Synthesis and Regioselective Reactions on Heterocyclic Derivatives

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Synthesis and Regioselective Reactions on Heterocyclic Derivatives

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La Faculté des sciences, sur le préavis de Monsieur J. LACOUR, professeur ordinaire et directeur de thèse (Département de chimie organique), Madame A. QUATTROPANI, docteure et co-directrice de thèse (Merck Serono S.A. – Genève, Suisse), Messieurs C. MAZET, docteur (Département de chimie organique), et L. S. LIEBESKIND, professeur (Emory University – Department of Chemistry – Atlanta, U.S.A.), autorise l'impression de la présente thèse, sans exprimer d'opinion sur les propositions qui y sont énoncées.

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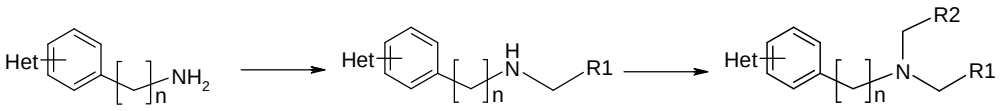
Résumé

De par la demande croissante de composés hétérocycliques dans le domaine pharmaceutique, le développement de méthodologies permettant leurs synthèses de façon efficace, tout en permettant une grande diversité, connaît un intérêt toujours grandissant. Le but de ce travail a été de développer la synthèse de divers hétérocycles originaux d'une façon robuste afin de pouvoir préparer des chimiothèques de composés de taille variable. Nous reportons dans ce travail de thèse l'optimisation de la synthèse en parallèle de dérivés portant des bioisostères d'acide carboxylique. Dans une deuxième partie, la synthèse et la transformation régioselective d'hétérocycles polyhalogénés, les trichloro-pyrido[3,2-*d*]pyrimidines, ont été investiguées.

1. Optimisation de la synthèse de dérivés portant des bioisostères d'acide carboxylique.

Le terme ''bioisostère'' est utilisé pour des composés ou des sous-structures qui partagent les mêmes formes, volumes, distributions éléctroniques et propriétés physico-chimiques et qui ont une activité biologique similaire. L'objectif d'un remplacement bioisostérique est de créer un nouveau composé ayant les mêmes propriétés biologiques que le composé parent, tout en ayant un profil biopharmaceutique différent. Dans le but de synthétiser des composés bioactifs ayant une fonctionnalité acide, nous nous sommes intéressés à la synthèse en parallèle de dérivés portant des hétérocycles acides, tel que le tétrazole ou le 1,3,4-oxadiazol-5-one. Cette synthèse a été développée en solution, en utilisant des réactifs sur support solide. La purification des produits finaux a été effectuée par extraction en phase solide (SPE). Notre approche a impliqué la préparation de phenyl- et benzylamines portant soit un tétrazole soit une 1,3,4-oxadiazol-5-one (dérivés **Ax**), sélectionnées de façon à avoir des composés offrant un large eventail de pKa (de 4.9 à 8.4). Ces amino-acides **Ax** ont ensuite réagit avec des aldehydes via deux alkylations réductrices successives, permettant d'accéder soit à des amines secondaires **AxBy** soit à des amines tertiaires **AxByCz** (*Schéma 1*).



Ax **AxBy** **AxByCz**

Het: tetrazol-5-yl
[1,3,4]oxadiazol-5-one
n = 0, 1

Schéma 1. Schéma général des composés des deux bibliothèques.

L'originalité dans l'élaboration de ces composés est amenée par les amino-acides **Ax** de départ, de même que par la voie de synthèse, ne demandant aucune protection de la fonction acide, contrairement à ce qui est généralement reporté dans la littérature.

Les amines secondaires ont été synthétisées par alkylation réductrice des amino-acides **Ax** avec des aldéhydes aromatiques et hétéroaromatiques **By**. Elles ont été obtenues avec une pureté entre 81 et 100% et un rendement entre 24 et 100%. Les amines tertaires **AxByCz** ont été synthétisées après une seconde alkylation réductrice, mettant en jeu les amines secondaires **AxBy** et des aldéhydes alkyle **Cz**. Ces amines tertiaires ont été isolées avec une pureté entre 80 et 97% et un rendement entre 33 et 100%.

