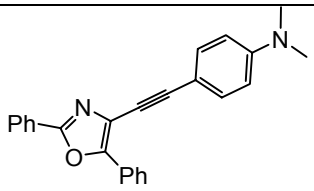
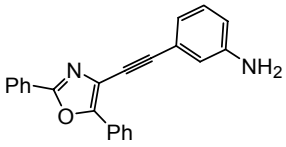
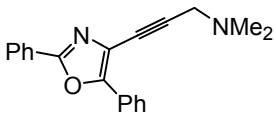
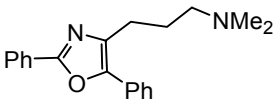
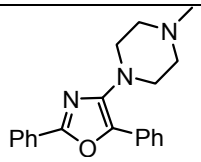
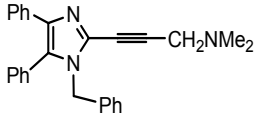
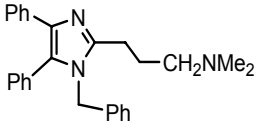
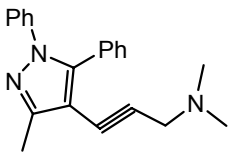
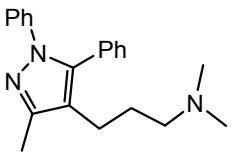
Table 5.3 Derivatives of pyrimidine

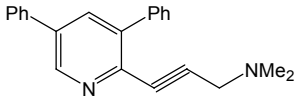
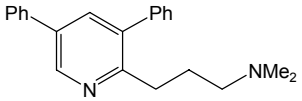
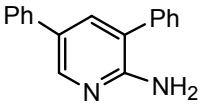
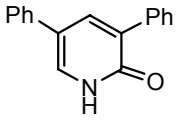
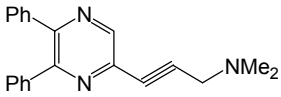
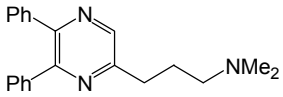
Structure	Name	Activity	Structure	Name	Activity
	**261a** Yl-211	IC_{50} =20 µM		**262** Yl-210	75 % activity at 20 µM
	**261b** Yl-314	61 % active at 20 µM		**263** Yl-212	76 % activity at 20 µM
	**259a** Yl-181	75 % activity at 20 µM		**260** Yl-383	46 % activity at 20 µM
	**259b** Yl-315	not active		**259c** Yl-322	not active
	**256** Yl-323	53 % activity at 20 µM		**257** Yl-330	50% activity at 20 µM
	**258** Yl-346	53 % activity at 20 µM			

Our synthetic methodology allowed to synthesize 4-dimethylaminopropyl pyrimidine **257**, which represents an example of structure **344** with X = CH_2, and to provide access to isomers **260**, **261a**, **261b**, **262** and **263**, where the saturated side chains were attached to position 2. It turned out that all these analogous or isomers showed a comparable activity. For improvement variation of the aryl groups would be advisable.

Calcineurin inhibitory activities of other momocyclic N-heterocycles substituted by ω-functionalized side chains and two aryl groups fitting into the general structure **8**, are shown in **Table 5.4**. Unfortunately all these compounds showed much lower activities than the corresponding pyrimidines **344**. Nevertheless, some surprising results are mentioned here: the dimethylaminopropynyl oxazole **311** showed a higher activity than the structure analogue **312**. 2-Amino-3,5-diphenylpyridine **283** and its oxygen-analogue **285** show a modest inhibiting activities, although they do not fit into the general structure **8**.

Table 5.4 Derivatives of other monocyclic heterocycle

Structure	name	activity	Structure	name	activity
	**335** Yl-219	66 % activity at 20 µM		**334** Yl-204	60 % activity at 20 µM
	**313a** Yl-249	91 % activity at 20 µM		**313** Yl-269	89 % activity at 20 µM
	**311** Yl-235	78 % activity at 20 µM		**312** Yl-367	88 % activity at 20 µM
	**314** Yl-263	68 % activity at 20 µM			
	**339** Yl-373	87 % activity at 20 µM		**340** Yl-377	71 % activity at 20 µM
	**322** Yl-321	not active		**323** Yl-332	72 % activity at 20 µM

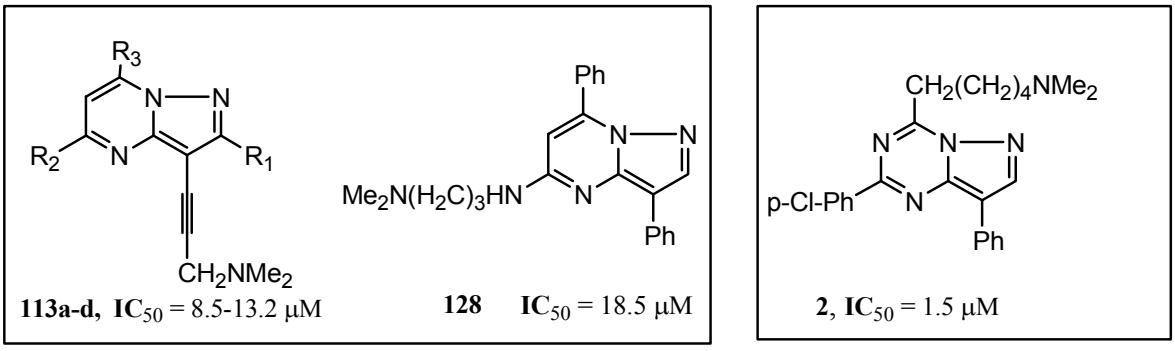
	**298** Yl-336	no active		**299** Yl-341	not active
	**283** Yl-317	68 % activity at 20 μM		**285** Yl-327	68 % activity at 20 μM
	**286** Yl-335	81 % activity at 20 μM		**287** Yl-345	62 % activity at 20 μM

Considering the calcineurin inhibitory effects of compounds obtained in our group so far, the following structure-activity relations can be summarized:

(1) Effect of core heterocycle

Pyrazolo[1,5-a]pyrimidine, pyrazolo[1,5-a]triazine and pyrimidine are preferable as core heterocycles in the general structure **8** of potential calcineurin inhibitors.

Some corresponding active calcinerine inhibitors are shown below. (**Figure 5.4**)



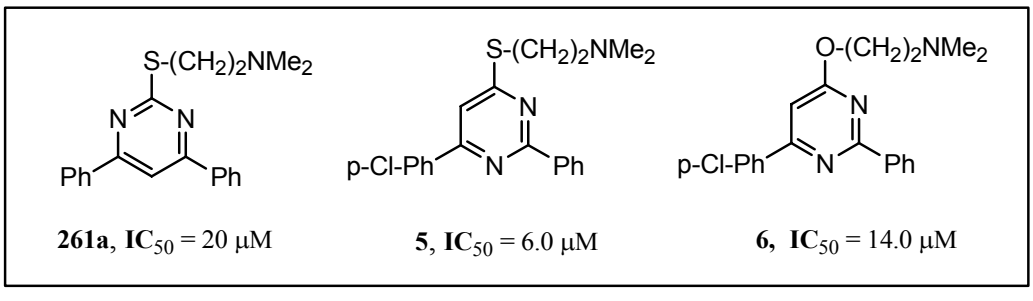
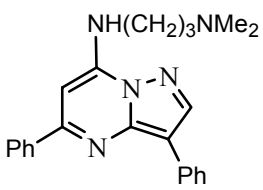


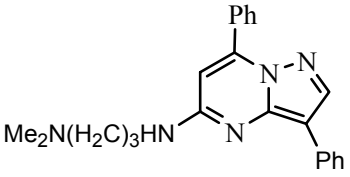
Figure 5.4

(2) The position of side chain

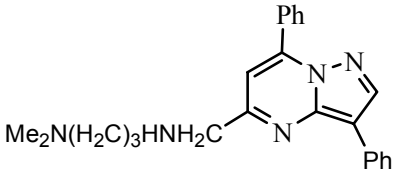
The optimal position of attachment of the side chain depends on the type of heterocycles. In the pyrazolo[1,5-a]pyrimidine series, position 7 of the pyrazolo[1,5-a]pyrimidine core is most effective for calcineurin inhibition, compared with connection sites 5 and 3. In addition, the $CH_2NH(CH_2)_3NMe_2$ side chain is less effective than $NH(CH_2)_3NMe_2$.(**Figure 5.5**)



3
IC_{50} = 7.5 μM



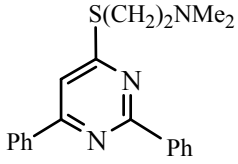
128
IC_{50} = 18.5 μM



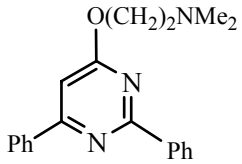
129
51 % activity at 20 μM

Figure 5.5

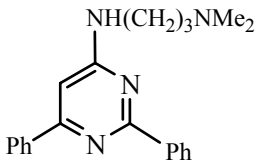
In the pyrimidine series, many target molecules with side chains at position 4, and position 2 were synthesized and tested. It was found that the calcineurin inhibitory activities of these two kinds of compounds are similar. (**Figure 5.6**)



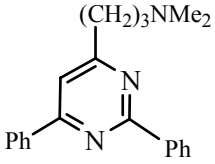
349
IC_{50} = 18 μM



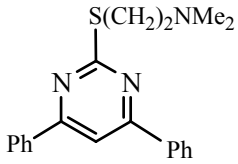
350
70 % activity
at 20 μM



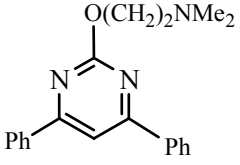
351
75 % activity
at 20 μM



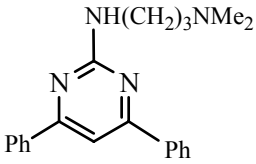
257
50 % activity
at 20 μM



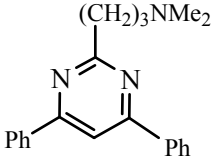
261a
IC_{50} = 20 μM



263
76 % activity
at 20 μM



262
75 % activity
at 20 μM



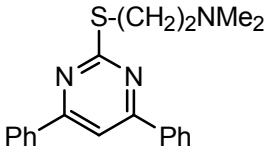
263
46 % activity
at 20 μM

Figure 5.6

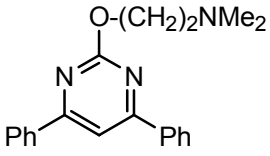
(3) The effect of substituted groups

Based on some preliminary conclusions of the effect of substituents at the side chain on the activity of calcineurin inhibitors of the general structure **8**, the following trends can be mentioned:

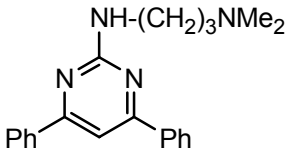
(a) Heterocycles with $Me_2N(CH_2)_2S$- side chain are more active than the compounds with $Me_2N(CH_2)_2O$- and $Me_2N(CH_2)_3NH$- side chain. (**Figure 5.7**)



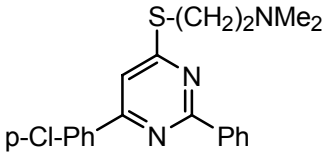
261a, IC_{50} = 20 μM



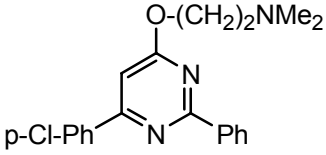
263, 76 % at 20 μM



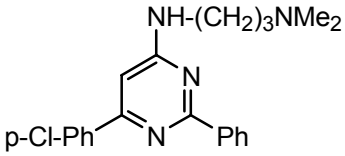
262, 75 % at 20 μM



5, IC_{50} = 6.0 μM



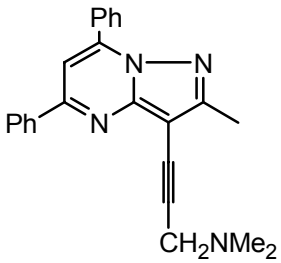
6, IC_{50} = 14.0 μM



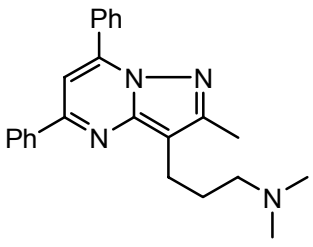
352, IC_{50} =10.0 μM

Figure 5.7

(b) Heterocycles with a $Me_2NCH_2C{\equiv}C$- side chain are more active than compounds with a saturated $Me_2N(CH_2)_3$- side chain. (**Figure 5.8**) This trend is similar to a report by Cheng [222] on the activities of nicotinic receptors [$Me_2N(CH_2)_2O$- > $Me_2N(CH_2)_2$- > $Me_2NCH_2C{\equiv}C$- > $Me_2N(CH_2)_3$-].



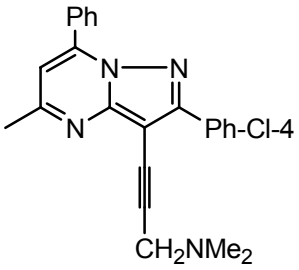
113a, IC_{50} = 13.2 μM



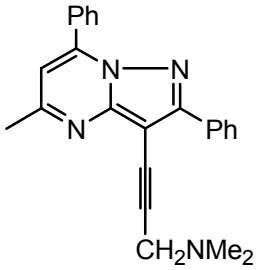
116a, 84 % at 20 μM

Figure 5.8

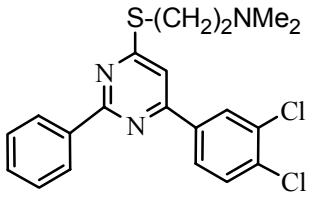
(c) In general, heterocycles with one 4-chlorophenyl or one 3,4-dichlorophenyl are more active than the compounds with phenyl. (**Figure 5.9**)



113d, IC$_{50}$ =8.5 μM

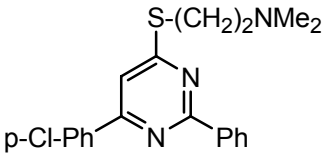


113c, IC$_{50}$ = 12.0 μM



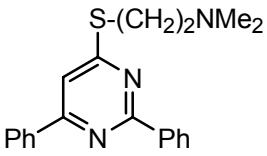
346

IC$_{50}$ = 1.5 μM



5

IC$_{50}$ = 6.0 μM



349

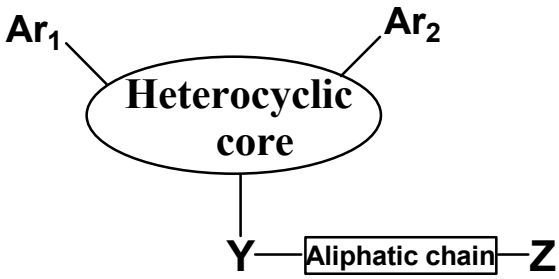
IC$_{50}$ =18.0 μM

Figure 5.9

On the other hand, our results demonstrated that it is impossible to deduce stringent roles for structure-activity relations from the data obtained so far. It would be extremely helpful if additional information (e.g. X-ray crystal analytical or NMR data), could be achieved about the interaction of an inhibitor with calcineurin. This would allow a prediction of optimized structure by the establishment of quantitative structure-activity-relation.

Chapter 6: Summary

Our research aimed to the development of new non-peptide calcineurin inhibitors. Such compounds are of eminent importance as immuno-suppressants and are used in the treatment of heart insufficiency. Based on a positive test of a few compounds (pyrazolopyrimidines and pyrazolotriazines), a general structure **8** (**Figure 6.1**) of potential calcineurin-inhibiting compounds was hypothesized in our group.

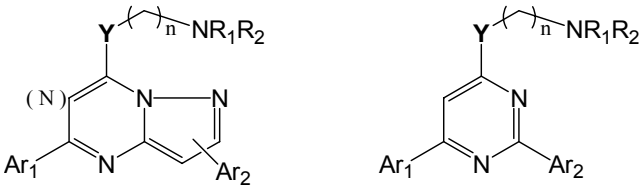


General structure **8**

Figure 6.1 General Structure **8**

The structural feature represents an assembly of a heterocyclic core (nitrogen containing aromatic heterocycle), furnished with two aryl groups and one side chain with a terminal heteroatom functionality. It was necessary to prove to what extend this hypothesis is valid and which structure-activity relations exist.

Investigations in Karanik's thesis [16b] concentrated on pyrazolo[1,5-a]pyrimidines, pyrazolo[1,5-a]triazines and pyrimidines, where the aryl groups and the saturated chain (Y = NH, O, or S) were varied (**Figure 6.2**).



350 **351**

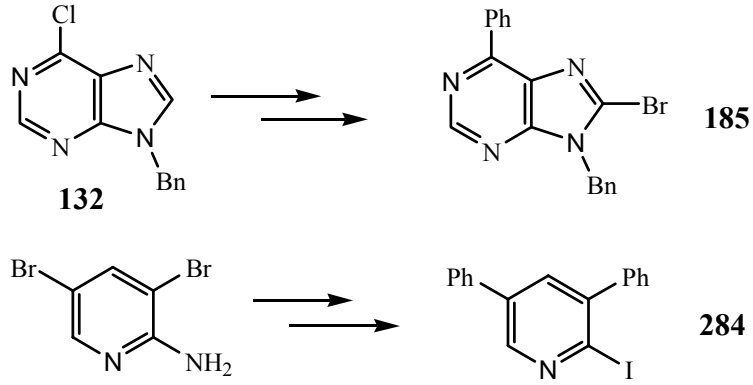
Figure 6.2 General Structures of Karanik's thesis

In the present thesis, we tried to vary the central N-heterocyclic cores, the side chains and its position of attachment. In the general structure **8**, **Y** can be CH_2 and CH_2NH, besides NH, O, and S, and the aliphatic chain can be saturated and unsaturated. As a synthetic strategy,

Pd-catalyzed coupling reactions were used to introduce side chains and/or aryl substituents into the central heterocycle. In this way the utility of such reactions to heterocyclic systems, which were neglected so far, could be figured out.

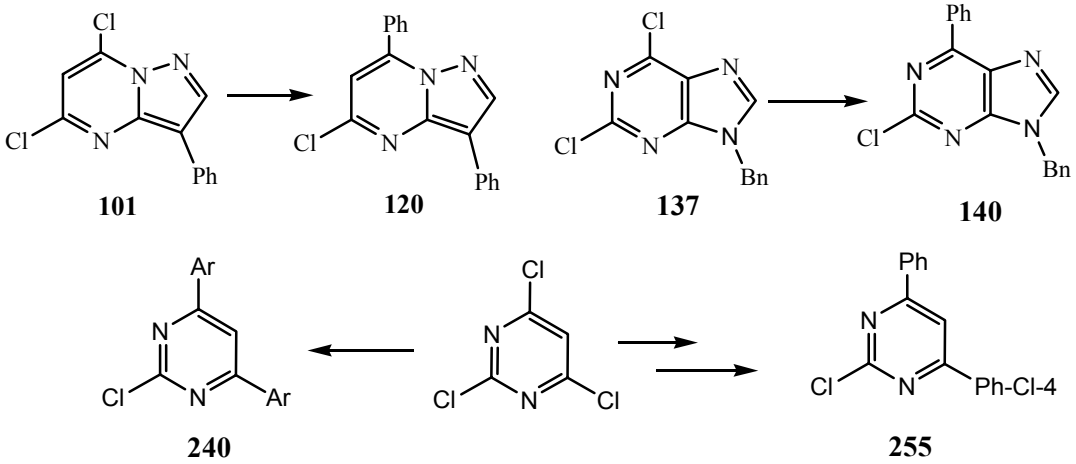
■ Synthesis of halogen subsitituted diaryl heterocycles

Halogen substituted diaryl heterocycles are important intermediates in the synthesis of general structures **8**. In order to introduce aryl groups into the heterocyclic core, Suzuki reaction was applied as the key step, for example, synthesis of 9-benzyl-8-bromo-6-phenylpurine (**185**) and 3,5-diphenyl-2-iodopyridine (**284**). (**Scheme 6.1**)



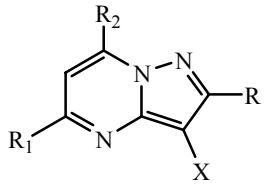
Scheme 6.1

If heterocycles with more than one halo-leaving group were used as starting materials, aryl group could be introduced by regioselective Suzuki coupling, e. g. synthesis of 5-chloro-3,7-diphenylpyrazolo[1,5-a]pyrimidine (**120**), 7 (or 9)-benzyl-2-chloro-6-phenylpurine (**140** and **184**) and 2-chloro-4,6-diarylpyrimidines (**240** and **255**). (**Scheme 6.2**)

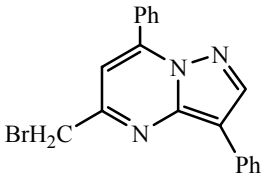


Scheme 6.2

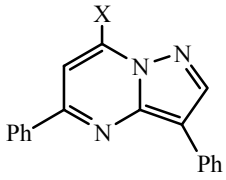
Other starting haloheterocycles were obtained either by replacement of hydroxyl groups or by halogenation of the unfunctionalized position of the heterocycles. More than 30 compounds of corresponding halo-heterocycles were synthesized. (**Figure 6.3**)



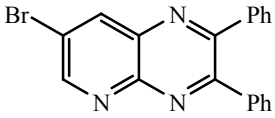
103, X = Br
104a-104h, X = I



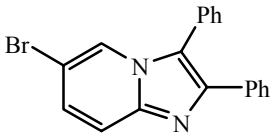
105



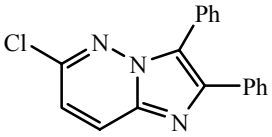
98, 99, 100
X = Cl, Br, I



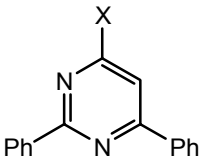
193



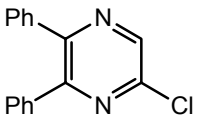
218



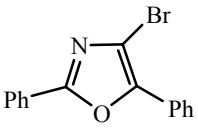
219



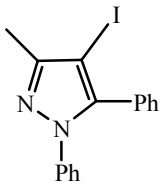
250, X = Cl
251, X = I



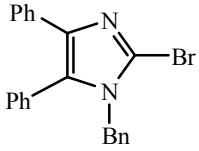
297



310



321



338

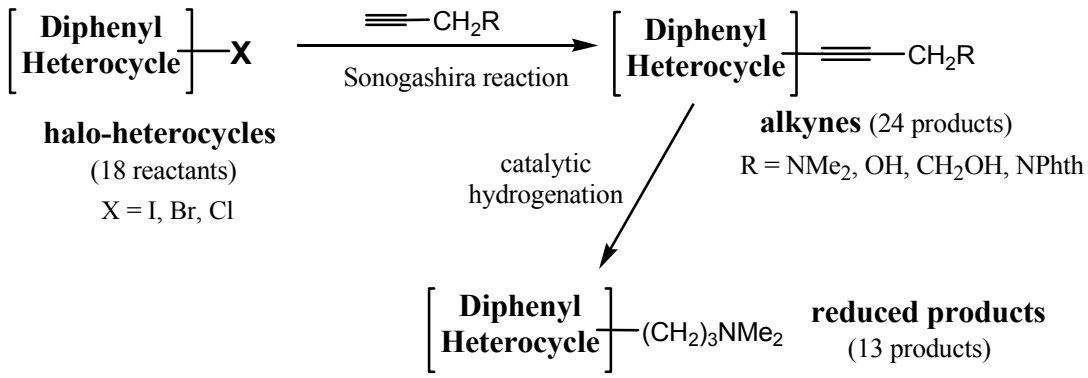
Figure 6.3

■ Introduction of side chains by Pd-catalyzed couplings and nucleophilic substitution

The introduction of the desired side chains by C-C bond formation reactions was achieved by Sonogashira coupling and Heck coupling. Buchwald-Hartwig amination and nucleophilic substitution were used to establish side chains which are connected to the core heterocycle by heteroatom-C bonds.

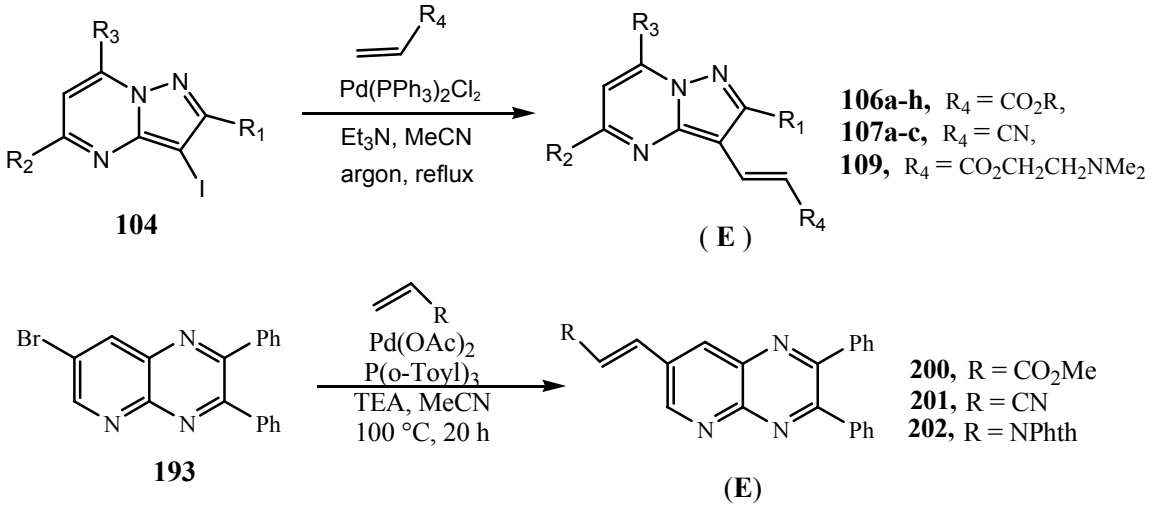
Sonogashira reaction turned out to be the most effective and convenient method to introduce ω-functionalized alkynyl group into the heterocyclic cores. Further catalytic hydrogenation of the alkyne moiets led to ω-functionalized alkyl substituted diaryl heterocycles. (**Scheme 6.3**) Five bicyclic and six monocyclic core heterocycles could be successfully submitted to this reaction sequence.

Several reaction conditions and Pd-catalysts were tested. It turned out that Pd/C was advantageous over other commonly used Pd(II) or Pd(0) pre-catalysts in a number of cases (**104a** and **321** as starting material).



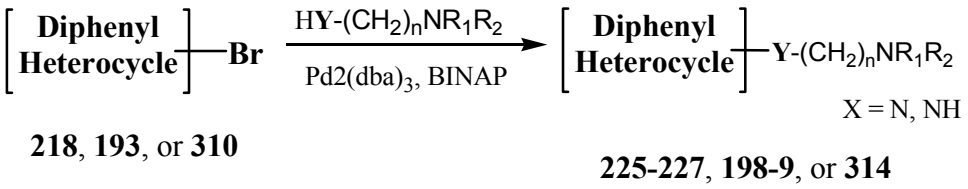
Scheme 6.3

Heck reaction of 3-iodopyrazolo[1,5-a]pyrimidines (**104a-h**) or 7-bromo-pyrido[2,3-b]pyrazine (**193**) with olefins, allowed to introduce ω-functionalized alkenyl groups into these heterocyclic cores. (**Scheme 6.4**)



Scheme 6.4

Buchwald-Hartwig amination of 6-bromoimidazo[1,2-a]pyridine (**218**), 7-bromo-pyrido[2,3-b]pyrazine (**193**) or 4-bromooxazole (**310**) with ω-functionalized alkylamines, allowed the introduction of aminoalkyl chains, which are tethered to the heterocyclic cores by a heteroatom. (**Scheme 6.5**)



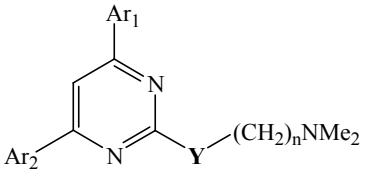
218, **193**, or **310**

225-227, **198-9**, or **314**

Scheme 6.5

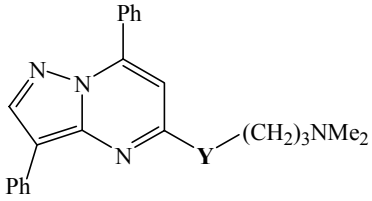
Our synthetic affords contributed to the general knowledge about the scope and limitation of Pd-catalyzed reactions in heterocyclic chemistry.

By nucleophilic substitution, a series of purines, pyrimidines, and pyrazolo[1,5-a]pyrimidines with a side chain (X = O, S, NH, or CH_2NH) were synthesized (**Figure 6.4**).



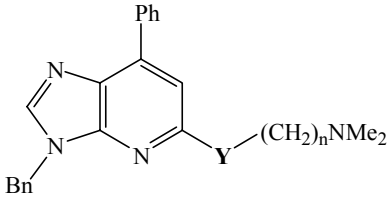
X = O, S, or NH, n = 2, or 3;

261-263



X = CH_2NH, or NH

128, 129



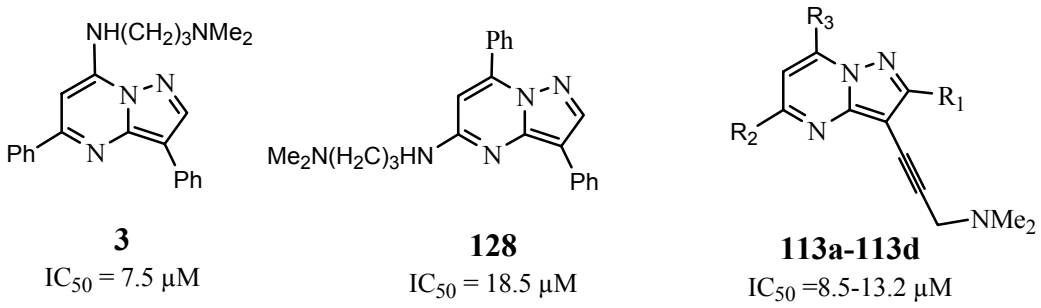
X = O, or NH, n = 2, or 3;

190, 191, 192 (7-benzyl)

Figure 6.4

■ Calcineurin inhibitory activities

Compared with the compounds of high activity independently obtained in our group by other methodology, the positions of connections of the side chains and aryl groups in the pyrazolo[1,5-a]pyrimidine series could be varied. According to the testing results of the compounds, we found out that the connection of the side chain to position 7 of pyrazolopyrimidine core is most effective for calcineurin inhibition as compared with other connection sites. The necessity of a basic amino group at the terminus of the side chain was manifested by our results. It was further detected, that the side chain can be unsaturated. (**Figure 6.5**)



3
IC_{50} = 7.5 µM

128
IC_{50} = 18.5 µM

113a-113d
IC_{50} =8.5-13.2 µM

Figure 6.5

Novel pyrimidines, where the amino substituted side chain was connected to position 2 rather than to position 4, revealed that these two positions are similar effective with respect to calcineurin inhibition.

Prior to the present thesis, compounds of the general structure **8** were investigated only with pyrazolopyrimidine, pyrazolotriazine and pyrimidine as central heterocyclic core. In the course of this thesis, novel compounds with purine, pyridopyrazine, imidazopyridine, imidazopyridazine, imidazole, oxazole, pyrazole, pyridine, and pyrazine were developed and tested.

The enzyme inhibiting test showed that, unfortunately, all these heterocyclic systems are not as effective as pyrazolopyrimidines, pyrazolotriazines and pyrimidines.

The structural model **8** of potential calcineurin inhibitors could be refined and important contributions to its scope and limitations were provided. The results further demonstrate the vast versatility of Pd-catalyzed coupling reactions in new areas of heterocyclic chemistry.

In the present work, more than 180 compounds were synthesized. Among them, about 130 compounds are new products. 86 of them fit into the general structure **8**.

Five publications arouse from these results. Two of them have been published, one is in press. Another two are under preparation.

Chapter7: Experimental

7.1 General Remarks

^{1}H NMR and **^{13}C NMR** spectra were recorded at 300 MHz and 75.5 MHz, respectively, with a Bruker AC-300 in deuterated solvent ($CDCl_3$, DMSO-d_6, D_2O, CD_3OD etc.), with TMS as internal standard. The following abbreviations are used in the splitting pattern of ^{1}H NMR**:** s (singlet), br (broad single), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet).

EI-Mass spectra (**MS**) (HP-5995 A) and EI-high resolution mass (**HRMS**) spectra (MAT 711, Varian) were measured at 70 eV.

Elemental analysis was measured at CHNS-932 (Leco) in the microanalytical lab of institute of chemistry.

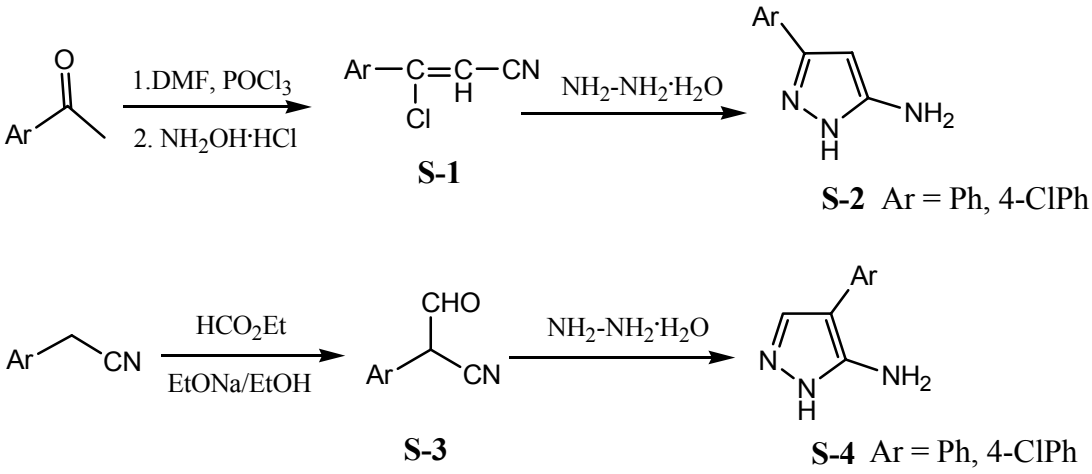
Melting points were determined on a Boetius hot-stage apparatus and were reported uncorrected.

TLC analysis was performed on Merck silica gel 60 F_{254} plates or Merck Al_2O_3 60F_{254} neutral (Typ E) plates and visualized with UV illumination.

Column chromatography was conducted with Merck silica gel 60 (400-639 mesh) or Merck neutral Al_2O_3 gel (90 standard). The normal solvents hexane, cyclohexane, ethyl acetate, dichloromethane were redistilled before use.

The cross-coupling reactions were carried out under argon in oven-dried glasswares. **Solvents** were dried and deoxygenated by standard procedures.

Starting materials were purchased from Aldrich, Lancaster, Acros, and Merck, except compounds **S1**-**S11** (see **Scheme7.1** to **7.4**).
3-amino-5-arylpyrazoles **S2** were prepared according to literatures [223, 224], 3-amino-4-arylpyrazoles **S4** were prepared as described in the literatures [225, 226]. (**Scheme 7.1)**



S-1

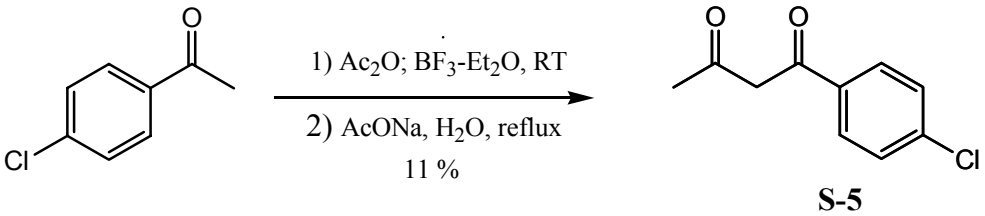
S-2 Ar = Ph, 4-ClPh

S-3

S-4 Ar = Ph, 4-ClPh

Scheme 7.1

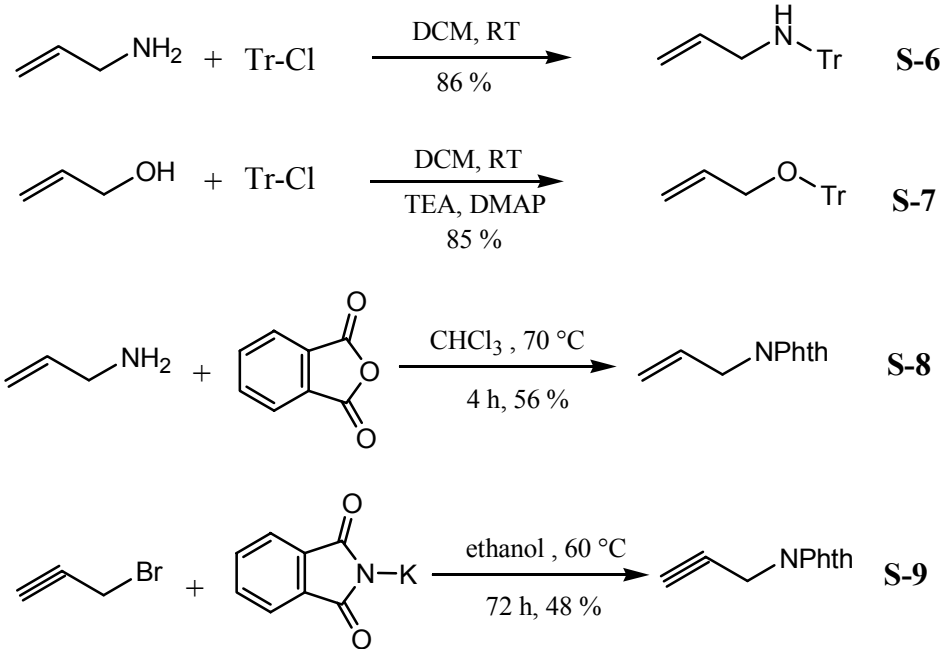
1-(4-chloro-phenyl)-butane-1,3-dione **S5** was prepared according to literature [227] (**Scheme 7.2**).



S-5

Scheme 7.2

Allyl-trityl-amine **S-6**, allyl trityl ether **S-7**, allyl-phthalamide **S-8**, and propargyl phthalamide **S-9** were prepared according to literatures [228-231], respectively (**Scheme 7.3**).



S-6

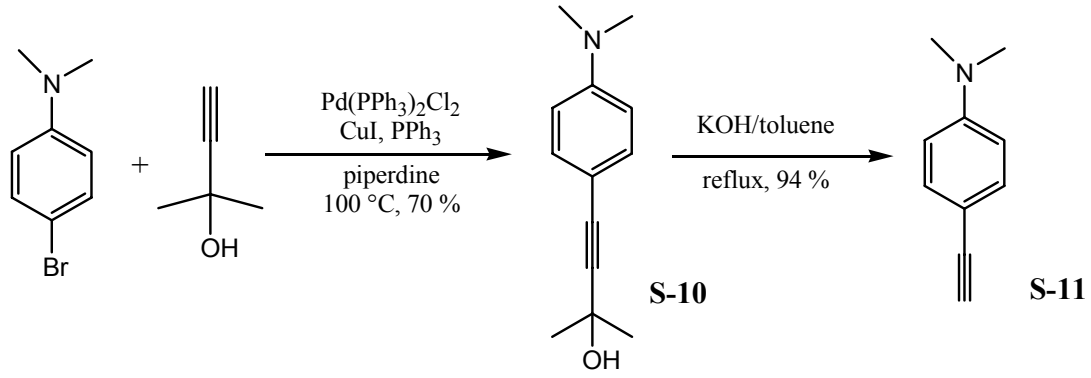
S-7

S-8

S-9

Scheme 7.3

4-Ethynyl-phenyl)-dimethylamine **S-11** was prepared according to literature procedures [232]. (**Scheme 7.4**).

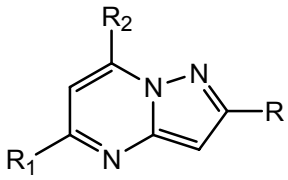


Scheme 7.4

7.2 Synthesis of pyrazolo[1,5-a]pyrimidine derivatives

7.2.1 Synthesis of pyrazolo[1,5-a]pyrimidines by ring closure

7.2.1.1 Synthesis of 2, 5, 7-tri-substituted pyrazolo[1,5-a]pyrimidines



88a-88h

General procedure:

A 50 ml round flask was charged with appropriate 5-substituted 3-aminopyrazole (20 mmol), appropriate 1,3-diketone (22 mmol) and 37 % hydrochloric acid (15 ml). The mixture was heated at reflux for 3 h. After the reaction was complete (from TLC), the mixture was cooled, neutralized with aq. Na_2CO_3 and extracted with $CHCl_3$ (3 × 40 ml). The combined organic layers were dried with anhydrous $MgSO_4$. The solvent was evaporated and the crude product was purified by recrystallization or column chromatography on silica gel.

5-Methyl-2,7-diphenylpyrazolo[1,5-a]pyrimidine (**88a**)

The crude product was purified by recrystallization with ethanol as solvent, and provided a light yellow solid, yield 89 %, mp 185-6 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.62 (s, 3 H, CH_3), 6.74 (s, 1 H, H-3), 6.90 (s, 1 H, H-6), 7.43-8.14 (m, 10 H, Ar-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 24.79 CH_3, 92.54 CH(C-3), 108.15CH(C-6), 126.58 CH, 128.50 CH, 128.64 CH, 129.45 CH, 129.70 CH, 130.90 CH, 131.15 C, 133.10 C, 145.73 C, 150.82 C, 155.72 C, 158.65 C.

HRMS(EI) calcd for $C_{19}H_{15}N_3(M^+)$ 285.12660, found 285.12656.

Anal. Calcd. for $C_{19}H_{15}N_3$: C, 79.98; H, 5.30; N, 14.73.
Found: C, 79.81; H, 5.34; N, 14.78.

2-(4-Chloro-phenyl)-5-methyl-7-phenylpyrazolo[1,5-a]pyrimidine (**88b**)

The crude product was purified by recrystallization with ethanol as solvent, and provided a light yellow solid, yield 66 %, mp 156-8 °C.