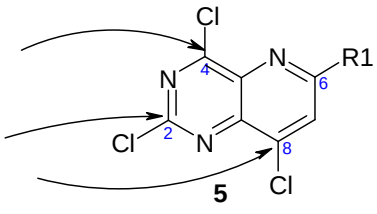
En conclusion, nous avons développés dans cette première partie, une méthode pratique et robuste permettant de synthétiser et de purifier en parallèle divers amino-acides portant un tétrazole ou une oxadiazolone comme fonction acide. Deux alkylations réductrices successives, partant des dérivés **Ax** et **AxBy** ont permis de synthetiser de nouveaux composés ayant des pKa entre 4.9 à 8.4.

2. Synthèse et régioséléctivité des trichloro-pyrido[3,2-*d*]pyrimidines.

Parmi les bioisostères connus des quinazolines, les pyridopyrimidines ont retenu l'attention des chimistes medicinaux en raison de leur activité biologique potentielle. Dans le but de synthétiser des composés nouveaux, nous avons selectionné cet hétérocycle comme squelette, et plus précisement, nous avons choisi la pyrido[3,2-*d*]pyrimidine qui a été peu explorée dans la littérature. Parmi les différents dérivés de ce régioisomère, nous nous sommes intéressés aux 2,4,8-trichloro-pyrido[3,2-*d*]pyrimidines substituées en position 6. En effet, le contrôle regioséléctif de la réactivité des trois chlores sur ces composés est apparu comme un défit intéressant.

Le but de ce second projet était dans un premier temps de trouver une voie de synthèse permettant l'accès à différentes 2,4,8-trichloro-pyrido[3,2-*d]*pyrimidines substituées en position 6, puisqu'aucune synthèse générale permettant leur formation n'a été reportée dans la litterature. Une nouvelle voie de synthèse pour la formation des 2,4,8-trichloro-pyrido[3,2-*d]*pyrimidines, substituées en position 6 avec des groupements alkyles ou aryles a donc été développée (composés **5 -** *Scheme 1*). D'après nos recherches, il s'agit de la première voie de synthèse générale développée pour de tels composés. Cette synthèse, en trois ou quatre étapes, a permis d'obtenir les composés **5** avec des rendements entre 30 et 52%.

SNAr reactions
Metal-catalyzed cross-coupling reactions
Chlorine reductions



R1=COOMe, Me, Ph

Figure 1. Réactions envisagées sur les trichloro-pyrido[3,2-d]pyrimidines **5**.

Dans un second temps, nous avons voulu explorer la réactivité des trois chlores présents sur ces composés en positions 2, 4 et 8, vis-à-vis de la substitution nucléophile aromatique et des réactions organo-metalliques (*Figure 1*). L'orthogonalité des trois centres réactifs, avec l'éventuelle différenciation des chlores, ainsi que l'influence du groupement en position 6 sur la réactivité des chlores, ont été investiguées. Lors de l'étude de la réactivité des trois chlores en positions 2, 4 et 8 sur ces composés, vis-à-vis des substitutions nucléophiles aromatiques, des amines primaires et secondaires, ainsi que des anilines ont pu être additionnées de façon regioselective en position 4. L'addition de thiols sur ces mêmes dérivés, a également eu lieu régiosélectivement en C-4. La liaison C-C en C-4, a quant à elle été introduite de façon selective en deux étapes à partir de la liaison C-S, formée par addition de thiols en C-4 sur les composés **5**, suivi de la réaction de couplage de Liebeskind-Srogl. Lors de ce couplage, aucune réaction secondaire n'a été observée sur les liaisons C-Cl. Sur les composés **5**, les réactions de couplages plus classiques sur les liaisons C-Cl, telles que les réactions de Suzuki, Stille ou Negishi, n'étaient pas régioselectives. L'introduction d'une liaison C-C en C-4 sur les 2,4,(6,7 or 8)-pyridopyrimidines, tous régioisomères confondus, n'a jamais été reporté précédemment.