^{1}H-NMR (CDCl3), δ(ppm): 2.64 (s, 3 H, CH_3), 6.78 (s, 1 H, H-3), 6.88 (s, 1 H, H-6), 7.37-8.12 (m, 9 H, Ar-H).
^{13}C-NMR (CDCl3), δ(ppm): 24.79 CH3, 92.50CH(C-3), 108.36 CH(C-6), 127.78 CH, 128.53 CH, 128.78 CH, 129.41 CH, 130.97 CH, 131.00 C, 131.49 C, 134.60 C, 145.74 C, 150.84 C, 154.49 C, 158.87 C.

Anal. Calcd. for $C_{19}H_{14}ClN_3$: C, 71.36; H, 4.41; Cl, 11.09; N, 13.41.
Found: C, 71.52; H, 4.50; Cl, 11.10; N, 13.24.

2-Methyl-5,7-diphenylpyrazolo[1,5-a]pyrimidine (**88c**)

The crude product was purified by recrystallization with ethanol as solvent, and provided a light yellow solid, yield 74 %, mp 113-4 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.53 (s, 3 H, CH_3), 6.58 (s, 1 H, H-3), 7.24 (s, 1 H, H-6), 7.49-8.09 (m, 10 H, Ar-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 14.92 CH_3, 96.47 CH(C-3), 104.42 CH(C-6), 127.20 CH, 128.68 CH, 128.87 CH, 129.26 CH, 130.09 CH, 130.87 CH, 131.66 C, 137.73 C, 146.15 C, 150.65 C, 155.44 C, 155.82 C.

Anal. Calcd. for $C_{19}H_{15}N_3$: C, 79.98; H, 5.30; N, 14.73.
Found: C, 79.83; H, 5.36; N, 14.74.

7-(4-Chloro-phenyl)-5-methyl-2-phenylpyrazolo[1,5-a]pyrimidine (**88d**)

The crude product was purified by recrystallization, using ethanol as solvent, and afforded a light yellow solid, yield 77 %, mp 155-7 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.63 (s, 3 H, CH_3), 6.74 (s, 1 H, H-3), 6.92 (s, 1 H, H-6), 7.37-8.13 (m, 9 H, Ar-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 24.80 CH_3, 92.69 CH(C-3), 107.95 CH(C-6), 126.53 CH, 128.69 CH, 128.80 CH, 128.91 CH, 129.50 C, 130.78 CH, 132.91 C, 137.02C, 144.49 C, 150.78 C, 155.79 C, 158.62 C.

Anal. Calcd. for $C_{19}H_{14}ClN_3$: C, 71.36; H, 4.41; Cl, 11.09; N, 13.41.
Found: C, 71.16; H, 4.58; Cl, 11.17; N, 13.09.

2,5-Dimethyl-7-phenylpyrazolo[1,5-a]pyrimidine (**88e**)

The crude product was purified by recrystallization, using ethanol as solvent, and provided a light yellow solid, yield 78 %, mp 81-2 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.50(s, 3 H, CH_3), 2.60(s, 3H, CH_3), 6.41(s, 1 H, H-3), 6.67(s, 1H, H-6), 7.52-8.03 (m, 5 H, Ar-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 14.83 CH_3, 24.69 CH_3, 95.18 CH(C-3), 107.50 CH(C-6), 128.60 CH, 129.20 CH, 130.80 CH, 131.13 C, 145.56 C, 150.37 C, 154.85 C, 158.29 C.

Anal. Calcd. for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82.
Found: C, 75.19; H, 5.98; N, 18.83.

2,5,7-Trimethylpyrazolo[1,5-a]pyrimidine (**88f**)

The crude product was purified by recrystallization, using diethyl ether/hexane (1/2) as solvent, and provided a light brown solid, yield 68 %, mp 69-70 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.52 (s, 3 H, CH_3), 2.54 (s, 3 H, CH_3), 2.71 (s, 3 H, CH_3), 6.36 (s, 1 H, H-3), 6.48(s, 1 H, H-6).
^{13}C-NMR($CDCl_3$), δ(ppm): 14.67 CH_3, 17.17 CH_3, 24.43 CH_3, 95.09 CH(C-3), 107.54 CH(C-6), 144.90 C, 149.08 C, 154.63 C, 157.98 C.

Anal. Calcd. for $C_9H_{11}N_3$: C, 67.06; H, 6.88; N, 26.07.
Found: C, 66.81; H, 7.01; N, 26.14.

2,5,7-Triphenylpyrazolo[1,5-a]pyrimidine (**88g**)

The crude product was purified by recrystallization with ethanol as solvent, and provided a light yellow solid, yield 77 %, mp 154-5 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 7.09 (s, 1 H, H-3), 7.24 (s, 1 H, H-3), 7.35-8.22 (m, 15 H, Ar-H).
^{13}C NMR($CDCl_3$), δ(ppm): 93.76 CH(C-3) , 105.04 CH(C-6), 126.61 CH, 127.22 CH, 128.57 CH, 128.68 CH, 128.88 CH, 128.93 CH, 129.52 CH, 130.25 CH, 131.46 C, 133.05 C, 137.61 C, 146.37 C, 151.15 C, 156.09 C, 156.26 C.

Anal. Calcd. for $C_{24}H_{17}N_3$: C, 82.97; H, 4.93; N, 12.09.
Found: C, 82.89; H, 4.99; N, 11.99.

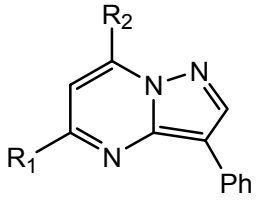
5,7-Diphenylpyrazolo[1,5-a]pyrimidine (**88h**)

The crude product was purified by column chromatography on silica gel, using hexane:ethyl acetate(4/1) as eluting solvent, and provide a yellow solid, yield 89 %, mp 85-6 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 6.30 (d, 1 H, *J* = 2.3, H-3), 7.28(s, 1 H, H-3), 7.44-8.08 (m, 10 H, Ar-H), 8.11 (d, 1H, *J* = 2.3, H-2).
^{13}C-NMR($CDCl_3$), δ(ppm): 97.19 CH(C-3), 105.22 CH(C-6), 127.29 CH, 128.74 CH, 128.95 CH, 129.24 CH, 130.31 CH, 130.97 CH, 131.51 C, 137.52 C, 145.21 CH(H-2), 146.85 C, 149.86 C, 156.22 C.

Anal. Calcd. for $C_{18}H_{13}N_3$: C, 79.68; H, 4.83; N, 15.49.
Found: C, 79.34; H, 5.06; N, 15.54.

7.2.1.2 Synthesis of 3,5,7-trisubstituted pyrazolo[1,5-a]pyrimidines



89a-89c

A 50 ml flask was charged with 3-amino-4-phenylpyrazole **S-4a** (3.18 g, 20 mmol), appropriate 1,3-diketone (22 mmol) and 37 % hydrochloric acid (15 mL). The mixture was heated at reflux for 10 hours. After the reaction was complete (check TLC), the mixture was cooled, neutralized with aq. Na_2CO_3 and extracted with $CHCl_3$ (3 × 40 ml). The combined organic layers were dried with anhydrous $MgSO_4$. The solvent was evaporated and the crude product was purified by recrystallization

5,7-Dimethyl-3-phenylpyrazolo[1,5-a]pyrimidine (**89a**)

The crude product was purified by recrystallization with ethanol:hexane(4/1) as solvent and provided a yellow solid, yield 75 %, mp 91-92 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.54 (s, 3 H, CH_3), 2.67 (s, 3 H, CH_3), 6.52 (s, 1 H, H-6), 7.17-8.02 (m, 5 H, Ph-H), 8.32 (s, 1 H, H-2).
^{13}C-NMR($CDCl_3$),δ(ppm): 17.08 CH_3(C-7), 24.93 CH_3(C-5), 108.74 CH(C-6), 109.54 C, 125.94 CH, 126.19 CH, 128.69 CH, 132.50 C, 142.14 CH(C-2), 144.81 C, 145.22 C, 158.74 C.

Anal. Calcd. for $C_{14}H_{13}N_3$ (223.28): C, 75.31; H, 5.87; N, 18.82.
Found: C, 75.25; H, 5.94; N, 18.84.

5-methyl-3,7-diphenylpyrazolo[1,5-a]pyrimidine (**89b**)

The crude product was purified by recrystallization with ethanol to provide a yellow solid, yield 86 %, mp 124-5°C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.61 (s, 3 H, CH_3), 6.70 (s, 1 H, H-6), 7.17-8.04 (m, 10 H, Ph-H), 8.32 (s, 1 H, H-2).
^{13}C-NMR ($CDCl_3$), δ(ppm): 25.06 CH_3, 108.71 CH(C-6), 109.57 C, 126.05 CH, 126.34 CH, 128.69 CH, 128.76 CH, 129.21 CH, 130.90 CH, 131.20 C, 132.41 C, 142.56 CH(C-2), 145.84 C, 146.24 C, 159.06 C.

Anal. Calcd. for $C_{19}H_{15}N_3$ (285.34): C, 79.98; H, 5.30; N, 14.73.
Found: C, 79.98; H, 5.41; N, 14.76.

3,5,7-Triphenylpyrazolo[1,5-a]pyrimidine (**89c**):

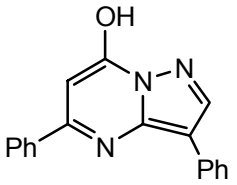
The crude product was purified by recrystallization with ethanol as solvent, and provided a yellow solid, yield 86 %, mp 163-4 °C.

^{1}H-NMR ($CDCl_3$),δ(ppm): 7.17 (s, 1 H, H-6), 7.31-8.18 (m, 15 H, Ph-H), 8.41 (s, 1 H, H-2).
^{13}C-NMR ($CDCl_3$),δ(ppm): 105.17 CH(C-6), 110.70 C, 126.14 CH, 126.37 CH, 127.35 CH, 128.74 CH, 128.78 CH, 129.95 CH, 129.28 CH, 130.43 CH, 131.01 CH, 131.39 C, 132.41 C, 137.38 C, 142.96 CH(C-2), 145.95 C, 147.02 C, 155.91 C.

Anal. Calcd. for $C_{24}H_{17}N_3$ (347.4): C, 82.97; H, 4.93; N, 12.10.
Found: C, 82.92; H, 5.01; N, 12.13.

7.2.1.3 Hydroxy-substituted pyrazolo[1,5-a]pyrimidines

7-hydroxy-3,5-diphenylpyrazolo[1,5-a]pyrimidine (**90**)



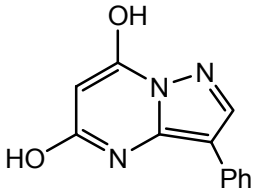
90

A mixture of 4-phenyl-3-aminopyrazole (3.18 g, 0.02 mol) and ethylbenzoyacetate (4.55 g, 0.022 mol) in acetic acid 5 ml was heated at reflux for 20 h, the solution was evaporated to dryness in vacuo and treated with diethyl ether, white solid was obtained, the crude product was recrystallized with ethanol, and 4.26 g white solid was obtained, yield 74 %, mp 250-2 °C.

^{1}H-NMR(DMSO-d_6), δ(ppm): 6.06 (s, 1 H, H-6), 7.28-7.85 (m, 10 H, Ph-H), 8.22 (s 1 H, H-2), 12.28 (br, 1 H, OH).
^{13}C-NMR(DMSO-d_6), δ(ppm): 95.22 CH,106.23 C, 126.56 CH, 127.67 CH, 128.05 CH, 128.21 Ch, 128.72 CH, 130.88 CH, 132.92 C, 136.23 C, 142.35 CH(C-2), 144,20 C, 150.67 C, 156.32 C.

Anal. Calcd. for $C_{18}H_{13}N_3O$(287.32): C, 75.25; H, 4.56; N, 14.63.
Found: C, 75.31; H, 4.68; N, 14.59.

5,7-dihydroxy-3-phenylpyrazolo[1,5-a]pyrimidine (**91**)

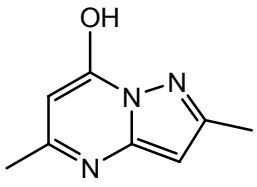


91

4-Phenyl-3-aminopyrazole **S-4a** (3.20 g, 0.02 mol) and diethyl malonate (3.23 g, 0.20 mol) were added to a solution of sodium (1.8g, 0.077mol) in 200 ml dry ethanol, the mixture was heated at reflux for 16 hours, after cooled the precipitate was collected by filter and washed with ethanol, and dried in vacuum, the solid (sodium salt) was dissolved in 150 ml water and the aqueous phase was acidified with 6 N HCl, the precipitate was collected and dried, the crude product was dissolved in 6N aqueous NaOH, and acidified the solution with 6N HCl, and provided a pure white solid 2.2 g, yield 50 %, mp 308-310 °C.

Anal. Calcd. for $C_{12}H_9N_3O_2$(227.22): C, 63.43; H, 3.99; N, 18.49.
Found: C, 63.20; H, 4.18; N, 18.32.

7-hydroxy-3,5-diphenylpyrazolo[1,5-a]pyrimidine (**92**)



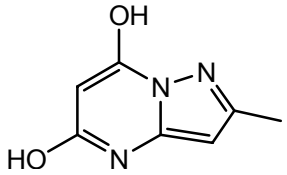
92

A mixture of 3-amino-2-methylpyrazole (1.95 g, 0.02 mol) and ethyl acetoactate (3.12 g, 0.024 mol) in 8 ml acetic acid was heated at reflux for 3 hours, after cooled, 40 ml water was added, the solution was cooled and the white solid was collected, washed with cold water and provided a white solid 2.32 g, yield 71 %, mp 226-8 °C.

^{1}H-NMR(DMSO-d_6), δ(ppm): 2.44 (s, 3H; CH_3), 2.49 (s, 3 H, CH_3), 5.27 (br, 1 H, OH), 5.69 (s, 1 H, H-3), 6.09 (s, 1 H, H-6).
^{13}C-NMR(DMSO-d_6), δ(ppm): 14.20 CH_3, 19.68 CH_3, 88.52 CH(C-2), 94.14 CH(C-6), 144.21 C, 151.33 C, 151.47 C, 156.58 C.

Anal. Calcd. for $C_8H_9N_3O$(163.18): C, 58.88; H, 5.56; N, 25.75.
Found: C, 58.78; H, 5.87; N, 25.64.

5,7-dihydroxy-3-methylpyrazolo[1,5-a]pyrimidine **(93)**



93

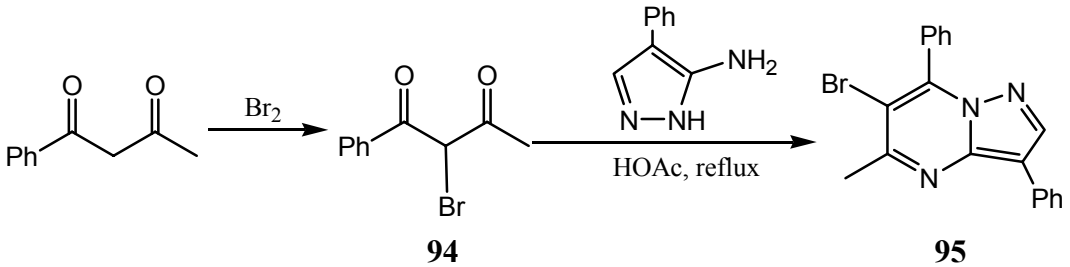
3-Amino-5-methylpyrazole (5.03 g, 51 mmol), diethyl malonate (9.60 g, 60 mmol) was added to a solution of sodium (3.2 g,0.14 mol) in 100 ml dry ethanol, the mixture was heated at reflux for 16hours, after cooled the precipitate was collected by filter and washed with ethanol, and dried in vacuum, the solid (sodium salt) was dissolved in 20ml water and the solution was acidified with 10 % HCl (to pH value <2), the solution was then cooled and the precipitate was collected, washed with cold 1 N HCl and dried, and provided a light yellow solid 6.9 g, yield 82 %, mp 244-6 °C.

Anal. Calcd. for $C_7H_7N_3O_2$(165.15): C, 50.91; H, 4.27; N, 24.55.
Found: C, 50.75; H, 4.48; N, 24.29.

7.2.2 Synthesis of halogen substituted pyrazolo[1,5-a]pyrimidines

7.2.2.1 Synthesis of 6-bromopyrazolo[1,5-a]pyrimidines

(a) 6-Bromo-5-methyl-3,7-diphenylpyrazolo[1,5-a]pyrimidine (**95**)



94 **95**

Scheme 7.5

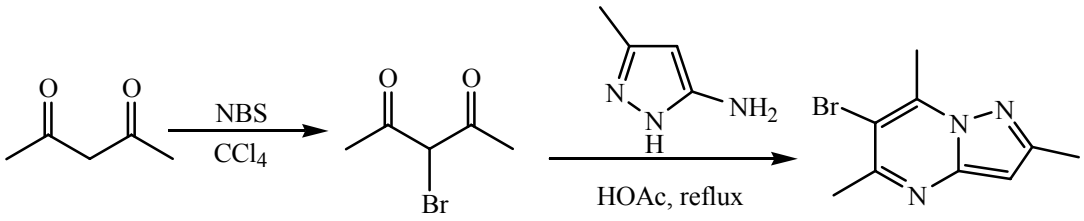
A solution of bromine (6.10 g, 0.038 mol) in 40 ml CCl_4 was added dropwise in 45 min to a vigorously stirring dispersion of benzoylacetone (6.16 g, 0.037 mol) in CCl_4 40 ml and water 40 ml at 0 °C, the mixture was continue to stir for 1 h, the mixture was separated and the aqueous layer was extracted with CCl_4 (2 × 30 ml), the combined organic phase was washed with brine (2 × 30 ml) and dried with anhydrous $MgSO_4$, the solvent was evaporated in high-vacuum and provide 9.30 g oily crude 2-bromo-1-phenyl-butane-1,3-dione **94**.

A 50 ml round flask was charged with 4-phenyl-3-aminopyrazole **S-2a** (3.18 g, 20 mmol), crude 2-bromo-1-phenyl-butane-1,3-dione **94** (5.8 g, >22 mmol) and conc. hydrochloric acid 15 ml. The mixture was heated at reflux for 10 h. After the reaction was complete, the mixture was cooled, neutralized with aq Na_2CO_3 and the orange precipitate was collected, washed with 1 N HCl and water, the crude product was purified by recrystallization from ethanol and 5.10 g orange solid was obtained, yield 70 %, mp.129-130 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.73 (s, 3 H, CH_3), 7.35-8.00 (m, 10 H, Ph-H), 8.25 (s, 1 H, H-2).
^{13}C-NMR($CDCl_3$), δ(ppm): 24.47 CH_3, 108.50 C, 126.32 CH, 126.57 CH, 128.76 CH, 129.08 CH, 129.61 CH, 130.70 CH, 131.09 C, 131.84 C, 142.92 CH(C-2), 146.24 C, 147.16 C, 157.45 C.

Anal. Calcd for $C_{19}H_{14}BrN_3$ (364.40): C, 62.63; H, 3.87; Br, 21.93; N, 11.53.
Found: C, 62.31; H, 4.09; Br, 22.02; N, 11.64.

(b) 6-Bromo-2,5,7-trimethylpyrazolo[1,5-a]pyrimidine **(97)**



96 **97**

Scheme 7.6

A soution of acetylacetone (2.02 g, 0.020 mol), NBS (3.60 g, 0.020 mol) in 20 ml CCl_4 was heated at reflux for 5 h, then filtered and the filtrate was evaporated to dryness and gave 3.4 g oily crude 3-bromo-acetylacetone **96**.

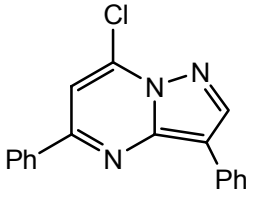
A mixture of 3-amino-2-methylpyrazole (1.65 g, 0.017 mol) and crude 3-bromo-acetylacetone **97** (3.10 g, 0.018 mol) in acetic acid 10 ml was heated at reflux for 3 h, after the mixture was cooled, 10 ml water was added, the solution was neutralized with 6 N NaOH, and extracted

with diethyl ether (2 × 40 ml), the extract was washed with water 30 ml, dried with anhydrous $MgSO_4$.the solvent was evaporated, the crude product was recrystallized with water and provided 3.64 g light brown solid, yield 89 %, mp 83-4 °C.

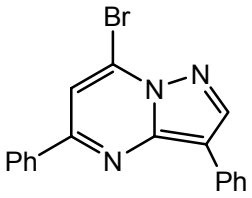
^{1}H-NMR($CDCl_3$), δ(ppm): 2.42 (s, 3 H, CH_3), 2.62 (s, 3 H, CH_3), 2.84 (s, 3 H, CH_3), 6.28 (s, 1 H, H-2).
^{13}C-NMR($CDCl_3$), δ(ppm): 14.63 CH_3, 17.30 CH_3, 26.17 CH_3, 95.64 CH(C-2), 105.73 C, 143.97 C, 147.27 C, 154.96 C, 156.50 C.

Anal. Calcd for $C_9H_{10}BrN_3$ (240.10): C, 45.02; H, 4.42; Br, 33.28; N, 17.50.
Found: C, 44.96; H, 4.42; Br, 33.49; N, 17.65.

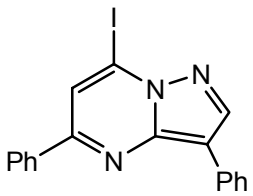
7.2.2.2 Synthesis of 7-halo-3,5-diphenylpyrazolo[1,5-a]pyrimidine



98



99



100

7-Chloro-3,5-diphenylpyrazolo[1,5-a]pyrimidine (**98**)

A solution of 7-hydroxy-5,7-diphenylpyrazolo[1,5-a]pyrimidine **90** (4.60 g, 16 mmol), $POCl_3$ (5 ml, 53 mmol) and N, N-dimethylaniline (0.4 ml, 3.1 mmol) was heated at reflux for 3 h. After the mixture was cooled to RT, ice (about 30 ml) was added slowly and carefully. The mixture was extracted with chloroform (3 × 30 ml), the combined organic layers were dried with anhydrous $MgSO_4$ and concentrated. The crude product was recrystallized with a mixture solvent of acetone and pentane, and a yellow crystal 4.81 g was obtained, yield 98 %, mp 159-60 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 7.49 (s, 1 H, H-6), 8.53 (s, 1 H, H-2), 7.28-8.17 (m, 10 H, Ar-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 105.59 CH(C-6),112.31 C, 126.43 CH, 126.63 CH, 127.40 CH, 128.81CH, 129.06 CH, 130.88 CH, 131.66 C, 136.29 C, 139.03 C, 143.54 CH(C-2), 145.81 C, 155.65 C.

Anal. Calcd for $C_{18}H_{12}ClN_3$ (305.77): C, 70.71; H, 3.96; Cl, 13.74; N, 11.60.
Found: C, 70.78; H, 3.94; Cl, 11.86; N, 13.77.

7-Bromo-3,5-diphenylpyrazolo[1,5-a]pyrimidine (**99**)

A solution of 7-hydroxy-5,7-diphenylpyrazolo[1,5-a]pyrimidine **90** (2.87 g, 10 mmol), $POBr_3$ (4.59 g, 16 mmol), and N, N-dimethylaniline (0.3 ml, 2.3 mmol) in dry toluene (10 mL) was heated at reflux for 3 h. After the solvent was evaporated, ice 30 g was added inside slowly and the mixture was extracted with $CHCl_3$ (3 × 30 ml). The combined organic layers were dried with anhydrous $MgSO_4$ and concentrated. The crude product was recrystallized with a mixture solvent of acetone and pentane to give a yellow crystal 3.35 g, yield 96 %, mp 164-5 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 6.77 (s, 1 H, H-6), 8.52 (s, 1 H, H-2), 7.27-8.16 (m, 10 H, Ar-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 109.72 CH (C-6), 112.46 C, 126.42 CH, 126.60 CH, 127.41 CH, 128.79 CH, 128.99 C, 129.04 CH, 130.84 CH, 131.77 C, 136.12 C, 143.28 CH (C-2), 145.30 C, 155.16 C.

Anal. Calcd for $C_{18}H_{12}BrN_3$ (350.21): C, 61.73; H, 3.45; Br, 22.82; N, 12.00.
Found: C, 61.71; H, 3.49; Br, 22.82; N, 12.00.

7-Iodo-3,5-diphenylpyrazolo[1,5-a]pyrimidine (**100**)

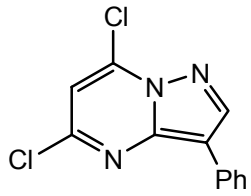
A mixture of 7-chloro-5,7-diphenylpyrazolo[1,5-a]pyrimidine (**98**) (1.53 g, 5 mmol) and 57 % aq HI (20 ml) was stirred at room temperature for 3 days, the mixture was diluted with H_2O (40 ml) and the mixture was extracted with $CHCl_3$ (3 × 40ml): The combined organic layers were washed with saturated aq $Na_2S_2O_3$ (2 × 30ml), 10 % aq Na_2CO_3 (2 × 30ml) and brine (30 ml). After dryed with anhydrous $MgSO_4$ and evaporated the solvent, 1.90 g yellow crystal was obtained, yield 95 %, mp 172-3 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 7.86 (s, 1 H, H-6), 8.51 (s, 1 H, H-2), 7.27-8.51 (m, 10 H, Ar-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 103.94 C, 112.79 C, 117.45 CH(C-6), 126.40 CH, 126.52 CH, 127.43 CH, 128.79 CH, 128.78 CH, 129.02 CH, 130.72 CH, 132.09 C, 135.90 C, 142.60 CH (C-2), 143.90 C, 154.47 C.

Anal. Calcd for $C_{18}H_{12}IN_3$ (397.21): C, 54.43; H, 3.05; I, 31.95; N, 10.58.
Found: C, 54.64; H, 2.89; I, 31.90; N, 10.66.

7.2.2.3 Synthesis of 5,7-dichloro-pyrazolo[1,5-a]pyrimidines

5,7-dichloro-3-phenylpyrazolo[1,5-a]pyrimidines (**101**)



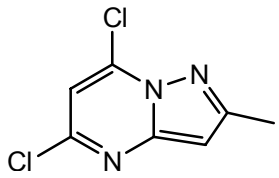
101

To a solution of 5,7-dihydroxy-2-phenylpyrazolo[1,5-a]pyrimidine **91** (2.20 g, 10 mmol) in phosphoryl chloride 30 ml, N,N-dimethylaniline 3 ml (as catalyst) was added, the resulting solution was heated at reflux for 20 hours, the mixture was evaporated in vacuum, 30 ml ice was added in the residue slowly and carefully, the mixture was extracted with ethyl acetate (3 × 40 ml), the combined organic phase was then washed with saturated aqueous sodium bicarbonate (2 × 30 ml), and dried with anhydrous $MgSO_4$, the solvent was evaporated, and the crude product was purified by recrystallization with hexane as solvent, and a yellow needle crystal 1.40 g was obtained, yield 53 %, mp 153-155 °C

^{1}H-NMR ($CDCl_3$), δ(ppm): 6.91 (s, 1 H, H-6), 7.20-7.91 (m, 5 H, Ph-H), 8.44 (s, 1 H, H-2).
^{13}C-NMR ($CDCl_3$), δ(ppm): 108.80 CH(C-6), 112.51 C, 126.46 CH, 127.16 CH, 128.89 CH, 130.46 C, 140.03 C, 144.10 CH(C-2), 149.18 C.

Anal. Calcd. for $C_{12}H_7Cl_2N_3$: C, 54.57; H, 2.67; Cl, 26.85; N, 15.91.
Found: C, 54.80; H, 2.69; Cl, 26.99; N, 15.83.

5,7-dichloro-2-methylpyrazolo[1,5-a]pyrimidines (**102**)



102

To a solution of 5,7-dihydroxy-3-methylpyrazolo[1,5-a]pyrimidine (6.60 g, 40 mmol) in phosphoryl chloride 60 ml, N,N-dimethylaniline 5 ml was added, the resulting red solution was refluxed for 20 hours, the mixture was evaporated in vacuum, 100ml ice was added in the residue slowly, and extracted with ethyl acetate (5 × 60 ml), the combined organic phase was then washed with saturated aqueous sodium bicarbonate (4 × 50 ml), and dried with anhydrous Na_2SO_4, the solvent was evaporated, and the crude product was purifed by recrystallization with hexane as solvent, and provided a yellow needle crystal 4.57 g, yield 57 %, mp 93-95 °C.

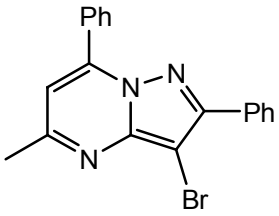
^{1}H-NMR ($CDCl_3$), δ(ppm): 2.56 (s, 3 H, CH_3), 6.52 (s, 1 H, H-6), 6.89 (s, 1 H, H-2).

^{13}C-NMR ($CDCl_3$), δ(ppm): 14.47 CH3, 98.08 CH(C-6), 107.49 CH(C-2), 139.15 C, 148.74 C, 148.94 C, 157.12 C

Anal. Calcd. for $C_7H_5ClN_3$: C, 41.61; H, 2.49; Cl, 35.09; N, 20.80.
Found: C, 41.65; H, 2.57; Cl, 35.14; N, 20.72.

7.2.2.4 Synthesis of 3-halo-2,5,7-trisubstituted-pyrazolo[1,5-a]pyrimidines

3-Bromo-5-methyl-2,7-diphenylpyrazolo[1,5-a]pyrimidine (**103**)



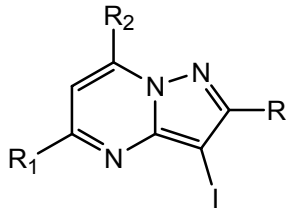
103

A solution of 5-methyl-2,7-diphenylpyrazolo[1,5-a]pyrimidine **88a** (2.85 g, 10 mmol), NBS (1.98 g, 11.0 mmol) in 30 ml CCl_4 was stirred at 50 °C for 0.5 h. After cooled, the solution was filtered and petroleum ether was added to the filtrate, causing precipitation of **7**. The product 3.15 g was collected as a light yellow crystal, yield 87 %, mp 136-138 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.64 (s, 3 H, CH_3), 6.77 (s, 1 H, H-6), 7.36-8.44 (m, 10 H, Ar-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 25.01 CH_3, 81.97 C, 109.29 CH(C-6), 128.41 CH, 128.63 CH, 128.92 CH, 129.03 CH, 129.45 CH, 130.29 C, 131.20 CH, 132.08 C, 146.08 C, 147.50 C, 152.44 C, 160.12 C.

Anal. Calcd for $C_{19}H_{14}BrN_3$ (364.24): C, 62.63; H, 3.87; Br, 21.93; N, 11.53.
Found: C, 62.65; H, 4.01; Br, 22.63; N, 11.66.

3-iodo-2,5,7-substituted-pyrazolo[1,5-a]pyrimidine (**104a-104h**)



104a-104h

General Procedure:

A 50ml round flask was charged with 10 mmol appropriate pyrazolo[1,5-a]pyrimidine **88**, N-iodosuccinimide, NIS (2.48 g, 11.0 mmol) and 20 ml dry THF. The mixture was heated at reflux 24 h. After the mixture was cooled, satd. aq. $Na_2S_2O_3$ (20 ml) was added and stirred for 30 min, then the mixture was extracted with AcOEt (4 × 40 ml). The combined organic layer

was dried with anhydrous $MgSO_4$, the solvent was evaporated and the crude products purified by column chromatography on silica gel using hexane-ethyl acetate (4/1) as eluting solvent and provided a pure yellow or orange product.

3-Iodo-5-methyl-2,7-diphenylpyrazolo[1,5-a]pyrimidine (**104a**)

The crude product was purified by column chromatography on silica gel, using hexane:ethyl acetate (8/1→3/1) as eluting solvent, and provided a light yellow solid, yield 70 %, mp 164-6 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.72 (s, 3 H, CH_3), 6.84 (s, 1 H, H-6), 7.55-8.09 (m, 10 H, Ar-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 25.03 CH_3, 49.02 C, 109.40CH(C-6), 126.58 CH, 128.88 CH, 128.96 CH, 129.41 CH, 129.65 CH, 130.33 CH, 131.13 C, 133.21 C, 146.24 C, 150.06 C, 155.50 C, 160.42 C.

HRMS(EI) calcd for $C_{19}H_{14}IN_3$ (M^+) 411.02325, found 411.02322.

Anal. Calcd. for $C_{19}H_{14}IN_3$: C, 55.49; H, 3.43; I, 30.86; N, 10.22.
Found: C, 55.87; H, 3.52; I, 30.56; N, 10.18.

3-Iodo-2-(4-chlorophenyl)-5-methyl-7-phenylpyrazolo[1,5-a]pyrimidine (**104b**)

The crude product was purified by column chromatography on silica gel, eluenting with hexane:ethyl acetate (8/1→3/1), and a light yellow solid was obtained, yield 69 %, mp 166-8 °C.

^{1}H-NMR($CDCl_3$),δ(ppm): 2.71 (s, 3 H, CH_3), 6.84 (s, 1 H, H-6), 7.41-8.04 (m, 9 H, Ar-H).
^{13}C-NMR($CDCl_3$),δ(ppm): 25.03 CH_3, 48.90 C, 109.60CH(C-6), 128.53 CH, 128.91 CH, 129.39 CH, 130.07 CH, 131.21 CH, 131.32 C, 135.03 C, 137.50 C, 146.24 C, 150.10 C, 154.28 C, 160.61 C.

Anal. Calcd. for $C_{19}H_{13}ClIN_3$: C, 51.20; H, 2.94; N, 9.43.
Found: C, 50.98; H, 3.15; N, 9.43.

3-Iodo-2-Methyl-5,7-diphenylpyrazolo[1,5-a]pyrimidine (**104c**)

The crude product was purified by column chromatography on silica gel, using hexane:ethyl acetate (8/1→3/1) as eluting solvent, and a yellow solid was obtained, yield 78 %, mp 138-40 °C.

H NMR($CDCl_3$), δ(ppm): 2.53 (s, 3 H, CH_3), 7.30 (s, 1 H, H-6), 7.49-8.18 (m, 10 H, Ar-H).

^{13}C NMR($CDCl_3$), δ(ppm): 15.34 CH_3, 53.24 C, 105.20 CH(C-6), 127.36 CH, 128.73 CH, 128.92 CH, 129.46 CH, 130.46 CH, 130.85 C, 131.13 CH, 137.06 C, 146.80 C, 149.46 C, 156.54 C, 156.75 C.

Anal. Calcd. for Calcd. for $C_{19}H_{14}IN_3$: C, 55.49; H, 3.43; I, 30.86; N, 10.22.
Found: C, 55.52; H, 3.64; I, 31.23; N, 10.27.

3-Iodo-7-(4-Chloro-phenyl)-5-methyl-2-phenylpyrazolo[1,5-a]pyrimidine (**104d**)

The crude product was purified by column chromatography on silica gel, using hexane:ethyl acetate (8/1→3/1) as eluting solvent and a light yellow solid was obtained, yield 83 %, mp 63-5 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.70 (s, 3 H, CH_3), 6.80 (s, 1 H, H-6), 7.45-8.05 (m, 9 H, Ar-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 25.02 CH_3, 49.26 C, 109.20 CH(C-6), 128.33 CH, 128.80 CH, 128.90 CH, 129.06 CH, 130.61 C, 130.75 CH, 132.67 C, 137.30 C, 144.96 C, 150.02 C, 155.54 C, 160.37 C

Anal. Calcd. for $C_{19}H_{13}ClIN_3$: C, 51.20; H, 2.94; N, 9.43.
Found: C, 50.96; H, 3.09; N, 9.46.

3-Iodo-2,5-dimethyl-7-phenylpyrazolo[1,5-a]pyrimidine (**104e**)

The crude product was purified by column chromatography on silica gel, using hexane:ethyl acetate (8/1→3/1) as eluenting solvent; and a yellow solid was obtained, yield 63 %, mp 90-1 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.49 (s, 3 H, CH_3), 2.67 (s, 3 H, CH_3) , 6.73 (s, 1 H, H-6), 7.54-7.99 (m, 5H, Ar-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 15.24 CH_3, 24.91 CH_3, 51.52 C, 108.69 CH(C-6), 128.64 CH, 129.23 CH, 130.85 C, 131.06 CH, 146.08 C, 149.27 C, 156.10 C, 160.09 C.

Anal. Calcd. for $C_{14}H_{12}IN_3$: C, 48.16; H, 3.46; I, 36.34; N, 12.03.
Found: C, 48.23; H, 3.50; I, 36.38; N, 12.14.

3-Iodo-2,5,7-trimethylpyrazolo[1,5-a]pyrimidine (**104f**)

The crude product was purified by column chromatography on silica gel, using hexane:ethyl acetate (8/1→3/1) as eluting solvent; and a brown solid was obtained, yield 45 %, mp 132-3°C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.51 (s, 3 H, CH_3), 2.60 (s, 3 H, CH_3), 2.70 (s, 3 H, CH_3), 6.53 (s, 1 H, H-6).
^{13}C-NMR($CDCl_3$), δ(ppm): 15.09 CH_3, 16.62 CH_3, 24.79 CH_3, 51.10 C, 108.77 CH(C-6) , 144.85 C, 148.73 C, 155.24 C, 160.01 C.

Anal. Calcd. for $C_9H_{10}IN_3$: C, 37.65; H, 3.51; I, 44.20; N, 14.64.
Found: C, 37.48; H, 3.72; I, 43.63; N, 14.60.

3-Iodo-2,5,7-triphenylpyrazolo[1,5-a]pyrimidine (**104g**)

The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate (8/1→3/1)as eluting solvent; and a yellow solid was obtained, yield 81 %, mp 202-3 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 7.24 (s, 1 H, H-6), 7.24-8.24 (m, 15 H, Ar-H).
^{13}C-NMR(CDCl3), δ(ppm): 50.67 C(C-3), 105.91 CH(C-6), 127.40 CH, 128.65 CH, 128.86 CH, 128.92 CH, 129.52 CH, 130.57 CH,130.82 C, 131.18 CH, 132.83 C, 136.99 C, 146.93 C, 150.2 C, 155.98 C, 156.99 C.

Anal. Calcd. for $C_{24}H_{16}IN_3$: C, 60.90; H, 3.41; I, 26.81; N, 8.88.
Found: C, 60.64; H, 3.45; I, 27.01; N, 8.82.

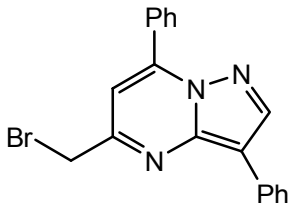
3-Iodo-5,7-diphenylpyrazolo[1,5-a]pyrimidine (**104h**)

The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate (10/1→4/1)as eluting solvent, and a yellow solid was obtained, yield 90 %, mp 160-1 °C.

^{1}H NMR($CDCl_3$), δ(ppm): 7.31 (s, 1 H, H-6), 7.44-8.15 (m, 10 H, Ar-H), 8.09 (s, 1 H, H-2).
^{13}C NMR($CDCl_3$), δ(ppm): 50.24 C(C-3), 105.74 CH(C-6), 127.46 CH, 128.80 CH, 128.98 CH,129.03 CH, 129.26 CH, 130.69 CH, 131.24 C, 136.90 C, 147.43CH(C-2), 149.01 C, 149.18 C, 157.22 C.

Anal. Calcd. for $C_{18}H_{12}IN_3$: C, 54.43; H, 3.05; I, 31.95; N, 10.58.
Found: C, 54.54; H, 3.18; I, 31.34; N, 10.39.

7.2.2.5 Synthesis of 5-bromomethyl-3,7-diphenylpyrazolo[1,5-a]pyrimidine (105)



105

To a solution of 5-methyl-3,7-diphenylpyrazolo[1,5-a]pyrimidine (**89b**) (1.43 g, 5 mmol), NBS (1.07 g, 6.0 mmol) in 20 ml CCl_4, catalytic amount of AIBN (80 mg) was added, the mixture was heated at reflux for 3 h, after the mixture was cooled, then filtered, petroleum ether (40-60 °C) was added to the filtrate, the precipitate was collected and washed with petroleum ether, 1.05 g orange solid was obtained, yield 58 %, mp 131-3 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 4.57 (s, 2 H, CH_2), 7.00 (s, 1 H, H-6), 7.16-8.04 (m, 10 H, Ar-H), 8.40 (s, 1 H, H-2).
^{13}C-NMR($CDCl_3$), δ(ppm): 33.31 CH_2, 107.58 CH(C-6), 111.11 C, 126.53 CH, 128.71 CH, 128.78 CH, 129.21 CH, 129.27 CH, 130.82 C, 131.26 CH, 131.82 C, 143.11 CH(C-2), 145.24 C, 147.48 C, 156.29 C.

Anal. Calcd for $C_{19}H_{14}BrN_3$ (364.24): C, 62.63; H, 3.87; Br, 21.93; N, 11.53.
Found:C, 62.65; H, 4.03; Br, 21.83; N, 11.60.

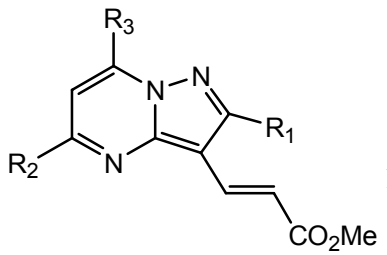
7.2.3 Synthesis of 3-alkenylpyrazolo[1,5-a]pyrimidines (Heck cross-coupling reactions)

Substituted 3-alkenylpyrazolo[1,5-a]pyrimidines 106a-h, 107a-c, 108, 109, 110, 111;

General Procedure:

A 50 ml round flask was charged with 3-iodopyrazolo[1,5-a]pyrimidine **104** (0.5 mmol)**,** $Pd(PPh_3)_{22}$ (18 mg, 0.025 mmol), MeCN (15 mL), triethylamine (203 mg, 2 mmol) and the corresponding alkene (1.5 mmol). The mixture was refluxed under argon for 24 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel.