La réactivité des deux autres chlores sur les 2,8-dichloro-pyrido[3,2-*d*]pyrimidines substituées en positions 4, *i.e.* les composés **12** et **15**, a ensuite été étudiée (*Figure 2*). L'addition d'amines primaires et secondaires, par substitution nucléophile aromatique, était régiosélective en position 2, indépendamment du substitutent en C-4 (*i.e.* amine ou aryle). De plus, lors de ces réactions, un seul régioisomère a été formé. Par contre, lorsque des thiols ont été additionnés sur ces mêmes composés, un mélange de deux régioisomères a été obtenu (*i.e.* produit d'addition en C-2 ou en C-8). Les conditions experimentales ont été ensuite optimisées sur les composés **12**, de façon à synthétiser l'un ou l'autre régioisomère: dans la DMF, l'addition en C-8 était favorisée, tandis que dans l'^{i}PrOH, l'addition en C-2 était majoritaire. L'application de ces conditions optimisées sur les dérivés **15** ont permis de constater que la régiosélectivité de l'addition de thiols dans la DMF était dépendante du substituant en position 4 (*i.e.* amine ou aryle). En effet, partant des dérivés **12** (ayant une amine en C4), le produit d'addition était majoritairement en C-8, tandis que partant des dérivés **15** (ayant un aryl en C4), le produit d'addition était majoritairement en C-2. Par contre, la régiosélectivité de cette même réaction dans l' ^{i}PrOH a été montrée comme indépendante du substituant en C-4, donnant pour les deux produits de départ (les composés **12** et **15**) majoritairement un produit d'addition en C-2. Les régioselectivité observées lors des réactions d'addition nucléophiles d'amines et de thiols sur les composés **12** et **15** sont résumées dans le *Schéma 2*.

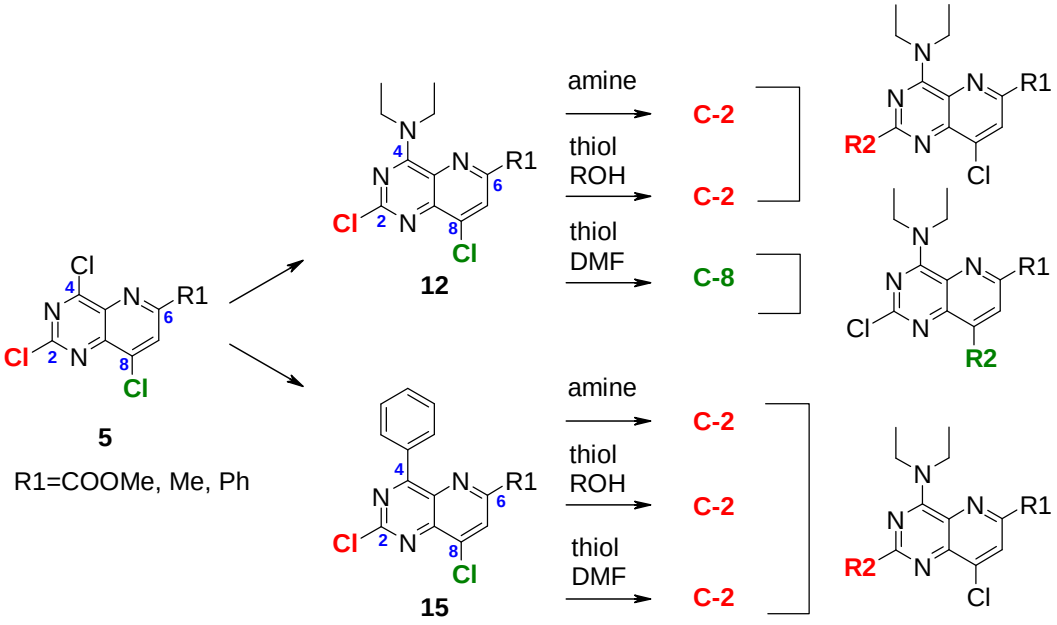


Figure 2. Résumé des régioselectivités observées pour les réactions de S_NAr sur les dérivés **12** et **15**.

La formation selective de liaisons C-C en positions 2 ou 8 sur les 4-amino(aryl)-pyrido[3,2-*d*]pyrimidines **12** et **15** a été effectuée après differenciation des deux chlores par addition regioselective de sodium methylthiolate. La présence de ces deux substituants orthogonaux, Cl et SMe, a permis la formation sélective sur la liaison C-Cl, d'une liaison C-C par réaction de couplage de Suzuki ainsi que de liaisons C-N et C-S. Dans un second temps, la liaison C-C a pu être formée à partir de la liaison C-S via la réaction de Liebeskind-Srogl. L'introduction de liaisons C-C en C-2 et/ou C-8 sur les pyrido[3,2-*d*]pyrimidines, n'a jamais été reporté précédemment.

En conclusion, nous avons développés une méthode pratique et robuste permettant de synthétiser des trichloro-pyrido[3,2-*d*]pyrimidines substituées en position 6 par divers groupes alkyles ou aryles. De plus, nous avons su contrôler la réactivité des trois chlores présents sur ces composés, pour des réactions de substitutions aromatiques nucléophiles et des réactions organo-metalliques. Enfin, nous avons démontré, pour la première fois, que des liaisons C-C pouvaient être introduites de façon sélective sur les dérivés de trichloro-pyrido[3,2-*d*]pyrimidines.