Substituted pyrazolo[1,5-a]pyrimidin-3-yl-acrylic acid methyl ester (**106a-h**)



106a-106h

3-(5-Methyl-2,7-diphenylpyrazolo[1,5-a]pyrimidin-3-yl)-acrylic acid methyl ester (**106a**)

The crude product was purified by column chromatography on silica gel, using hexane:ethyl acetate (2/1) as eluting solvent; and a yellow solid was obtained, yield 91 %, mp 155-6 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.73 (s, 3 H, CH_3), 3.80 (s, 3 H, CH_3), 6.92 (s, 1 H, H-6), 7.31 (d, 1 H, *J* = 16Hz, =C-H), 7.98 (d, 1 H, *J* = 16Hz, =C-H), 7.47-8.10 (m, 10 H, Ar-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 25.08 CH_3 , 51.97 CH_3 , 102.97 C, 109.74 CH(C-6), 116.20 CH(=CH), 128.66 CH, 128.73 CH, 128.88 CH, 129.05 CH, 129.52 CH, 130.60 C, 131.19 CH, 132.40 C, 135.15 CH(=CH), 146.26 C, 148.56 C, 157.15 C, 160.80 C, 168.81C(C=O).

HRMS(EI) calcd for $C_{23}H_{19}N_3O_2$ (M^+) 369.14773, found 369.14773.

Anal. Calcd. for $C_{23}H_{19}N_3O_2$: C 74.78; H, 5.18; N, 11.37.
Found: C, 74.89; H, 5.33; N, 11.17.

3-[2-(4-Chloro-phenyl)-5-methyl-7-phenylpyrazolo[1,5-a]pyrimidin-3-yl]-acrylic acid methyl ester (**106b**)

The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate (2/1) as eluting solvent , and a yellow solid was obtained, yield 93 %, mp 149-51 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.73 (s, 3 H, CH_3), 3.81 (s, 3 H, CH_3), 6.93 (s, 1 H, H-6), 7.30 (d, 1 H, *J* = 15.4Hz, =C-H), 7.92 (d, 1 H, *J* = 15.4Hz, =C-H), 7.48-8.21 (m, 9 H, Ar-H)
^{13}C-NMR($CDCl_3$),δ(ppm): 25.08 CH_3, 51.44 CH_3 , 102.99 C, 106.38 CH(C-6), 116.59 CH(=CH), 128.70 CH, 128.83 CH, 129.49 CH, 130.73 CH, 130.90 C, 131.27 CH, 134.58 CH(=CH), 135.28 C, 146.28 C, 148.25 C, 155.86 C, 161.00 C, 168.68 C(C=O).

Anal. Calcd. for $C_{23}H_{19}ClN_3O_2$: C, 68.40; H, 4.49; Cl, 8.78; N, 10.40.
Found: C, 68.41; H, 4.56; Cl, 9.15; N, 10.34.

3-(2-Methyl-5,7-diphenylpyrazolo[1,5-a]pyrimidin-3-yl)-acrylic acid methyl ester (**106c**)

The crude product was purified by column chromatography on silica gel, using hexane:ethyl acetate (3/1) as eluting solvent; and a orange solid was obtained, yield 89 %, mp 164-5 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.60(s, 3H, CH_3), 3.85(s, 3 H, CH_3), 7.11(d, 1H, *J* =16Hz, =C-H), 7.26(s, 1H, H-6), 7.97(d, 1H, *J* =16 Hz, =C-H), 7.40-8.24(m, 10H, Ar-H)
^{13}C-NMR($CDCl_3$),δ(ppm): 13.63 CH_3, 51.44 CH_3, 104.76 C, 105.50 CH(C-6), 114.87 CH(=CH), 127.47 CH, 128.79 CH, 129.42 CH, 129.63 CH, 130.79 CH, 131.00 C, 131.29 CH, 134.48 CH(=CH), 136.87 C, 146.85 C, 148.50 C, 156.54 C, 157.25 C, 168.76 C(C=O).

Anal. Calcd. for $C_{23}H_{19}N_3O_2$: C, 74.78; H, 5.18; N, 11.37.
Found: C, 74.30; H, 5.31; N, 11.35.

3-[7-(4-Chloro-phenyl)-5-methyl-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl]-acrylic acid methyl ester (**106d**)

The crude product was purified by column chromatography on silica gel, using hexane:ethyl acetate (2/1) as eluting solvent; and a yellow solid was obtained, yield 94 %, mp 162-4 °C;

^{1}H-NMR($CDCl_3$), δ(ppm): 2.72 (s, 3 H, CH_3), 3.80 (s, 3 H, CH_3), 6.89 (s, 1 H, H-6), 7.30 (d, 1 H, *J* = 16 Hz, =C-H), 7.97 (d, 1 H, *J* = 16 Hz, =C-H), 7.47-8.06 (m, 9 H, Ar-H).
^{13}C-NMR($CDCl_3$),δ(ppm): 25.07 CH_3, 51.40 CH_3, 103.09 C, 109.50 CH(C-6), 116.48 CH(=CH), 128.77, 128.97, 128.90, 129.14, 129.46, 130.86, 132.25, 134.94 (=CH), 137.41, 144.99, 148.48, 157.16, 160.75, 168.74 (C=O).

Anal. Calcd. for $C_{23}H_{19}ClN_3O_2$: C, 68.40; H, 4.49; Cl, 8.78; N, 10.40.
Found: C, 68.44; H, 4.64; Cl, 8.53; N, 10.28.

3-(2,5-Dimethyl-7-phenylpyrazolo[1,5-a]pyrimidin-3-yl)-acrylic acid methyl ester (**106e**)

The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate(4/1) as eluting solvent; and a yellow solid was obtained, yield 90 %, mp 194-6 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.57 (s, 3 H, CH_3), 2.58 (s, 3 H, CH_3), 3.82 (s, 3 H, CH_3), 6.81 (s, 1 H, H-6), 7.01 (d, 1 H, *J* = 16 Hz, =C-H), 7.91 (d, 1 H, *J* = 16Hz, =C-H), 7.57-8.01 (m, 5 H, Ar-H).
^{13}C-NMR($CDCl_3$),δ(ppm): 13.58 CH_3, 24.96 CH_3, 51.39 CH_3, 103.68 C, 109.11 CH(C-6), 114.43 CH(=C-H), 128.71CH, 129.35 CH, 130.83 C, 131.16 CH, 134.56 CH(=C-H), 146.04 C, 148.37 C, 155.36 C, 160.70 C, 168.85 C(C=O).

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67.
Found: C, 70.23; H, 5.57; N, 13.76.

3-(2,5,7-Trimethylpyrazolo[1,5-a]pyrimidin-3-yl)-acrylic acid methyl ester (**106f**)

The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate (4/1) as eluting solvent; and a light yellow solid was obtained, yield 62 %, mp 171-3 °C;

^{1}H-NMR($CDCl_3$), δ(ppm): 2.58 (s, 3 H, CH_3), 2.60 (s, 3 H, CH_3), 2.70 (s, 3 H, CH_3), 3.81 (s, 3 H, CH_3), 6.60 (s, 1 H, H-6), 6.98 (d, 1 H, *J* = 16 Hz, =C-H), 7.86 (d, 1 H, *J* = 16 Hz, =C-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 13.38 CH_3, 17.06 CH_3, 24.80 CH_3, 51.37 CH_3, 103.71 C, 109.27 CH(C-6), 114.30 CH(=C-H), 134.60 CH(=C-H), 145.29 C, 147.43 C, 155.06 C, 160.40 C, 168.83 C(C=O).

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13.
Found: C, 63.40; H, 6.21; N, 17.05.

3-(2,5,7-Triphenylpyrazolo[1,5-a]pyrimidin-3-yl)-acrylic acid methyl ester (**106g**)

The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate (2/1) as eluting solvent; and a yellow solid was obtained, yield 90 %, mp 215-6 °C;

^{1}H-NMR($CDCl_3$), δ(ppm): 3.83 (s, 3 H, CH_3), 7.26 (s, 1H, H-6), 7.54 (d, 1 H, *J* = 19Hz, =C-H), 8.05 (d, 1 H, *J* = 19 Hz, =C-H), 7.59-8.27 (m, 15 H, Ar-H).
^{13}C-NMR($CDCl_3$),δ(ppm): 51.43 CH_3, 104.03 C(C-3), 106.16 CH(C-6), 116.66 CH(=CH), 127.90 CH, 128.76 CH, 128.80 CH, 129.20 CH, 129.55 CH, 129.58 CH, 129.81 CH, 130.41 CH, 130.64 C, 130.91 CH, 132.34 C, 135.04 CH(=CH), 136.86 C, 147.07 C, 148.71 C, 157.34 C, 157.40 C, 168.82 C(C=O).

Anal. Calcd. for $C_{28}H_{21}N_3O_2$: C, 77.94; H, 4.91; N, 9.74.
Found: C, 77.33; H, 5.01; N, 9.58.

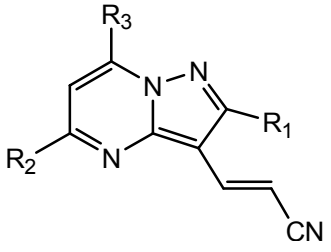
3-(5,7-Diphenylpyrazolo[1,5-a]pyrimidin-3-yl)-acrylic acid methyl ester (**106h**)

The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate(6/1) as eluting solvent, and a yellow solid was obtained, yield 86 %, mp.134-5 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 3.77 (s, 3 H, CH_3), 6.87 (d, 1 H, *J* = 16 Hz, =C-H), 7.39 (s, 1H, H-6), 7.95 (d, 1 H, *J* = 16 Hz, =C-H), 7.47-8.15 (m, 10 H, Ar-H), 8.23 (s, 1 H, H-2).
^{13}C NMR(CDCl3), δ(ppm): 51.50 CH_3, 106.11 CH(H-6), 107.20 C(C-3), 105.74 CH(C-6), 115.49 CH(=CH), 127.52 CH, 128.84 CH, 129.07 CH, 129.11 C, 129.34 CH, 130.95 CH, 131.34 CH, 134.42 CH(=CH), 136.70 C, 145.58 CH(C-2), 147.55 C, 157.55 C, 168.39 C(C=O).

Anal. Calcd. for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82.
Found: C, 74.17; H, 4.92; N, 11.71.

Substituted pyrazolo[1,5-a]pyrimidin-3-yl-acrylonitrile (107a-107c)



107a-107c

3-(5-Methyl-2,7-diphenylpyrazolo[1,5-a]pyrimidin-3-yl)-acrylonitrile (**107a**)

The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate (2/1) as eluting solvent; and a yellow solid was obtained, yield 52 %, mp 206-8 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.73(s, 3 H, CH_3), 6.85(d, 1H, *J* =16.2 Hz, =C-H), 6.96 (s, 1 H, H-6), 7.59 (d, 1 H, *J* = 16.2 Hz, =C-H), 7.48-8.10 (m, 10 H, Ar-H).

^{13}C-NMR($CDCl_3$),δ(ppm): 25.06 CH_3 , 93.95 C, 102.56 CH(=CH), 110.04 CH(C-6), 120.26 C, 127.49 C, 128.72 CH, 128.84 CH, 129.38 CH, 129.41 CH, 129.54 CH, 130.29 C, 131.39 CH, 140.48 CH(=CH), 146.56 C, 148.62 C, 156.68 C, 161.44 C(CN).

HRMS(EI) calcd for $C_{22}H_{16}N_4$ (M^+) 336.13750, found 369.13753.

Anal. Calcd. for $C_{22}H_{16}N_4$: C, 78.55; H, 4.79; N, 16.66.
Found: C, 78.80; H, 4.82; N, 16.38.

3-[2-(4-Chloro-phenyl)-5-methyl-7-phenylpyrazolo[1,5-a]pyrimidin-3-yl]-acrylonitrile (**107b**)

The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate (2/1) as eluting solvent, and a yellow solid was obtained, yield 43 %, mp180-2 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.74(s, 3 H, CH_3), 6.86(d, 1 H, *J* =15.6 Hz, =C-H), 6.98(s, 1H, H-6), 7.49(d, 1 H, *J* = 15.6 Hz, =C-H), 7.46-8.07 (m, 9 H, Ar-H).
^{13}C-NMR($CDCl_3$),δ(ppm): 25.08 CH_3, 94.46 CH(=CH), 102.56 C, 110.23 CH (C-6), 120.08 C, 128.77 CH, 129.13 CH, 129.52 CH, 130.19 C, 130.3, 130.62 CH, 131.49 CH, 135.67 C, 139.96 CH(=CH), 146.61C, 148.62 C, 155.41 C, 161.67 C(CN).

Anal. Calcd. for $C_{22}H_{15}ClN_4$: C, 71.75; H, 4.08; Cl, 9.56; N, 15.11.
Found: C, 72.29; H, 4.17; Cl, 9.21; N, 14.92.

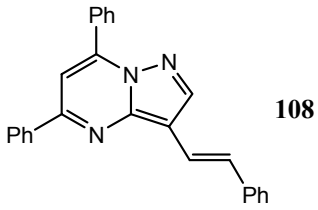
3-(2-Methyl-5,7-diphenylpyrazolo[1,5-a]pyrimidin-3-yl)-acrylonitrile (**107c**)

The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate (2/1) as eluting solvent; and a orange solid was obtained, yield 79 %, mp 164-5 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.56 (s, 3 H, CH_3), 6.73 (d, 1 H, *J* = 16.2 Hz, =C-H), 7.44 (s, 1 H, H-6), 7.54 (d, 1 H, *J* = 16.2 Hz, =C-H), 7.56-8.19 (m, 10 H, Ar-H).
^{13}C-NMR($CDCl_3$),δ(ppm): 13.15 CH_3 , 92.75 CH(=CH), 104.41 C, 105.83 CH(C-6), 120.33 C, 127.45 CH, 128.86 CH, 129.13 CH, 129.46 CH, 130.71 C, 131.10 CH, 131.49 CH, 136.59 C, 139.71CH(=CH), 147.18 C, 148.48 C, 155.45 C, 157.88 C(CN).

Anal. Calcd. for $C_{22}H_{16}N_4$: C, 78.55; H, 4.79; N, 16.66.
Found: C, 78.71; H, 4.86; N, 16.52.

5,7-Diphenyl-3-styrylpyrazolo[1,5-a]pyrimidine (**108**)

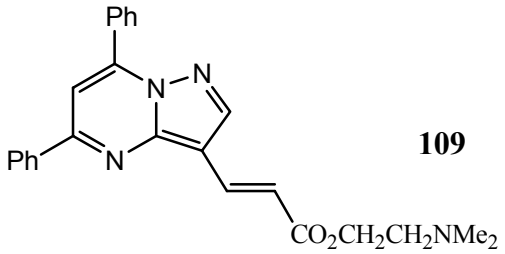


108

The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate(4/1) as eluting solvent , and a red solid was obtained, yield 36 %, mp 174-6 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 7.30 (s, 1 H, H-6), 7.41 (d, 1 H, *J* = 16.2 Hz, =C-H), 7.55 (d, 1 H, *J* = 16.2 Hz, =C-H), 7.19-8.21 (m, 15 H, Ar-H), 8.29 (s, 1 H, H-2).
^{13}C-NMR($CDCl_3$),δ(ppm): 105.26 CH(C-6), 109.68 C(C-3), 117.68(=CH), 126.03 CH, 126.87 CH, 127.25 CH, 128.57 CH, 128.70 CH, 128.89 CH, 129.20 CH, 130.39 CH, 130.98CH(=CH), 131.25 CH, 137.20 C, 138.19 C, 143.13 CH (C-2) , 143.15 C, 146.22 C, 146.84 C, 155.71 C
Anal. Calcd. for $C_{26}H_{19}N_3$: C, 83.62; H, 5.13; N, 11.25.
Found: C, 83.84; H, 5.15; N, 11.07.

3-(5,7-Diphenylpyrazolo[1,5-a]pyrimidin-3-yl)-acrylic acid 2-dimethylamino-ethyl ester (**109**)



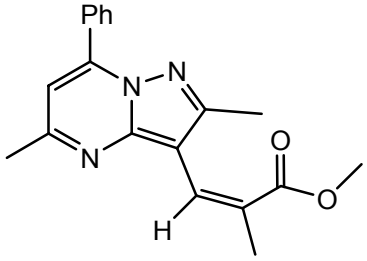
109

The crude product was purified by column chromatography on silica gel, using ethyl acetate:methanol (5/1) as eluting solvent and provided a yellow glass material, yield 57 %.

^{1}H-NMR($CDCl_3$), δ(ppm**)**: 2.26(s, 3H, CH_3), 2.61(t,2H, J=5.9 Hz), 4.25 (t, 2H, J=5.9 Hz , CH_2), 6.81(d, 1H, J=15.8Hz, =CH), 7.30(s, 1H, H-6), 7.39-7.48(m, 6H, Ph-H), 7.89-7.92(dd, 2H, Ph-H), 7.91(d, 1H, J=15.8Hz, =CH), 8.16(s, 1H, H-2).
^{13}C-NMR($CDCl_3$), δ(ppm): 45.00 CH_3, 57.83 CH_2, 61.83 CH_2, 105.97 CH, 107.16 C, 115.45 CH, 127.43 CH, 128.73 CH, 128.95 CH, 129.31 CH, 130.87 CH, 131.26 CH, 134.46 CH, 136.54 C, 145.35 C, 145.37 CH, 147.36, 147.53 C, 157.39 C, 167.84 C.

HRMS (EI) calcd for $C_{19}H_{15}N_3$ (M^+) 412.18993, found 412.18964.

3-(2,5-Dimethyl-7-phenylpyrazolo[1,5-a]pyrimidin-3-yl)-2-methyl-acrylic acid methyl ester (**110**)



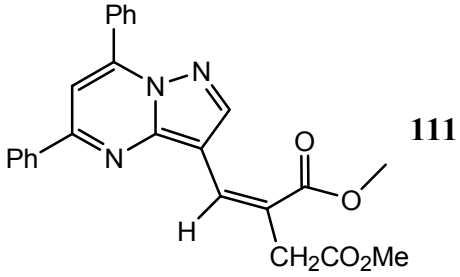
110

The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate (4/1) as eluting solvent; and provided a yellow solid, yield 27 %, mp. 122-3 °C;

^{1}H-NMR($CDCl_3$), δ(ppm): 2.08 (d, 3 H, *J* = 1.5Hz, =C-CH_3), 2.43 (s, 3 H, CH_3), 2.61 (s, 3 H, CH_3), 3.80 (s, 3 H, O-CH_3), 6.72 (s, 1 H, H-6), 7.51-7.54(m, 3 H, Ph-H), 7.71 (d, 1 H, *J* = 1.5 Hz, =C-H), 7.98 (dd, 2 H, Ph-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 13.95 CH_3, 15.79 CH_3, 24.95 CH_3, 51.87 CH_3, 10438 C, 108.33 CH(C-6), 128.17 C, 128.66 CH, 128.71 CH, 129.29 CH, 130.99 CH(=C-H), 131.27 C, 145.76 C, 146.93 C, 154.24 C, 159.04 C, 169.12 C.

Anal. Calcd. for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08.
Found: C, 71.13; H, 6.00; N, 13.00.

2-(5,7-Diphenylpyrazolo[1,5-a]pyrimidin-3-ylmethylene)-succinic acid dimethyl ester (**111**)



111

The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate (6/1) as eluting solvent; and get yellow solid, yield: 14 %, mp. 128-9 °C;

^{1}H-NMR($CDCl_3$), δ(ppm): 3.63 (s, 3 H, CH_3), 3.80 (s,3 H, CH_3), 3.82 (s, 2 H, CH_2), 7.39 (s, 1H, H-6), 7.46-7.54 (m, 6 H, Ph-H), 7.96 (dd, 2 H, Ph-H), 8.12 (dd, 2 H, Ph-H), 8.27 (s, 1H, =C-H), 8.29 (s, 1H, H-2).
^{13}C-NMR($CDCl_3$), δ(ppm): 34.45 CH_2, 52.15 CH_3, 52.21 CH_3, 106.36 CH(C-6), 106.98 C, 120.71C, 127.50 CH, 128.83 CH, 129.02 CH, 129.32 CH, 130.76 C, 130.94 CH, 131.13 CH, 131.36 CH(=C-H), 136.74 C, 144.90 CH(C-3), 147.37 C, 148.20 C, 157.39 C, 168.37 C, 171.62 C.

Anal. Calcd. for $C_{25}H_{21}N_3O_4$: C, 70.25; H, 4.95; N, 9.83.
Found: C, 70.38; H, 5.09; N, 9.75.

7.2.4 Synthesis of 3-alkynylpyrazolo[1,5-a]pyrimidines and related compounds (Sonogashira cross-coupling reaction)

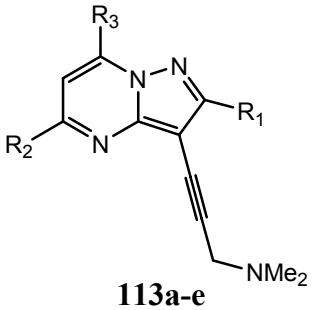
(1) Pd/C catalyzed Sonogashira reaction

Synthesis of substituted 3-alkynylpyrazolo[1,5-a]pyrimidines (113a-k, 114)

General Procedure:

A 25ml Schlenk flask was charged with 3-iodopyrazolo[1,5-a]pyrimidine (**104a-d**, or **104h**) (0.5 mmol), K_2CO_3 (166 mg, 1.2 mmol), CuI (10 mg, 0.05 mmol), 10% Pd/C (22 mg, 0.02

mmol), and PPh_3 (21 mg, 0.08 mmol) in DME (5 ml) and water (5 ml). Argon was passed through the flask 3 times and the mixture was stirred at 25 °C for 0.5 h, then the alkyne (0.6 mmol) was added via syringe. The mixture was heated at 80 °C for 24 h, then cooled to RT, and filtered through a pad of celite, washing with EtOAc, the combined crude solution was washed with water (2 × 30 ml) twice. The organic layer was dried with anhydrous $MgSO_4$, concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel, eluting with EtOAc:MeOH (1:0→6:1) for products **113a-113e**, with hexane:EtOAc (1:1→0:1) for products **113f-113k**.



113a-e

	R^1	R^2	R^3
a	H	Ph	Ph
b	Me	Ph	Ph
c	Ph	Me	Ph
d	Ph	Me	4-ClPh
e	4-ClPh	Me	Ph

3-(5,7-Diphenyl-pyrazolo[1,5-a]pyrimidin-3-yl)-prop-2-ynyl]-dimethylamine (**113a**)

Yellow solid, yield 91 %, mp 102-3 °C

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.41 (s, 6 H, $2CH_3$), 3.58 (s, 2 H, CH_2), 7.32 (s, 1 H, H-6), 7.43-8.13 (m, 10 H, Ph-H), 8.15 (s, 1H, H-2).
^{13}C-NMR ($CDCl_3$), δ(ppm): 44.15 CH_3, 49.03 CH_2, 76.23 C, 87.69 C, 93.99 C, 105.89 CH(H-6), 127.50 CH, 128.79 CH, 128.93 CH, 129.26 CH, 129.36 C, 130.71 CH,130.92 C, 131.24 CH, 136.93 C, 147.34 CH(C-2), 150.11 C, 157.01 C.

Anal. Calcd. for $C_{23}H_{20}N_4$ (352.43): C, 78.38; H, 5.72; N, 15.66.
Found: C, 78.50; H, 5.94; N, 15.66.

Dimethyl-[3-(2-methyl-5,7-diphenyl-pyrazolo[1,5-a]pyrimidin-3-yl)-prop-2-ynyl]-amine (**113b**)

Yellow solid, yield 76 %, mp 109-11 °C

^{1}H NMR ($CDCl_3$), δ(ppm): 2.50 (s, 3 H, CH_3), 2.64 (s, 6 H, $2CH_3$), 3.87(s, 2 H, CH_2), 7.27 (s, 1 H, H-6), 7.43-7.52 (m, 6 H, Ph-H), 7.96-8.00 (dd, 2 H, Ph-H), 8.08-8.11 (dd, 2 H, Ph-H).
^{13}C NMR ($CDCl_3$) δ(ppm): 13.87 CH_3, 42.91 CH_3, 48.62 CH_2, 85.26 C, 92.14 C, 105.58 CH (C-6), 127.41 CH, 128.78 CH, 128.94 CH, 129.33 CH, 130.70 CH, 130.91 C, 131.29 CH, 136.95 C, 146.91 C, 150.94 C, 157.10 C, 157.65 C .

Anal. Calcd. for $C_{24}H_{22}N_4$ (366.46): C, 78.68; H, 6.05; N, 15.29.
Found: C, 78.44; H, 6.25; N, 15.01.

Dimethyl-[3-(5-methyl-2,7-diphenyl-pyrazolo[1,5-a]pyrimidin-3-yl)-prop-2-ynyl]-amine (**113c**)**:**

Yellow solid, yield 70 %, mp 152-4 °C

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.44 (s, 6 H, $2CH_3$), 2.63 (s, 3 H, CH_3), 3.70 (s, 2 H, CH_2), 6.77 (s, 1 H, H-6), 7.35-7.51 (m, 6 H, Ph-H), 8.04 (dd, 2 H, Ph-H), 8.21 (dd, 2 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 25.03 CH_3, 43.96 CH_3, 49.18 CH_2, 77.93 C, 88.79 C, 89.93 C, 109.50 CH(H-6), 127.81 CH, 128.41 CH, 128.59 CH, 129.18 CH, 129.47 CH, 130.53 C, 131.19 CH, 132.52 C, 146.09 C, 151.75 C, 155.56 C, 160.22 C.

HRMS (EI) calcd for $C_{24}H_{22}N_4$ (M^+) 366.18445, found, 366.18447.

Anal. Calcd. for $C_{24}H_{22}N_4$ (366.46): C, 78.68; H, 6.05; N, 15.29.
Found: C, 78.65; H, 6.28; N, 15.05.

{3-[7-(4-Chloro-phenyl)-5-methyl-2-phenyl-pyrazolo[1,5-a]pyrimidin-3-yl]-prop-2-ynyl}-dimethylamine (**113d**)

Yellow solid, yield 54 %, mp 177-8 °C;

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.44 (s, 6 H, $2CH_3$), 2.71 (s, 3 H, CH_3), 3.68 (s, 2 H, CH_2), 6.84 (s, 1 H, H-6), 7.40-7.59 (m, 5 H, Ph-H), 8.09 (dd, 2 H, Ph-H), 8.26 (dd, 2 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 25.03 CH_3, 44.35 CH_3, 49.26 CH_2, 76.50 C, 90.34 C, 90.66 C, 109.62 CH(H-6), 128.58 CH, 128.61 CH, 129.03 CH, 129.43 CH, 130.51 C, 131.16 C, 131.20 CH, 134.98 C, 146.04 C, 151.65 C, 154.20 C, 160.23 C.

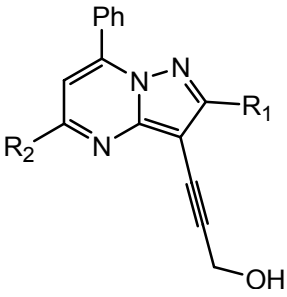
Anal. Calcd. for $C_{24}H_{21}ClN_3$ (400.90): C, 71.90; H, 5.28; Cl, 8.84; N, 13.86.
Found: C, 71.82; H, 5.42; Cl, 8.89; N, 13.58.

{3-[2-(4-Chloro-phenyl)-5-methyl-7-phenyl-pyrazolo[1,5-a]pyrimidin-3-yl]-prop-2-ynyl}-dimethylamine (**113e**)

Yellow solid, yield 69 %, mp 80-2 °C

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.50 (s, 6 H, $2CH_3$), 2.68 (s, 3 H, CH_3), 3.79 (s, 2 H, CH_2), 6.81 (s, 1 H, H-6), 7.43-7.54 (m, 5 H, Ph-H), 8.06 (dd, 2 H, Ph-H), 8.26 (dd, 2 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 24.97 CH_3, 43.12 CH_3, 48.32 CH_2, 77.94 C, 88.41 C, 90.03 C, 109.30 CH(H-6), 127.74 CH, 128.45 CH, 128.88 CH, 129.27 CH, 130.70 C, 130.79 CH, 132.33 C, 137.32 C, 144.82 C, 151.68 C, 155.59 C, 160.21 C.

Anal. Calcd. for $C_{24}H_{21}ClN_3$ (400.90): C, 71.90; H, 5.28; Cl, 8.84; N, 13.86.
Found: C, 72.18; H, 5.38; Cl, 9.02; N, 13.57.



113f, R_1 = H, R_2 = Ph

113g, R_1 = Ph, R_2 = Me

3-(2-Methyl-5,7-diphenyl-pyrazolo[1,5-a]pyrimidin-3-yl)-prop-2-yn-1-ol (**113f**)

Yellow solid, yield 78 %, mp 152-4 °C;

^{1}H-NMR ($CDCl_3$), δ(ppm): 4.58 (s, 2 H, CH_2), 7.37 (s, 1 H, H-6), 7.50-7.61 (m, 6 H, Ph-H), 8.01 (dd, 2 H, Ph-H), 8.17 (dd, 2 H, Ph-H), 8.22(s, 1H, H-2).
^{13}C-NMR ($CDCl_3$), δ(ppm): 51.99 CH_2, 76.10 C, 91.51 C, 93.48 C, 106.13 CH(H-6), 127.58 CH, 128.77 CH, 128.93 CH, 129.29 CH, 130.77 CH, 131.29 CH, 136.83, 147.45 CH(C-2), 150.04 C, 157.45 C.

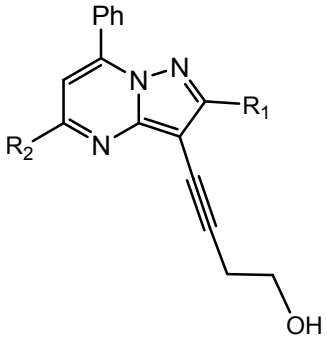
Anal. Calcd. for $C_{21}H_{15}N_3O$ (325.30):C, 77.52; H, 4.65; N, 12.91.
Found: C, 77.40; H, 4.80; N, 12.67.

3-(5-Methyl-2,7-diphenyl-pyrazolo[1,5-a]pyrimidin-3-yl)-prop-2-yn-1-ol (**113g**)

Yellow solid, yield 72 %, mp 85-6 °C

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.56 (s, 3 H, CH_3), 4.56 (s, 2 H, CH_2), 6.67 (s, 1 H, H-6), 7.33-7.48 (m, 6 H, Ph-H), 7.96 (dd, 2 H, Ph-H), 8.15 (dd, 2 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 24.78 CH3, 51.94 CH_2, 77.17 C, 89.56 C, 93.58 C, 109.52 CH(H-6), 127.58 CH, 128.43 CH, 128.59 CH, 129.19 CH, 129.50 CH, 130.36 C, 131.22 CH, 132.33 C, 146.14 C, 151.62 C, 155.17 C, 160.32.

Anal. Calcd. for $C_{22}H_{17}N_3O$ (339.39):C, 77.86; H, 5.05; N, 12.38.
Found: C, 77.64; H, 5.20; N, 12.11



113h, R_1 = Ph, R_2 = Me
113i, R_1 = H, R_2 = Ph
113j, R_1 = Me, R_2 = Ph

4-(5-Methyl-2,7-diphenyl-pyrazolo[1,5-a]pyrimidin-3-yl)-but-3-yn-1-ol (**113h**)

Yellow solid, yield 71 %, mp 182-3 °C

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.66 (s, 3 H, CH_3), 2.86 (t, 2 H, *J* = 6.4 Hz, CH_2), 3.91 (t, 2 H, *J* = 6.4 Hz, CH_2), 7.06 (s, 1 H, H-6), 7.31-7.44 (m, 6 H, Ph-H), 8.05 (dd, 2 H, Ph-H), 8.22 (dd, 2 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 24.68 CH_2, 24.91 CH_3, 61.18 CH_2, 74.25 C, 91.47 C, 92.37 C, 106.08 CH(C-6), 127.48 CH; 127.59 CH, 128.52 CH, 128.87 CH, 129.14 CH, 130.47 CH, 132.69 C, 137.02 C, 146.24 C, 150.72 C, 155.49 C, 156.49 C.

Anal. Calcd. for $C_{23}H_{19}N_3O$ (353.42):C, 73.16; H, 5.42; N, 11.89.
Found: C, 73.28; H, 5.59; N, 11.68.

4-(5,7-Diphenyl-pyrazolo[1,5-a]pyrimidin-3-yl)-but-3-yn-1-ol (**113i**)

Yellow solid, yield 75 %, mp 132-3 °C

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.74 (t, 2 H, *J* = 6.4 Hz, CH_2), 3.80 (t, 2 H, *J* = 5.7 Hz, CH_2), 7.30 (s, 1 H, H-6), 7.44-7.52 (m, 6 H, Ph-H), 7.94 (dd, 2 H, Ph-H), 8.10 (dd, 2 H, Ph-H), 8.13 (s, 1H, H-2).
^{13}C-NMR ($CDCl_3$), δ(ppm): 24.42 CH_2, 61.18 CH_2, 72.75 C, 90.35 C, 94.26 C, 105.94 CH(C-6), 127.54 CH; 128.78 CH, 128.96 CH, 129.28 CH, 130.71 CH, 130.94 C, 131.24 CH, 136.94 C, 147.17 CH(C-2), 147.36 C, 150.01 C, 157.07 C.

Anal. Calcd. for $C_{22}H_{17}N_3O$ (339.39):C, 77.86; H, 5.05; N, 12.38.
Found: C, 77.91; H, 5.19; N, 12.23

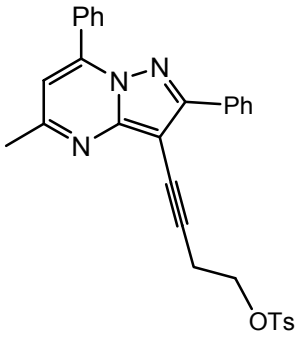
4-(2-Methyl-5,7-diphenyl-pyrazolo[1,5-a]pyrimidin-3-yl)-but-3-yn-1-ol (**113j**)

Yellow solid, yield 70 %, mp 128-9 °C

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.56 (s, 3 H, CH_3), 2.84 (t, 2 H, *J* = 6.4 Hz, CH_2), 3.88 (t, 2 H, *J* = 5.8 Hz, CH_2), 7.29 (s, 1 H, H-6), 7.50-7.60 (m, 6 H, Ph-H), 8.06 (dd, 2 H, Ph-H), 8.18 (dd, 2 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 13.72 CH_3, 24.53 CH_2, 61.29 CH_2, 73.10 C, 91.64 C, 93.37 C, 105.31 CH(C-6), 127.46 CH; 128.73 CH, 128.87 CH, 129.32 CH, 130.49 CH, 131.04 C, 131.16 CH, 137.13 C, 146.69 C, 150.46 C, 156.66 C, 157.34 C.

Anal. Calcd. for $C_{23}H_{19}N_3O$ (353.42):C, 73.16; H, 5.42; N, 11.89.
Found: C, 73.32; H, 5.50; N, 11.74.

Toluene-4-sulfonic acid 4-(5-methyl-2,7-diphenyl-pyrazolo[1,5-a]pyrimidin-3-yl)-but-3-ynyl ester (**113k**)



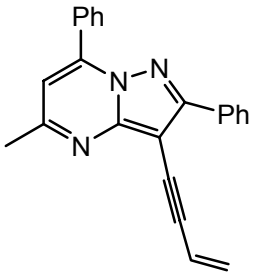
113k, Ts = p-toluenesulfonyl

Brown solid, yield 18 %, mp 158-9 °C;

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.36 (s, 3 H, CH_3), 2.67 (s, 3 H, CH_3), 2.95 (t, 2 H, *J* = 7.1 Hz, CH_2), 4.26 (t, 2 H, *J* = 7.1 Hz, CH_2), 6.81(s, 1 H, H-6), 7.25 (d, 2 H, *J* = 8.3 Hz, Ph-H), 7.42-7.45 (m, 6 H, Ph-H), 7.79 (d, 2 H, *J* = 8.3 Hz, Ph-H), 8.09 (dd, 2 H, Ph-H), 8.24 (dd, 2 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm):14.18 CH_3, 21.17 CH2, 24.96 CH_3, 67.99 CH_2, 74.30 C, 89.33 C, 89.83 C, 109.44 CH(C-6), 127.56 CH, 127.97 CH, 128.49 CH, 128.55 CH, 129.17 CH, 129.45 CH, 129.85 CH, 130.44 C, 131.17 CH, 132.42 C, 132.78 C, 144.86 C, 146.02 C, 151.46 C, 155.49 C, 160.16 C.

Anal. Calcd. for $C_{30}H_{25}N_3O_3S$ (507.60):C, 70.98; H, 4.96; N, 8.28, S, 6.32.
Found: C, 70.84; H, 5.17; N, 8.05, S, 6.17.

3-(But-3-en-1-ynyl)-5-methyl-2,7-diphenyl-pyrazolo[1,5-a]pyrimidine (**114**)



114

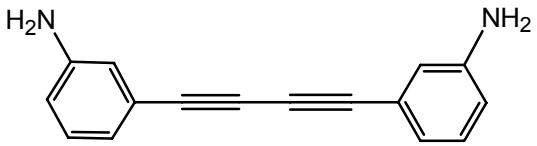
The crude product was purified by flash column chromatography on silica, eluting with cyclohexane:EtOAc (4:1→2:1) to provide a yellow solid 123 mg, yield 36 %, mp. 186-8 °C;

^{1}H NMR($CDCl_3$, 300 MHz), δ(ppm): 2.71 (s, 3 H, CH_3), 5.53 (dd, 1 H, J_1 = 11.3 Hz, J_2 = 2.3 Hz, CH=C<u>H</u>$_2$), 5.77 (dd, 1 H, J_1 = 17.9 Hz, J_2 = 2.3Hz, CH=C<u>H</u>$_2$), 6.19 (dd, 1H, J_1 = 17.9 Hz, J_2 = 11.3 Hz, C<u>H</u>=CH_2), 6.85 (s, 1 H, H-6), 7.40-7.58 (m, 6 H, Ph-H), 8.11 (dd, 2 H, Ph-H), 8.29 (dd, 2 H, Ph-H).
^{13}C NMR ($CDCl_3$), δ(ppm): 25.0 CH_3, 81.7 C, 90.3 C, 93.9 C, 109.6 CH(C-6), 117.9 CH(<u>C</u>H=), 125.6 CH_2(=<u>C</u>H_2), 127.8 CH, 128.4 CH, 128.6 CH, 129.2 CH, 129.5 CH, 130.5 C, 131.2 CH, 132.5 C, 146.1 C, 151.3 C, 155.5 C, 160.3 C.

Anal. Calcd. for $C_{23}H_{17}N_3$ (335.40):C, 82.32; H, 5.11; N, 12.53.
Found: C, 82.07; H, 5.30; N, 12.28.

Using the same procedure, **104h** reacted with 3-amino-phenylacetylene, no desired coupling product was obtained, but a nearly quantitative homo-coupling product **115** was isolated**.**

2-[4-(2-Amino-phenyl)-1,3-butadiynyl]phenyl-amine **(115)**



115

The crude product was purified by flash column chromatography on silica gel, eluting with cyclohexane:EtOAc (3:1 → 1:1) to afford a grey-green solid, yield: 100 %, mp.124-5°C.

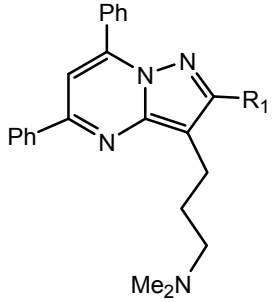
^{1}H-NMR ($CDCl_3$, 300MHz), δ(ppm): 3.70 (s, br, 4 H, $2NH_2$), 6.69 (m, 2 H, Ph-H), 6.81 (t, 2 H, J = 1.9 Hz, Ph-H), 6.93 (dt, 2 H, J_1 = 7.5 Hz, J_2 = 1.2 Hz, Ph-H), 7.11 (t, 2 H, J = 7.9 Hz, Ph-H).
^{13}C NMR ($CDCl_3$, 75MHz), δ(ppm): 73.4 C, 81.7 C, 116.3 CH, 118.4 CH, 122.4 C(C-3), 123.0 CH, 129.4 CH, 146.3 C(C-1).

Anal. Calcd. for $C_{16}H_{12}N_2$ (232.28): C, 82.73; H, 5.21; N, 12.06.
Found: C, 82.84; H, 5.40; N, 12.01.

(2) Catalytic hydrogenation of 113a and 113b

General Procedure:

A 25 ml Schlenk-flask was charged with **113a** or **113b** 0.3 mmol, 10 % Pd/C (67 mg, 0.06 mmol, 0.2 equiv) and EtOH (15ml). The mixture was stirred under hydrogen at atmospheric pressure (balloon) and room temperature for 16h. It was filtered through a pad of Celite, washed with EtOAc. The solvent was evaporated and the residue was purified by flash column chromatography on standard neutral Al_2O_3, eluting with EtOAc:MeOH(1:0→10:1) to provide the product **116a** or **116b**.



116a (R_1=Me)
116b (R_1=H)

[3-(5,7-Diphenyl-pyrazolo[1,5-a]pyrimidin-3-yl)-propyl]-dimethylamine (**116a**)**:**

Yellow solid, Yield 37 %, mp 72-74 °C;

^{1}H-NMR($CDCl_3$, 300 MHz), δ(ppm,): 1.95-2.06 (m, 2 H, CH_2), 2.28 (s, 6 H, $2CH_3$), 2.44 (t, 2 H, *J* = 7.5 Hz, CH_2), 2.95 (t, 2H, *J* = 7.9Hz, CH_2), 7.31 (s, 1 H, H-6), 7.50-8.05 (m, 10 H, Ph-H), 8.07 (s, 1 H, H-2).
^{13}C NMR ($CDCl_3$, 75MHz), δ(ppm): 21.0 CH_2, 28.3 CH_2, 45.5 CH_3, 59.4 CH_2, 104.7 CH(C-6), 110.8 C, 127.2 CH, 128.7 CH, 128.9 CH, 129.2 CH, 130.1 CH, 130.8 CH, 131.7 C, 137.7 C, 144.5 CH, 146.5 C, 147.1 C, 154.5 C.

Anal. Calcd. for $C_{23}H_{24}N_4$(356.46): C, 77.50; H, 6.79; N, 15.72.
Found: C, 77.62; H, 6.95; N, 15.48.

N,N-Dimethyl-[3-(2-methyl-5,7-diphenyl-pyrazolo[1,5-a]pyrimidin-3-yl)-propyl]-amine (**116b**)

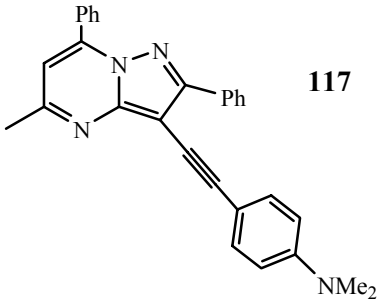
Yellow solid, Yield 40 %, mp 93-4 °C;

^{1}H NMR ($CDCl_3$, 300 MHz), δ(ppm): 1.82-1.91 (m, 2 H, CH_2), 2.18 (s, 6 H, CH_3), 2.32 (t, 2 H, *J* = 7.5 Hz, CH_2), 2.40 (s, 3 H, CH_3), 2.81 (t, 2 H, *J* = 7.5 Hz, CH_2), 7.13 (s, 1 H, H-6), 7.40-7.49 (m, 6 H, Ph-H), 7.99-8.02 (dd, 2 H, Ph-H), 8.06-8.09 (dd, 2 H, Ph-H).
^{13}C NMR ($CDCl_3$, 75MHz), δ(ppm): 13.2 CH_3, 20.6 CH_2, 28.3 CH_2, 45.6 CH_3, 59.6 CH_2, , 103.8 CH (C-6), 108.3 C, 127.1 CH, 128.7 CH, 128.8 CH, 129.2 CH, 129.9 CH, 130.7 CH, 131.9 C, 137.9 C, 145.7 C, 147.9 C, 153.6 C, 154.2 C.

Anal. Calcd for $C_{24}H_{26}N_4$ (370.49): C, 77.80; H, 7.07; N, 15.12.
Found: C, 77.92; H, 7.14; N, 15.07.

(3) Other Sonogashira reaction

Synthesis of dimethyl-[4-(5-methyl-2,7-diphenyl-pyrazolo[1,5-a]pyrimidin-3-ylethynyl)-phenyl]-amine (**117**)



117

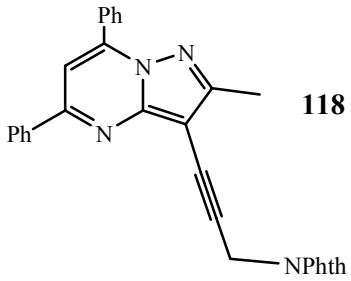
A 25 ml flask was charged with 3-iodo-5-methyl-2, 7-diphenylpyrazolo[1, 5]pyrimidine **104a** (206 mg, 0.5 mmol), $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol), (4-ethynyl-phenyl)dimethylamine (73 mg, 0.5 mmol), and piperdine 2 ml Argon was passed three times and the mixture was heated at 80 °C for 24 h, the solvent was evaporated in vacuum, the residue was purified by column

chromatography on silica gel, eluting with cyclohehane:ethyl acetate (6/1→1/1), and 94 mg brown solid was obtained, yield 44 %, mp 150-2 °C.

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.86 (s, 3 H, CH_3), 2.98 (s, 6 H, $2CH_3$), 6.69 (d, 2 H, *J* = 9.0 Hz, Ph-H), 7.18 (s, 1 H, H-6), 7.48-8.21 (m, 10 H, Ph-H), 8.44 (d, 2 H, *J* = 9.0 Hz, Ph-H).
^{13}C NMR ($CDCl_3$), δ(ppm): 26.90 CH_3, 40.28 CH_3, 78.96 C, 92.42 C, 95.98 C, 105.84 CH(C-6), 111.87 CH, 127.46 CH, 127.74 CH, 128.47 CH, 128.61 C, 128.79 C, 128.99 CH, 130.34 CH, 132.57 CH, 132.94 C, 137.13 C, 146.08 C, 149.86 C, 149.98 C, 155.41 C, 155.99 C.

Anal. Calcd. for $C_{30}H_{24}N_4$ (428.53): C, 81.28; H, 5.65; N, 13.07.
Found: C, 81.40; H, 6.71; N, 13.18.

Synthesis of 2-[3-(2-Methyl-5,7-diphenyl-pyrazolo[1,5-a]pyrimidin-3-yl)-prop-2-ynyl]-isoindole-1,3-dione (**118**)



118

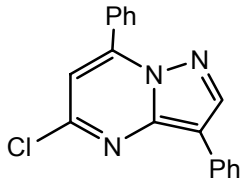
A 25 ml flask was charged with 3-iodo-2-methyl-5, 7-diphenylpyrazolo[1, 5]pyrimidine **104c** (206 mg, 0.5 mmol), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), CuI (10 mg, 0.05 mmol), TEA 5 ml**,** DMF 5 ml and N-propargyl-phthalamide 111 mg (0.6 mmol), Argon was passed three times and the mixture was heated at 50 °C for 24 h, the solvent was evaporated in vacuum, the residue was purified by column chromatography on silica gel, eluting with cyclohehane:ethyl acetate (5/1→1/1), and 89 mg light brown solid was obtained, yield 38 %, mp 163-5 °C.

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.47 (s, 3 H, CH_3), 4.77 (s, 2 H, CH_2), 7.24 (s, 1 H, H-6), 7.42-8.14 (m, 14 H, Ph-H).
^{13}C NMR ($CDCl_3$), δ(ppm): 13.74 CH_3, 28.61 CH_2, 74.24 C, 88.07 C, 92.46 C, 105.37 CH(C-6), 123.49 CH, 127.52 CH, 128.73 CH, 128.80 C, 128.88 CH, 129.32 CH, 130.54 CH, 131. 16 CH, 132.22 C, 134.07 CH, 134.32 C, 137.01 C, 146.72 C, 156.89 C, 158.23 C, 167.22 C(C=O).

Anal. Calcd. for $C_{30}H_{20}N_4O_2$(468.50): C, 76.91; H, 4.30; N, 11.96.
Found: C, 76.78; H, 4.51; N, 11.78.

7.2.5 Synthesis of substituted pyrazolo[1,5-a]pyrimidines via Suzuki cross-coupling reaction

Synthesis of 5-chloro-3,7-diphenylpyrazolo[1,5-a]pyrimidine (**120**)



A 50 ml Schlenk flask was charged with 5,7-dichloro-3-phenylpyrazolo[1,5-a]pyrimidine **101** (528 mg, 2 mmol), phenylboronic acid (244 mg, 2 mmol), anhydrous K_2CO_3 (331 mg, 2.4 mmol), $Pd(PPh_3)_4$ (70 mg, 0.06 mmol), and toluene 30 ml. Argon was passed inside the flask and the mixture was heated at 100 °C for 20 h, after cooled, the solid was filtered out, the filtrate was evaporated and the residue was separated by column chromatography on silica gel, eluting with hexane and then hexane:ethyl acetatate (10/1), the coupling product 5-chloro-3,7-diphenylpyrazolo[1,5-a]pyrimidine **120** 347 mg (54 %) was first isolated, eluting with hexane:ethyl acetatate (5/1) and isolated 7-chloro-3,5-diphenylpyrazolo[1,5-a]pyrimidine **98** (138 mg yield 23 %).

Orange solid, yield 54 %, mp 121-3 °C;

^{1}H-NMR ($CDCl_3$), δ(ppm): 6.80 (s, 1 H, H-6), 7.18-7.96 (m, 10 H, Ph-H), 8.38 (s, 1 H, H-2).
^{13}C-NMR ($CDCl_3$), δ(ppm): 108.20 CH(C-6), 110.82 C, 126.42 CH, 126.68 CH, 128.84 CH, 129.31 CH, 129.98 C, 131.23 C, 131.66 CH, 143.48 CH(C-2), 144.70 C, 148.35 C, 150.47 C.

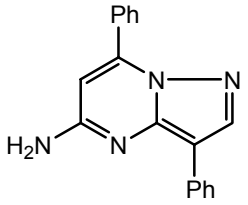
Anal. Calcd for $C_{18}H_{12}ClN_3$ (305.76): C, 70.71; H, 3.96; Cl, 11.60; N, 13.74
Found: C, 70.77; H, 4.06; Cl, 11.62; N, 13.53.

Using the same conditions, **101** was coupled with 3 equiv. of phenylboronic acid, 3,5,7-triphenylpyrazolo[1,5-a]pyrimidine (**89c**) was obtained in 86 % yield. **100** or **104h** was coupled with 1.5 equiv. of phenylboronic acid, 89c was obtained in 99 % and 62 % respectively.

Attempt to undergo regioselective Suzuki coupling, and chose $Pd(PPh_3)_4$ (0.05 equiv.) as catalyst, DME as solvent, 2 M aqueous (2 equiv.) Na_2CO_3 as base, and at 80 °C 16 h, **101** was treated with equal equivalent of phenylboronic acid, 5-chloro-3,7-diphenylpyrazolo-[1,5a]pyrimidine **120** was obtained in 72 % yield

7.2.6 Synthesis of substituted pyrazolo[1,5-a]pyrimidines by Nucleophilic substitution

3,7-Diphenylpyrazolo[1,5-a]pyrimidin-5-ylamine (**127**)



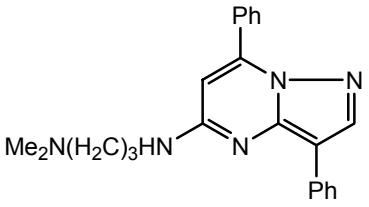
127

A 500 ml autoclave was charged 5-Chloro-3,7-diphenylpyrazolo[1,5-a]pyrimidine **120** (162 mg**,** 0.53 mmol) and liquid ammonia 20ml, the mixture was heated at 100 °C for 24 h, after cooled the autoclave was opened, the residue was dissolve in 60 ml CH_2Cl_2, washed with water (2 × 30 ml), and dried with anhydrous $MgSO_4$, the solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with cyclohexane:ethyl acetate (1/1), and provided a yellow solid 126 mg, yield 83 %, mp 214-5 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 4.88 (s, 2 H, NH_2), 6.09 (s, 1 H, H-6), 7.11-7.93 (m, 10 H, Ph-H), 8.16 (s, 1 H, H-2).
^{13}C-NMR ($CDCl_3$), δ (ppm): 98.10 CH(H-6), 106.56 C, 125.38 CH, 125.87 CH, 128.59 CH, 128.63 CH, 129.15 CH,130.72 CH, 131.42 C, 142.61 CH(H-2), 145.74 C, 148.00 C, 156.17 C.

Anal. Calcd. for $C_{18}H_{14}N_4$: C,75.50; H, 4.93; N, 19.57.
Found: C, 75.43; H, 5.04; N, 19.55.

N'-(3,7-Diphenyl-pyrazolo[1,5-a]pyrimidin-5-yl)-N,N-dimethyl-propane-1,3-diamine (**128**)



128

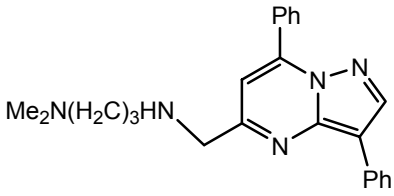
A solution of 5-chloro-3,7-diphenylpyrazolo[1,5-a]pyrimidine **47** (58 mg**,** 0.19 mmol) in N,N-dimethyl-propane-1,3-diamine 3 ml was heated at 100 °C for 24 h, the mixture was evaporated in vacuum, 30 ml water was added, the solution was extracted with chloroform (3 × 30 ml), the extract was washed with 10 % NaOH 30 ml and water 30 ml, then dried with anhydrous MgSO4, the solvent was evaporated and the residue was purified by flash column chromatography on standard neutral Al_2O_3 gel, eluting with EtOAc:MeOH(10:1)**,** yellow solid 61 mg was obtained, yield 87 %, mp 195-7 °C.

^{1}H-NMR ($CDCl_3$), δ(ppm): 1.76 (m, 2 H, CH_2), 2.18 (s, 6 H, CH_3), 2.38 (t, 2 H, *J* = 6.8Hz, CH_2), 3.54(m, 2 H, CH_2), 5.94 (s, 1 H, H-6), 6.31 (br, 1H, NH), 7.09-8.02 (m, 10 H, Ph-H), 8.14 (s, 1 H, H-2).
^{13}C-NMR ($CDCl_3$), δ(ppm): 24.27 CH_2, 38.26 CH_2, 43.30 CH_3, 56.13 CH_2, 99.35 CH(C-6), 105.81 C, 125.22 CH, 125.38 CH, 128.48 CH, 128.59 CH, 129.12 CH, 130.44 CH, 131.47 C, 133.54 C, 141.81 CH(C-2), 145.93 C, 146.85 C, 155.95 C.

HRMS (EI) calcd for $C_{23}H_{25}N_5$ (M^+) 371.21100, found 371.21108.

Anal. Calcd. for $C_{23}H_{25}N_5$ (371.48): C, 74.36; H, 6.78 N, 18.85.
Found: C, 74.46; H, 6.90; N, 18.61.

N'-(3,7-Diphenyl-pyrazolo[1,5-a]pyrimidin-5-ylmethyl)-N,N-dimethyl-propane-1,3-diamine (**129**)



129

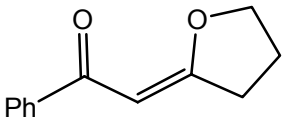
A solution of 5-bromomethyl-3,7-diphenylpyrazolo[1,5-a]pyrimidine **105** (146 mg, 0.4 mmol) in N,N-dimethyl-propane-1,3-diamine 2 ml was stirred at RT for 12 h, then the solution was treated with saturated aq. $NaHCO_3$ 30 ml, the mixture was extracted with ethyl acetate (3 × 30 ml), the extract was dried with anhydrous $MgSO_4$, the solvent was evaporated and the residue was purified by flash column chromatography on standard neutral Al_2O_3 gel, eluting with EtOAc:MeOH(10:1) and provided a brown glass material 50 mg, yield 33 %.

^{1}H-NMR($CDCl_3$), δ(ppm): 1.76 (m, 2 H, CH_2), 2.22 (s 6 H, $2CH_3$), 2.38 (t, 2 H, *J* = 7.5Hz, CH_2), 2.49 (br, 1 H, NH), 2.80 (t, 2 H, *J* = 6.9Hz, CH_2), 4.05 (s, 2 H, CH_2), 6.99 (s, 1 H, H-6), 7.26-8.12 (m, 10 H, Ph-H), 8.43 (s, 1 H, H-2).
^{13}C-NMR($CDCl_3$), δ(ppm): 28.13 CH_2, 45.53 CH_3, 48.13 CH_2, 54.99 CH_2, 57.95 CH_2, 107.00 CH(C-6), 109.86 C, 126.10 CH, 126.31 CH, 128.67 CH, 129.23 CH, 130.94 CH, 131.20 CH, 132.31 C, 142.59 CH(C-2), 145.62 C, 146.66 C, 160.67 C.

HRMS(EI) calcd for $C_{24}H_{26}N_5$(M^+) 385.22665, found 385.22662.

7.2.7 Synthesis of pyrazolo[1,5-a]pyrimidine derivatives by ring-chain-transformation

2-(Dihydro-furan-2-ylidene)-1-phenyl-ethanone (**130**)



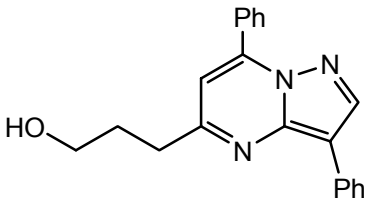
130

A 250 ml flask was charged with 95 % NaH (1.01 g, 0.04 mol), and dry ether 120 ml, ethanol 0.1 ml was added dropwise(as catalyst), 4-butyrolactone (1.80 g, 0.02 mol) was added inside in one portion, and the mixture was cooled to 15 °C, then a solution of acetophenone (2.40 g, 0.02 mol) in 20 ml ether was added dropwise over 1 h, the resulting mixture was stirred at RT for 24 h, and cooled to 0°C, 2 ml ethanol was added to destroy the excess NaH, then cold 10 % aq. ammonium sulphate 40 ml was added, and separated, the ether solution was dried with anhydrous sodium sulphate, evaporated the solvent, the residue was purified by column chromatography on silica gel, eluting with cyclohexane:ethyl acetate (4/1→1/1), and provided a yellow solid 1.05 g, yield 28 %, mp 36-8 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 1.95 (m, 2 H, CH_2), 2.58 (t, 2 H, J = 6.1 Hz, CH_2), 3.73 (t, 2 H, J = 7.3 Hz, CH_2), 6.21 (s, 1 H, C=C<u>H</u>), 7.42-7.90 (m, 5 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ (ppm): 28.34 CH_2, 36.13 CH_2, 62.08 CH_2, 96.31 CH, 126.98 CH, 128.64 CH, 132.34 CH, 134.60 C, 182.45 C, 197.59 C.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 76.57; H, 6.43;
Found: C, 76.34; H, 6.60;

3-(3,7-Diphenyl-pyrazolo[1,5-a]pyrimidin-5-yl)-propan-1-ol (**131**)



55

A 50ml flask was charged with 2-(dihydro-furan-2-ylidene)-1-phenyl-ethanone **130** (395 mg, 2.1 mmol, 3-amino-4-phenylpyrazole (320 mg, 2 mmol), ethanol 15 ml and 37 % HCl 1 ml, the mixture was heated at reflux for 6 h, ethanol was evaporated and neutralized with aq. Na_2CO_3, the mixture was extracted with ethyl acetate (3 × 30 ml), and dried with anhydrous $MgSO_4$, the solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with CH_2Cl_2:ethyl acetate (4/1), and provided a yellow solid 546 mg, yield 83 %, mp 147-8 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.13-2.21 (m, 2 H, CH_2), 2.24 (br, 1 H, OH), 3.07 (t, 2 H, J = 7.4 Hz, CH_2), 3.83 (t, 2 H, J = 6.0 Hz, CH_2), 6.82 (s, 1 H, H-6), 7.26-8.07 (m, 10 H, Ph-H), 8.42 (s, 1 H, H-2)

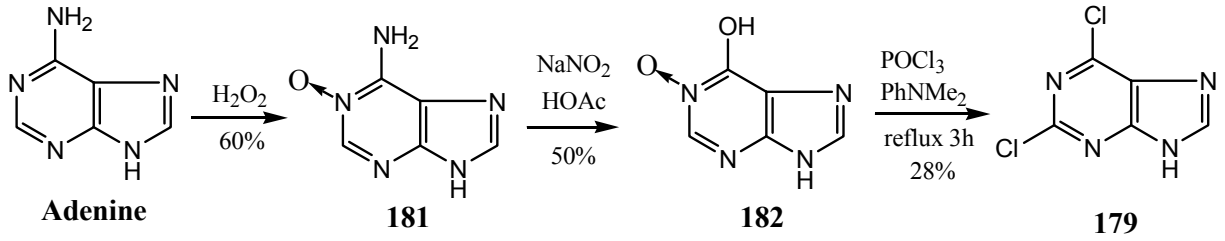
^{13}C-NMR($CDCl_3$), δ (ppm): 30.81 CH_2, 34.80 CH_2, 62.15 CH_2, 108.34 CH(C-6), 109.83 C, 126.19 CH, 126.42 CH, 128.72 CH, 128.75 CH, 129.22 CH, 131.00 CH, 131.13 C, 142.76 CH(C-2), 145.59 C, 146.65 C, 162.07 C, .

Anal. Calcd. for $C_{21}H_{19}N_3O$: C,76.57; H, 5.81; N, 12.76
Found: C, 76.27; H, 6.12; N, 12.59.

7.3 Synthesis of purine derivatives

7.3.1 Synthesis of 2,6-dichloropurine

2,6-Dichloropurine was prepared from commercial available adenine. The synthetic route is as below (**Scheme 7.7**):



Scheme 7.7

Adenine 1-N-oxide (**181**)

Adenine (20.0 g, 0.15mol) was suspended in 120 ml of acetic acid and the mixture was heated at reflux for 1 h. After the solid was dissolved completely, the solution was cooled to room temperature. To this solution, 74 ml of 30 % H_2O_2 was added dropwise and then the solution was allowed to stand for 3 days at room temperature. The precipitate was collected and washed with water to give **51** as a white solid 13.60 g, yield 60 %, mp>300 °C.

Hypoxanthine 1-N-oxide (**182**)

Adenine 1-N-oxide (**181**) (7.19 g, 0.053 mol) was suspended in a solution containing $NaNO_2$ (33.07 g, 0.48 mol) in 500 ml water. The mixture was cooled to 10 °C in an ice bath, and 300 ml of 30 % aqueous was added dropwise with stirring over a period of 30 min. After the addition of acid was complete, the solution was heated at 70-80 °C for 2 h, then cooled to room temperature and allowed to stand for 4 days. The precipitate was collected and washed with water, alcohol, and ether to afford **52** as a yellow solid 4.0 g, yield 50 %, mp>300 °C.

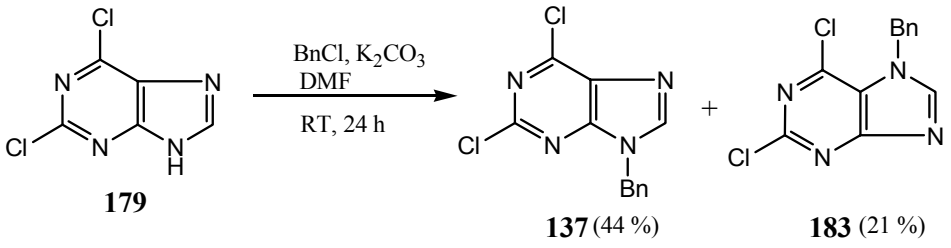
2,6-dichloropurine (**179**)

Hypoxanthine 1-N-oxide (**182**) (3.6 g, 0.024 mol) was suspended in a mixture of 180 ml of phosphoryl chloride and 6 ml N,N-dimethylaniline and was was heated at reflux for 3 h under Argon. After the mixture was cooled to room temperature, excess phosphoryl chloride was distilled off under reduced pressure. The residue was dissolved in 100 ml water and extracted with CH_2Cl_2 (3 × 100 ml), the solvent was evaporated in vacuum to give a crude oil, which was chromatography on silica gel, eluting with ethyl acetate: hexane (1/1→1/0) to give a white solid 1.28 g, yield 28 %, mp 184-6 °C.

Anal. Calcd. for $C_5H_2Cl_2N_4$: C, 31.77; H, 1.07; Cl, 37.52; N, 29.64.
Found: C, 31.79; H, 1.13; Cl, 36.72; N, 29.35.

7.3.2 Benzylation of 2,6-dichloropurine and 6-chloropurine

(1) Benzylation of 2,6-dichloropurine



179 **137** (44 %) **183** (21 %)

Scheme 7.8

A flask was charged with 2,6-dichloropurine (1.27 g, 6.6 mmol), anhydrous potassium carbonate (2.72 g, 20 mmol), and dry DMF 40 ml, Argon was passed, the mixture was stirred for 30 min, then benzylchloride (1.27 g, 16 mmol) was added, and stirred at room temperature for 2 days.The solid was filtered off, the filtratet was evaporated, and the residue was purified by column chromatography on silica gel.

9-Benzyl-2,6-dichloro-purine (**137**)

Eluting with hexane:ethyl acetate (2/1), and provide 0.81 g white solid, yield 44 %, mp 125-7 °C.

^{1}H-NMR ($CDCl_3$), δ(ppm): 5.34 (s, 2 H, CH_2), 7.30-7.56 (m, 5 H, Ph-H), 7.98 (s, 1 H, H-8)
^{13}C-NMR ($CDCl_3$), δ(ppm): 48.04 CH_2, 127.84 C, 128.09 CH, 129.03 C,129.09 CH, 129.39 CH, 133.99 C, 145.54 CH(H-8), 151.89 C, 153.02 C.

Anal. Calcd. for $C_{12}H_8Cl_2N_4$ (279.13): C, 51.64; H, 2.89; Cl, 25.40; N, 20.07.
Found: C, 51.58; H, 2.94; Cl, 25.27; N, 19.96.

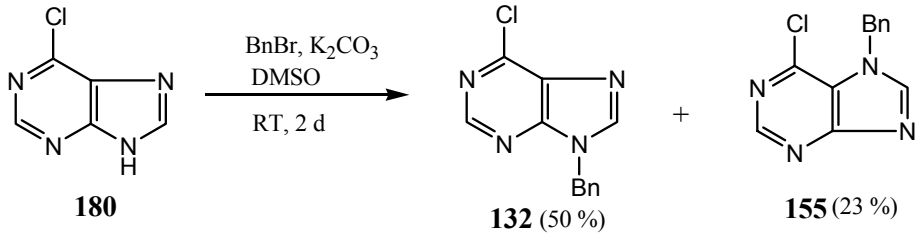
7-Benzyl-2,6-chloro-purine (**183**)

Eluting with hexane:ethyl acetate (1/1), and obtain 0.36 g white solid, yield 21 %, mp 144-6 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 5.74 (s, 2 H, CH_2), 7.23-7.45 (m, 5 H, Ph-H), 9.06 (s, 1 H, H-8).
^{13}C-NMR($CDCl_3$), δ(ppm): 49.8 CH2, 121.9 C(C-5), 126.8 CH, 128.0 CH, 128.9 CH, 136.3 C, 143.4 C, 151.2 C, 152.8 CH(C-8), 163.4 C.

Anal. Calcd. for $C_{12}H_8Cl_2N_4$ (279.13): C, 51.64; H, 2.89; Cl, 25.40; N, 20.07.
Found: C, 51.50; H, 2.98; Cl, 25.21; N, 19.99.

(2) Benzylation of 6-chloropurine



180 **132** (50 %) **155** (23 %)

Scheme 7.9

A mixture of 6-chloropurine (2.47 g, 16 mmol), anhydrous potassium carbonate (2.76 g, 20 mmol), DMSO 40 ml and benzylbromide (2.74 g, 16 mmol) was stirred at room temperature for 2 days.

The reaction solution was decanted from the solid, ice water 50 ml was poured inside, the solution was acidified to PH = 5 with formic acid, the mixture was extracted with ethyl acetate (4 × 80ml), the combined extract was washed with water 100 ml, dried with anhydrous MgSO4, evaporated the solvent, the residue was separated by column chromatography on silica gel.

9-Benzyl-6-chloro-purine (**132**)

Eluting with hexane:ethyl acetate (2/1), 1.98 g white solid was obtained, yield 50 %, mp 80-2 °C.

^{1}H-NMR ($CDCl_3$), δ(ppm): 5.46 (s, 2 H, CH_2), 7.30-7.39 (m, 5 H, Ph-H), 8.10 (s, 1 H, H-8), 8.19 (m, 1 H, H-2)
^{13}C-NMR ($CDCl_3$), δ(ppm): 47.91 CH_2, 127.96 CH, 128.90 CH, 129.30 CH, 131.55 C, 134.52 C, 144.96 CH(C-8), 151.19 C, 151.88 C, 152.21 CH(C-2).

Anal. Calcd. for $C_{12}H_9ClN_4$ (244.69): C, 58.91; H, 3.71; Cl, 14.49; N, 22.90.
Found: C, 58.74; H, 3.86; Cl, 14.35; N, 22.71.

7-Benzyl-6-chloro-purine (**155**)

Eluting with hexane:ethyl acetate (1/1), and get 0.91 g white solid, yield 23 %, mp 144-6°C.

^{1}H-NMR ($CDCl_3$), δ(ppm): 5.71 (s, 2 H, CH_2), 7.17-7.38 (m, 5 H, Ph-H), 8.25 (s, 1 H, H-8), 8.89 (s, 1 H, H-2).
^{13}C-NMR ($CDCl_3$), δ(ppm): 50.74 CH_2, 122.56 C, 127.08 CH, 128.94 CH, 129.39 CH, 134.64 C, 143.24 C, 149.16 CH(C-8), 152.62 CH(C-2), 162.05 C.

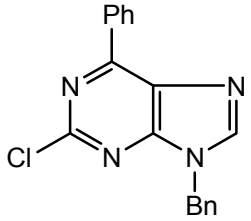
Anal. Calcd. for $C_{12}H_9ClN_4$ (244.69): C, 58.91; H, 3.71; Cl, 14.49; N, 22.90.
Found: C, 58.74; H, 3.86; Cl, 14.35; N, 22.71.

7.3.3 Suzuki cross-coupling of halopurines

General procedure:

A flask was charged with halopurine (**137**, **183**, or **132**) 0.6 mmol, phenboronic acid (79 mg, 0.6 mmol), K_2CO_3 (100 mg, 0.72 mmol), $Pd(PPh_3)_4$ (35 mg, 0.03 mmol), and dry toluene 10 ml. Argon was passed three times and heated at 100 °C for 20 h, the solvent was evaporated, and the residue was purified by column chromatography on silica gel.

9-Benzyl-2-chloro-6-phenylpurine (**140**)



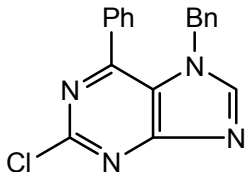
140

Eluting with hexane:ethyl acetate (1:1), and a white solid 112 mg was obtained, yield 70 %, mp 141-3 °C.

^{1}H-NMR ($CDCl_3$), δ(ppm): 5.36 (s, 2 H, CH_2), 7.30-7.49 (m, 8 H, Ph-H), 7.96 (s, 1 H, H-8), 8.72-8.78 (dd, 2H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 47.41 CH_2, 128.01 CH, 128.72 CH, 128,80 CH, 129.25 CH, 130.06 CH, 131.74 CH, 134.49 C, 134.76 C, 144.67 CH(C-8), 154.39 C, 154.43 C, 156.77 C, 160.11 C.

Anal. Calcd for $C_{18}H_{13}ClN_4$ (320.78): C, 67.40; H, 4.08; Cl, 11.05; N, 17.47
Found: C, 67.67; H, 4.36; Cl, 10.92; N, 17.23.

7-Benzyl-2-chloro-6-phenylpurine (**184**)



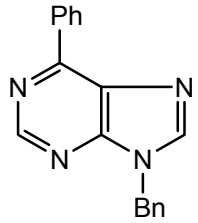
184

Eluting with hexane:ethyl acetate (1:3), and a white solid was obtained, yield 66 %, mp 154-5 °C.

^{1}H-NMR ($CDCl_3$), δ(ppm): 5.12 (s, 2 H CH_2), 6.45-7.45 (m, 10 H, Ph-H), 8.22 (s, 1 H, H-8).
^{13}C-NMR ($CDCl_3$), δ(ppm): 51.31 CH_2, 122.02 C, 126.46 CH, 128.53 CH, 128.63 CH, 128.98 CH, 130.43 CH, 133.98 C, 134.47 C, 150.70 CH(C-8), 154.41 C, 154.66 C, 164.04 C.

Anal. Calcd for $C_{18}H_{13}ClN_4$ (320.78): C, 67.40; H, 4.08; Cl, 11.05; N, 17.47
Found: C, 67.34; H, 4.33; Cl, 10.87; N, 17.52.

9-Benzyl-6-phenylpurine (**134a**)



134a

Eluting with hexane:ethyl acetate (1:1), and a white solid was obtained, yield 75 %, mp 124-5 °C.

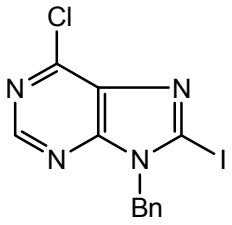
^{1}H-NMR ($CDCl_3$), δ(ppm): 5.43 (s, 2 H, CH_2), 7.26-7.50 (m, 8 H, Ph-H), 8.04 (s, 1 H, H-8), 8.71 (dd, 2 H, Ph-H), 8.99 (s, 1 H, H-2)
^{13}C-NMR ($CDCl_3$), δ(ppm): 47.32 CH_2, 127.83 CH, 128.61 CH, 128.70 CH, 129.17 CH, 129.80 CH, 130.93 C, 131.06 CH, 135.16 C, 135.48 C, 144.21CH(C-8), 149.45 C, 151.34 C, 152.55 CH(C-2).

Anal. Calcd for $C_{18}H_{14}N_4$ (286.33): C, 75.50; H, 4.93; N, 19.57
Found: C, 75.44; H, 5.14; N, 19.64.

9-Benzyl-8-iodo-6-chlorol-purine (**152**)

A 50 ml flask was charged with 9-Benzyl-6-chloro-purine (**132**) (367 mg, 1.5 mmol), NIS (1.01 g, 4.5 mmol), and THF 20 ml. The flask was draped with aluminium-foil, and the mixture was heated at reflux under Ar for 3 days. The solvent was evaporated, 60 ml CH_2Cl_2 was added inside, the solution was washed with sat. aq. $Na_2S_2O_3$ (2 × 30 ml), and water 30 ml, then dried with anhydrous $MgSO_4$, evaporated the solvent, the residue was separated by flash column

chromatography on silica gel, eluting with hexane:ethyl acetate (2/1), to provide a white solid 254 mg, yield 46 %, mp 135-6 °C.



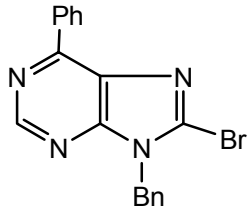
152

^{1}H-NMR ($CDCl_3$), δ(ppm): 5.47 (s, 2 H, CH_2), 7.32-7.34 (m, 5 H, Ph-H), 8.71 (s, 1 H, H-2).
^{13}C-NMR ($CDCl_3$), δ(ppm): 49.69 CH_2, 108.17 C, 127.89 CH, 128.62 CH, 128.99 CH, 133.81 C, 134.27 C, 149.36 C, 152.09 CH(H-2), 153.06 C.

Anal. Calcd for $C_{12}H_8ClIN_4$ (370.58): C, 38.89; H, 2.18; N, 15.12
Found: C, 39.00; H, 2.20; N, 15.01

7.3.4 Sonogashira cross-coupling of halo-purines

(1) 9-Benzyl-8-bromo-6-phenylpurine (**185**)



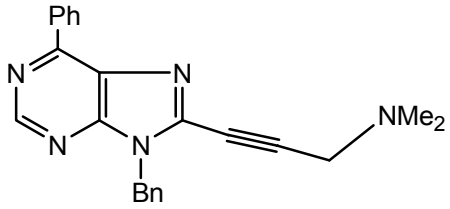
185

A 50 ml flask was charged with 9-benzyl-6-phenylpurine **134a** (358 mg, 1.25 mmol), NBS (1.35 g, 7.5 mmol), and THF 20 ml. The mixture was heated at reflux for 2 days. The solvent was evaporated, the residue was separated by flash column chromatography on silica gel, eluting with hexane:ethyl acetate (3/1) to provide a white solid 255 mg, yield 56 %, mp 112-4 °C.

^{1}H-NMR ($CDCl_3$), δ(ppm): 5.43 (s, 2 H, CH_2), 7.23-8.69 (m, 10 H, Ph-H), 8.91 (s, 1 H, H-2).
^{13}C-NMR ($CDCl_3$), δ(ppm): 47.64 CH_2, 127.84 CH, 128.43 CH, 128.74 CH, 128.94 CH, 129.72 CH, 131.20 CH, 131.31 C, 133.07 C, 134.77 C, 135.13 C, 152.09 CH(H-2), 153.59 C, 153.73 C.

Anal. Calcd for $C_{18}H_{13}BrN_4$ (365.23): C, 59.19; H, 3.59; Br, 21.88; N, 15.12
Found: C, 59.02; H, 3.75; Br, 22.03; N, 15.00

(2) [3-(9-Benzyl-6-phenyl-purin-8-yl)-prop-2-ynyl]-dimethylamine (**186**)



186

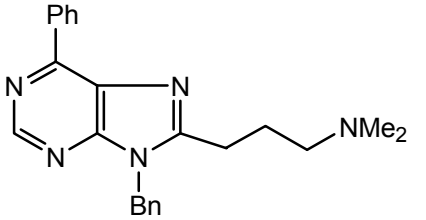
A 25 ml schlenk flask was charged 9-Benzyl-8-bromo-6-phenylpurine **185** (182 mg, 0.5 mmol), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), CuI (10 mg, 0.05 mmol), triethylamine 10 ml, and N, N-dimethylpropargylamine (83 mg, 1.0 mmol), Argon was passed three times and the mixture was heated at 80 °C for 24 h. The mixture was concentrated, the residue was purified by column chromatography on silica gel, eluting with ethyl acetate:methanol (1/0→8/1), and provided a brown solid 158 mg, yield 86 %, mp 134-6 °C.

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.34 (s, 6 H, $2CH_3$), 3.63 (s, 2 H, CH_2), 5.58 (s, 2 H, CH_2), 7.29-8.80 (m, 10 H, Ph-H), 9.03 (s, 1 H, H-2).
^{13}C-NMR ($CDCl_3$), δ(ppm): 44.21 CH_3, 46.90 CH_2, 47.64 CH_2, 75.13 C, 94.23 C, 127.60 CH, 128.22 CH, 128.69 CH, 128.80 C, 128.86 CH, 129.87 CH, 130.88 C, 131.08 CH, 135.46 C, 138.42 C, 152.32 C, 152.09 CH(H-2), 154.61 C.

Anal. Calcd for $C_{23}H_{21}N_5$ (367.45): C, 75.18; H, 5.76; N, 19.06.
Found: C, 75.05; H, 5.98; N, 19.01

(**3**) [3-(9-Benzyl-6-phenyl-purin-8-yl)-propyl]-dimethylamine (**187**)

A mixture of [3-(9-benzyl-6-phenyl-purin-8-yl)-prop-2-ynyl]-dimethylamine **186** (100 mg, 0.27 mmol), 10 % palladium on charcoal (65mg, 0.054 mmol on Pd, 0.2 equiv) in ethanol (15 mL) were stirred under hydrogen at room temperature and atmosphere 16 hours. After complete conversion (TLC monitoring), the catalyst was filtered off through a pad of celite, washed with ethyl acetate, the solvents were removed under reduced pressure, and the residue was purified by column chromatography on neutral Al_2O_3 gel, eluting with cyclohexane:ethyl acetate (1:1) to provide a white solid 71 mg, yield 70 %, mp 81-3 °C.



187

^{1}H-NMR ($CDCl_3$), δ(ppm): 1.94-2.02 (m, 2 H, CH_2), 2.13 (s, 6 H, $2CH_3$), 2.27 (t, 2 H, J = 7.2Hz, CH_2), 2.82 (t, 2 H, J = 7.4 Hz, CH_2), 5.45 (s, 2 H, CH_2), 7.07-8.78 (m, 10 H, Ph-H), 8.91 (s, 1 H, H-2).

^{13}C-NMR ($CDCl_3$), δ(ppm): 25.01 CH_2, 25.54 CH_2, 45.42 CH_3, 45.51 CH_2, 58.68 CH_2, 126.85 CH, 128.08 CH, 128.60 CH, 129.00 C, 129.73 CH, 130.64 CH, 130.88 C, 132.16 C, 135.80 C, 151.76 CH(H-2), 152.86 C, 154.09 C, 157.42 C.

Anal. Calcd for $C_{23}H_{25}N_5$ (371.48): C, 74.36; H, 6.78; N, 18.85.
Found: C, 74.56; H, 6.91; N, 18.77.

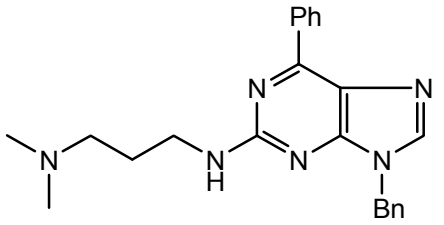
7.3.5 Nucleophilic substitution of halopurines

(a) Introducing $Me_2N(CH_2)_3NH$ to 2-position of purines

General procedure:

A solution of 2-Cl-substituted purine 0.3 mmol in 3 ml N,N-dimerhyl-1,3-propan-diamine was heated at 150 °C for 18 h, then evaporated in vacuum, the residue was dissolved in 50 ml chloroform, washed with aq. 10 % NaOH 30 ml and water 30 ml, dried with anhydrous $MgSO_4$, evaporated the solvent, and purified by column chromatograph on standard neutral Al_2O_3 gel.

N'-(9-Benzyl-6-phenyl--purin-2-yl)-N,N-dimethyl-propane-1,3-diamine (**190**)



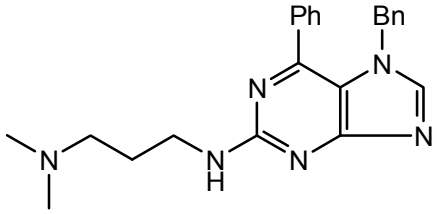
190

Eluting with chloroform:methol (50/1) to provide a light brown solid, yield 98 %, mp 81-2 °C.

^{1}H-NMR ($CDCl_3$), δ(ppm): 1.73 (m, 2 H, CH_2), 2.14 (s, 6 H, $2CH_3$), 2.31 (t, 2 H, J = 7.6 Hz, CH_2), 3.48 (m, 2 H, CH_2), 5.17 (s, 2 H, CH_2), 5.60 (t, 1 H, J = 5.3 Hz, NH), 7.19-7.60 (m, 8 H, Ph-H), 7.62 (s, 1 H, H-8), 8.59-8.62 (dd, 2 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 27.46 CH_2, 40.68, 45.54 CH_3, 46.54 CH_2, 57.81 CH_2, 124.70 C, 127.77 CH, 128.26 CH, 128.39 CH, 128.90 CH, 129.48 CH, 130.43 CH, 136.08 CH, 140.72 CH(C-8), 154.56, 155.44 C, 159.72 C.

Anal. Calcd. for $C_{23}H_{26}N_6$: C, 71.48; H, 6.78; N, 21.74.
Found: C, 71.36; H, 6.87; N, 21.51.

N'-(7-Benzyl-6-phenyl-7H-purin-2-yl)-N,N-dimethyl-propane-1,3-diamine (**189**)



189

Eluting with ethyl acetate:methol (5/1) to give a light brown oil, yield 98 %.