Abbreviations

δ	chemical shift
µL	microliter
µM	micromolar
µmol	micromole
%	percent
% inh.	percentage of inhibition
ACN	acetonitrile
aq.	aqueous
Ar	aryl
Atm.	atmosphere
Boc	*tert*Butoxycarbonyl
br s	broad singulet
℃	degree Celcius
calcd	calculated
cat.	catalyst
Cbz	benzyloxycarbonyl
CDI	1,1'-carbodiimidazole
conc.	concentration
conv.	conversion
COSY	correlation spectroscopy
CuTc	Copper (I) thiophene carboxylate
CuMeSal	Copper (I) methyl salycilate
d	doublet
DCB	dichlorobenzene
DCM	dichloromethane
DIEA	diisopropylethylamine
DMA	dimethylacetamide
DMAD	dimethyl acetylenedocarboxylate
DME	ethylene glycol dimethyl ether
DMF	*N*,*N*-dimethylfromamide
DMSO	dimethylsulfoxide
EDG	electron donating group
equiv	equivalent
ESI	electronspray ionization
ES-MS	ElectroSpray ionization Mass Spectroscopy
ET	electron transfer

Et_2O	diethyl ether
EWG	electron withdrawing group
g	gram
HBA	Hydrogen Bond Acceptor
HBD	Hydrogen Bond Donor
het	heterocycle
hr	hour
HMBC	Heteronuclear Multiple Bond Connectivity
HPLC	High Performance Liquid Chromatography
HSQC	Heteronuclear Single Quantum Coherence
IC_{50}	inhibition concentration for 50% of blockage
^{i}PrOH	isopropanol
IR	infra-red
J	coupling constant
LS	Liebeskind-Srogl
M	molar, mole per liter
m	multiplet
Maj.	Major
MeOH	methanol
mg	milligram
MHz	Megahertz
min	minute
min.	minor
mL	milliliter
mM	millimolar
mmol	millimole
mol	mole
M.S.	molecular sieve
Mw	molecular weight
MW	Microwave
mp	melting point
MP	macroporous
MS	mass spectroscopy
m/z	mass over charge ratio
n.d.	not determined
nM	nanomolar
NOESY	Nuclear Overhauser Effect Spectroscopy
NMR	nuclear magnetic resonance
o.n.	over night

ppm	parts per million
PPh3	triphenyl phosphine
PSA	Polar Surface Area
q	quadriplet
quant.	quantitative
Rf	retention factor
RotIbonds	Rotable Bonds
rt	room temperature
s	singulet
S_NAr	Aromatic Nucleophilic Substitution
solv.	Solvent
SPE	Solid Phase Extraction
t	time
t	triplet
T	temperature
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
t_R	retention time
1D	one-dimensional
2D	two-dimensional

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General Introduction.

The construction of heterocycles is a significant endeavor in synthetic organic methodology. They occur in a multitude of biochemically important compounds including drugs in development and on the market. Given the vastness of the chemical space, the challenge for medicinal chemists and biochemists is to identify the compounds that are more likely to be drugs.[1] A survey of the literature reveals that several biologically active molecules bear an acid functionality. Another class, the kinase inhibitors, consists of planar heterocycles that present hydrogen bond donating and/or accepting functionalities.[2] Some drugs belonging to these two classes of molecules, *i.e.* derivatives bearing acid functionality and kinases inhibitors, as well as combination of these, are represented in *Figure 1*.

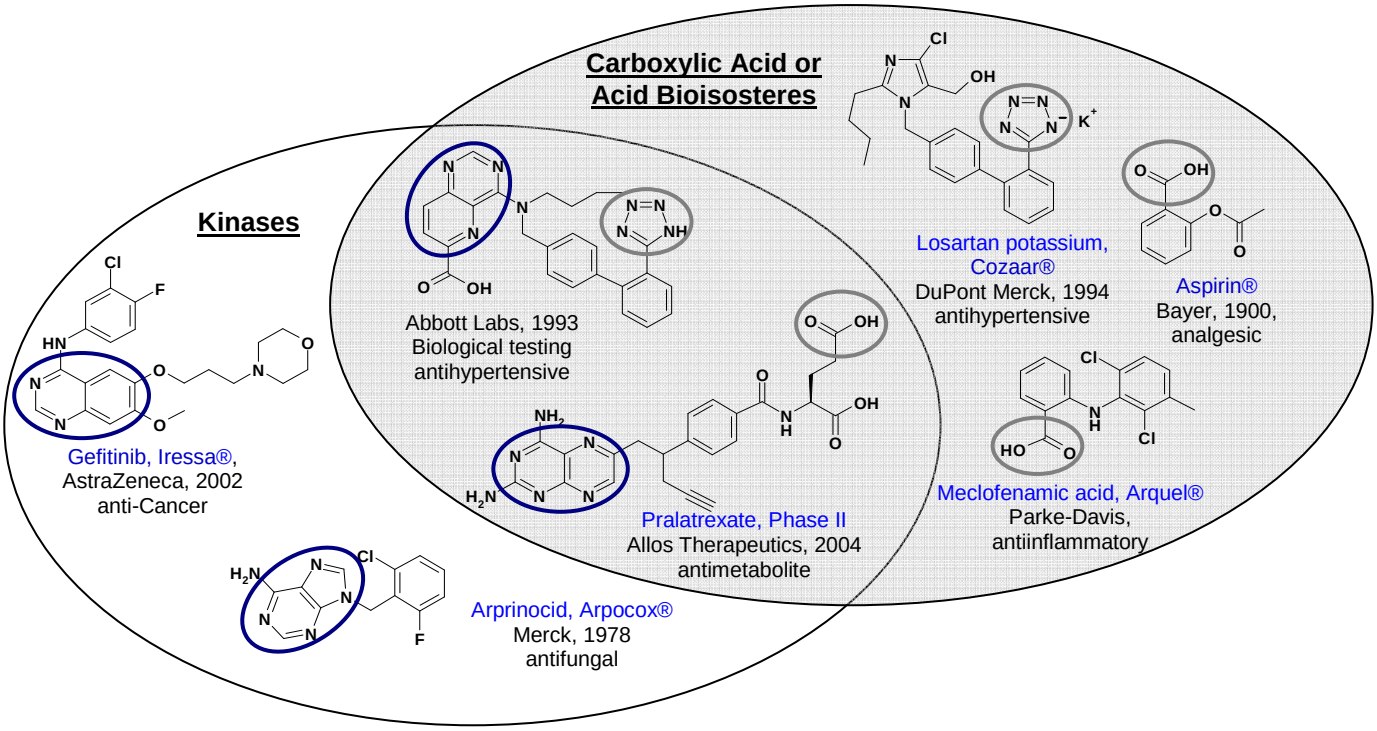


Figure 1. Representatives of drugs bearing an acid functionality and/or as heterocycles.

In the present work, we focused on the access to members of both classes of molecules. The scope of all reactions for the preparation of these molecules was explored to define the best experimental conditions to fit a wide range of reactants. In parallel, methodologies were developed around the derivatization of acid bioisosteres and pyridopyrimidine scaffolds, to provide robust protocols allowing the production of libraries of compounds.

[1] Lipinski, C.; Hopkins, A. *Nature*, **2004**, *432*, 855-412.
[2] (a) McMahon, G.; Sun, L.; Liang, C.; Tang, C. *Curr. Opin. Drug Dis. DeVelop.* **1998**, *1*, 131. (b) Adams, J. L.; Lee, D. *Curr. Opin. Drug Dis. DeVelop.* **1999**, *2*, 96. (c) Garcia-Echeverria, C.; Traxler, P.; Evans, D. B. *Med. Res. ReV.* **2000**, *20*, 28 and references therein.

In the first part, the parallel preparation of bioisosteres of acid derivatives via two successive reductive alkylations is reviewed (*Figure 2*).

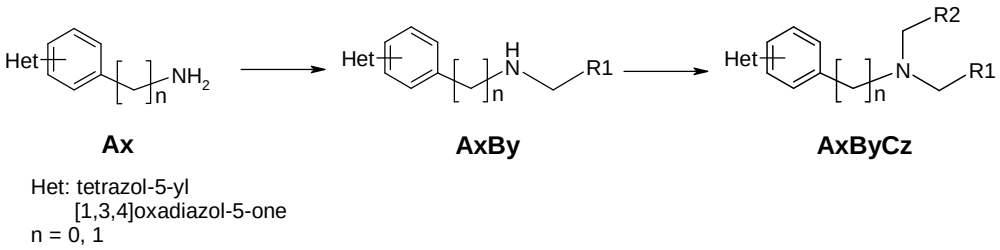
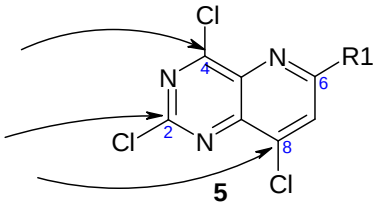


Figure 2. Synthesis of bioisosteres of acid derivatives **Ax**, **AxBy** and **AxByCz**.