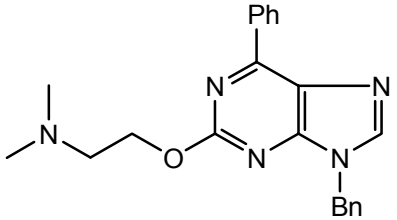
^{1}H-NMR ($CDCl_3$), δ(ppm): 2.17 (m, 2 H, CH_2), 2.71 (s, 6 H, $2CH_3$), 3.07 (t, 2 H, J = 7.5 Hz, CH_2), 3.59 (m, 2 H, CH_2), 5.04 (s, 2 H, CH_2), 6.07 (br, 1 H, NH), 6.52 (dd, 2 H, J = 6.7 Hz, Ph-H), 7.12-7.40 (m, 8 H, Ph-H), 8.05 (s, 1 H, H-8)
^{13}C-NMR ($CDCl_3$), δ(ppm):): 24.90 CH_2, 40.68 CH_2, 43.03 CH_3, 50.96 CH_2, 555.78 CH_2, 116.86 C, 126.42 CH, 128.11 CH, 128.44 CH, 128.58 CH, 128.75 CH, 129.74 CH, 134.82 C, 136.37 C, 148.44 CH(C-8), 154.01 C, 159.70 C, 163.88 C, 175.94 C.

HRMS (EI) calcd for $C_{23}H_{26}N_6$ (M^+) 386.22189; found 386.22182.

(b) Introducing $Me_2N(CH_2)_3O$- to 2 position of purine

[2-(9-Benzyl-6-phenyl-purin-2-yloxy)-ethyl]-dimethylamine (**191**)

A 10 ml flask was charged with 9-benzyl-2-chloro-6-phenylpurine **141** (51 mg, 0.16 mmol), t-BuOK (23 mg, 0.2 mmol) and 2-dimethylamino-ethanol 3 ml. Argon was passed and the mixture was heated at 150 °C for 16 h, evaporated in vacuum, the residue was dissolved in 60 ml chloroform, washed with sat. aq. $NaHCO_3$ 30 ml, then water 30 ml, dried with anhydrous $MgSO_4$, evaporated the solvent, and purified by column chromatograph on standard neutral Al_2O_3 gel, eluting with ethyl acetate:methol (10/1) to give a light brown oil 41 mg, yield 68 %.



191

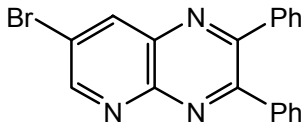
^{1}H-NMR ($CDCl_3$), δ(ppm): 2.48 (s, 6 H, $2CH_3$), 3.00 (t, 2 H, J = 6.0 Hz, CH_2), 4.73 (t, 2 H, J = 6.0 Hz, CH_2), 5.38 (s, 2 H, CH_2), 7.32-7.52 (m, 8 H, Ph-H), 7.93 (s, 1 H, H-8), 8.78 (dd, 2 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 45.13 CH_3, 47.01 CH_2, 57.29 CH_2, 64.84 CH_2, 127.85 CH, 128.47 CH, 128.54 CH, 129.08 CH, 129.79 CH, 131.17 CH, 135.35 C, 135.45 C, 143.12 CH(C-8), 154.78 C, 155.97 C, 161.18 C, 175.72 C.

HRMS (EI) calcd for $C_{22}H_{23}N_5O$ (M^+) 373.19026, found 373.19029.

7.4 Synthesis of pyrido[2,3-b]pyridazine derivatives

7.4.1 Synthesis of 7-bromo-2,3-diphenylpyrido[2,3-b]pyrazine (**193**)

A 100ml flask was charged with 2,3-diamino-5-bromopyridine (965mg, 5.0 mmol), benzil (1.26g, 6.0 mmol), ethanol 30 ml and 3 drops of hydrochloric acid, the mixture was heated at reflux for 12 h, the alcohol was evaporated, the solid was dissolve in 60 ml dichloromethane, and washed with water (2 × 30 ml), dried with anhydrous $MgSO_4$, evaporated the solvent, the residue was purified by column chromatography on silica gel, eluting with cyclohexane:ethyl acetate (4/1) and afforded a yellow solid 1.33 g, yield 73 %, mp 149-50 °C.



193

^{1}H-NMR ($CDCl_3$), δ(ppm): 7.27-7.63 (m, 10 H, Ph-H), 8.67 (d, 1 H, $J_{6,8}$ = 2.6 Hz, H-8), 9.15 (d, 1 H, $J_{6,8}$ = 2.6 Hz, H-6).
^{13}C-NMR ($CDCl_3$), δ(ppm): 120.92 C(C-7), 128.24 CH, 128.45 CH, 129.60 CH, 129.68 CH, 129.83 CH, 130.19 CH, 136.40 C, 137.78 C, 138.09 C, 139.37 CH(C-8), 148.25 C, 155.11 CH(C-6), 155.47 C, 156.48.

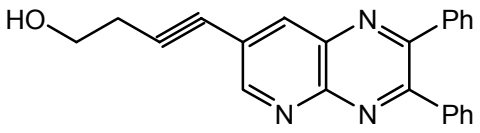
Anal. Calcd. for $C_{19}H_{12}BrN_3$ (362.22): C, 63.00; H, 3.34; Br, 22.06; N, 11.60.
Found: C, 62.83; H, 3.45; Br, 22.29; N, 11.63.

7.4.2 Synthesis of 7-alkynyl-2,3-diphenylpyrido[2,3-b]pyrazine

General procedure of Sonogashira reaction:

A 25 ml Schlenk flask was charged with 7-bromo-2,3-diphenylpyrido[2,3-b]pyrazine (181 mg, 0.5 mmol), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), CuI (10 mg, 0.05 mmol), dry TEA 5 ml**,** dry DMF 5 ml and alkyne (1.0 mmol), Argon was passed three times and the mixture was heated at 100 °C for 24 h, the solvent was evaporated in vacuum, and the residue was purified by column chromatography on silica gel.

4-(2,3-Diphenyl-pyrido[2,3-b]pyrazin-7-yl)-but-3-yn-1-ol (**194a**)



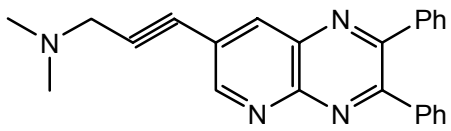
194a

The residue was purified by column chromatography on silica gel, eluting with ethyl acetate: and provided a yellow solid 172 mg, yield 98 %, mp 165-7 °C.

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.06 (br, 1 H, OH), 2.79 (t, 2 H, *J* = 6.4 Hz, CH_2), 3.90 (t, 2 H, *J* = 6.4 Hz, CH_2), 7.29-7.61 (m, 10 H, Ph-H), 8.44 (d, 1 H, *J* = 3.0 Hz, H-8), 9.09 (d, 1 H, *J* = 3.0 Hz, H-6).
^{13}C-NMR ($CDCl_3$), δ(ppm): 24.00 CH_2, 60.81 CH_2, 78.59 C, 93.42 C, 128.20 CH, 128.43 CH, 129.44 CH, 129.59 CH, 129.81CH, 130.23 CH, 135.33 C, 137.84 C, 138.27 C, 139.53 CH (C-8), 148.46 C, 155.32 C, 156.09 C, 156.24 CH(C-6).

Anal. Calcd. For $C_{23}H_{17}N_3O$: C, 78.61; H, 4.88; N, 11.96.
Found: C, 78.90; H, 5.12; N, 11.65.

[3-(2,3-Diphenyl-pyrido[2,3-b]pyrazin-7-yl)-prop-2-ynyl]-dimethylamine (**194b**)



194b

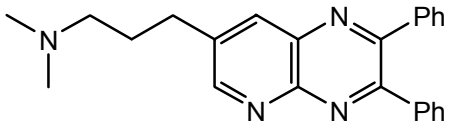
The residue was purified by column chromatography on silica gel, eluting with ethyl acetate: methanol (4/1), and get light yellow solid 133 mg, yield 76 %, mp 101-3 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.32 (s, 6 H, $2CH_3$), 3.47 (s, 2 H, CH_2), 7.20-7.7.53 (m, 10 H, Ph-H), 8.40 (d, 1 H, *J* = 2.3 Hz, H-8), 8.40 (d, 1 H, *J* = 2.3 Hz, H-6).
^{13}C-NMR ($CDCl_3$), δ(ppm): 44.34 CH_3, 48.64 CH_2, 81.67 C, 91.01 C, 121.71 C, 128.13 CH, 128.37 CH, 129.37 CH, 129.52 CH, 129.77 CH, 129.77 CH, 130.21 CH, 135.25 C, 137.86 C, 138.27 C, 139.61 CH(C-8), 148.60 C, 155.22 C, 156.07 CH(C-6).

Anal. Calcd. for $C_{24}H_{20}N_4$(364.44): C, 79.10; H, 5.53; N, 15.73.
Found: C, 78.94; H, 5.69; N, 15.46.

N'-(2,3-Diphenyl-pyrido[2,3-b]pyrazin-7-yl)-N,N-dimethyl-propane-1,3-diamine (**195**)

A solution of [3-(2,3-diphenyl-imidazo[1,2-a]pyridin-6-yl)-prop-2-ynyl]-dimethylamine (81 mg, 0.22 mmol), ethanol (15 ml) and 10 % palladium on charcoal (46 mg, 0.044 mmol on Pd, 0.2 equiv) was stirred under hydrogen at room temperature and atmosphere for 16 hours. After complete conversion (TLC monitoring), the catalyst was filtered off through a pad of celite, washed with ethyl acetate, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on neutral Al_2O_3 gel, eluting with ethyl acetate:methanol (10:1) to provide 44 mg brown liquid, yield, 54 %.



195

^{1}H-NMR ($CDCl_3$), δ(ppm): 1.85-1.92 (m, 2 H, CH_2), 2.18 (s, 6 H; $2CH_3$), 2.30 (t, 2 H, J = 7.2 Hz, CH_2), 2.88 (t, 2 H, J = 7.2 Hz, CH_2), 7.26-7.30 (m, 6 H, Ph-H), 7.46 (dd, 2 H, Ph-H), 7.51 (dd, 2 H, Ph-H), 8.21 (d, 1 H, $J_{6,8}$ = 2.3 Hz, H-8), 8.96 (d, 1 H, $J_{6,8}$ = 2.3 Hz, H-6).
^{13}C-NMR ($CDCl_3$), δ(ppm): 28.71 CH2, 30.70 CH2, 45.43 CH3, 58.67 CH2, 128.11 CH, 128.39 CH, 129.17, CH, 129.24 CH, 129.79 CH, 130.23 CH, 135.84 CH(C-8), 136.04 C, 138.23 C, 138.72 C, 140.24 C, 148.44 C, 154.52 C, 155.31 C, 155.84 CH(C-6).

HRMS (EI) calcd for $C_{24}H_{24}N_3$ (M^+) 368.2001, found 368.2001.

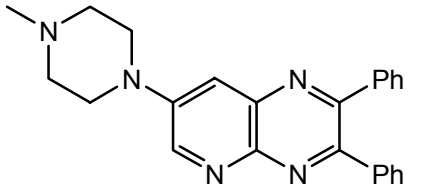
Anal. Calcd. for $C_{24}H_{24}N_4$(368.47): C, 78.23; H, 6.57; N, 15.21.
Found: C, 78.32; H, 6.75; N, 15.09.

7.4.3 Buchwald-Hartwig amination of 7-bromo-2,3-diphenylpyrido[2,3-b]pyrazine

General procedure:

A 25 ml schlenk flask was charged with 7-bromo-2,3-diphenylpyrido[2,3-b]pyrazine (181 mg, 0.5 mmol), $Pd_2(dba)_3$ (10 mg, 0.01 mmol), BINAP (19 mg, 0.03mmol), t-BuONa (68 mg, 0.7mmol), appropriate substituted amine1.0 mmol, dry toluene 5 ml, Argon was passed three times and the mixture was heated at 110 °C for 20 h, after cooled, 50 ml water was added, the mixture was extracted with ethyl acetate (3 × 40ml), the extract was washed with water (2 × 40 ml), dried with anhydrous $MgSO_4$, evaporated the solvent, the residue was purified by column chromatography

7-(4-Methyl-piperazin-1-yl)-2,3-diphenylpyrido[2,3-b]pyrazine (**198**)



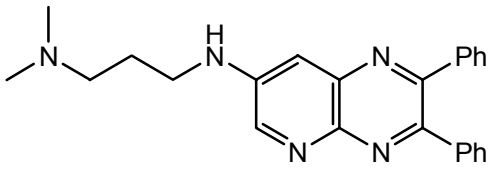
198

The crude product was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2:MeOH(10:1)and provided a brown sold 122 mg, yield 68 %, mp.164-6 °C;

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.28 (s, 3 H, CH_3), 2.55 (t, 4 H, J = 4.9 Hz, $2CH_2$), 3.38 (t, 4 H, J = 4.9 Hz, $2CH_2$), 7.20-7.51 (m, 11 H, 10Ph-H and H-8), 8.94 (d, 1H, $J_{6,8}$ = 3.0 Hz, H-6).
^{13}C-NMR ($CDCl_3$), δ(ppm): 46.05 CH3, 48.05 CH2, 54.45 CH2, 116.13 CH(C-8),128.00 CH, 128.29 CH, 128.73 CH, 128.92 CH, 129.73 CH, 130.11 CH, 137.25 C, 138.98 C, 138.98 C, 144.27 C, 147.29 CH(H-6), 147.80 C, 152.22 C, 154.54 C.

Anal. Calcd. for $C_{24}H_{23}N_5$(381.47) C, 75.56; H, 6.08; N, 18.36.
Found: C, 75.44; H, 6.32; N, 18.07.

N'-(2,3-Diphenyl-pyrido[2,3-b]pyrazin-7-yl)-N,N-dimethyl-propane-1,3-diamine (**199**)



199

The crude product was purified by flash column chromatography on standard neutral Al_2O_3 gel, eluting with ethyl acetate:methanol (10/1) and provided a brown solid 140 mg, yield:73 %, mp 150-2°C.

^{1}H-NMR ($CDCl_3$), δ(ppm):1.83 (m, 2 H, CH_2), 2.25(s, 6H, $2CH_3$), 2.43 (t, 2 H, *J* = 5.7 Hz, CH_2), 3.30 (m, 2 H, CH_2), 6.42 (s, 1 H, NH), 7.20 (d, 1 H, *J* = 3.0 Hz, H-8), 7.27-7.57 (m, 10 H, Ph-H), 8.68 (d, 1 H, *J* = 3.0 Hz, H-6).
^{13}C-NMR ($CDCl_3$), δ(ppm): 25.37 CH_2, 43.26 CH_2, 45.47 CH_3, 58.49 CH_2, 108.36 CH(C-8), 127.92 CH, 128.21 CH, 128.34 CH, 128.68 CH, 129.76 CH, 130.07 CH, 138.54 C, 138.76 C, 139.29 C, 143.64 C, 145.91 C, 147.86 CH(C-6), 150.02 C, 154.03 C.

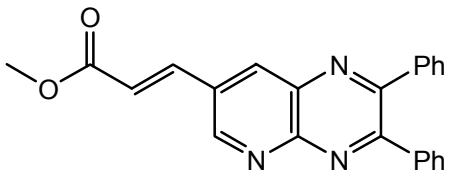
Anal. Calcd. for $C_{24}H_{25}N_5$(383.49) C, 75.17; H, 6.57; N, 18.26.
Found: C, 75.21; H, 6.72; N, 17.99.

7.4.4 Synthesis of 7-alkenyl-2,3-diphenylpyrido[2,3-b]pyrazine (Heck reaction)

General procedure:

A 25 ml schlenk flask was checked with 7-bromo-2,3-diphenylpyrido[2,3-b]pyrazine (181 mg, 0.5 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mol), P(o-tolyl)$_3$ (15 mg, 0.05 mmol), TEA (200 mg, 2 mmol), and MeCN 10 ml, Argon was passed inside, appropriate alkene 1.5 mmol was added inside with a syringe, the mixture was heated at 100 °C for 20 h, the solvent was evaporated and the residue was purified by column chromatography on silica gel.

3-(2,3-Diphenyl-pyrido[2,3-b]pyrazin-7-yl)-acrylic acid methyl ester (**200**)



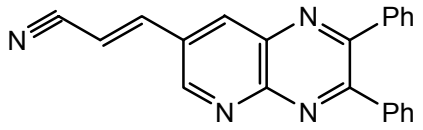
200

The crude product was purified by flash column chromatography on silica gel, eluting with cyclohexane:ethyl acetate (5/1→1/1), and provided a yellow solid 176 mg, yield 96 %, mp 197-8°C;

^{1}H-NMR ($CDCl_3$), δ(ppm): 3.88 (s, 3 H, CH_3), 6.77 (d, 1 H, *J* = 16.2 Hz, =C-H), 7.34-7.65 (m, 10 H, Ph-H), 7.91 (d, 1 H, *J* = 16.2 Hz, =C-H), 8.58 (d, 1 H, *J* = 2.6 Hz, H-8), 9.32 (d, 1 H, *J* = 2.6 Hz, H-6).
^{13}C-NMR ($CDCl_3$), δ(ppm): 52.14 CH_3, 121.99 CH(=C-H), 128.23 CH, 128.49, 129.54, 129.74 CH, 129.79 CH, 130.30 CH, 131.64 C, 135.65 C, 136.37 CH(=C-H), 137.80 C, 138.26 C, 140.00 CH(C-8), 150.32 C, 153.06 CH(C-6), 155.58 C, 156.79 C, 166.47 C(C=O).

Anal. Calcd. for $C_{23}H_{17}N_3O_2$ (367.40): C, 75.19; H, 4.66; N, 11.44.
Found: C, 75.19; H, 4.85; N, 11.28.

3-(2,3-Diphenyl-pyrido[2,3-b]pyrazin-7-yl)-acrylonitrile (**201**)



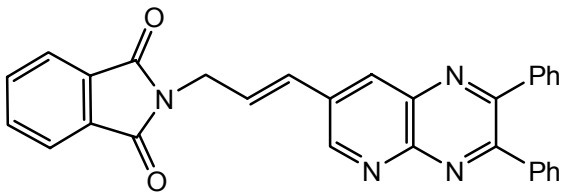
201

The crude product was purified by flash column chromatography on silica with cyclo-hexane:ethyl acetate (3/1-1/1) as eluting solvent and provided a yellow solid 109 mg, yield: 65 %, mp.188-9 °C;

^{1}H-NMR ($CDCl_3$), δ(ppm): 6.23 (d, 1 H, *J* = 17.0 Hz, =C-H), 7.60 (d, 1 H, *J* = 17.0 Hz, =C-H), 7.32-7.66 (m, 10 H, Ph-H), 8.53 (d, 1 H, *J* = 2.3 Hz, H-8), 9.32 (d, 1 H, *J* = 2.3 Hz, H-6).
^{13}C-NMR ($CDCl_3$), δ(ppm):100.84 CH(=C-H), 117.07 C, 128.29 CH, 128.52 CH, 129.72 CH, 129.95 CH, 130.28 CH, 130.52 C, 135.34 C, 136.00 CH(=C-H), 137.62 C, 138.04 C,145.84 CH(C-8), 150.64 C, 151.93 CH(C-6), 155.94 C, 157.36 C.

Anal. Calcd. for $C_{22}H_{14}N_4$ (334.37): C, 79.02; H, 4.22; N, 16.76.
Found: C, 79.14; H, 4.35; N, 16.67

2-[3-(2,3-Diphenyl-pyrido[2,3-b]pyrazin-7-yl)-allyl]-isoindole-1,3-dione (**202**)



The crude product was purified by flash column chromatography on silica, eluting with cyclohexane:ethyl acetate (3/1→1/1) and provided a light yellow solid 78 mg, yield:33 %, mp 89-91 °C;

^{1}H-NMR ($CDCl_3$), δ(ppm): 4.57 (dd, 2 H, J_1 = 6.3 Hz, J_2 = 1.1 Hz, CH_2), 6.63 (dt, 1 H, J_1 = 16.0 Hz, J_2 = 6.3 Hz, =C-H), 6.87 (d, 1 H, J = 16.0 Hz, 7.31-7.63 (m, 10 H, Ph-H), 7.75 (dd, 2 H, J_1 = 5.7 Hz, J_2 = 3.0 Hz, Ph-H), 7.90 (dd, 2 H, J_1 = 5.7 Hz, J_2 = 3.0 Hz, Ph-H), 8.37 (d, 1H, J = 2.3 Hz, H-8), 9.19 (d, 1 H, J = 2.3 Hz, H-6).
^{13}C-NMR ($CDCl_3$), δ(ppm):39.54 CH_2, 123.52 CH(=C-H), 127.95 CH, 128.13 CH, 128.39 CH, 129.10 CH, 129.29 CH, 129.41 CH, 129.81 CH, 130.26 CH, 132.04 C, 133.57 C, 133.93CH(=C-H), 134.21(C-8), 135.94 C, 138.01 C, 138.50 C, 149.25 C, 152.92 (C-6), 155.04 C, 155.70 C, 167.89 C.

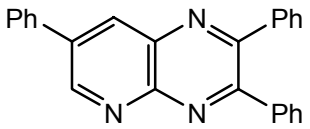
Anal Calcd for $C_{30}H_{20}N_4O$ (468.50): C, 76.91; H, 4.30; N, 11.96.
Found: C, 76.70; H, 4.48; N, 11.83.

7.4.5 Synthesis of 7-aryl-2,3-diphenylpyrido[2,3-b]pyrazine (Suzuki reaction)

General procedure of Suzuki reaction:

A 25ml schlenk flask was charged with 7-bromo-2,3-diphenylpyrido[2,3-b]pyrazine (181 mg, 0.5 mmol), K_2CO_3 (97 mg, 0.7 mmol), arylbronic acid (0.7 mmol), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol), and dry toluene 10 ml**,** Argon was passed three times and the mixture was heated at 100 °C for 16 h, the solvent was evaporated in vacuum, the residue was dissolved in 50 ml CH_2Cl_2, washed with water (2 × 30 ml), the solution was dried with anhydrous $MgSO_4$. The solvent was evaporated, and the residue was purified by column chromatography.

2,3,7-Triphenylpyrido[2,3-b]pyrazine (**203**)



203

The crude product was purified by flash column chromatography on silica gel, eluting with cyclohexane:ethyl acetate (6/1→2/1),and provide yellow solid 172 mg, yield 96 %, mp: 172-3 °C. (lit. [9], 282-4 °C)

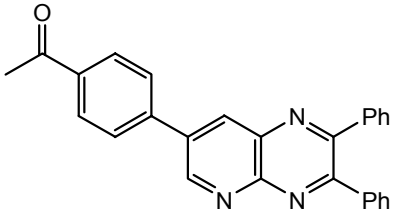
^{1}H-NMR ($CDCl_3$), δ(ppm): 7.31-7.82 (m, 15 H, Ph-H), 8.67 (d, 1 H, J = 2.6 Hz, H-8), 9.45 (d, 1 H, J= 2.6 Hz, H-6).

^{13}C-NMR ($CDCl_3$), δ(ppm): 127.56 CH, 128.16 2CH, 128.45 CH, 128.95 CH, 129.32 CH, 129.44 CH, 129.81 CH, 130.29 CH, 134.50 CH, 136.01 C, 136.50 C, 138.11 C, 138.60 C, 149.06 C, 153.61 CH, 155.12 C, 155.90 C.

HRMS (EI) calcd for $C_{25}H_{17}N_3$ (M^+) 359.14225, found 359.14226.

Anal. Calcd. for $C_{25}H_{17}N_3$: C, 83.54; H, 4.77; N, 11.69.
Found: C, 83.69; H, 4.83; N, 11.48.

1-[4-(2,3-Diphenyl-pyrido[2,3-b]pyrazin-7-yl)-phenyl]-ethanone (**204**)



204

The crude product was purified by flash column chromatography on silica gel, eluting with cyclohexane:ethyl acetate (4/1→1/1), and provided a yellow solid 101 mg, yield 50 %, mp 273-4 °C;

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.66 (3, 3 H, CH_3), 7.32-7.65 (m, 10 H, Ph-H), 7.88 (d, 2 H, J = 10.3 Hz, Ph-H), 8.13 (d, 2 H, J = 10.3 Hz, Ph-H), 8.69 (d, 1 H, $J_{6,8}$ = 2.6 Hz, H-8), 9.43 (d, 1 H, $J_{6,8}$ = 2.6 Hz, H-6).
^{13}C-NMR ($CDCl_3$), δ(ppm): 26.79 CH_3, 127.71 CH, 128.21 CH, 128.48 CH, 129.39 CH, 129.46 CH, 129.61 CH, 129.80 CH, 130.28 CH, 135.16 CH(C-8), 135.78 C, 136.75 C, 137.04 C, 137.94 C, 138.41 C, 140.88 C, 149.40 C, 153.09 CH(C-6), 155.41 C, 156.42 C, 197.45 C(C=O).

HRMS (EI) calcd for $C_{27}H_{19}N_3O$(M^+) 401.15285, found 401.15281.

Anal. Calcd. for $C_{27}H_{19}N_3O$: C, 80.78; H, 4.77; N, 10.47.
Found: C, 81.01; H, 4.92; N, 10.24.

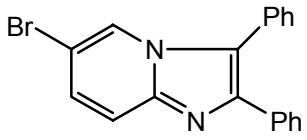
7.5 Synthesis of imidazo[1,2-a]pyridine derivatives

7.5.1 Synthesis of 6-bromo-2,3-diphenyl-imidazo[1,2-a]pyridine (**218**)

A 50 ml flask was charged 2-amino-5-bromopyridine (892 mg, 5 mmol), 2-bromo-2-phenyl-acetophenone (desyl bromide) (1.70 g, 6 mmol), $NaHCO_3$ (491 mg (6 mmol), and iso-propanol 15 ml, the mixture was heated at reflux for 12 h, the alcohol was evaporated, then 30 ml water and 60 ml dichloromethane were added, the mixture was separated and the organic phase was

washed with water (2 × 30 ml), dried with anhydrous $MgSO_4$, evaporated the solvent, the residue was purified by column chromatography on silica gel, eluting with cyclohexane:ethyl acetate(3/1) and provided white solid 1.17 g, yield 67 %, mp 198-9 °C.

6-Bromo-2,3-diphenylimidazo[1,2-a]pyridine (**218**)



218

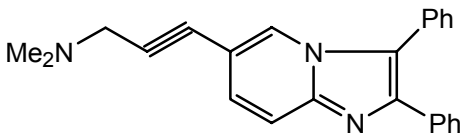
^{1}H-NMR ($CDCl_3$), δ(ppm): 7.23-7.66 (m, 12 H, Ph-H H-7 and H-8), 8.05 (dd, 1 H, J_1 = 1.8 Hz, J_2 = 0.8 Hz, H-5)
^{13}C-NMR ($CDCl_3$), δ(ppm): 107.11 C, 118.20 CH(C-8), 121.44 C(C-7), 123.32 CH(C-5), 127.77 CH, 128.03 CH, 128.06 CH, 128.34 CH, 129.20 C, 129.30 CH, 129.75 CH, 130.64 CH(C-5), 133.62 C, 143.17 C.

Anal. Calcd. for $C_{19}H_{13}BrN_2$ (349.22): C, 65.35; H, 3.75; Br, 22.88 N, 8.02.
Found: C, 65.09; H, 3.97; Br, 23.17; N, 7.91.

7.5.2 Synthesis of [3-(2,3-diphenyl-imidazo[1,2-a]pyridin-6-yl)-prop-2-ynyl]-dimethylamine and related compounds (Sonogashira reaction)

[3-(2,3-Diphenyl-imidazo[1,2-a]pyridin-6-yl)-prop-2-ynyl]-dimethylamine (**220**)

A 25 ml flask was charged with 6-bromo-2,3-diphenylimidazo[1,2-a]pyridine **218** (153 mg, 0.5 mmol), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), CuI (10 mg, 0.5 mmol), TEA 5 ml**,** DMF 5 ml and N,N-dimethylpropargylamine 83 mg (1.0 mmol), Argon was passed and the mixture was heated at 100 °C for 24 h, the solvent was evaporated in vacuum, the residue was purified by column chromatography on silica gel, eluting with ethyl acetate: methanol (4/1), and afforded a light yellow solid 130 mg, yield 74 %, mp 136-7 °C.



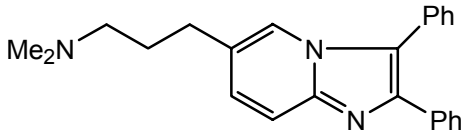
220

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.27 (s, 6 H, CH_3), 3.34 (s, 2 H, CH_2), 7.15-7.59 (m, 12 H, Ph-H, H-7 and H-8), 7.98 (s, 1 H, H-5).
^{13}C-NMR ($CDCl_3$), δ(ppm): 44.43 CH_3, 48.57 CH_2, 81.43 C, 86.28 C, 108. 91 C, 117.2 CH(C-8), 126.22 CH(C-7), 127.66 CH, 127.83 CH, 128.02 CH, 128.30 CH, 129.15 CH, 129.67 CH, 130.73 CH(C-5)132.02 C, 132.15 C, 133.76 C, 143.09 C, 143.62.

Anal. Calcd. for $C_{24}H_{21}N_3$ (351.44): C, 82.02; H, 6.02; N, 11.96.
Found: C, 82.06; H, 6.26; N, 11.78.

[3-(2,3-Diphenyl-imidazo[1,2-a]pyridin-6-yl)-propyl]-dimethylamine (**221**)

A solution [3-(2,3-diphenyl-imidazo[1,2-a]pyridin-6-yl)-prop-2-ynyl]-dimethylamine **220** (84 mg, 0.24 mmol), ethanol (15 ml) and 10 % palladium on charcoal (52 mg, 0.048 mmol on Pd, 0.2 equiv) was stirred under hydrogen at room temperature and atmosphere 16 hours. After complete conversion (TLC monitoring), the catalyst was filtered off through a pad of celite, washed with ethyl acetate, the solvents were removed under reduced pressure, and the residue was purified by column chromatography on neutral Al_2O_3 gel, eluting with ethyl acetate:methanol (10:1) to give 40 mg light brown solid, yield, 47 %, mp 70-1 °C.



221

^{1}H-NMR ($CDCl_3$), δ(ppm): 1.67 (m, 2 H, CH_2), 2.12 (s, 3 H, CH_3), 2.19 (t, 2 H, J = 7.2 Hz, CH_2), 2.49(t, 2 H, J = 7.7 Hz, CH_2), 7.01 (dd, 1 H, J_1 = 9.0 Hz, J_2 = 1.5 Hz , H-7), 7.16-7.58 (m, 11 H, Ph-H and H-8), 7.67 (s, 1 H, H-5)
^{13}C-NMR ($CDCl_3$), δ(ppm): 28.74 CH2, 30.39 CH2, 45.44 CH3, 58.70 CH_2, 117.9 CH, 120.81 CH, 126.26 C, 126.85 CH, 127.31 CH, 128.01 CH, 128.21 CH, 128.77 Ch, 129.52 CH, 130.08 C,130.74 CH,132.15 C, 134.34 C, 142.38 C, 142.38 C, 144.06 C.

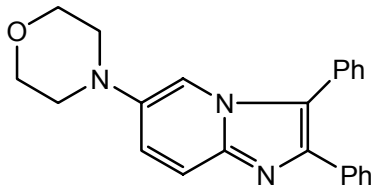
HRMS (EI) calcd for $C_{24}H_{25}N_3$ (M^+) 355.2048, found 355.2045.

7.5.3 Buchwald-Hartwig amination of 6-bromo-2,3-diphenylimidazo[1,2-a]pyridine

General procedure:

A schlenk 25ml flask was charged with 6-bromo-2,3-diphenyl-imidazo[1,2-a]pyridine **218** (175 mg, 0.5 mmol), $Pd_2(dba)_3$ (10 mg, 0.01 mmol), BINAP (19 mg, 0.03 mmol), t-BuONa 68 mg (0.7 mmol), appropriate substituted amine 1.0 mmol, dry toluene 5 ml, Argon was passed three times and the mixture was heated at 110 °C for 20 h, after cooled, 50 ml water was added, the mixture was extracted with ethyl acetate (3 × 40 ml), the extract was washed with water (2 × 40 ml), dried with anhydrous $MgSO_4$, evaporated the solvent, the residue was purified by column chromatography.

6-Morpholin-4-yl-2,3-diphenylimidazo[1,2-a]pyridine (**225**)



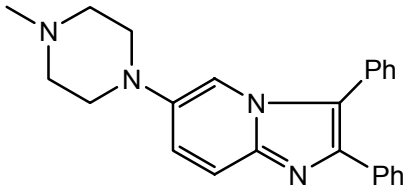
225

The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate, and provided a grey needle crystal 142 mg, yield 80 %, mp 201-2 °C.

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.90 t, 4 H, *J* = 4.6 Hz, $2CH_2$), 3.76 (t, 4 H, *J* = 4.6 Hz, $2CH_2$), 7.01 (dd, 1 H, J_1 = 9.8 Hz, J_2 = 2.2 Hz, Ar-H), 7.14-7.22 m, 3 H, Ph-H), 7.29 (d, 1 H, *J* = 1.9 Hz, Ar-H), 7.37-7.53 (m, 7 H, Ph-H), 7.56 (d, 1 H, *J* = 1.9 Hz, Ar-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 50.66 CH_2, 66.68 CH_2, 108.74 CH(C-8), 117.55 CH(C-7),121.07 CH(C-5), 121.71 C, 127.24 CH, 127.88CH, 128.22 CH, 128.82 CH, 129.60 CH, 130.16 C, 130.60 CH, 134.34 C, 139.90 C, 142.01 C, 142.45 C.

Anal. Calcd. for $C_{23}H_{31}N_3O$ (355.439): C, 77.72; H, 5.96; N, 11.82.
Found: C, 77.62; H, 6.22; N, 11.50.

6-(4-Methyl-piperazin-1-yl)-2,3-diphenylimidazo[1,2-a]pyridine (**226**)



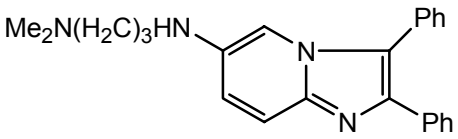
226

The product was purified by column chromatography on silica gel, eluting with ethyl acetate:methanol:TEA (10/1/0.2), and get grey needle crystal 112 mg, yield 61 %, mp 229-230 °C.

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.33 (s, 3 H, CH_3), 2.56 (t, 4 H, *J* = 4.5 Hz, $2CH_2$), 3.01 (t, 4 H, *J* = 4.5 Hz, $2CH_2$), 7.10 (dd, 1 H, J_1 = 9.4 Hz, J_2 = 2.2 Hz, Ar-H), 7.21-7.29 (m, 3 H, Ph-H), 7.38 (d, 1 H, *J* = 1.9 Hz, Ar-H), 7.44-7.60 (m, 7 H, Ph-H), 7.62 (d, 1 H, *J* = 1.9Hz, Ar-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 46.07 CH3, 50.38 CH2, 54.86 CH2,108.83CH(C-8),117.38 CH(C-7), 121.48 CH(C-5), 121.66 C, 127.17 CH, 127.89 CH, 128.19 CH, 128.73 CH, 129.55 CH, 130.22 C, 130.60 C, 134.45 C, 139.88 C, 141.98 C, 142.37 C.

Anal. Calcd. for $C_{24}H_{24}N_4$ (368.47): C, 78.23; H, 6.57; N, 15.21.
Found: C, 78.22; H, 6.58; N, 15.22.

N'-(2,3-Diphenyl-imidazo[1,2-a]pyridin-6-yl)-N,N-dimethyl-propane-1,3-diamine (**227**)



227

The product was purified by column chromatography on neutral Al_2O_3 gel, eluting with ethyl acetate:methanol 20:1 to give 40 mg brown solid, yield 22 %, mp 125-6 °C

^{1}H-NMR ($CDCl_3$), δ(ppm): 1.70-1.79 (m, 2 H, CH_2), 2.21 (s, 6H, $2CH_3$), 2.37 (t, 2H, *J* = 6.4 Hz, CH_2), 2.97 (t, 2 H, *J* = 6.4 Hz, CH_2), 6.75 (dd, 1 H, Ar-H), 7.11 (s, 1 H, N-H), 7.19-7.62 (m, 12 H, Ph-H and Ar-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 26.22 CH_2, 43.99 CH_2, 45.54 CH_3, 58.48 CH_2, 102.21 CH(C-8),117.41 CH(C-7), 120.24 CH(C-5), 121.31 C, 126.93 CH, 127.79 CH, 128.13 CH, 128.52 CH, 129.43 C, 129.44 CH, 130.65 CH, 134.69 C, 136.98 C. 141.47 C, 141.61.

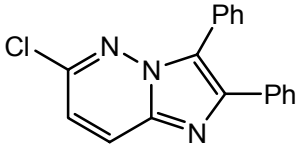
Anal. Calcd. for $C_{24}H_{26}N_4$ (370.49): C, 77.80; H, 7.07; N, 15.12.
Found: C, 77.81; H, 6.98; N, 15.03.

7.6 Synthesis of imidazo[1,2-b]pyridazine derivatives

7.6.1 Synthesis of 6-chloro-2,3-diphenylimidazo[1,2-b]pyridazine (**219**)

A 50 ml flask was charged with 3-amino-6-chloropyridazine (1.30 g, 10 mmol), 2-bromo-2-phenyl-acetophenone (desyl bromide) (3.40 g, 12 mmol), $NaHCO_3$ (982 mg, 12 mmol), and iso-propanol 30 ml, the mixture was heated at reflux for 12 h, the alcohol was evaporated, then 50 ml water and 100 ml dichlomethane was added inside, separated and the organic phase was washed with water (2 × 30 ml), dried with anhydrous $MgSO_4$, evaporated the solvent, the residue was purified by column chromatography on silica gel, eluting with cyclohexane:ethyl acetate(2/1) and provided a yellow needle crystal 2.35 g, yield 77 %, mp 207-8 °C.

6-Chloro-2,3-diphenylimidazo[1,2-b]pyridazine (**219**)



219

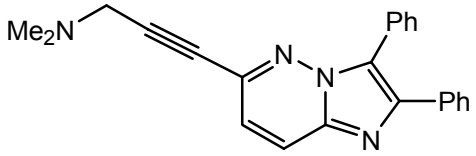
^{1}H-NMR ($CDCl_3$), δ (ppm): 7.07 (d, 1 H, *J* = 9.0 Hz, H-7), 7.31-7.67 (m,10 H, Ph-H), 7.94 (d, 1 H, *J* = 9.0 Hz, H-8)

^{13}C-NMR ($CDCl_3$), δ (ppm): 118.83 CH, 126.56 CH, 128.03 C, 128.24 CH, 128.39 CH, 128.47 CH, 128.78 CH, 128.95 CH, 130.41 CH, 133.63 C, 137.29 C, 144.09 C, 146.49.

Anal. Calcd. for $C_{18}H_{12}ClN_3$ (305.76): C, 70.71; H, 3.96; Cl, 11.60; N, 13.74.
Found: C, 70.64; H, 3.93; Cl, 11.80; N, 13.63.

7.6.2 Synthesis of [3-(2,3-diphenyl-imidazo[1,2-b]pyridazin-6-yl)-prop-2-ynyl]-dimethylamine (**223**)

A 25ml flask was charged with 6-Chloro-2,3-diphenylimidazo[1,2-b]pyridazine **219** (153mg, 0.5mmol), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), CuI (10mg, 0.5mmol), TEA 5 ml**,** DMF 5 ml and N,N-dimethylpropargylamine (83 mg, 1.0 mmol), Argon was passed three times and the mixture was heated at 100 °C for 24 h, the solvent was evaporated in vacuum, the residue was purified by column chromatography on silica gel, eluting with ethyl acetate:methanol (6/1), and provided a light yellow solid 160 mg, yield 86 %, mp 144-5 °C.



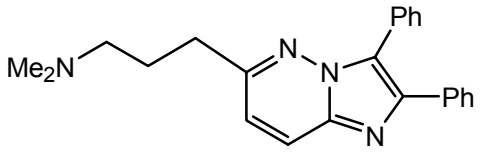
223

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.38 (s, 6 H, CH_3), 3.50 (s, 2 H, CH_2), 7.15 (d, 1 H, J = 9.3 Hz, H-7), 7.28-7.66 (m, 10 H, Ph-H), 7.98 (d, 1 H, J = 9.1 Hz, H-8)
^{13}C-NMR ($CDCl_3$), δ (ppm): 44.47 CH3, 48.53 CH2, 81.66 C, 88.59 C, 120.99 CH, 124.70 CH, 125.32 C, 128.06, 128.34 CH, 128.45 CH, 128.67 CH, 128.71 CH, 130.55 CH, 133.71 C, 137.59 C, 138.01, 143.88 C, 146.57 C.

Anal. Calcd. for $C_{23}H_{20}N_4$ (352.43): C, 78.38; H, 5.72; N, 15.90.
Found: C, 78.22; H, 5.91; N, 15.86.

7.6.3 Synthesis of [3-(2,3-diphenyl-imidazo[1,2-b]pyridazin-6-yl)-propyl]-dimethylamine (**224**)

A solution [3-(2,3-Diphenyl-imidazo[1,2-b]pyridazin-6-yl)-prop-2-ynyl]-dimethylamine **223** (130 mg, 0.37 mmol), ethanol (15 ml) and 10 % palladium on charcoal (82 mg, 0.074 mmol on Pd, 0.2 equiv) was stirred under hydrogen at room temperature and atmosphere 16 hours. After complete conversion (TLC monitoring), the catalyst was filtered off through a pad of Celite, washed with ethyl acetate, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on neutral Al_2O_3 gel, eluting with ethyl acetate:methanol (10:1) to give 96 mg of light brown solid, yield, 73 %, mp 112-3 °C



224

[1]H-NMR ($CDCl_3$), δ (ppm): 1.80 (m, 2 H, CH_2), 2.11 (s, 3 H, CH_3), 2.23 (t, 2 H, *J* = 7.3 Hz, CH_2), 2,73 (t, 2 H, *J* = 7.7 Hz, CH_2), 6.85 (d, 1 H, *J* = 9.1 Hz, H-7), 7.19-7.60 (m, 10 H, Ph-H), 7.79 (d, 1 H, *J* = 9.0 Hz, H-8).
[13]C-NMR ($CDCl_3$), δ (ppm): 26.64 CH_2, 33.30 CH_2, 45.46 CH_3, 58.86 CH_2, 118.50 CH, 124.89 CH, 127.74 CH, 128.29 CH, 128.34 CH, 128.40 CH, 128.44 CH, 129.05 C, 130.53 CH,134.38 C, 137.92 C, 142.85 C, 154.92 C.

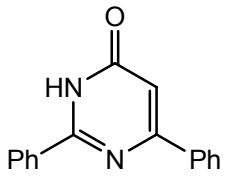
Anal. Calcd. for $C_{23}H_{24}N_4$ (356.46): C, 77.50; H, 6.79; N, 15.72.
Found: C, 77.52; H, 6.82; N, 15.62.

7.7 Synthesis of pyrimidine derivatives

7.7.1 Synthesis of aryl substituted chloro- or iodopyrimidine

7.7.1.1 Using general methods and starting with benzamidine

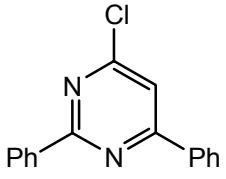
2,6-Diphenyl-3H-pyrimidin-4-one (**249**)



249

Benzamidine hydrochloride hydrate (10.48 g, 0.067mol) and ethyl benzolacetate (14.82 g, 0.074 mol) were added to a solution of sodium (1.8 g, 0.077 mol) in 80 ml dry ethanol, the mixture was heated at reflux for 16 hours. Ethanol was evaporated in vacuum to dryness and the residue was dissolve in 100 ml water, the mixture was acidified with concentrated hydrochloric acid (pH = 3), the precipitate was collected, washed with water, the crude product was recrystallized with ethanol and provided a white solid 12.70 g, yield 76 %, mp 296-7 °C.

4-Chloro-2,6-diphenylpyrimidine (**250**)



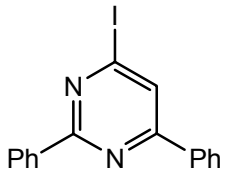
250

A 100 ml flask was charged with 2,6-diphenyl-3H-pyrimidin-4-one **249** (12.70 g, 0.051 mol), phosphoryl chloride (36.0 ml, 59.20 g, 0.38 mol), phosphorpentachloride (10.20 g, 0.049 mol). The mixture was heated at reflux for 3 h, the excess of phosphoryl chloride was evaporated in vacuum, then 100 g ice was added slowly and carefully, the solid was collected and washed with water completely. The crude product was recrystallized with petroether (40-60 °C), and provided a white solid 10.20 g, yield 75 %, mp 103-4 °C.

^{1}H-NMR ($CDCl_3$), δ(ppm): 7.43-7.49 (m, 6 H, Ph-H), 7.55 (s, 1 H, H-5), 8.11-8.14 (dd, 2 H, Ph-H), 8.48-8.52 (dd, 2 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 114.47 CH(C-5), 127.40 CH, 128.58 CH, 128.65 CH, 129.01 CH, 131.42 CH, 131.51 CH,135.90 C, 136.48 C, 162.22 C, 165.21 C, 165.67 C.

Anal. Calcd for $C_{16}H_{11}ClN_2$ (266.72): C, 72.05; H, 4.16; Cl, 13.29; N, 10.50
Found: C, 72.15; H, 4.29; Cl, 13.14; N, 10.36

4-Iodo-2,6-diphenylpyrimidine (**251**)



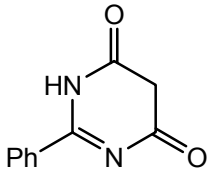
251

A mixture of 4-Chloro-2,6-diphenylpyrimidine **250** (3.0 g, 8.3 mmol) and 57 % HI (30 ml, 0.23 mol) was stirred at room temperature for 20 h, then 100 ml cold 10 % NaOH was added, the precipitate was collected and washed with cold water, the crude product was recrystallized with petroether (40-60 °C), and provided a light brown solid 1.70 g, yield 42 %, mp 98 °C.

^{1}H-NMR ($CDCl_3$), δ(ppm): 7.41-7.48 (m, 6 H, Ph-H), 7.95 (s, 1 H, H-5), 8.06-8.10 (dd, 2 H, Ph-H), 8.44-8.48 (dd, 2 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 125.57 CH(C-5), 127.33 CH, 128.52 CH, 128.57 CH, 128.99 CH, 130.80 (C-4) 131.32 CH, 131.40 CH,135.46 C, 136.34 C, 163.44 C, 164.60 C.

Anal. Calcd for $C_{16}H_{11}IN_2$ (358.18): C, 53.65; H, 3.10; I, 35.43; N, 7.82.
Found: C, 53.79; H, 3.24; I, 35.27; N, 7.58.

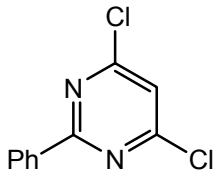
2-Phenyl-1H-pyrimidine-4,6-dione (**252**)



252

Benzamidine hydrochloride hydrate (10.90 g, 0.070mol) and diethyl malonate (11.20 g, 0.070mol) were added to a solution of sodium (4.30 g, 0.19mol) in 70 ml dry ethanol, the mixture was heated at reflux for 3 hours. Ethanol was evaporated in vacuum to dryness and the residue was dissolve in 80 ml warm water, the mixture was acidified with concentrated hydrochloric acid (pH = 3), the precipitate was collected, washed with water, the crude product was recrystallized with DMF/water and afforded a white solid 6.90 g, yield 52 %, mp 324-5 °C.

4,6-Dichloro-2-phenylpyrimidine (**253**)



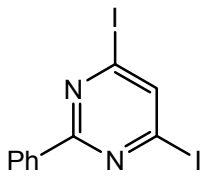
253

A mixture of 2-Phenyl-pyrimidine-4,6-dione (2-phenyl-4,6-dihydroxypyrimidine) **252** (6.90 g, 0.037 mol), phosphoryl chloride (18 ml, 0.19 mol), N,N-dimethylaniline (4.4 g, 0.036 mol), was heated at reflux for 2 h, the excess $POCl_3$ was evaporated in vacuum, then 50 g ice was added inside slowly and carefully, the solid was collected and washed with water completely. The crude product was recrystallized with ethanol, and provided a light yellow solid 7.5 g, yield 89 %, mp 93-4°C.

^{1}H-NMR ($CDCl_3$), δ(ppm): 7.20 (s, 1 H, H-5), 7.42-7.46 (m, 3 H, Ph-H), 8.35-8.38 (dd, 2 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 118.8 CH(C-5), 128.73 CH, 128.87 CH, 132.26 CH, 134.87 C, 162.03 C, 165.76. C.

Anal. Calcd for $C_{10}H_6Cl_2N_2$ (225.07): C, 53.36; H, 2.69; Cl, 31.50; N, 12.45.
Found: C, 53.24; H, 2.86; Cl, 31.75; N, 12.32.

4,6-Diiodo-2-phenylpyrimidine (**254**)



254

A mixture of 2-phenyl-4,6-dichloropyrimidine **254** (2.0 g, 9.0 mmol), NaI (2.7 g, 18 mmol) and 57 % HI 40 ml was stirred at 40 °C under Argon for 24 h, 50 g ice was added, the mixture was neutralizd with 40 % NaOH, and extracted with CH_2Cl_2 (3 × 40 ml), the extract was washed

with water, dried with anhydrous $MgSO_4$, the solvent was evaporated, and the crude product was recrystallized with with petroether (40-60 °C), and provided a yellow solid 3.30 g, yield 91 %, mp 103-5 °C.

^{1}H-NMR ($CDCl_3$), δ(ppm): 7.38-7.46 (m, 3 H, Ph-H), 8.05 (s, 1 H, H-5), 8.28-8.33 (dd, 2 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 128.67 CH, 128.84 CH, 132.07 CH, 134.73 C, 139.67 CH(C-5), 164.94. C.

Anal. Calcd for $C_{10}H_6I_2N_2$ (407.98): C, 29.44; H, 1.48; I, 62.21; N, 6.87.
Found: C, 29.60; H, 1.63; I, 62.01; N, 6.72.

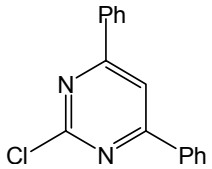
7.7.1.2 Using Suzuki cross-coupling and starting with 2,4,6-trichloropyrimidine

(a) 2-Chloro-4,6-diarylpyrimidine

General procedure:

To a solution of 2,4,6-trichloropyrimidine (1.0 g, 5.5 mmol) in 50 ml DME, appropriate arylboronic acid (11.0 mmol, 2.0 equiv), sodium carbonate (3.61 g, 34.1 mmol, 6.2 equiv, dissolve in a minimium amount of water) was added. The active catalyst was generated by the addition of palladium acetate (31 mg, 0.14 mmol, 2.5 % equiv), and triphenylphosphine (72 mg, 0.28 mmol, 5 % equiv) to the mixture. Argon was passed, and the mixture was heated at 70 °C for 24 h. The solvent was removed by rotary evaporation and the product was extracted with methylene chloride (3 × 50 ml), the organics washed with water (2 × 50 ml), and dried over anhydrous magnesium sulphate. The solvent was evaporated, and the residue was purified by column chromatography on silica gel, eluting with cyclohexane:ethyl acetate(15/1→6/1).

2-Chloro-4,6-diphenylpyrimidine (**240a**)

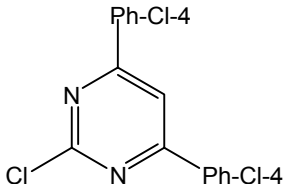


White solid, yield 67 %, mp 106-8 °C;

^{1}H-NMR($CDCl_3$), δ(ppm): 7.53-7.55 (m, 6 H, Ph-H), 8.01 (s, 1 H, H-5), 8.12-8.16 (m, 4 H, Ph-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 110.93 CH(H-5), 127.46 CH, 129.09 CH, 131.66 CH, 135.65 C, 162.07 C, 167.64 C.

Anal. Calcd. for $C_{16}H_{11}ClN_2$(266.73): C, 72.05; H, 4.16; Cl, 13.29; N, 10.50.
Found: C, 72.21; H, 4.30; Cl, 13.47; N, 10.50.

2-Chloro-4,6-bis-(4-chloro-phenyl)-pyrimidine



White solid, yield: 82%; mp.151-3°C;

^{1}H-NMR($CDCl_3$), δ(ppm): 7.42 (dd, 4 H, *J* = 8.7 Hz. Ph-H), 7.85 (s, 1 H, H-5), 8.01 (dd, 4 H, *J* = 8.7 Hz, Ph-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 110.31CH(H-5), 128.73 CH, 129.41 CH, 133.83 C, 138.19 C, 162.17 C, 166.52 C.

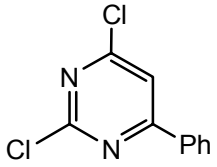
Anal. Calcd. for $C_{16}H_9Cl_3N_2$(335.62): C, 57.26; H, 2.70; Cl, 31.69; N, 8.35.
Found: C, 57.23; H, 2.61; Cl, 31.80; N, 8.44.

(b) 2,4-dichloro-6-arylpyrimidine

General procedure:

To a solution of 2,4,6-trichloropyrimidine (1.0 g, 5.5 mmol) in 50 ml DME, appropriate arylboronic acid (5.5 mmol, 1.0 equiv), sodium carbonate (1.80 g, 17.0 mmol, 3.1 equiv, dissolve in a minimium amount of water) was added. The active catalyst was generated by the addition of palladium acetate (31 mg, 0.14 mmol, 2.5 % equiv), and triphenylphosphine (72 mg, 0.28 mmol, 5 % equiv) to the mixture. Argon was passed, and the mixture was heated at 70 °C for 24 h. The solvent was removed by rotary evaporation and the product was extracted with methylene chloride (3 × 50 ml), the organic layer was washed with water (2 × 50 ml), and dried over anhydrous magnesium sulphate. The solvent was evaporated, and the residue was purified by column chromatography on silica gel, eluting with cyclohexane:CH_2Cl_2 (5/1→1/1).

2,4-dichloro-6-phenylpyrimidine (**239a**)

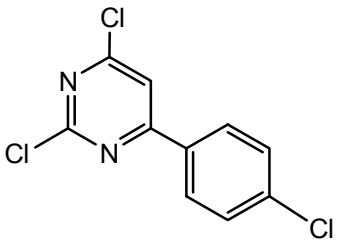


White solid, yield: 81 %; mp 83-4 °C;

^{1}H-NMR($CDCl_3$), δ(ppm): 7.44-7.48 (m, 3 H, Ph-H), 7.59 (s, 1 H, H-5), 7.96-8.01 (dd, 2 H, *J* = 8.7 Hz, Ph-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 115.33 CH(H-5), 127.61 CH, 129.24 CH, 132.48 CH, 134.09 C, 160.97 C, 162.93 C, 168.20 C.

Anal. Calcd. for $C_{10}H_6Cl_2N_2$(225.08): C, 53.36; H, 2.69; Cl, 31.50; N, 12.45.
Found: C, 53.41; H, 2.51; Cl, 31.20; N, 12.68.

2,4-Dichloro-6-(4-chloro-phenyl)-pyrimidine (**239b**)

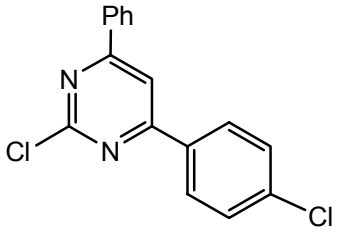


White solid, yield: 78 %; mp.123-5 C;

^{1}H-NMR($CDCl_3$), δ(ppm): 7.41-7.45 (dd, 2 H, Ph-H), 7.57 (s, 1 H, H-5), 7.93-7.96 (dd, 2 H, Ph-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 115.12CH(H-5), 128.87 CH, 129.56 CH, 132.49 C, 138.97 C, 161.07 C, 163.17 C, 166.88 C.

Anal. Calcd. for $C_{10}H_5Cl_3N_2$(259.52): C, 46.28; H, 1.94; Cl, 40.98; N, 10.79.
Found: C, 46.32; H, 2.04; Cl, 40.70; N, 10.48.

(c) 2-Chloro-4-(4-chloro-phenyl)-6-phenylpyrimidine (**255**)



To a solution of 2,4-dichloro-6-(4-chloro-phenyl)-pyrimidine **239b** (290 mg, 1.1 mmol) in 15 ml DME, phenyllboronic acid (134 mg, 1.1 mmol, 1.0 equiv), sodium carbonate (360 mg, 3.4 mmol, 3.1 equiv, dissolve in a minimium amount of water) was added. The active catalyst was generated by the addition of palladium acetate (12 mg, 0.055 mmol, 5 % equiv), and triphenylphosphine (29 mg, 0.11 mmol, 10 % equiv) to the mixture. Argon was passed, and the mixture was heated at 70 °C for 24 h. The solvent was removed by rotary evaporation and the product was extracted with methylene chloride (3 × 20 ml), the organic layer was washed with water (2 × 20 ml), and dried over anhydrous $MgSO_4$. The solvent was evaporated, the residue

was purified by flash column chromatography on silica gel, eluting with cyclohexane:CH_2Cl_2 (5/1→1/1), and provided a white solid 274 mg, yield 82 %, mp 97-9 °C;

^{1}H-NMR ($CDCl_3$), δ(ppm): 7.39-7.46 (m, 5 H, Ph-H), 7.87 (s, 1 H, H-5), 7.98-8.05 (m, 4 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 110.63 CH(C-5), 127.46 CH, 128.73 CH, 129.12 CH, 129.35 CH, 131.80 CH, 134.05 C, 135.84 C, 138.02 C, 162.13 C, 166.31 C, 167.86 C.

Anal. Calcd. for $C_{16}H_{10}Cl_2N_2$: C, 63.81; H, 3.35; Cl, 23.54; N, 9.30.
Found: C, 63.71; H, 3.46; Cl, 23.66; N, 9.13.

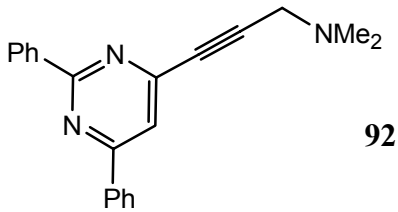
7.7.2 Sonogashira cross-coupling of halopyrimidines

7.7.2.1 From 4-iodo-2,6-diphenylpyrimidine 251

General procedure:

A 25 ml flask was charged with 4-iodo-2,6-diphenylpyrimidine **251** (358 mg, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol), cuprous iodide (19 mg, 0.10 mmol), dry triethylamine 10 ml, and appropriate alkyne 1.5 mmol. Argon was passed inside and the mixture was stirred at room temperature for 24 h, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel.

[3-(2,6-Diphenyl-pyrimidin-4-yl)-prop-2-ynyl]-dimethylamine (**256**)



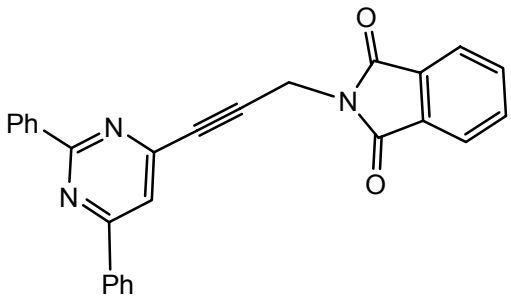
92

The product was purified by column chromatography on silica gel, eluting with ethyl acetate:methanol (8:1) and provided 237 mg brown solid, yield 76 %, mp 62-3 °C.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.29 (s, 6 H, CH_3), 3.44 (s, 2 H, CH_2), 7.35-7.37 (m, 6 H, Ph-H), 7.51 (s, 1 H, H-5), 8.05 (dd, 2 H, Ph-H), 8.48 (dd, 2 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ (ppm): 44.47 CH_3, 48.59 CH_2, 84.19 C, 89.11 C, 116.91 CH(H-5), 127.20 CH, 128.46 CH, 128.52 CH, 128.92 CH, 130.89 CH, 132.15 CH, 136.44 C, 137.44 C, 151.39 C, 164.01 C, 164.70 C.

Anal. Calcd. for $C_{21}H_{19}N_3$ (313.4): C, 80.48; H, 6.11; N, 13.41.
Found: C, 80.30; H, 6.35; N, 13.24.

2-[3-(2,6-Diphenyl-pyrimidin-4-yl)-prop-2-ynyl]-isoindole-1,3-dione (**258**)



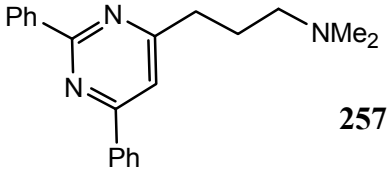
The product was purified by column chromatography on silica gel, ethyl acetate:cyclohexane (1:1) was as eluting solvent and provided a brown solid, yield 84 %, mp 221-2 °C.

^{1}H-NMR ($CDCl_3$), δ (ppm): 4.71 (s, 2 H, CH_2), 7.40-7.46 (m, 6 H, Ph-H), 7.60 (s, 1 H, H-5), 7.67-7.70 (dd, 2 H, Ph-H), 7.83-7.86 (dd, 2 H, Ph-H), 8.10-8.13 (dd, 2 H, Ph-H), 8.46-8.49 (dd, 2 H, Ph-H)
^{13}C-NMR ($CDCl_3$), δ (ppm): 27.73 CH_2, 81.42 C, 86.28 C, 117.12 CH(C-5), 123.70 CH, 127.24 CH, 128.49 CH, 128.95 CH, 130.92 CH, 131.24 CH, 131.99 C, 134.35 CH, 136.34 C, 137.27 C, 150.74 C, 164.17 C, 164.78 C, 166.94 C.

Anal. Calcd. for $C_{27}H_{17}N_3O$ (415.44): C, 78.06; H, 4.12; N, 10.11.
Found: C, 78.16; H, 4.28; N, 10.05

[3-(2,6-Diphenyl-pyrimidin-4-yl)-propyl]-dimethylamine (**257**)

A solution [3-(2,6-diphenyl-pyrimidin-4-yl)-prop-2-ynyl]-dimethylamine **256** (126 mg, 0.4 mmol), ethanol (15 ml) and 10 % palladium on charcoal (89 mg, 0.08 mmol on Pd, 0.2 equiv) was stirred under hydrogen at room temperature and atmosphere 16 hours. After complete conversion (TLC monitoring), the catalyst was filtered off through a pad of Celite, washed with ethyl acetate, the solvents were removed under reduced pressure, and the residue was purified by column chromatography on neutral Al_2O_3 gel, using ethyl acetate:Methanol (10:1) as eluting solvent to provide 96 mg light brown oil, yield 76 %.



257

^{1}H-NMR ($CDCl_3$), δ(ppm): 1.91-2.01 (m, 2 H, CH_2), 2.17(s, 3 H, CH_3), 2.31 (t, 2 H, J = 7.3 Hz, CH_2), 2.79 (t, 2 H, J = 7.5 Hz, CH_2), 7.35 (s, 1 H, H-5), 7.38-7.41 (m, 6 H, Ph-H), 8.11 dd, 2 H, Ph-H), 8.51 (dd, 2 H, Ph-H)

^{13}C-NMR ($CDCl_3$), δ(ppm): 26.46 CH_2, 35.77 CH_2, 45.35 CH_3, 58.99 CH_2, 113.54 CH(C-5), 127.10 CH, 128.38 CH, 128.42 CH, 128.85 CH, 130.46 CH, 130.65 CH, 137.34 C, 138.21 C, 163.71 C, 164.22 C, 171.00 C.

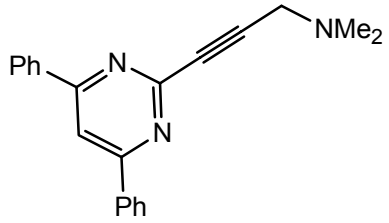
HRMS (EI) calcd for $C_{21}H_{23}N_3$ (M^+) 317.18920, found 317.18920.

7.7.2.2 From 2-chloro-4,6-diarylsubstituted pyrimidine

General procedure:

A 25 ml flask was charged with appropriate 2-chloro-4,6-diarylpyrimidine (0.5 mmol), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), CuI (10 mg, 0.05 mmol), TEA 5 ml**,** DMF 5 ml and N,N-dimethylpropargylamine 83 mg (1.0 mmol), Argon was passed three times and the mixture was heated at 100 °C for 24 h, the solvent was evaporated in vacuum, the residue was purified by column chromatography on silica gel, eluting with ethyl acetate: methanol (5/1),

[3-(4,6-Diphenyl-pyrimidin-2-yl)-prop-2-ynyl]-dimethylamine (**259a**)



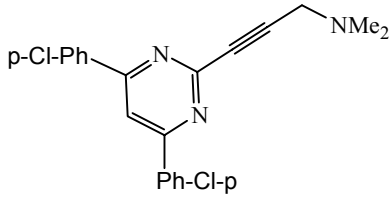
Brown solid 60 mg was obtained, yield 38 %, mp 101-3 °C. When using KOAc as base, 112 mg brown solid was obtained, yield 70 %.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.39 (s, 6 H, CH_3), 3.54(s, 2 H, CH_2), 7.43-7.46 (m, 6 H, Ph-H), 7.93 (s, 1 H, H-5), 8.06-8.10 (dd, 4 H, Ph-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 44.35 CH_3, 48.44 CH_2, 83.07 C, 85.40 C, 111.55CH(H-5), 127.37 CH, 128.96 CH, 131.08 CH, 136.56C, 153.09C, 165.16 C

HRMS (EI) calcd for $C_{21}H_{19}N_3$ (M^+) 313.15790, found , 313.15785

Anal. Calcd. for $C_{21}H_{19}N_3$ (313.40) C, 80.48; H, 6.11; N, 13.41.
Found: C, 80.14; H, 6.12; N, 13.37.

{3-[4,6-Bis-(4-chloro-phenyl)-pyrimidin-2-yl]-prop-2-ynyl}-dimethylamine (**259b**)

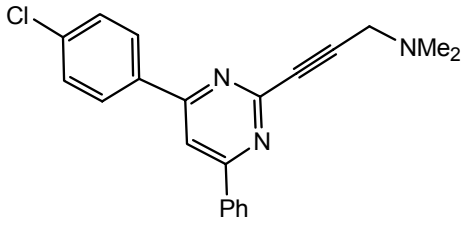


Brown solid 98 mg was obtained, yield: 51 %, mp 112-4 °C.

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.35 (s, 6 H, CH_3), 3.50 (s, 2 H, CH_2), 7.37 (d, 4 H, *J* = 8.7 Hz), 7.80 (s, 1 H, H-5), 7.98 (d, 4 H, *J* = 8.7 Hz)
^{13}C-NMR ($CDCl_3$), δ(ppm): 44.38 CH_3, 48.40 CH_2, 83.72 C, 85.06 C, 111.77 CH(H-5), 128.63 CH, 129.18 CH, 134.67 CH, 137.47 C, 153.09 C, 163.97 C

Anal. Calcd. for $C_{21}H_{17}Cl_2N_3$ (382.28): C, 65.98; H, 4.48; Cl, 18.55; N, 10.99.
Found: C, 65.84; H, 4.61; Cl, 18.73; N, 10.81.

{3-[4-(4-Chloro-phenyl)-6-phenyl-pyrimidin-2-yl]-prop-2-ynyl}-dimethylamine (**259c**)

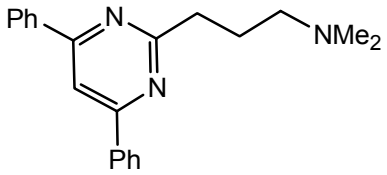


Brown solid 88 mg was obtained, yield 51 %, mp 86-8 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.35 (s, 6 H, CH_3), 3.50 (s, 2 H, CH_2), 7.36-7.42(m, 5 H, Ph-H), 7.84 (s, 1 H, H-5), 7.97-8.05 (m, 4 H, Ph-H).
^{13}C-NMR($CDCl_3$), δ (ppm): 44.39 CH_3, 48.44 CH_2, 83.45 C, 85.22 C, 111.13CH(H-5), 127.34 CH, 128.64 CH, 128.96 CH, 129.16 CH, 131.20 CH, 134.89 C, 136.32 C, 137.33 C, 153.10C, 163.80 C, 165.30 C

Anal. Calcd. for $C_{21}H_{18}ClN_3$ (347.84): C, 72.51; H, 5.22; Cl, 10.19; N, 12.08.
Found: C, 72.66; H, 5.41; Cl, 10.26; N, 11.94.

[3-(4,6-Diphenyl-pyrimidin-2-yl)-propyl]-dimethylamine (**260**)



A solution [3-(4,6-diphenyl-pyrimidin-2-yl)-prop-2-ynyl]-dimethylamine **259a** (76mg, 0.24 mmol) in ethanol (15 ml) and 10 % palladium on charcoal (51 mg, 0.048 mmol on Pd, 0.2equiv) was stirred under hydrogen at room temperature and atmosphere 16 hours. After complete conversion (TLC monitoring), the catalyst was filtered off through a pad of Celite, washed with ethyl acetate, the solvents were removed under reduced pressure, the residue was purified by column chromatography on neutral Al_2O_3 gel, using ethyl acetate:cyclohexane (1:1) as eluting solvent to provide 55 mg light brown oil, yield 72 %.

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.04-2.14 (m, 2 H, CH_2), 2.20 (s, 2 × 3 H, CH_3), 2.37 (t, 2 H, J = 7.5 Hz, CH_2), 3.03 (t, 2 H, J = 7.7 Hz, CH_2), 7.41-7.44 (m, 6 H, Ph-H), 7.81 (s, 1 H, H-5), 8.05-8.08 (m, 4 H, Ph-H),
^{13}C-NMR ($CDCl_3$), δ(ppm): 26.53 CH_2, 37.52 CH_2, 45.61 CH_3, 59.56CH_2, 110.03 CH(C-5), 127.25 CH, 128.91 CH, 130.62 CH, 137.56 C, 164.66 C, 171.27 C.

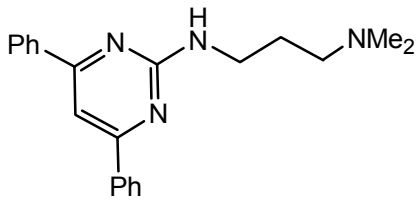
HRMS (EI) calcd for $C_{21}H_{23}N_3$ (M^+) 317.18920, found 317.18920.

259b and **259c** were hydrogenated with hydrogen, using the same conditions, only **260** was obtained, and the yields were 37 % and 44 %, respectively.

7.7.3 Nucleophilic substitution of 2-chloropyrimidine

7.7.3.1 To introduce 3-dimethylamino-propylamino group

N'-(4,6-Diphenyl-pyrimidin-2-yl)-N,N-dimethyl-propane-1,3-diamine (**262**)



A mixture of 2-chloro-4,6-diphenylpyrimidine (107 mg, 0.4 mmol) in N,N-dimethyl-propanediamine 3 ml was heated at 110 °C for 16 h, then evaporated the solvent to dryness in high vacuum, the residue was dissolved in 20 ml 2 N HCl, and washed with dichloromethane (2 × 20 ml), the aqueous layer was basified with solid potassium carbonate (ph > 10), then extracted with dichloromethane (4 × 20 ml), the organic phase was dried with anhydrous $MgSO_4$, evaporated the solvent, and provide yellow solid 105 mg, yield 79 %, mp 62-4 °C;

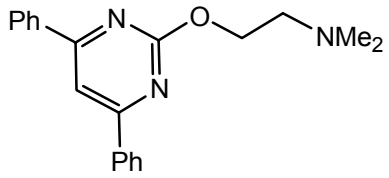
^{1}H-NMR ($CDCl_3$), δ(ppm): 1.73 (m, 2 H, CH_2), 2.14 (s, 3 H, CH_3), 2.31 (t, 2 H, J = 7.2 Hz, CH_2), 3.51 (dt, 2 H, J_1 = 6.0 Hz, J_2 = 6.7 Hz, CH_2), 5.73 (t, 1 H, J = 6.0 Hz, NH), 7.29 (s, 1 H, H-5), 7.35-7.38 (m, 6 H, Ph-H), 7.99 (dd, 4 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 27.50 CH_2, 40.32 CH_2, 45.57 CH_3, 57.82 CH_2, 102.67 CH(C-5), 127.10 CH, 128.66 CH, 130.28 CH, 138.12 C, 163.11 C, 165.57 C.

HRMS (EI) calcd for $C_{21}H_{24}N_4$ (M^+) 332.20010, found 332.20014.

7.7.3.2 To introduce 2-dimethylamino-ethoxy group

[2-(4,6-Diphenyl-pyrimidin-2-yloxy)-ethyl]-dimethylamine (**263**)

A mixture of 2-chloro-4,6-diphenylpyrimidine **240a** (107 mg, 0.4 mmol) and t-BuOK (56 mg, 0.5 mmol) in 2-(dimethylamino)-ethanol 3 ml was heated at 110 °C for 16 h, then evaporated to dryness in high vacuum, the residue was dissolved in 20 ml 2 N HCl, and washed with dichloromethane (2 × 20 ml), the aqueous layer was basified with solid potassium carbonate (pH > 10), then extracted with dichloromethane (4× 20 ml), the organic phase was dried with anhydrous $MgSO_4$, evaporated the solvent, and provided a yellow glass 38 mg, yield 30 %.



^{1}H-NMR ($CDCl_3$), δ(ppm): 2.35 (s, 6 H, CH_3), 2.84 (t, 2 H, J = 6.0 Hz, CH_2), 4.62 (t, 2 H, J = 6.0 Hz, CH_2), 7.41-7.44 (m, 6 H, Ph-H), 7.70 (s, 1 H, H-5), 8.08 (dd, 4 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 45.81 CH_3, 57.83 CH_2, 65.01 CH_2, 106.65 CH(C-5), 127.30 CH, 128.83 CH, 130.98 CH, 136.87 C, 165.64 C, 167.05 C.

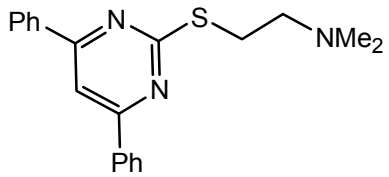
HRMS (EI) calcd for $C_{20}H_{21}N_3O$ (M^+) 319.16846, found 319.16852.

7.7.3.3 To introduce 2-dimethylamino-ethylsulfanyl group

General procedure:

A 50 ml flask was charged with appropriate 2-chloro-4,6-diarylpyrimidine (0.4 mmol), 2-(dimethylamino)-ethanethiol hydrochloride (N, N-dimethylamino-2-mercaptoethyl ammonium chloride) (63 mg, 0.42 mmol), sodium hydroxide (40 mg, 1.0 mmol) and ethanol 20 ml. The mixture was refluxed overnight (16 h), evaporated the solvent, 30 ml water was added, and neutralized the mixture with 2 N HCl. The mixture was extracted dichloromethane (3 × 30 ml), washed with water 30 ml, the organic phase was dried with anhydrous magnesium sulphate, evaporated the solvent, the residue was column chromatography on silica gel.

[2-(4,6-Diphenyl-pyrimidin-2-ylsulfanyl)-ethyl]-dimethylamine (**261a**)

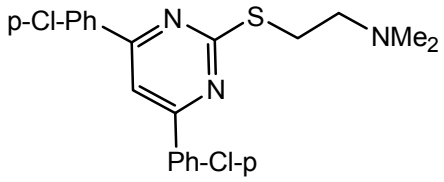


Eluting with ethyl acetate: methanol (9:1) to provide light yellow solid 47 mg, yield: 35 %, mp. 86-8 °C;

^{1}H-NMR ($CDCl_3$), δ(ppm): 2.30 (s, 6 H, CH_3), 2.71 (t, 2 H, *J* = 7.5 Hz, CH_2), 3.35 (t, 2 H, *J* = 7.5 Hz, CH_2), 7.42-7.43 (m, 6 H, Ph-H), 7.68 (s, 1 H, H-5), 8.05 (dd, 4 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 28.52 CH_2, 45.33 CH_3, 58.80 CH_2, 107.98 CH(C-5), 127.20 CH, 128.84 CH, 130.95 CH, 136.78 C, 164.75 C, 172.06 C.

HRMS (EI) calcd for $C_{20}H_{21}N_3S$ (M^+) 335.14562, found 335.14558.

{2-[4,6-Bis-(4-chloro-phenyl)-pyrimidin-2-ylsulfanyl]-ethyl}-dimethylamine (**261b**)



Eluting with ethyl acetate: methanol (10:1) to provide light yellow solid 54 mg, yield 33 %, mp 131-2 °C;

^{1}H-NMR($CDCl_3$), δ(ppm): 2.29 (s, 6 H, CH_3), 2.69 (t, 2 H, *J* = 7.5 Hz,CH_2), 3.34 (t, 2 H, *J* = 7.5 Hz,CH_2), 7.40 (dd, 4 H, Ph-H), 7.60 (s, 1 H, H-5), 8.00 (dd, 4 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ (ppm): 28.68 CH_2, 45.37 CH_3, 58.71 CH_2, 107.38 CH(H-5), 128.52 CH, 129.18 CH,135.04 C, 137.34 C, 163.70 C, 172.49.

HRMS (EI) calcd for $C_{20}H_{19}Cl_2N_3S$ (M^+): 403.06767, found 403.06746.

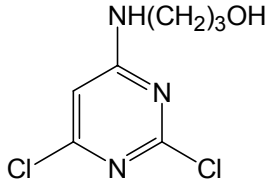
7.7.3.4 To introduce 3-hydroxypropylamino group

A solution of 2,4,6-trichloropyrimidine (1.83 g, 10 mmol) in THF (10ml) was added dropwise to a stirred solution of propanlamine (1.50 g, 20 mmol) in THF 20ml at room temperature. The

turbid mixture was allowed to stir at room temperature overnight (about 16 h). The solvent was removed by evaporation under vacuum to give a white solid. The crude product was separated by flash chromatograph on silica gel.

3-(2,6-Dichloro-pyrimidin-4-ylamino)-propan-1-ol (**264b**)

264b was eluted with hexane:ethyl acetate (1/2), a white solid 0.882 g was obtained, yield 40 %, mp 91-2 °C.



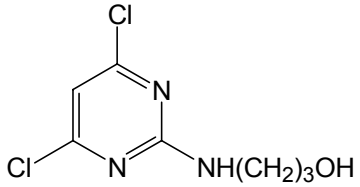
264b

^{1}H-NMR($CDCl_3$), δ(ppm): 1.81-1.90 (m, 2 H, CH_2), 3.49-3.56(m, 2 H, CH_2), 3.63-3.68 (m, 2H, CH_2), 4.85 (t, 1 H, *J* = 4.7 Hz, NH), 6.69(s, 1 H, H-6), 8.39 (br, 1 H, OH).
^{13}C-NMR($CDCl_3$), δ(ppm): 31.52 CH_2, 37.76 CH_2, 58.26 CH_2, 102.70 CH(C-6), 156.74 C, 159.17 C, 164.12 C.

Anal. Calcd. for $C_7H_9Cl2N2O$ (222.08): C, 37.86; H, 4.08; Cl, 31.93; N, 18.92.
Found: C, 38.02; H, 4.03; Cl, 31.69; N, 18.95.

3-(4,6-Dichloro-pyrimidin-2-ylamino)-propan-1-ol (**264a**)

264a was eluted with ethyl acetate, a white solid 1.089 g was obtained, yield 49 %, mp 118-9 °C.



264a

^{1}H-NMR($CDCl_3$), δ(ppm): 1.36-1.45 (m, 2 H, CH_2), 3.00-3.06(m, 2 H, CH_2), 3.17-3.23 (m, 2 H, CH_2), 4.36 (t, 1 H, *J* = 4.9 Hz, NH), 6.57(s, 1 H, H-6), 7.81 (br, 1 H, OH).
^{13}C-NMR($CDCl_3$), δ(ppm): 31.63 CH_2, 38.30 CH_2, 58.49 CH_2, 107.23 CH(C-6), 160.80 C, 161.50 C.

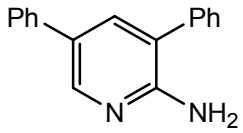
Anal. Calcd. for $C_7H_9Cl2N2O$ (222.08): C, 37.86; H, 4.08; Cl, 31.93; N, 18.92.
Found: C, 38.10; H, 4.08; Cl, 31.99; N, 19.04.

7.8 Synthesis of pyridine derivatives

7.8.1 Synthesis of 2-amino-3,5-diphenylpyridine (283):

2-Amino-3,5-dibromopyridine (2.52 g, 10.0 mmol) and phenylboronic acid (2.53 g, 21.0 mmol) were dissolved in methanol (20 ml). Na_2CO_3 (25 g, 0.24 mol) in water (50 ml) and then toluene (100 ml) were added, and the suspension was degassed with evaporating for 10 min and then passing Argon. Pd $(PPh_3)_2Cl_2$ (177 mg, 0.25 mmol) was then added, and the mixture was heated under reflux under argon with vigorous stirring for 66 h. The organic solvents were removed under reduced pressure, followed by extraction with ethyl acetate (3 × 50 ml), washed with water (2 × 50 ml), and dried with anhydrous $MgSO_4$, evaporated the solvents, the residue

was separated with column chromatography on silica (eluting with diethyl ether) and provide 1.37 g light brown solid, yield: 53 %, mp 106 °C.

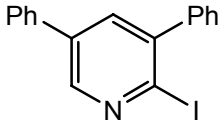


^{1}H-NMR($CDCl_3$), δ(ppm): 4.83 (s, 2 H, NH_2), 7.39-7.64 (m, 10 H, Ph-H), 7.69 (d, 1 H, *J* = 2.3 Hz, H-4), 7.81 (d, 1 H, *J* = 2.3 Hz, H-6).
^{13}C-NMR($CDCl_3$), δ(ppm): 121.74 C, 126.29 CH, 126.94 CH, 127.86 CH, 127.94 CH, 128.76 CH, 128.93 CH, 129.18 CH, 136.60 CH(C-4), 137.98 C, 138.20 C, 145.48 CH(C-6), 155.21 C.

Anal. Calcd. for $C_{17}H_{14}N_2$ (246.30): C, 82.90; H, 5.73; N, 11.37.
Found: C, 82.83; H, 5.93; N, 11.41.

7.8.2 Synthesis of 2-iodo-3,5-diphenylpyridine (284):

Aminopyridine **283** (1.00 g, 4.0 mmol) was dissolved in CH_2I_2 (13 ml), aided by ultrasound. *tert*-Butyl nitrite (0.65 g, 6.0 mmol) and I_2 (1.02 g, 4.0 mmol) were then added, and the reaction mixture was stirred at room temperature for 24 h under exclusion of light. To complete the reaction (TLC monitoring), additional of *tert*-butyl nitrite (0.32 g 3.0 mmol) was added and the mixture was stirred for further 12 h. The reaction was stopped by addition of 30 ml of satd. Na_2CO_3 solution and an excess of solid $Na_2S_2O_3$. The solvents were evaporated to dryness under reduced pressure, followed by addition of 40 ml water and extraction with ethyl acetate (3 × 40 ml). The combined organic layers were dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel, eluting with cyclohexane:ethyl acetate (10:1-3:1), to provide 660 mg light brown solid, yield 46 %, mp 86-7 °C.

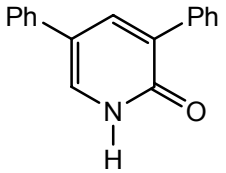


^{1}H-NMR ($CDCl_3$), δ(ppm*):* 7.31-7.44 (m, 10 H, Ph-H), 7.54 (d, 1 H, *J* = 2.6 Hz, H-4), 8.43 (d, 1 H, *J* = 2.6 Hz, H-4).
^{13}C-NMR ($CDCl_3$), δ(ppm): 120.77 C, 127.08 CH, 128.40 CH, 128.53 CH, 128.67 CH, 129.31 CH, 129.38 CH, 135.39 CH(C-4), 136.05 C, 136.27 C, 141.36 C, 144.05 C, 147.46 CH(C-6).

Anal. Calcd. for $C_{17}H_{12}IN$ (357.19): C, 57.16; H, 3.39; I, 35.53; N, 3.93.
Found: C, 57.48; H, 3.60; I, 35.30; N, 3.98.

3,5-Diphenyl-1H-pyridin-2-one (**285**):

Further elution of the crude product described above with ethyl acetate, 161 mg light yellow solid was obtained, yield: 16 %, mp 192-3 °C.