In the second part of this work, the synthesis and the regioselective substitutions on trichloro-pyrido[3,2-*d*]pyrimidine scaffolds **5** are discussed (*Figure 3*).

SNAr reactions
Metal-catalyzed cross-coupling reactions
Chlorine reductions



R1=COOMe, Me, Ph

Figure 3. Synthesis and regioselectivity of trichloro-pyrido[3,2-*d*]pyrimidines **5**.

Part 1. Optimized Parallel Preparation of Acid Bioisosteres.

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1. Introduction.

Among the pharmacologically active compounds, a large number are organic acids or bases, capable of partial ionization in the physiological pH range.[1] This behaviour is of great importance because the ionized molecule, due to its electronical charge, possesses physical and chemical properties, which differ from those of its uncharged form. As consequence, ionization state plays an important role as a factor in drug absorption (lipophilicity) and distribution (bioavailability).[1] For these reasons, replacement of the acid functionality in drug-like compounds by acid bioisosteres is a frequently used strategy to modulate their overall biopharmaceutical profile.

Bioisosterism is the rational modification of lead compounds into more clinically effective agents.[2,3] The term “bioisostere” refers to compounds or substructures that share similar shapes, volumes, electronic distributions, physicochemical properties and have similar biological activity. The objective of a bioisosteric replacement is to create a new compound with similar biological properties to the parent compound but with a different overall biopharmaceutical profile, such as permeability, solubility, microsome stability, etc… Its systematic application has resulted in a broad variety of therapeutically used drugs, many of them finally having the desired combination of favorable properties.

In our continuing efforts to synthesize drug-like compounds, we report our investigations on the parallel synthesis of compounds bearing acid heterocycles. Tetrazole, a common isosteric replacement for the carboxylic acid moiety, and more recently the 1,3,4-oxadiazol-5-one have been chosen in this study as carboxylic acid bioisosteres. For the production of this primary library, we have developed a solution phase parallel synthesis, using solid supported reagents. Optimization of reaction conditions and the isolation process are described later in this part.

1.1. Chemical and Pharmacological Properties of Acid Bioisosteres.

Tetrazoles and oxadiazolones are heterocyclic acids that have attracted a lot of interest in medicinal chemistry.[4] For some time, 5-substituted-1*H*-tetrazoles have been used as isosteric replacements for the carboxylic acid moiety in biologically active molecules.[4]

It has been shown that aliphatic and aromatic tetrazoles have pKa values that are similar to the corresponding carboxylic acids (4.5-4.9 vs 4.2-4.4, respectively), due to the ability of the moiety to stabilize a negative charge by electron delocalization.[5] In general, tetrazolic acids exhibit physical characteristics similar to carboxylic acids and are strongly influenced by the effect of a substituent at the C5 position.[5]

Like their carboxylic acid counterparts, tetrazoles are ionized at physiological pH (7.4), and both exhibit a planar structure. However, Hansch has shown that anionic tetrazoles are almost 10 times more lipophilic than the corresponding carboxylates,[6] which is an important factor to bear in mind when designing a drug molecule to pass through cell membranes.

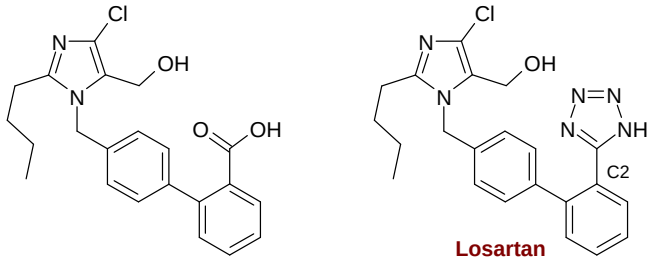
Another important factor when considering a tetrazole as a replacement is the effect of delocalization of the negative charge around the tetrazole ring. The distribution of charge over a great molecular surface area may be favourable for a receptor-substrate or enzyme-substrate interaction, or may complicate the contact, depending on the local charge density available at the interface. The larger size of the heterocycle (vs. a carboxyl group) may also change the interactions at the active site, either by less favourable orientation of functional groups, or by steric hindering of an active conformational change of the target.