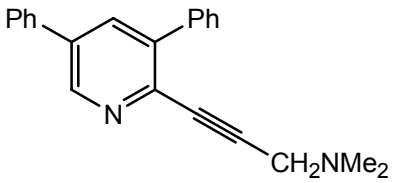


^{1}H-NMR($CDCl_3$), δ(ppm): 7.30-7.46(m, 8H, Ph-H), 7.62(d, 1H, J=2.6Hz, H-4), 7.76-7.79(dd, 2H, J=5.4Hz, Ph-H), 7.90(d, 1H, J=2.6Hz, H-6), 13.63(s, 1H, N-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 121.32 C, 125.83 CH, 127.35 CH, 128.03 CH, 128.41 CH, 128.63 CH, 129.10 CH, 131.29 CH(C-4), 131.35 C, 136.49 C, 139.50 CH(C-6), 163.45 C.

Anal. Calcd. for $C_{17}H_{13}NO$ (247.29): C, 82.57; H, 5.30; N, 5.66.
Found: C, 82.68; H, 5.42; N, 5.57.

7.8.3 Synthesis of 3-(3,5-diphenyl-pyridin-2-yl)-prop-2-ynyl]-dimethylamine(286):

2-Iodo-3,5-diphenylpyridine **284** (250 mg, 0.7 mmol) CuI (13 mg, 0.10 equiv.), $Pd(PPh_3)_2Cl_2$ (25 mg, 0.05 equiv), N,N-dimethyl-propargylamine (116 mg, 1.4 mmol 2 equiv) was suspended in triethylamine (10 ml) and pass the Argon, the suspension was stired at room temperature 24 hours, The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (ethyl acetate:methanol 6:1) and provided 196 mg of **286** as a brown crystal yield, 89 %, mp 82-83 °C.



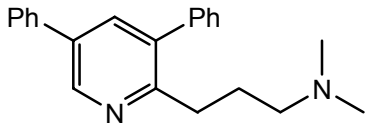
^{1}H-NMR($CDCl_3$), δ(ppm): 2.08 (s, 6 H, CH_3), 3.35 (s, 2 H, CH_2), 7.28-7.51 (m, 10 H, Ph-H), 7.74 (d, 1H, *J* = 1.8 Hz, H-4), 8.70 (d, 1 H, *J* = 1.8 Hz, H-6).
^{13}C-NMR ($CDCl_3$), δ(ppm): 44.00 CH_3, 48.47 CH_2, 84.68 C, 88.34 C, 127.07 CH, 128.12 CH, 128.29 CH, 128.42 CH, 129.16 CH, 129.26 CH, 135.06 CH(C-4), 135.54 C, 136.95 C, 138.29 C, 139.60 C, 139.84 C, 146.97 CH(C-6).

HRMS (EI) calcd for $C_{22}H_{20}N_2$ (M^+) 312.16265, found 312.16260.

Anal. Calcd. for $C_{22}H_{20}N_2$ (312.41): C, 84.58; H, 6.45; N, 8.97.
Found: C, 84.52; H, 6.50; N, 8.94.

7.8.4 Synthesis of 3,5-diphenyl-2-(3-dimethylaminopropyl)-pyridine (287):

A solution [3-(3,5-diphenyl-pyridin-2-yl)-prop-2-ynyl]-dimethylamine **286** (125 mg, 0.4 mmol) in ethanol (15 ml) and 10 % palladium on charcoal (89 mg, 0.08 mmol on Pd, 0.2 equiv) wase stirred under hydrogen at room temperature and atmosphere 16 hours. After complete conversion (TLC monitoring), the catalyst was filtered off through a pad of Celite, washed with ethyl acetate, the solvents were removed under reduced pressure, and the residue was purified by column chromatography on neutral Al_2O_3 gel (ethyl acetate and ethyl acetate:Methanol 10:1) to provide 90 mg of **287** as a light brown oil, yield 71%.



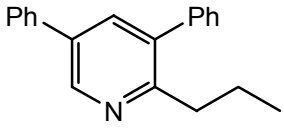
^{1}H-NMR($CDCl_3$), δ(ppm): 1.73-1.83 (m, 2 H, CH_2), 2.08 (s, 6 H, $2CH_3$), 2,20 (t, 2 H, *J* = 7.5 Hz, CH_2), 2.73 (t, 2 H, *J* = 7.9 Hz, CH_2), 7.26-7.52 (m, 10 H, Ph-H), 7.61 (d, 1 H, *J* = 2.3 Hz, H-4), 8.70 (d, 1 H, *J* = 2.3 Hz, H-6).
^{13}C-NMR ($CDCl_3$), δ(ppm): 27.39 CH_2, 33.08 CH_2, 45.02 CH_3, 59.26 CH_2, 127.00 CH, 127.59 CH, 127.90 CH, 128.47 CH, 129.04 CH, 129.08 CH, 133.86 C, 135.89 C, CH(C-4), 136.83 C, 137.59 C, 139.72 C, 146.45 CH(C-6), 157.97 C.

HRMS (EI) calcd for $C_{22}H_{24}N_2$ (M^+) 316.1940, found 316.1937.

Anal. Calcd. for $C_{22}H_{24}N_2$ (316.44): C, 83.50; H, 7.64; N, 8.85.
Found: C, 83.40; H, 7.80; N, 8.85.

3,5-Diphenyl-2-propylpyridine (**288**):

The crude product described above was purified by column chromatography on neutral Al_2O_3 gel, 17 mg of **288** was at first isolate (eluting with cyclohexane:ethyl acetate 1:1) as a light yellow liquid, yield 16 %.



^{1}H-NMR($CDCl_3$), δ(ppm): 0.80 (t, 3 H, *J*= 7.3 Hz, CH_3), 1.60-1.69 (m, 2 H, CH_2), 2.71 (t, 2H, *J* = 7.9 Hz, CH_2), 7.27-7.55 (m, 10 H, Ph-H), 7.63 (d, 1 H, *J* = 2.3 Hz, H-4), 8.72 (d, 1 H, *J* = 2.3 Hz, H-6).

^{13}C-NMR ($CDCl_3$), δ(ppm): 14.11 CH_3, 23.09 CH2, 37.16 CH_2, 127.02 CH, 127.50 CH, 127.87 CH, 128.39 CH, 129.04 CH, 129.12 CH, 133.69 C, 135.85 CH(C-4), 136.83 C, 137.70 C, 139.95 C, 146.43 CH(C-6). 158.42 C.

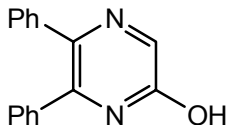
HRMS (EI) calcd for $C_{20}H_{19}N$ (M^+) 273.15175, found 273.15174.

7.9 Synthesis of pyrazine derivatives

7.9.1 Synthesis of 5-chloro-2,3-diphenylpyrazine

5-Chloro-2,3-diphenylpyrazine was chosen as the starting diphenyl-haloheterocycle, 2-hydroxy-5,6-diphenylpyrazine was prepared at first.

2-Hydroxy-5,6-diphenylpyrazine (**296**)

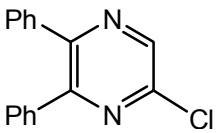


To a stirring and refluxing mixture of glycine amide hydrochloride 6.6 g (0.06 mol) and benzyl 12.6g (0.06 mol) in 150 ml methanol, a solution of 12 N aq. NaOH 9.6 ml (0.12 mol) was added dropwise over 20 min, the mixture was continue refluxing for 2 h and cooled, treated with 12 N hydrochloric acid 7.5 ml, follow by 6 g solid $KHCO_3$, the yellow solid was filtered off, washed well with water and methanol, dried in air, recrystallized from butanol, and provided a yellow solid 10.56 g, yield 71 %, mp 225-7°C.

^{1}H-NMR(DMSO-d_6), δ(ppm): 7.21-7.34 (m, 10 H, Ph-H), 8.13 (s, 1 H, H-3), 12.23 (s, 1 H, N-H)
^{13}C-NMR(DMSO-d_6), δ(ppm): 117.84 C, 127.04 CH, 127.68 CH, 128.05 CH, 128.78 CH, 129.03 CH, 129.43 CH, 137.75 C, 156.68 C.

Anal. Calcd. for $C_{16}H_{12}N_2O$ (248.28): C, 77.40; H, 4.87; N, 11.28.
Found: C, 77.24; H, 4.94; N, 11.20.

5-Chloro-2,3-diphenylpyrazine (**297**)



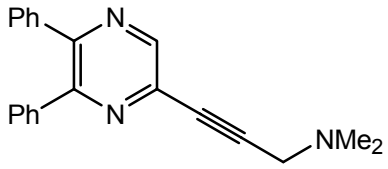
A solution of 2-hydroxy-5,6-diphenylpyrazine **296** (5.0 g, 0.02 mol), phosphoryl chloride 20 ml, and one drop of sulphuric acid was refluxed for 16 h, after cooled, the mixture was poured slowly onto 200 g chopped ice, stirred to complete hydrolysis, then the mixture was neutralized with 28 % ammonia while keeping it below 10°C, the mixture was extracted with chloroform (3 × 50 ml), the extract was dried with anhydrous $MgSO_4$, evaporated the solvent, the crude product was recrystallized with methanol, and provided a light yellow solid 4.94 g, yield 93 %, mp 124-5 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 7.30-7.47 (m, 10 H, Ph-H), 8.60 (s, 1 H, H-6).
^{13}C-NMR ($CDCl_3$), δ(ppm): 128.38 CH, 128.40 CH, 128.96 CH, 129.23 CH, 129.59 CH, 129.74 CH, 137.11 C, 137.47 C, 141.58 CH(C-6), 146.45 C, 150.78 C, 152.22 C.

Anal. Calcd. for $C_{16}H_{11}Cl\,N_2$ (266.72): C, 72.05; H, 4.16; Cl, 13.29; N, 10.50.
Found: C, 72.05; H, 4.24; Cl, 13.33; N, 10.56.

7.9.2 Synthesis of [3-(5,6-diphenyl-pyrazin-2-yl)-prop-2-ynyl]-dimethylamine (**298**):

A 25 ml schlenk flask was charged with 5-chloro-2,3-diphenylpyrazine **297** 267 mg (1.0 mmol), $Pd(PPh_3)_2Cl_2$ 36 mg (0.05 mmol), CuI 20 mg (0.1mmol), KOAc 147 mg (1.5 mmol), DMF 5 ml and N,N-dimethylpropargylamine 125 mg (1.5 mmol), Argon was passed and the mixture was heated at 100 °C for 24 h, DMF was evaporated in vacuum, the residue was purified by column chromatography on neutral Al_2O_3 gel, eluting with cyclohexane:ethyl acetate (1/1) to give 165 mg light brown oil 163 mg, yield 52 %.



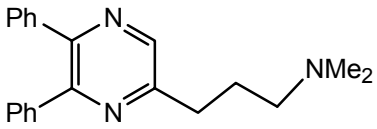
^{1}H-NMR($CDCl_3$), δ(ppm): 2.31 (s, 6 H, $2CH_3$), 3.48 (s, 2 H, CH_2), 7.18-7.37 (m, 10 H, Ph-H), 8.58 s, 1 H, H-3)
^{13}C-NMR($CDCl_3$), δ(ppm): 44.42 CH_3, 48.61 CH_2, 82.49 C, 89.23 C, 128.27 CH, 128.82 CH, 128.86 CH, 129.64 CH, 129.74 CH, 136.95 C, 138.10 C, 138.13 C, 144.73 CH(C-3), 150.81 C, 152.30 C.

HRMS (EI) calcd for $C_{21}H_{19}N_3$ (M^+) 313.1579, found 317.1576.

Anal. Calcd. for $C_{21}H_{19}N_3$(313.40): C, 80.48; H, 6.11; N, 13.41.
Found: C, 80.65; H, 6.30; N, 13.37.

7.9.3 Synthesis of [3-(5,6-diphenyl-pyrazin-2-yl)-propyl]-dimethylamine (**299**):

A solution 3-(5,6-diphenyl-pyrazin-2-yl)-prop-2-ynyl]-dimethylamine **298** (84 mg, 0.27 mmol) in ethanol (15 ml) and 10 % palladium on charcoal (67 mg, 0.06 mmol on Pd, 0.2 equiv) was stirred under hydrogen at room temperature and atmosphere 16 hours. After complete conversion (TLC monitoring), the catalyst was filtered off through a pad of Celite, washed with ethyl acetate, the solvents were removed under reduced pressure, and the residue was purified by column chromatography on neutral Al_2O_3 gel eluting with ethyl acetate:methanol 10:1) to provide 58 mg of brown oil, yield, 58 %.



^{1}H-NMR($CDCl_3$), δ(ppm): 1.89-1.99 (m, 2 H, CH_2), 2.18 (s, 6 H, $2CH_3$), 2.32 (t, 2 H, *J* = 7.3 Hz, CH_2), 2.86 (t, 2 H, *J* = 7.7Hz, CH_2),7.20-7.36 (m, 10 H, Ph-H), 8.40 (s, 1 H, H-3).
^{13}C-NMR($CDCl_3$), δ(ppm): 27.31 CH_2, 32.84 CH_2, 45.49 CH_3, 59.09 CH2, 128.21 CH, 128.31 CH, 128.47 CH, 129.60 CH, 129.74 CH, 138.75 C, 138.85 C, 141.60 CH(C-3), 149.96 151.62 C, 154.54 C.

HRMS (EI) calcd for $C_{21}H_{23}N_3$ (M^+) 317.1892, found 317.1890.

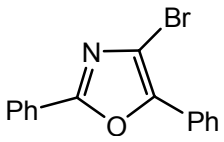
Anal. Calcd. for $C_{21}H_{23}N_3$(317.43): C, 79.46; H, 7.30; N, 13.24.
Found: C, 79.66; H, 7.46; N, 13.12..

7.10 Synthesis of oxazole derivatives

7.10.1 Synthesis of 4-bromo-2,5-diphenyloxazole (**310**):

To a solution of 2,5-diphenyloxazole (2.21 g, 10 mmol), NBS (2.14 g, 12 mmol), in CCl4 20 ml, a few (5~6) drops of hydrobromic acid was added as catalyst, the mixture was heated at reflux for 4 hours, cooled and filtered, the filtrate was evaporate, the crude product was purified by recrystallization from methanol, and provide white solid 1.30 g, yield 43 %, mp 64-5 °C.

4-Bromo-2,5-diphenyloxazole (**310**)



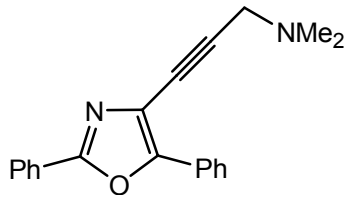
^{1}H-NMR($CDCl_3$), δ(ppm): 7.29-7.43 (m, 6 H, Ph-H), 7.93 (dd, 2 H, Ph-H), 8.00-8.03 (m, 2 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 112.72 C, 124.27 C, 125.39 CH, 126.37 CH, 127.03 C, 128.79 CH, 128.83 CH, 128.90 CH, 130.89 CH, 146.14 C, 160.07 C.

Anal. Calcd. for $C_{15}H_{10}BrNO$(300.15): C, 60.02; H,3.36; Br, 26.62, N, 4.67.
Found: C, 60.13; H, 3.52; Br, 25.81; N, 4.77.

7.10.2 Synthesis of 4-alkyl-2,5-diphenyloxazole by Sonogashira reactions

[3-(2,5-Diphenyl-oxazol-4-yl)-prop-2-ynyl]-dimethylamine (**311**)

A 25ml flask was charged with 4-bromo-2,5-diphenyloxazole (150 mg, 0.5 mmol), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), CuI (10mg, 0.05mmol), TEA 5 ml**,** DMF 5 ml and N,N-dimethylpropargylamine (83 mg, 1.0 mmol), Argon was passed and the mixture was heated at 100 °C for 24 h, the solvent was evaporated in vacuum, the residue was purified by column chromatography on silica gel, eluting with ethyl acetate: methanol (6/1), and provided a brown glass material 63 mg, yield 42 %. When using TEA as base and solvent and reacted at 80 °C 24 h, **311** was isolated in 10 %, When using KOAc as base and DMF as solvent and reacted at 100 °C 24 h, **311** was isolated in 66 %.



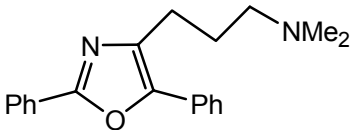
^{1}H-NMR($CDCl_3$), δ(ppm): 2.35 (s, 6 H, CH_3), 3.58 (s, 2 H, CH_2), 7.37-8.02 (m, 10 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 44.07 CH_3, 48.62 CH_2, 77.86 C, 91.06 C, 119.23 C, 124.99 CH, 126.55 CH, 128.79 CH, 128.97 CH, 130.79 CH, 132.01 CH, 133.08 C, 135.18 C, 151.78 C, 159.64 C.

HRMS (EI) calcd for $C_{20}H_{18}N_2O$ (M^+) 302.14191, found 302.14193.

[3-(2,5-Diphenyl-oxazol-4-yl)-propyl]-dimethylamine (**312**)

A solution [3-(2,5-diphenyl-oxazol-4-yl)-prop-2-ynyl]-dimethylamine(112 mg, 0.37 mmol) in ethanol (15 ml) and 10 % palladium on charcoal (83 mg, 0.074 mmol on Pd, 0.2 equiv) was stirred under hydrogen at room temperature and atmosphere 16 h. After complete conversion (TLC monitoring), the catalyst was filtered off through a pad of Celite, washed with ethyl acetate, the solvents were removed under reduced pressure, and the residue was purified by

column chromatography on neutral Al_2O_3 gel, eluting with cyclohexane:ethyl acetate(1:1) to provide 66 mg of brown oil, yield, 58 %.



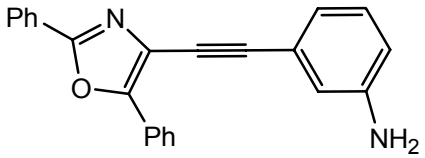
313

^{1}H-NMR($CDCl_3$), δ(ppm): 1.78-1.88 (m, 2 H, CH_2), 2.09(s, 6 H, CH_3), 2.25 (t, 2 H, *J* = 7.4 Hz, CH_2), 2.70 (t, 2 H, *J* = 7.7 Hz, CH_2),7.17-7.95 (m, 10 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 25.06 CH_2, 26.81 CH_2, 45.49 CH_3, 59.16 CH_2, 125.59 CH, 126.28 CH, 127.57 C, 127.71 CH, 128.73 CH, 128.81 CH, 129.13 C, 130.11 CH, , 133.08 C, 137.54 C, 145.39 C, 159.53 C.

HRMS (EI) calcd for $C_{20}H_{22}N_2O$ (M^+) 306.17321, found 306.17321.

Synthesis of 3-(2,5-diphenyl-oxazol-4-ylethynyl)-phenylamine (**313**)

A 25 ml flask was charged with 4-bromo-2,5-diphenyloxazole (150 mg, 0.5 mmol), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), CuI (10 mg, 0.05mmol), TEA 5 ml**,** and 3-ethynyl-phenylamine (117 mg, 1.0 mmol), Argon was passed and the mixture was heated at 80 °C for 24 h, the solvent was evaporated in vacuum, the residue was purified by column chromatography on silica gel, eluting with cyclohexane:ethyl acetate(2/1), and gave a light yellow solid 125 mg, yield 74 %, mp 195-6 °C.



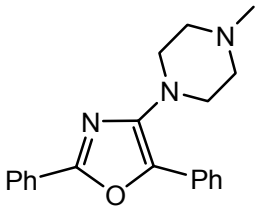
^{1}H-NMR($CDCl_3$), δ(ppm): 3.74 (s, 2 H, NH_2), 6.69-6.72 (dd, 1 H, *J* = 8.8 Hz, Ph-H), 6.93 (t, 1 H, *J* = 1.9 Hz, Ph-H), 7.17 (t, 1 H, *J* = 7.9 Hz, Ph-H), 7.39 (t, 1 H, Ph-H), 7.47-7.52 (m, 5 H, Ph-H), 8.13-8.16 (m, 4 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 80.88 C, 95.66 C, 115.89 CH, 117.74 CH, 119.68 C, 122.13 CH, 123.22 C, 125.06 CH, 126.61 CH,126.71 C, 127.75 C, 128.84 CH, 128.97 CH, 129.39 CH, 130.81 CH, 146.37 C, 151.87 C, 159.81 C.

Anal. Calcd. for $C_{23}H_{16}N_2O$ (336.39): C, 82.12; H,4.79; N,8.33.
Found: C, 81.94; H, 4.90; N, 8.19.

7.10.3 Buchwald-hartwig amination of 4-bromo-2,5-diphenyloxazole

Synthesis of 1-(2,5-diphenyl-oxazol-4-yl)-4-methyl-piperazine (**314**):

A schlenk 25 ml flask was charge with 4-bromo-2,5-diphenyloxazole **310** (150 mg, 0.5 mmol), $Pd_2(dba)_3$ (10 mg, 0.01 mmol), BINAP (19 mg, 0.03 mmol), t-BuONa (68 mg, 0.7 mmol), 4-methyl-piperazine (100 mg, 1.0 mmol), dry toluene 5 ml, Argon was passed three times and the mixture was heated at 110 °C for 20 h, evaporated the solvent, the residue was purified by column chromatography on neutral Al_2O_3 gel, eluting with ethyl acetate, and get light yellow solid 22 mg, yield 14 %, mp 110-2 °C;



^{1}H-NMR($CDCl_3$), δ(ppm): 2.38 (s, 3 H, CH_3), 2.60 (t, 4 H, J = 4.8 Hz, CH_2), 3.20 (t, 4 H, J = 4.8 Hz, CH_2), 7.23-7.45 (m, 6 H, Ph-H), 7.84 (dd, 2 H, J_1 = 8.2Hz, J_2 = 1.0 Hz, Ph-H), 8.06 (dd, 2 H, J_1 = 8.4 Hz, J_2 = 1.5 Hz, Ph-H),
^{13}C-NMR ($CDCl_3$), δ(ppm): 46.38 CH_3, 50.20 CH_2, 55.28 CH_2, 124.45 CH, 126.15 CH, 126.74 CH, 127.70 C, 128.56 CH, 128.67 CH, 129.35 C, 129.97 CH, 135.93 C, 146.61 C, 157.54.

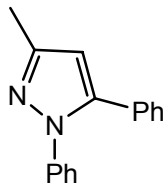
HRMS (EI) calcd for $C_{20}H_{21}N_3O$ (M^+) 319.16846, found 319.16845.

7.11 Synthesis of Pyrazole derivatives

7.11.1 Synthesis of 4-iodo-3-methyl-1,5-diphenylpyrazole

4-Iodo-3-methyl-1,5-diphenylpyrazole was started from 3-methyl-1,5-diphenylpyrazole.

3-Methyl-1,5-diphenylpyrazole (**320**)



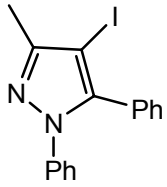
A 250ml flask was charged with phenylhydrazine (6.68 g, 0.06mol), sodium acetate (3.28 g, 0.04mol), benzoylacetone (9.74 g, 0.06mol), ethanol 80 ml and water 40 ml, the mixture was heated at reflux for 3 h and concentrated the solvent in vacuum, 40 ml ether and 40 ml water were added inside the flask, separated, the aqueous layer was extracted with ether (40 2 × 40

ml), the combined extracts were washed with 1 N NaOH 30 ml, brine 30 ml, and dried with anhydrous $MgSO_4$, the solvent was evaporated in vacuum and provided an orange oil 13.03 g, yield 93 %.

^{1}H-NMR($CDCl_3$), δ(ppm): 2.56 (s, 3 H, CH_3), 6.48 (s 1 H, H-4), 7.39-7.46 (m, 10 H, Ph-H).
^{13}C-NMR($CDCl_3$), δ (ppm): 13.63 CH_3, 107.79 CH(C-4), 125.13 CH, 127.09 CH, 128.08 CH, 128.42 CH, 128.65 CH, 128.86 CH, 130.77 C, 140.19 C, 143.69 C, 149.45 C.

HRMS (EI) calcd for $C_{16}H_{14}N_2(M^+)$ 234.11570, found 234.11575.

4-Iodo-3-methyl-1,5-diphenylpyrazole (**321**)



A 100ml flask was charged with 4-methyl-1,2-diphenylpyrrole **320** (2.34 g,10 mmol), 50 ml DMF, the solution was cooled to 0 °C and passed Argon, NIS (2.70 g, 12 mmol) was added and stirred at room temperature overnight (16 h), then the solution cooled again to 0°C, NIS (0.13 g, 0.5 mmol) was added and continue to stir at RT for another 12 h, 250 ml water was added inside, the mixture was extracted with ether (2 × 120 ml), ethyl acetate 100 ml and hexane 100 ml, the combined extract was washed with water 50 ml, 10 % aq. $Na_2S_2O_3$ 50ml, water 50 ml, and dried with anhydrous $MgSO_4$, the solvent was concentrated and provided a brown solid 2.12 g, yield 59 %, mp 94-6 °C.

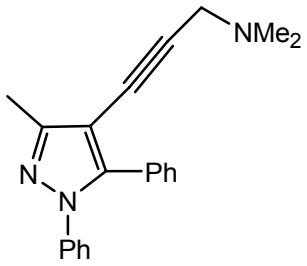
^{1}H-NMR($CDCl_3$), δ(ppm): 2.33 (s, 3 H, CH_3), 7.08-7.19 (m, 10 H, Ph-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 14.39 CH_3, 66.23 C, 124.64 CH, 127.27 CH, 128.27 C, 128.44 CH, 128.79 CH, 128.85 CH, 130.15 CH, 139.93 C, 144.02 C, 151.64 C.

HRMS (EI) calcd for $C_{16}H_{13}IN_2$ (M^+) 360.01235, found 360.01241.

7.11.2 Dimethyl-[3-(3-methyl-1,5-diphenyl-pyrazol-4-yl)-prop-2-ynyl]-amine (**322**)

A 25ml Schlenk flask was charged with 4-Iodo-3-methyl-1,5-diphenylpyrazole (320 mg, 1.0 mmol), K_2CO_3 (332 mg, 2.4 mmol), CuI (20 mg, 0.1 mmol), 10 % Pd/C (44 mg, 0.04 mmol), and PPh_3 (42 mg, 0.16 mmol) in DME (10 ml) and water (10 ml). Argon was passed through the flask 3 times and the mixture was stirred at 25 °C for 0.5 h, then N,N-dimethylpropargyl amine 100 mg (1.2 mmol) was added. After refluxing under argon for 24 h the mixture was

cooled to 25 °C and filtered through a pad of Celite. After washing with EtOAc, the combined crude solution was washed with water (50 mL) twice. The organic layer was dried with anhydrous $MgSO_4$, concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel, eluting with EtOAc:MeOH(1:0→6:1) and provided a light brown solid 306 mg, yield 97 %, mp 66-7 °C.

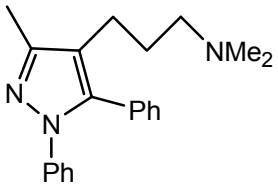


^{1}H-NMR($CDCl_3$), δ(ppm) : 2.23 (s, 6 H, CH_3), 2.36 (s, 3 H, CH_3), 3.40 (s, 2 H; CH_2), 7.14-7.61 (m, 10 H, Ph-H).
^{13}C-NMR($CDCl_3$), δ (ppm): 12.65 CH_3, 44.01 CH_3, 48.73 CH_2, 88.05 C, 104.10 C, 125.04 CH, 127.32 CH, 128.26 CH, 128.50 CH, 128.89 CH, 129.39 CH,132.02 C, 133.24 C, 139.75 C, 144.21 C, 151.95 C.

Anal. Calcd. for $C_{21}H_{21}N_3$: C, 79.97; H, 6.71; N, 13.32.
Found: C, 80.12; H, 6.72; N, 13.15.

7.11.3 Dimethyl-[3-(3-methyl-1,5-diphenyl-pyrazol-4-yl)-propyl]-amine (**323**)

A solution dimethyl-[3-(3-methyl-1,5-diphenyl-pyrazol-4-yl)-prop-2-ynyl]-amine **322** (158 mg, 0.5 mmol) in ethanol (15 ml) and 10 % palladium on charcoal (111 mg, 0.1 mmol on Pd, 0.2 equiv) was stirred under hydrogen at room temperature and atmosphere 16 h. After complete conversion (TLC monitoring), the catalyst was filtered off through a pad of Celite, washed with ethyl acetate, the solvents were removed under reduced pressure, and the residue was purified by column chromatography on neutral Al_2O_3 gel, eluting with ethyl acetate:methanol (10:1) to give 122 mg of brown oil, yield, 76 %.



^{1}H-NMR($CDCl_3$), δ(ppm): 1.48-1.58 (m, 2 H, CH_2), 2.06 (s, 3 H, CH_3), 2.12 (t, 2 H, J = 7.4 Hz, CH_2), 2.28 (s, 3 H, CH_3), 2.37 (t, 2 H, J = 7.9 Hz, CH_2), 7.07-7.62 (m,10 H, Ph-H).
^{13}C-NMR($CDCl_3$), δ(ppm): 12.19 CH_3, 21.30 CH_2, 28.91 CH_2, 45.39 CH_3, 59.44 CH_2, 119.42 C, 124.39 CH, 126.30 CH, 128.05 CH, 128.40 CH, 128.58, 129.80 CH, 131.12 C, 140.10 C, 140.39 C, 148.31 C.

HRMS (EI) calcd for $C_{21}H_{25}N_3$ (M^+) 319.2049, found 319.2046.

Anal. Calcd. for $C_{21}H_{25}N_3$ (319.44): C, 78.96; H, 7.89; N, 13.15.
Found: C, 78.83; H, 8.02; N, 13.07.

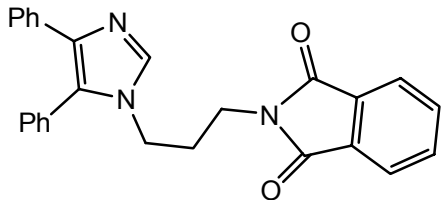
7.12 Synthesis imidazole derivatives

7.12.1 Nucleophilic substitution of 4,5-diphenylimidazole

Synthesis of 3-(4,5-diphenyl-imidazol-1-yl)-propylamine **335**

(**1**) 2-[3-(4,5-Diphenyl-imidazol-1-yl)-propyl]-isoindole-1,3-dione **334**

A mixture of 4,5-diphenylimidazole (440 mg, 2.0 mmol), N-3-bromopropylphthalimide (1.07 g, 4.0 mmol), cesium carbonate (1.30 g, 4.0 mmol) and DMF 15 ml was heated at 60 °C for 4 h, then the mixture was cooled and diluted with 30 ml water, the mixture was extracted with ethyl acetate (3 × 40 ml), the combined extract was washed with water (3 × 30 ml) and then brine 30 ml, the solution was dried with anhydrous sodium sulphate. Evaporated the solvent and the residue was purified by column chromatography on SiO_2 gel, eluting with ethyl acetate and ethylacetate: methanol(10/1) and provided a white solid 767 mg, yield 94 %, mp 109-110 °C.



334

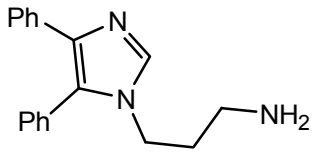
^{1}H-NMR($CDCl_3$), δ(ppm): 1.79-1.89 (m, 2 H, CH_2), 3.53 (t, 2 H, J = 6.6 Hz, CH_2), 3.79 (t, 2 H, J = 7.5 Hz, CH_2), 7.01-7.37 (m, 10 H, Ph-H), 7.61 (s, 1 H, H-2), 7.64-7.76 (m, 4 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 30.07 CH_2, 35.02 CH_2, 42.80 CH_2, 123.33 CH, 126.28 CH, 126.47 CH, 128.08 CH, 128.63 CH, 129.00 CH, 130.61 C, 130.68 CH, 131.86 C, 134.09 CH, 134.48 C, 136.72 CH(C-2), 138.38 C, 168.09 C(C=O).

HRMS (EI) calcd for $C_{26}H_{21}N_3O_2$ (M^+) 407.16338, found 407.16330.

(**2**) 3-(4,5-Diphenyl-imidazol-1-yl)-propylamine (**335**)

A soution of 2-[3-(4,5-diphenyl-imidazol-1-yl)-propyl]-isoindole-1,3-dione **334** (408 mg, 1.0 mmol) 80 % hydrazine hydrate (75 mg, 1.2 mmol), and ethanol 15 ml was heated at reflux for 8 h, then the solution was cooled, 4 N HCl solution 20 ml was added, and the solution was heated at reflux for 6 h, after cooled, the white precipitate was filtered away, the solution was

concentrated, the precipitate was removed again, then 30 ml water and excess Na_2CO_3 solid was added, the mixture was extracted with dichloromethane (4 × 30 ml), and dried the solution with anhydrous $MgSO_4$, evaporated the solvent and 235 mg white solid was obtained, yield 85 %, mp 42-4 °C.



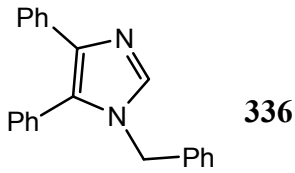
335

^{1}H-NMR($CDCl_3$), δ(ppm): 1.26 (m, 2 H, CH_2), 1.66 (t, 2 H, J = 6.8 Hz, CH_2), 2.58 (br, 2 H, NH_2), 3.89 (t, 2 H, J = 7.2 Hz, CH_2), 7.12-7.48 (m, 10 H, Ph-H), 7.63 (s, 1 H, H-2).
^{13}C-NMR($CDCl_3$), δ(ppm): 34.23 CH_2, 38.72 CH_2, 42.59 CH_2, 126.22 CH, 126.50 CH, 128.09 CH, 128.70 CH, 129.01 C, 129.10 CH, 130.80 CH, 130.84 C, 134.60 C, 136.78 CH(C-2), 138.13 C.

HRMS (EI) calcd for $C_{18}H_{19}N_3$ (M^+) 277.15790, found 277.15794.

7.12.2 Sonogashira cross-coupling of 1-benzyl-2-bromo-4,5-diphenylimidazole

1-Benzyl-4,5-diphenylimidazole (**336**)



336

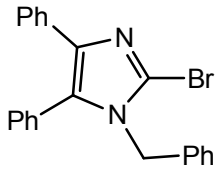
A mixture of 4,5-diphenylimidazole (6.61 g, 30 mmol), potassium carbonate (2.40 g, 17 mmol) and dry DMF 90 ml was passed with Argon, and heated to 80 °C, benzyl chloride (3.80 g, 30 mmol) was added inside slowly, then stirred over night (16 h), the solid was filtered away, and the solvent was evaporated, the crude product was purified by column chromatography on silica gel, eluting with ethyl acetate: hexane (2/1), and a white solid 8.68 g was obtained, yield 93 %, mp 112-4 °C.

^{1}H-NMR($CDCl_3$), δ(ppm): 4.96 (s, 2 H, CH_2), 6.94-7.50 (m, 15 H, Ph-H), 7.61(s, 1 H, H-2)
^{13}C-NMR($CDCl_3$), δ(ppm): 48.79 CH_2, 126.25 CH, 126.56 CH, 126.94 CH, 127.68 CH, 127.99 CH, 128.15 CH, 128.79 CH, 128.93 CH, 130.94 CH, 133.23 C, 134.45 C, 134.90 C, 136.50 C, 137.09 CH(C-2), 138.27 C.

Anal. Calcd. for $C_{22}H_{18}N_2$(310.39): C, 85.13; H, 5.85; N, 9.03
Found: C, 85.33; H, 5.99; N, 8.91

1-Benzyl-2-bromo-4,5-diphenylimidazole (**338**)

A 50 ml flask was charged 1-benzyl-4,5-diphenylimidazole **336** (1244 mg, 4.0 mmol) NBS (890 mg, 5.0 mmol) and CH_3CN 30 ml, the mixture was stirred at room temperature 2 h. The solvent was concentrated and the residue was purified by column chromatography on silica gel, eluting with ethyl acetate: hexane (1/6→1/2), and a yellow solid 929 mg was obtained, yield 60 %, mp 106-8 °C.



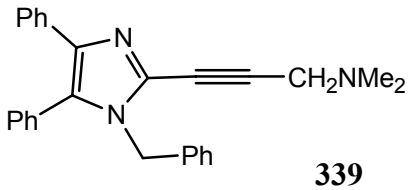
338

^{1}H-NMR($CDCl_3$), δ(ppm): 5.09 (s, 2 H, CH_2), 6.98-7.55 (m, 15 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 48.99 CH_2, 120.58 C(C-2), 126.34 CH, 126.51 CH, 126.76 CH, 127.71 CH, 128.15 CH, 128.71 CH, 129.02 CH, 129.17 CH, 130.24 C, 130.92 CH, 131.39 C, 133.52 C, 136.05 C, 139.17 C.

Anal. Calcd. for $C_{22}H_{17}BrN_2$(389.29): C, 67.88; H, 4.40; Br, 20.53; N, 7.20.
Found: C, 67.65; H, 4.59; Br, 20.80; N, 7.02.

[3-(1-Benzyl-4,5-diphenyl-imidazol-2-yl)-prop-2-ynyl]-dimethylamine (**339**)

A 25 ml schlenk flask was charged 1-benzyl-2-bromo-4,5-diphenylimidazole **338** (195 mg, 0.5 mmol), $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol), CuI (10 mg, 0.05 mmol), triethylamine 10 ml, and N, N-dimethylpropargylamine (83 mg, 1.0 mmol), Argon was passed three times and heated at 80 °C for 24 h. The mixture was concentrated, the residue was purified by column chromatography on neutral Al_2O_3 gel, eluting with ethyl acetate: hexane (1/3→1/1), and provided a brown oil 85 mg, yield 43 %. When using DMF as solvent and reacted at 100 °C 24 h, **339** was isolated in 27 % yield.



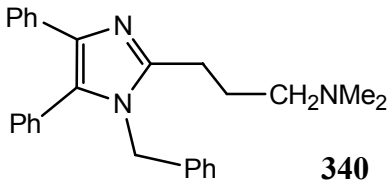
339

^{1}H-NMR($CDCl_3$), δ(ppm): 2.20 (s, 6 H, $2CH_3$), 3.49 (s, 2 H, CH_2), 5.09 (s, 2 H, CH_2), 6.88-7.48 (m, 15 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 43.98 CH_3, 48.34 CH_2, 48.42 CH_2, 75.58 C, 89.24 C, 126.57 CH, 126.65 CH, 126.75 CH, 126.92 C, 127.57 CH, 128.07 CH, 128.58 C, 128.77 CH, 128.92 CH, 130.28 C, 130.82 CH, 131.64 C, 133.86 C, 136.63 C, 138.49 C.

HRMS (EI) calcd for $C_{27}H_{25}N_3$ (M^+) 391.20485, found 391.20462.

[3-(1-Benzyl-4,5-diphenyl-imidazol-2-yl)-propyl]-dimethylamine (**340**)

A solution [3-(1-benzyl-4,5-diphenyl-imidazol-2-yl)-prop-2-ynyl]-dimethylamine **339** (70 mg, 0.18 mmol), ethanol (15 ml) and 10 % palladium on charcoal (40 mg, 0.036 mmol on Pd, 0.2 equiv) was stirred under hydrogen at room temperature and atmosphere 16 h. After complete conversion (TLC monitoring), the catalyst was filtered off through a pad of Celite, washed with ethyl acetate, the solvents were removed under reduced pressure, and the residue was purified by column chromatography on neutral Al_2O_3 gel, eluting with ethyl acetate to provide 45 mg of yellow oil, yield, 63 %.



340

^{1}H-NMR($CDCl_3$), δ(ppm): 1.92-2.02 (m, 2 H, CH_2), 2.19 (s, 6 H, $2CH_3$), 2,35 (t, 2 H, J = 7.8 Hz, CH_2), 2,70 (t, 2 H, J = 7.58 Hz, CH_2), 5.01 (s, 2 H, CH_2), 6.92-7.52 (m, 15 H, Ph-H).
^{13}C-NMR ($CDCl_3$), δ(ppm): 25.14 CH_2, 26.04 CH_2, 45.34 CH_3, 46.84 CH_2, 59.05 CH_2, 125.80 CH, 126.07 CH, 126.69 CH, 127.45 CH, 128.07 C, 128.47 CH, 128.78 CH, 128.87 CH, 130.98 CH, 132.43 C, 134.79 C, 136.70 C, 137.41 C, 148.28.

HRMS (EI) calcd for $C_{27}H_{29}N_3$ (M^+) 395.2362, found 395.2359.

References

1. Wang, J. H.; Desai, R. *Biochem. Biophys. Res. Commun.* **1976**, 72, 926-932.

2. Watterson, D. M.; Vanaman, T. C. *Biochem. Biophys. Res. Commun.* **1976**, 73, 40-46.

3. Rusnak, F.; Mertz, P. *Physiolog. Rev.* **2000**, 80, 1483-1521.

4. Loh, C.; Shaw, K. T. Y.; Carew, J.; Viola, J. P. B. *J. Biol. Chem.* **1996**, 271, 10884-10891.

5. Perrino, B. A.; Fong, Y. L.; Brickey, D. A. *J. Biol. Chem*. **1992**, 267, 15965-15969.

6. Lai, M. M.; Burnett, P. E.; Woloker, H.; Blackshaw, S.; Snyder, S. H. *J. Biol. Chem.* **1998**, 273, 18325-18331.

7. Kashishian, A.; Howard, M.; Loh, C. *J. Biol. Chem*. **1996**, 271, 10884-10891.

8 Sussman, M. A.; Lim, H. W.; Gude, N.; Taigen, T. *Science* **1998**, 281, 1690-1693.

9. Glynne, R.; Akkaraju, S.; Healy, J. I.; Bayner, J.; Coodnoow, C. C.; Mack, D. H. *Nature* **2000**, 403, 672-676.

10. Matin B. L.; Spannaus-Matin, D. J. *Biochem. Pharmacol.* **2000**, 60, 803-888.

11. Fischer, G.; Bang, H.; Mech, C. *Biomed. Biochim. Acta* **1984**, 43, 1101-1111.

12. Fischer, G.; Grabley, S.; Thiericke, R. *Drug Discovery from Nature*, Springer-Verlag **1999**, 257-280.

13. Liebscher, J.; Pätzel, M. *Synlett* **1994**, 471-478.

14. Pätzel, M.; Liebscher, J. *Synthesis* **1995**, 879-894.

15. Pätzel, M.; Knoll, A.; Steinke, T.; Löwis, M.; Liebscher, J. *J. Prakt. Chem.* **1993**, 335, 639-643.

16. (a) Karanik, M.; Pätzel, M.; Liebscher, J. *Synthesis* **2003**, 1201-1208. (b) Karanik, M. *Ph. D. Thesis,* **2004**, Humboldt University.