Compared to tetrazoles, the use of oxadiazolone heterocycles as acid bioisosteres is less described in literature and few physicochemical data are available. Depending on the regioisomer, calculated pKa of oxadiazolones range between 6,5 and 11,9. It has been shown that these heterocycles are more lipophilic than carboxylic acids.[1] As previously said for the tetrazole moiety, the larger size of the oxadiazolones heterocycle versus a carboxyl group, and the changes in the global geometry of the resulting molecule may modify the interaction with the target.

As an illustration, we will present two examples taken from the literature to represent the various classes of acid bioisostere-containing substances that emerged from research efforts.

1.2. Medicinal Chemistry Case Studies in literature.

A well known bioisosteric replacement of a carboxylic acid by a tetrazole is the example of Losartan, a DuPont's non-peptidic selective angiotensin II receptor antagonist, launched in 1994 to treat hypertension (*Figure 1.1*).[7a-d]



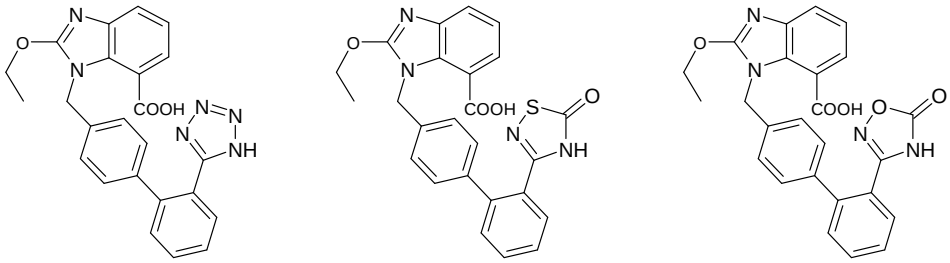
	1	2
IC_{50}	0.23 μM	0.02 μM
EC_{30} iv	3 mg/kg	0.8 mg/kg
EC_{30} po	11 mg/kg	0.6 mg/kg
pKa	4.5	5.0
logP	1.2	4.5

Figure 1.1. Comparison of Losartan and its carboxylic acid analogue.

While investigating new series of analogues derived from a biphenyl scaffold, it was found that compound **1** was active by i.v. injection in renal hypertensive rat models. Unfortunately, the effect was minimized upon oral administration. In an effort by the research team to find compounds with greater potency and bioavailability, a series of carboxylic acid isosters was prepared.

Interestingly, no carboxamide nor sulfonamide compounds were found to improve the oral activity, but when tetrazole was introduced at the C2 position (compound **2**), a dramatic enhancement in binding affinity and oral potency was observed, due to the greater ability of the heterocycle to distribute a negative charge at physiological pH. The observed increase in oral bioavailability of Losartan **2** compared to compound **1** may be due to the greater lipophilicity of the tetrazole, which can be correlated to logP values (4.5 vs 1.2 for compounds **2** and **1** respectively). The introduction of Losartan in the literature was followed by a great number of papers relating the use of bioisosteric replacement to improve the biopharmaceutical properties of lead compounds.[7e-g]

Based on these results, Naka's group in Japan has developed 2-substituted (1-benzylimidazol-5-yl)acetic acids as selective angiotensin II receptor antagonist.[8] By analogy to the strategy followed by DuPont's group, they incorporated the tetrazolylbiphenylmethyl moiety leading the discovery of Candesartan **3**. Few years later, Losartan **2** has been reported to be metabolized by *N*-glucuronidation on the tetrazole ring, which could shorten the duration of its effects *in vivo*. Naka's group investigated the replacement of the tetrazole ring by other more lipophilic acidic groups to improve oral bioavailability, which could also solve the metabolic problems. Investigations were done on the replacement of the tetrazole ring of **3** by other ionisable five-membered rings, such as oxadiazolone, oxathiadiazole and thioxadiazole. The 5-oxa-1,2,4-thiadiazole **4** and 2-oxa-1,2,4-oxadiazole **5** derivatives were found to be as potent as the tetrazole **3** derivatives (*Figure 1.2*). Each compound was further evaluated *in vivo* for inhibition of the pressor response induced by Angiotensin II in conscious rats. Derivatives **4** and **5** (TAK-536) showed higher inhibitory potencies than the tetrazole **3** after oral administration. These results were correlated with a higher oral bioavailability of these two compounds. TAK-536 was selected as a new highly potent AT2-selective receptor antagonist and is currently in phase II for the treatment of hypertension.