17. Brown, D. J.; Cowden, W. B.; Lan, S. B.; Mori, K. *Aust. J. Chem.* **1984**, 37, 155-163.

18. Diederich, F.; Stang. J. *Metal-catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weihein, Germany, **1998**.

19. Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, Chichester, UK, **1995**.

20. Malleron, J. L.; Fiaud, J. C.; Legros, J. Y. *Handbook of Palladium-Catalyzed Organic Reactions*, Academic Press, **1997**.

21. Tsuji, J. *Perspectives in Organopalladium Chemistry for the 21st Century*, Elsevier, **1999**.

22. Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, 103, 1875-1916.

23. Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules,* 2nd Ed., University Science Books, Mill Valley, USA, **1999**.

24. Negishi, E.; Baba, S. *J. Chem. Soc., Chem. Commun*. **1976**, 596-597.

25. Negishi, E. *Acc. Chem. Res*. **1982**, 15, 340-348

26. Erdric, E. *Tetrahedron* **1992**, 48, 9577-9648.

27. Sakamoto, T.; Nishimura, S.; Kondo, Y.; Yamanaka, H. *Synthesis* **1988**, 485-486.

28. Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, 100, 3636-8; **1979**, 101, 4992-4998.

29. Stile, J. K. *Angew. Chem., Int. Ed.* **1986**, 25, 508-524.

30. Farina, V.; Krishnamurphy, V.; Scott, W. *Organic Reactions* **1997**, 50, 1-652.

31. Sandosham, J.; Undheim, K. *Acta Chem. Scand.* **1989,** 43, 684-689.

32. Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, 95, 2457-2483.

33. Suzuki, A. *J. Organomet. Chem.* **1999**, 576, 147-168.

34. Chemler, S. R.; Trauner, D. *Angew. Chem. Int. Ed.* **2001**, 40, 4544-4568.

35. Thompson, W. J.; Gaudino, J. *J. Org. Chem*. **1984**, 49, 5237-5243.

36. Kamatatant, A.; Overman, L. E. *J. Org. Chem.* **1999**, 64, 8743-8744

37. Tamao, K.; Sumitani, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, 49, 1958-1969.

38. Amatore, C.; Jutand, A.; Fauvarque, J. F. *J. Organomet. Chem.* **1990**, 390, 389-398.

39. Minato, A; Suzuki, K; Tamao, K; Kumada, M. *Tetrahedron Lett.* **1981**, 22, 5319-5322.

40. Minato, A.; Suzuki, K.; Kumada, M. *J. Chem. Soc.*, *Chem. Commun.* **1984**, 511-513

41. Hatanaka, Y.; Fukushima, S.; Hiyama, T. *Heterocycles* **1990**, 30, 303-306.

42. Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.* **1994**, 66, 1471-1478.

43. Schibata, K.; Miyazawa, K.; Goto, Y. *Chem. Commun.* **1997**, 1309-1310.

44. Sonagashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, 17, 4467-4470.

45. Rossi, R.; Carpita, A.; Belina, F. *Org. Prep. Proc. Int.* **1995**, 27, 129-160.

46. Negishi, E.; Anastasia, L. *Chem. Rev*. **2003**, 103, 1979-2017.

47. Edo, kiyoto.; Yamanaka, H.; Sakamoto, T. *Heterocycles* **1978**, 9, 271-274.

48. Bleicher, L. S.; Cosford, N. D. P.; Herbaut, A. *J. Org. Chem.* **1998**, 63, 1109-1118.

49. Mizoroki, J. F.; Mori, K.; Ozaki, A.; *Bull. Chem. Soc. Jpn.* **1971**, 44, 581-584.

50. Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, 37, 2320-2322.

51. Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, 7449-7476.

52. Sakamoto, T.; Arakida, H.; Edo, Kiyota; Yamanaka, H. *Heterocycles* **1981**, 16, 965-968.

53. Busacca, C. A.; Dong, Y. *Tetrahedron Lett.* **1996,** 37, 3947-3950.

54. Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, 116, 5969-5970.

55. Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, 116, 7901-7902.

56. A Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, 68, 2861-2873.

57. Viciu, M. S.; Kelly, R. A.; Stevens, E. D.; Nolan, S. *Org. Lett.* **2003**, 5, 1479-1482.

58. Kalinin, V. N. *Synthesis* **1992**, 413-432.

59. Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*, Pergamon Press, **2000**.

60. Undheim, K.; Benneche, T. *Adv. Heterocycl. Chem.* **1995**, 62, 305-418.

61. Stanforth, S. P. *Tetrahedron* **1998**, 54, 263-303.

62. Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1988,** 27, 2225-2249.

63. Aoyaki, Y.; Inoue, A.; Koizumi, I.; Ohta, A. *Heterocycles* **1992**, 33, 257-272.

64 Sandosham, J.; Undheim, K. *Acta. Chem. Scand.* **1989**, 43, 62-68.

65. Cruskie, M. P.; Zoltewicz, J. A.; Abboud, K. A. *J. Org. Chem.* **1995**, 60, 7491-7495.

66. Wu, G. G.; Wong, Y. W.; Poirier, M. *Org. Lett.* **1999**, 1, 745-747.

67. Meyers, C.; Maes, B. U. W.; Loones, K. T. J. *J. Org. Chem.* **2004**, 69, 6010-6017.

68. Malpass, J. R.; Cox, C. D. *Tetrahedron Lett*. **1999**, 40, 1419-1422.

69. Cox, C. D.; Malpass, J. R. *Tetrahedron* **1999**, 55, 11879-11888.

70. Bracher, F.; Daab, J. *Eur. J. Org. Chem.* **2002,** 14, 2288-2291.

71. Havelková, M.; Hocek, M.; Česnek, M.; Dvoák, D. *Synlett* **1999**, 1145-1147.

72. Novinson, T.; Bhooshan, B.; Okabe, T.; Revankar, G. R.; Wilson, H. R. *J. Med. Chem.* **1976**, 19, 512-516.

73. Senga, K.; Novinson, T.; Wilson, H. R. *J. Med. Chem.* **1981**, 24, 610-613.

74. Suzuki, M.; Iwasaki, H.; Fujikawa, Y.; Sakashita, M.; Kitahara, M.; Sakoda, R. *Bioorg. Med. Chem. Lett.* **2001**, 11, 1285-1288.

75. Al-mansa, C.; Arriba, A. F.; Cavalcanti, F. L.; Gomez, L. A.; Miralles, A.; Forn J. *J. Med. Chem.* **2001**, 44, 350-361.

76. Fraley, M. E.; Rubino R. S.; Hoffman, W. F.; Hambaugh S. R.; Thomas K. A. *Bioorg. Med. Chem. Lett*. **2002**, 12, 3537-3541.

77. Novinson, T.; Hanson, R.; Dimmitt, M. K.; Simmon , L. N.; Robins, R. K.; O'Brien, D. E. *J. Med. Chem.* **1974**, 17, 645-648.

78. Selleri , S.; Bruni , F.; Costagli, C.; Costanzo, A.; Guerrini, G.; Ciciani, G.; Costa, B.; Martini, C. *Bioorg. Med. Chem.* **2001**, 9, 2661-2671.

79. Kirkpatrick, W. E.; Okabe, T.; Hillyard, I. W.; Robin, R. K.; Dren, A. T. *J. Med. Chem.* **1977**, 20, 386-393.

80. Shioto, T.; Yamamori, T. *J. Org. Chem.* **1999**, 64, 453-457.

81. Vattoly J. M.; Jaya P. J.; John M. J. S.; Dileep, K. *Adv. Synth. Catal.* **2003**, 345, 620-624.

82. Fraley, M. E.; Hoffman, W. F.; Rubino, R. S.; Hungate, R.W.; Thomas, K. A. *Bioorg. Med. Chem. Lett.* **2002**, 12, 2767-2770.

83. Bellec, C.; Lhommet, G. *J. Heterocycl. Chem.* **1995**, 32, 1793-1800.

84. Danagulyan, G. G.; Pannosyan, G. A.; Boyakhchyan, A. P. *Chem. Heterocycl. Comp.* **2002**, 38, 581-585.

85. Petrov, A. A.; Emelina, E. E.; Firsov, A. V. *Russ. J. Org. Chem.* **2000**, 36, 1027-1032.

86. Emelina, E. E.; Petrov, A. A.; Firsov, A. V. *Russ. J. Org. Chem.* **2001**, 37, 852-8

87. Springer, R. H. *J. Med. Chem.* **1976**, 19, 291-296.

88. Hori, I. Bull. *Chem. Soc. Jpn.* **1970**, 43, 849-855.

89. Brindley, J. C.; Caldwell, J. M.; Meakins, G. D.; Plackett, S. J.; Price, S. J. *J. Chem. Soc.* , *Perkin Trans*, *1* **1987**, 1153-1158.

90. Caldwell, J. M.; Meakins, G. D; Jones, R. H.; Kidd, T. R.; Prout, K. *J. Chem. Soc. Perkin Trans*, *1* **1987**, 2305-2310.

91. Robins, R. K.; Revankar, G. R.; O'Brien, D. E.; Springer, R. H. *J. Heterocycl. Chem.* **1985**, 22, 601-634.

92. Novinson,T. *J. Med. Chem*. **1977**, 20, 296-299, *J. Med. Chem.* **1976**, 19, 517-519.

93. Allen, W. E.; Fowler, C. J.; Lynch, V. M.; Sessler, J. L. *Chem. Eur. J.* **2001**, 7, 721-729.

94. Whitcombe, N. J.; Hii, K. K.; Gibson; S. E. *Tetrahedron* **2001**, 57, 7449-7476.

95. Kundu, N. G.; Nandi, B. *J. Org. Chem.* **2001**, 66, 4563-4575**.**

96. Heidenreich, R. G.; Köhler, K.; Krauter, J. K.; Pietsch, J. *Synlett* **2002**, 1118-1122.

97. (a) Gala, D.; Jenkins, S. J.; Kugelman, M. *Organic Progress Research & Development* **1997**, 1, 163-164. (b) Dyer, U. C.; Shapland, P. D.; Tiffin, P. D. *Tetrahadron Lett.* **2002**, 42, 1765-1767. (c) McClure, M. S.; Roschangar, F.; Hodson, S. J.; Millar, a.; Osterhout, M. H. *Synthesi*s **2001**, 1681-1685. (d) Sakurai, H.; Tsukuda, T.; Hirao, T. *J. Org. Chem.* **2002**, 67, 2721-2722. (e) Tagata, T.; Nishida, M. *J. Org. Chem.* **2003**, 68, 9412-9415. (f) LeBlond, C. R.; Andrews, A. T.; Sun, Y. K.; Sowa, Jr. J. R. *Org. Lett.* **2001**, 3, 1555-1557. (g) Organ, M. G.; Mayer, S. *J. Comb. Chem.* **2003**, 5, 118-124. (h) Accadi, A.; Cerichelli, G.; Chiarini, M.; Correa, M.; Zorzan, D. *Eur. J. Org. Chem.* **2003**, 4080-4086.

98. (a) Reardon, P.; Metts, S.; Crittendon, C.; Dangherity, P.; Parson, E. J. *Organometallics* **1995**, 14, 3810-3816. (b) Hagiwara, H.; Shimizu, Y.; Hoshi, T.; Suzuki, T. etal. *Tetrahedron Lett.* **2001**, 42, 4349-4351. (c) Xie, X. F.; Lu, J. P.; Chen, B.; Han, J. J.; She, X. G.; Pan, X. F. *Tetrahedron Lett*. **2004**, 45, 809-811. (d) Mehnert, C. P.; Weaver, D. W.; Ying, J. Y. *J. Am. Chem. Soc.* **1998**, 120, 12289-12296. (e) Khan, S. I.; Grinstaff, M. W. *J. Org. Chem*. **1999**, 64, 1077-1078.

99. (a) Potts, K. T.; Horwitz, C. P.; Fessak, A.; Keshavarz-K, M.; Nash, K. E.; Toscano, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 10444-10445. (b) Bleicher, L.; Cosford, N. D. P. *Synlett* **1995**, 1115-1116. (c) Cosford, N. D. P.; Bleicher, C. L.; Herbaut, A. *J. Med. Chem.* **1996**, *39*, 3235-3237. (d) Bleicher, L. S.; Cosford, N. D. P.; Herbaut, A.; McCallum, J. S.; McDonald, I. A. *J. Org. Chem.* **1998**, 63, 1109-1118. (e) Novak, Z.; Szabo, A.; Kotschy, A. *J. Org. Chem*. **2003**, 68, 3327-3329. (f) Lopez-Deber; M.P., Castedo, L.; Granja, J.R. *Org. Lett.* **2001**, 3, 2823-2826. (g) Pal, M.; Subramanian, V.; Yeleswarapu, K. R.*Tetrahedron Lett*. **2003**, 44, 8221-8225 (h) Novak, Z.; Szabo, A.; Repasi, J. *J. Org. Chem.* **2003**, 68, 3327-3329.

100. Fairlamb, I. J. S.; Bäuerlein, P. S.; Marrison, L. R. M. *Chem. Commun.* **2003**, 632-633

101. Hyun Oh, C.; Lee, S. C.; Lee, K. S.; Woo, E. R.; Hong, C. Y.; Cho, J. H. *Arch. Pharm. Pharm. Med. Chem.* **1999**, 332, 187-190.

102. Detty, M. R. *J. Org. Chem.* **1979**, 44, 2073-2077.

103. (a) Kelley, J. L.; Krochmal, M. P.; Linn, J. A.; Mclean, E. W.; Sooko, F. E. *J. Med. Chem.* **1988**, 31, 606-612.(b) Kelley, J. L.; Linn, J. A.; Krochmal, M. P. *J. Med. Chem.* **1988**, 31, 2001-2004.

104. Imbach, P.; Carpraro, H. G.; Furet, P.; Mett, H.; Meyer, T.; Zimermann, J. *Bioorg. Med. Chem. Lett.* **1999**, 9, 91-96.

105. Bakkestuen, A. K.; Gundersen, L. L.; Langli, G.; Liu, F. Nolsøe, J. M. J. *Bioorg. Med. Chem. Lett.* **2000**, 10, 1207-1210.

106. Brathe, A.; Gundersen, L. L.; Meyer, J. N.; Rise, F.; Spilsberg, B. *Bioorg. Med. Chem. Lett.* **2003**, 13, 877-880.

107. Hocek, M.; Vortruba, I. *Bioorg. Med. Chem. Lett.* **2002**, 12, 1055-1058.

108. Matsuda, A.; Shinozaki, M.; Yamaguchi, T.; Homma, H, Nomoto, R. *J. Med. Chem.* **1992**, 35, 241-252.

109. Cristalli, G.; Volpini, R.; Vittori, S.; Campioni, E.; Monopoli, A.; Conti, A. *J. Med. Chem*. **1994**, 37, 1720-1726.

110. LaMontagne, M. P.; Smith, D. C.; Wu, G. S. *J. Heterocycl. Chem.* **1983**, 20, 295-299.

111. Chapman, E.; Ding, S.; Schultz, P. G.; Wong, C. H. *J. Am. Chem. Soc.* **2002**, 124, 14524-14525.

112. Marasco, Jr.C. J.; Kramer, D. L.; Miller, J.; Porter, C. W.; Bacchi, C. J.; Rattendi, D. *J. Med. Chem*. **2002**, 45, 5112-5122.

113. Havelková, M.; Dvořák, D.; Hocek, M. *Synthesis* **2001**, 1704-1710.

114. Hocek, M.; Hocková, D.; Dvořáková, H. *Synthesis* **2004**, 889-894.

115. Gunderson, L. L.; Rise, F. *Tetrahedron* **1994**, 50, 9743-9756.

116. Gunderson, L. L. *Tetrahedron Lett.* **1994**, 35, 3155-3158.

117. Liu, F. S.; Dalhaus, B.; Gunderson, L. L.; Rise, F. *Acta Chem. Scand.* **1999**, 53, 269-279.

118. Langli, G.; Gunderson, L. L.; Rise, F. *Tetrahedron Lett.* **1995**, 36, 1945-1948.

119. Langli, G.; Gunderson, L. L.; Rise, F. *Tetrahedron Lett.* **1996**, 52, 5625-5638.

120. Nolsøe, J. M.; Gunderson, L. L.; Rise, F. *Acta Chem. Scand.* **1999**, 53, 366-72.

121. Bergstrom, D. E.; Reday, P. A. *Tetrahedron Lett.* **1982**, 23, 4191-4194.

122. Cong-Danh, N.; Beaucourt, J. P.; Pichat, L. *Tetrahedron Lett.* **1979**, 20, 3159-3162.

123. Hirota, K.; Kitade, Y.; Kanbe, Y. *J. Org. Chem.* **1992**, 57, 5268-6270.

124. Hocek, M.; Stará, I. G.; Dvořáková, H. *Collect. Czech. Chem. Commun.* **2002**, 67, 1223-1235.

125. Harada, H.; Asano, O.; Hoshiro, Y.; Yoschikawa, S.; Matskura, M.; Abe, S. *J. Med. Chem.* **2001**, 44, 170-179.

126. Oh, C. H.; Lee, S. C.; Lee, K. S.; Woo, E. R.; Cho, J. H. *Arch. Pharm. Pharm. Med. Chem*. **1999**, 332, 187-190.

127. Geir, L.; Lise-Lotte, G.; Frode, R. *Tetrahedron* **1996**, 52, 5625-5638.

128. Cavier, R. *Chim. Ther.* **1966**, 66, 327-330.

129. Haley, T. J.; Flesher A. M.; Vcomelt, R. *Proc. Soc. Biol. Med.* **1957**, 96, 579-584.

130. Cavallini, G.; Massarani, E.; Nardi, D.; Magrassi, F.; Altucci, P. *J. Med. Pharm. Chem*. **1959**, 1, 327-332.

131. Kumari, S.; Ghai, P.; Sexsena, A. *Indian J. Chem. B*, **1992**, 31, 92-97.

132. Vinot, M. *Bull. Soc. Chim. Fr.* **1976,** 251-253.

133. Armand, J.; Chekir, K.; Pinson, J. *Can. J. Chem.* **1978**, 56, 1804-1816.

134. Sanfilippo, P. J.; Urbanski, M.; Press, J. B. *J. Med. Chem.* **1988**, 31, 2221-2217.

135. Kaminiski, J: J.; Puchalski, C.; Solomon, D. L. *J. Med. Chem.* **1989**, 32, 1686-1700.

136. Gyoten, M.; Nagaya, H.; Fukuda, S.; Ashida, Y. *Chem. Pharm. Bull.* **2003**, 51, 122-133.

137. Ishikawa, T.; Lizawa, Y.; Okonogi, K.; Miyake, A. *J. Antibiot.* **2000**, 53, 1053-1070.

138. Enguehard, C.; Renou, J. L.; Collot, V. *J. Org. Chem.* **2000**, 65, 6572-6575.

139. Enguehard, C.; Hervet, M.; Théry, I. *Helv. Chim. Acta*, **2001***,* 84, 3610-3615.

140. Thomas, A. P.; Allott, C. P.; Gibson, K. H. *J. Med. Chem*. **1992**; 35, 877-885.

141. Enguehard, C.; Allouchi, H.; Gueiffier, A. Buchwald, S. L. *J. Org. Chem*. **2003**, 68, 4367-4370.

142. Gudmundsson, K. S.; Williams, J. D.; Duach, J. C.; Townsend, L. B. *J. Med. Chem.* **2003**, 46, 1449-1455.

143. (a) Enguehard, C.; Hervet, M.; Thery, I.; Renou, J. L. Fauvelle, F.; Gueiffier, A. *Helv. Chim. Acta* **2001**, 84, 3610-3615. (b) Yananaka, M.; Miyake, S.; Suda, S.; Ohhara, H.; Ogawa, T. *Chem. Pharm. Bull.* **1991**, 39, 1556-1567.

144. Salimbeni, A.; Canevotti, R.; Paleari, F.; Poma, D.; Caliari, S.; Subissi, A. *J. Med. Chem.* **1995**, 38, 4806-4820

145. Ban, M.; Taguchi, H.; Katsushima, T.; Aoki, S.; Watanabe, A. *Bioorg. Med. Chem.* **1998**, 6, 1057-1067.

146. Dinan, F. J.; Bardos, T. J. *J. Med. Chem.* **1980**, 23, 569-572.

147. Wright, G. E.; Brown, N, C. *J. Med. Chem.* **1980**, 23, 34-38.

148. Hendry, J. A.; Homer R. F. *J. Chem. Soc.* **1952**, 328-333.

149. Koga, M.; Schneller, S. W. *J. Heterocycl. Chem*. **1992**, 29, 1741-1747.

150. Borowski, T.; Krol, M.; Broclwwic, E, Baranowski, T. C.; Mokrosz, M. J. *J. Med. Chem.* **2000**, 43, 1901-1909.

152. Wellmar, U.; Hörnfeld, A. B.; Gronowitz, S. *J. Heterocycl. Chem.* **1995,** 32, 1159-63.

153. Ali, N. M.; McKillop, A.; Mitchell, M. B.; Rebelo, R.A.; Walbank, P. J. *Tetrahedron* **1992**, 48, 8117-8126.

153. Edo, K.; Sakamoto, T. *Heterocycles* **1978**, 9, 271-274.

154. Bleicher, L.S.; Cosford, N.D.; Herbaut, A.; McCallum, J. S.; McDonald, I.A. *J. Org. Chem.* **1998**, 63, 1109-1118.

155. Varlhac, J. B.; Pereyre, M.; Shin, H. *Organomatallics* **1991**, 10, 3007-3009.

156. Sakamoto, T.; Nishimura, S.; Kondo, Y.; Yamanka, H. *Synthesis* **1988**, 485-486.

157. Miller, W. H.; Seefeld, M. A.; Newlander, K. A. *J. Med. Chem.* **2002**, 45, 3246-3256.

158. Sakamoto, T.; Arakida, H.; Edo, K.; Yamanaka, H. *Heterocycles* **1981**, 16, 965-968.

159. Majeed, A. J.; Antonsen, Ø.; Benneche, T. *Tetrahedron* **1989**, 45, 993-1006.

160. Schomaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, 66, 7125-7128.

161. Mangalagiu, I, Benneche, T, Undheim, K. *Acta Chem. Scand.* **1996**, 50, 914-917.

162. Shibata, T.; Yonebubo, S.; Soai, K. *Angew. Chem. Int. Ed.* **1999**, 38, 659-661.

163. Edo, K.; Sakamoto, T.; Yamanaka, H. *Heterocycles* **1979**, 12, 383-386.

164. Brown, D. J.; Cowden, W. B.; Lan, S. B.; Mori, K. *Aust. J. Chem.* **1984**, 37, 155-163.

165. (a) Vlad, G.; Horvath, I. T. *J. Org. Chem*. **2002**, 67, 6550-6552. (b) Lepretre, A.; Turck, A.; Ple, N.; Knochel, P.; Queguiner, G. *Tetrahedro,* **2000**, 56, 265-273. (c) Ple. N.; Turck, A. Heynderickx, A.; Queguiner, G. *Tetrahedron* **1998**, 54, 9701-9710. (d) Maes, B. U. W.; Lemiere, G. L. F. *Tetrahedron* **2000**, 56, 1777-1781.

166. Hendry, H. *J. Chem. Soc.* **1952**, 328-333.

167. (a) Sajiki, H.; Kume, A.; Hattori, K.; Hirota, K. *Tetrahedron Lett.* **2002**, 43, 7247-7250. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2002**, 102, 4009-4091. (c) Hassan, J.; Gozzi, C.; Schulz, E.; Lemaire, M. *J. Organomet. Chem.* **2003**, 687, 280-283. (d) Cortese, N. A.; Heck, F. R. *J. Org. Chem.* **1977**, 42, 3491-3494.

168. Delia, T.J.; Stark, D.; Glenn, S. K. *J. Heterocycl. Chem*. **1995**, 32, 1177-1780.

169. Lednicer, D. *In Strategies for Organic Drug Synthesis and Design*, John Wiley & Sons: New York, **1988**, 242-257.

170. (a) Barbera, J.; Melendez, E.; Remero, P. *Mol. Cryst. Liq. Cryst.* **1985**, 126, 259-264. (b) Seto, K.; Shimojitosyo, H.; Matsubara, H.; Takahashi, S. *Chem. Lett.* **1990**, 323-3.

171. Lee, A. W. M.; Chan, W. H.; Wong, M. S. *J. Chem. Soc., Chem. Commun.* **1988**, 1585-1586.

172. (a) Meyer, T. *Acc. Chem. Res*. **1989**, 22, 163-170. (b) Pyle, A. M.; Barton, J. K. *Prog. Inorg. Chem.* **1990**, 38, 413-416. (c) Gittins, D. I.; Bethell, D.; Nichols, R. J.; Schiffrin, D. J. *Adv. Mater.* **1999**, 737-740.

173. Brandao, M. A.; Oliveria, A. B.; Snieckus, V. *Tetrahedron Lett.* **1993**, 34, 2437-2440.

174. Prim, D.; Kirsch, G. *J. Chem. Soc.*, *Perkin Trans. 1*, **1994**, 2603-2606.

175. Cross, P. E.; Dickinson, R. P.; Parry, M. J. *J. Med. Chem.* **1986**, 29, 1637-1643.

176. Sandosham, J.; Undlheim, K. *Acta Chem. Scand.* **1989**, 43, 684-689.

177. Tiley, J. W.; Levitan, P.; Lind, J.; Welton, A. F. *J. Med. Chem.* **1987**, 30, 185-193.

178. Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, 61, 7240-7241.

179. Niu, C.; Li, J.; Doyle, T. W.; Chen, S. H. *Tetrahedron* **1998**, 54, 6311-6318.

180. Minato, A.; Suzuki, K.; Tamao, K. *J. Chem. Soc., Chem. Commun.* **1984**, 511-513.

181. Tilley, J.; Zawoiski, S. *J. Org. Chem.* **1988**, 53, 386-390.

182. Ernst, A.; Gobbi, L.; Vasella, A. *Tetrahedron Lett.* **1996**, 37, 7959-62.

183. Chapman, G. M.; Stanforth, S. P.; Tarbit, B.; Watson, M. D. *J. Chem. Soc.*, *Perkin Trans. 1,* **2002**, 581-582.

184. Cruskie, M. P.; Zoltewicz, J. A.; Abboud, K. A. *J. Org. Chem.* **1995**, 60, 7491-7495.

185. Bargar, T. M.; Wilson, T.; Daniel, J. K. *J. Heterocycl. Chem.* **1985,** 22, 1583-1592**.**

186. Cox, C. D.; Malpass, J. R. *Tetrahedron* **1999**, 55, 11879-11888.

187. Bessard, Y.; Roduit, J. P. *Tetrahedron* **1999**, 55, 393-404.

188. Meyers, C.; Maes, B. U. W.; Loones, K. T. J. *J. Org. Chem*. **2004**, 69, 6010-6017

189. (a) Johnstone, R. A. W.; Wilby, A. H. *Chem. Rev.* **1985**, 85, 129-170. (b) Weil, J. R.; Pater, B. A.; Heck, F. R. *J. Org. Chem.* **1980**, 45, 4926-4931.

190. Robertson, D. W.; Beedle, E. E.; Jones, N. D. *J. Med. Chem*. **1986**, 29, 635-640. (b) Colucci, W. S.; Wright, R. F.; Braunwald, E. *New Eng. J. Med.* **1986**, 314, 349-355.

191. Watanabe, T.; Hayashi, K.; Sakurada, J.; Ohki, M. *Heterocycle,* **1989**, 29, 123-131.

192. Jones, K.; Keenan, M.; Hibbert, F. *Synlett* **1996,** 509-510.

193. Yang, Y.; Martin, A. R. *Heterocycles* **1992**, 34, 1395-1398

194. Akita, Y.; Kanekawa, H.; Kawasaki, T. *J. Heterocycl. Chem.* **1988**, 25, 975-977.

195. Turck, A.; Plé, N.; Dognon, D.; Harmoy, C, Quéguiner, G. *J. Heterocycl. Chem.* **1994**, 31, 1449-1453.

196. Akita, Y.; Inoue, A.; Mori, Y.; Ohta, A. *Heterocycles* **1986**, 24, 2093-2097.

197. Aoyagi, Y.; Inoue, A.; Koizumi, I.; Hashimoto, R. *Heterocycles* **1992**, 33, 257-272.

198. Karmas, G.; Spoerrt, P. E. *J. Am. Chem. Soc.* **1952**, 74, 1580-1584.

199. Hodgetts, K. J.; Kershaw, M. T. *Org. Lett.* **2002**, 4, 2905-2907.

200. Sakamoto, T.; Nagata, H.; Kondo, Y. *Chem. Pharm. Bull.* **1987**, 35, 823-828.

201. Gilchrist, T. L.; Pearson, D. P. J. *J. Chem. Soc.*, *Perkin Trans. 1,* **1976**, 989-993.

202. Genin, M. J.; Biles, C.; Kaiser, B. J.; Poppe, S, M. *J. Med. Chem.* **2000**, 43, 1034-1040.

203. (a) Penning, T. D.; Talley, J. J. Bertenshaw, S. R. *J. Med. Chem.* **1997**, 40, 1347-65. (b) Almansa, C.; Alfon, J. Arriba, A. F.; Cavalcanti, F. L. *J. Med. Chem.* **2003**, 46, 3463-3475.

204. Siskovic, D. R.; Roth, B. D.; Wilson, M. W. *J. Med. Chem.* **1990**, 33, 31-38.

205. (a) Regan, J.; Breitifelder, S.; Cirillo, P.; *J. Med. Chem*. **2002**, 45, 2994-3008. (b) Dumas, J.; Mokdad, H. H.; Silbley, R. *Bioorg. Med. Chem. Lett.* **2000**, 10, 2051-2054.

206. Stauffer, S. R.; Huang, Y.; Cooletta, C. J.; Tedesco, R.; Katzenebogen, J. A. *Bioorg. Med. Chem.* **2001**, 9, 141-150.

207. Chupp, J. P. *J. Heterocycl . Chem.* **1994**, 1377-1380.

208. Organ, M. G.; Mayer, S. *J. Comb. Chem.* **2003**, 118-124.

209. Huang, Y. R.; Katzenllenbogen, J. A. *Org. Lett.* **2000**, 2, 2833-2336.

210.Tolf, B. R.; Dahlbom, R.; Theorellel, H. *Acta Chem. Scand. B*, **1982**, 36, 101-1077.

211. Higley, C. A.; Wilde, R. G.; Maduskuie, T. P. *J. Med. Chem.* **1994**, 37, 3511-3522.

212. Khanna, I. K.; Weier, R. M.; Xiang, Y. Y. *J. Med. Chem.* **1997**, 40, 1634-1647.

213. Wadsworth, S. A.; Cavender, D. E. *Pharm. Experi. Ther.* **1999**, 291, 680-687

214. Elz, S.; Krammer, K.; Pertz, H. H. Detert, H. *J. Med. Chem.* **2000**, 43, 1071-1084.

215. Wang, D. M.; Haseltine, J. *J. Heterocycl. Chem.* **1994**, 31, 1637-1639.

216. Ali, N, M.; Mckillop, A.; Mitchell, M. B. *Tetrahedron* **1992**, 48, 8117-8126

217. Dobler, M. R. *Tetrahedron Lett.* **2003**, 44, 7115-7117.

218. Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M. *Heterocyles* **1990**, 31, 1951-1957.

219. Ohta, A.; Itoh, R.; Kaneko, Y.; Koike, H. Yuwsa, K. *Heterocycles* **1989**, 29, 939-945.

220. Evans, D. A.; Bach, T. *Angew. Chem. Int. Ed.* **1993**, 32, 1326-1327.

221. Milgrom, L. R.; Dempsey, P. J. F.; Yahioglu, G. *Tetrahedron* **1996**, 52, 9877-9890.

222. Cheng, Y. X.; Dukat, M, Dowd, M.; Fiedler, W. Glennon, R. A. *Eur. J. Med. Chem.* **1999**, 34, 177-190.

223. Liebscher, J.; Neumann, B.; Hartmann, H. *J. Prakt. Chem.* **1983**, 325, 915-918.

224. Hartmann, H.; Liebscher, J. *Synthesis* **1984**, 276-277.

225. Jourdan, F.; Ladurée, D.; Robba, M. *J. Heterocycl. Chem.* **1994**, 31, 305-312.

226. Joshi, K. C.; Pathak, V. N.; Garg, U. *J. Indian Chem. Soc.* **1983**, 60, 1074-1076

227. Chen, L. S.; Cummings, S. C. *Inorg. Chem.* **1978**, 17, 2358-2361.

228. Arthur A. V; Piet, H.; Hubert, V. *Nucleosides Nucleotides* **1988**, 7, 75-90.

229. (a) Janine, C.; Samir, B.; Claude, C. J. *Tetrahedron-Asymmetry* **1999**, 10, 3859-3862. (b) Chaudhary, S. K.; Hernardez, O. *Tetrahedron*, *Lett.* **1979**, 20, 95-98.

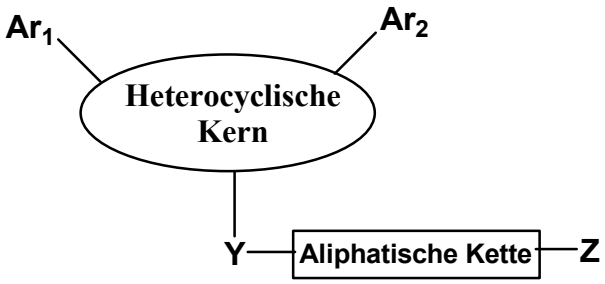
230. Palucki, M.; Hughes, D. L.; Yasuda, N. *Tetrahedron Lett*. **2001**, 42, 6811-6814.

231. Paul, M.; Hassan, I. *Tetrahedron-Asymmetry* **1998**, 9, 4419-4428.

232. Kankare, J.; Haenninen, E. *Acta Chem*. *Scand. Ser. B*, **1988**, 42, 448-454.

Zusammenfassung

Unsere Forschungsziele sind die Entwicklung von neuen nichtpeptidischen Calcineurin-Inhibitoren. Nach einem positiven Test von einigen Substanzen (Pyrazolopyrimidinen und Pyrazolotriazinen) wurde eine allgemeine Struktur **8** mit calcineurin-inhibierenden Potential formuliert.



Allgemeine Struktur 8

Die Struktur besteht aus einem heterocyclischen Kern, zwei Aryl-Gruppen und einer Seitenkette.

In dieser Dissertation versuchen wir, die zentralen N-heterocyclischen Kerne, die Seitenketten und deren Position zu variieren. In der allgemeinen Struktur **8**, kann Y nicht nur NH, O und S sondern auch CH_2 und CH_2NH sein und die aliphatische Kette kann gesättigt und ungesättigt sein. Als synthetische Strategie wurden Palladium-katalysierte Kupplungsreaktionen verwendet, um Seitenketten und/oder Aryl-Substituenten einzuführen.

Synthese von Halogensubstituierten Diarylheterocylen

Halogensubstituierte Diarylheterocyclen sind wichtige Intermediate in der Synthese der allgemeine Strukture **8**. Um Aryl-Gruppen einzuführen, ist die Suzuki-Reaktion der Schlüsselschritt.

Andere Halo-Heterocyclen werden entweder durch Substitutionen von Hydroxylgruppen mit einem Halogen oder durch Halogenierung der unfunktionalisierten Position der Heterocyclen erreicht. Mehr als 30 Substanzen entsprechender Halo-Heterocyclen wurden synthetisiert.

Einführung der Seitenketten durch Palladium-katalysierte Kupplungen

Die Einführung der gewünschten Seitenketten durch C-C und C-N-Bindungsknüpfung wurde durch Sonogashira-Kupplung, Heck-Kupplung und Buchwald-Hartwig-Aminierung erzielt

Mit der Sonogashira-Reaktion kann eine ω-funktionalisierte Alkynylgruppe in die heterocyclischen Kerne effektiv und bequem eingeführt werden. Eine anschliessende katalytische Hydrierung der Alkynylgruppe führt zu ω-funktionalisierten Alkyl substituierten Diarylheterocyclen. Fünf bicyclische und sechs monocyclische heterocyclischen Kerne können durch diese Reaktionsreinfolge erfolgreich dargestellt werden.
Durch Heck-Reaktion von 3-Iodopyrazolo[1,5-a]pyrimidinen oder von 7-Bromopyrido[2,3-b]pyrazinen mit Olefinen können ω-funktionalisierten Alkenylgruppen in diese heterocyclischen Kerne eingeführt werden.
Durch Buchwald-Hartwig-Aminierung von 6-Bromoimidazo[1,2-a]pyridinen ,von 7-Bromo-pyrido[2,3-b]pyrazinen oder von 4-Bromooxazolen mit den ω-funktionalisierten Alkylaminen, können die Aminoalkylketten in diese heterocyclischen Kerne eingeführt werden.
Wir haben allgemeine Beiträge zu diesem Bereich und in Bezug auf die Beschränkung der Palladium-katalysierten Reaktionen in der Chemie der Heterocyclen geleistet.

Calcineurin-inhibierende Aktivität

Im Verlauf dieser Dissertation wurden Heterocyclen mit Grundkörpern von Purin, Pyridopyrazin, Imidazopyridin, Imidazopyridazin, Imidazol, Oxazol, Pyrazol, Pyridin und Pyrazin entwickelt und getestet. Die Ergebnisse zeigen, dass nur Pyrazolopyrimidine, Pyrazolotriazine und Pyrimidine wirkungsvoll sind.
Das strukturelle Modell **8** der möglichen Calcineurin-Inhibitoren kann verfeinert werden. Wichtige Beiträge zu diesem Bereich und Beschränkungen wurden so mit zur Verfügung gestellt. Weitere Resultate zeigen die beträchtliche und vielseitige Verwendbarkeit der Palladium-katalysierten Kupplungsreaktionen in diesen neuen Bereichen der Chemie der Heterocyclen.

In der vorliegenden Arbeit wurden mehr als 180 Substanzen synthetisiert. Unter ihnen sind ungefähr 130 neue Substanzen. 86 von ihnen passen in die allgemeine Struktur **8**.

Fünf Publikationen entstanden aus diesen Resultaten. Zwei von ihnen sind schon erschienen. Eine ist im Druck, zwei weitere sind in Vorbereitung.

Lebenslauf

Persönlishe Daten

Name	Lunxiang Yin
Geburtsdatum	26. 03. 1966
Geburtsort	Anhui, V. R. China
Nationalität	Chinesisch

Schulausbildung

- ♦ 1972-1977 Grundschule in Ningguo, Anhui
- ♦ 1977-1980 Heli-Gymnasium, in Ningguo, Anhui
- ♦ 1980-1983 Xuncheng-Gymnasium, in Xuancheng, Anhui
- ♦ July 7-9, 1983 Abitur

Studium

- ♦ 1983-1987 Studium der Fachrichtung Chemie an dem Institut für Chemie der **Shandong Universität**, V. R. China,
  B.Sc. in Chemie

- ♦ 1987-1990 Anfertigung der Masterarbeit am dem Institut für Chemie der **Shandong Universität**, V. R. China,
  M.Sc. in Organischer Chemie (von Prof. Lunji Jiao)
  Thema der Masterarbeit: "*Synthesis of substituted trimethylsilyl-cyclopentadienes starting from 6,6-dialkylfulenes*".

- ♦ 2001-2005 Anfertigung der Doktorarbeit am dem Institut für Chemie der **Humboldt Universität zu Berlin**, Germany,
  Ph.D. in Organischer Chemie (von Prof. Jürgen Liebscher)
  Thema der Doktorarbeit: "*Synthesis of new calcineurin inhibitors via Pd-catalyzed cross-coupling reactions*"

Beruflicher Werdegang

- ■ 1990-1994 Mitarbeit an dem Institut für Industriechemie der Hochschule der Shandong Leichtindustrie, V. R. China

- ■ 1994-1999 Mitarbeit an dem Institut für Chemie der Shandong Pädagogische Universität, V. R. China

- ■ 1999-2000 Wissenschaftlicher Angestellter am dem Instititut für Chemie der Bar-Ilan Universität, Israel

- ■ 2001-2005, Wissenschaftlicher Angestellter am dem Instititut für Chemie der Humboldt Universität zu Berlin, Germany

Selbständigkeitserklärung

Hiermit erkläre ich, Lunxiang Yin, dass ich diese Dissertation selbständig und ohne unerlaubte Hilfe angefertigt habe.

Berlin, den 26. Jan. 2005

Lunxiang Yin (殷伦祥)

Publications from the thesis

(1) **L. X. Yin**, J. Liebscher, "Convenient synthesis of substituted 3-alkenyl-pyrazolo[1,5-a] pyrimidines via Heck cross-coupling reaction", *Synthesis*, **2004**, 2329-2334.

(2) **L. X. Yin**, J. Liebscher, "ω-functionalized 3-alkynylpyrazolo[1,5-a] pyrimidines by Sonogashira coupling", *Synthesis*, **2005**, 131-135.

(3) **L. X. Yin**, J. Liebscher, "Pd-catalyzed cross-coupling of 7-bromo-2,3-diphenyl-pyrido[2,3-b]pyrazine", *Synthesis,* **2005**, 1345-1349.

(4) **L. X. Yin**, J. Liebscher, "Synthesis of 3-dimethylamino-propynyl and 3-dimethylamino-propyl substituted diarylheterocycles via Sonogashira reactions"*, J. Heterocyclic Chem*. (accepted)

(5) **L. X. Yin**, J. Liebscher, "Application of heterogenous palladium catalysts in cross-coupling reactions" (review article), *Submitted to Chem. Rev.*