Candesartan
3

IC_{50} iv 0.11 µM
% inh. 3h/7h
1 mg/kg 100/92
0.1mg/kg 67/91
pKa 5.3
logP 0.32
Bioavailability 5%

4

IC_{50} iv 0.25 µM
% inh. 3h/7h
1 mg/kg 100/100
0.1mg/kg 100/100
pKa 6.6
logP 1.58
Bioavailability 51%

TAK-536
5

IC_{50} iv 0.42 µM
% inh. 3h/7h
1 mg/kg 100/100
0.1mg/kg 75/64
pKa 6.1
logP 0.90
Bioavailability 20%

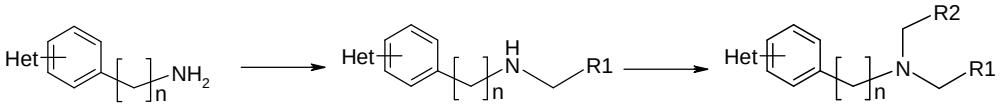
Figure 1.2. Comparison of Candesartan and its bioisostere analogues.

The improvement in *in-vitro* and *in vivo* ADME profile, associated with bioisosterism replacement of carboxylic acid by acid heterocycles, which has been demonstrated in the literature, together with the frequency of acid functionality found in pharmacologically active compounds, encourage us to design a novel library of compounds bearing acid heterocycle as one point of diversity.

1.3. A Library of heterocycles bearing an acid functionality.

1.3.1. General presentation of the library.

Combinatorial chemistry for the synthesis of a large number of organic compounds is recognized now as a key element of early drug discovery. Our approach involved the elaboration of tetrazole and [1,3,4]oxadiazol-2-one phenyl- and benzyl-amines (**Ax**) with two successive reductive alkylation reactions to provide two libraries, **AxBy** and **AxByCz**, respectively (*Scheme 1.1*). The two libraries were designed to incorporate a wide range of pKa and to introduce groups R1 and R2 which possess drug-like properties. Indeed, selection of R1 and R2 was based on three criteria: Lipinski's rules,[9] PSA,[10] and toxicity predictions of the final prepared compound.[11]



Ax **AxBy** **AxByCz**

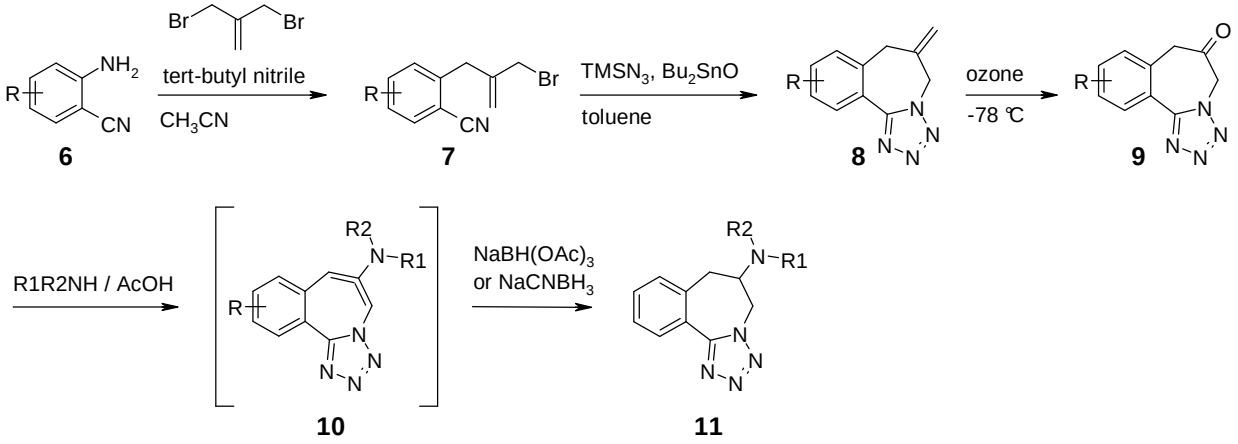
Het: tetrazol-5-yl
[1,3,4]oxadiazol-5-one
n = 0, 1

Scheme 1.1. General structure of the library derivatives.

Although solution-phase and solid-phase parallel synthesis have become a leading discovery and optimization tool for the library generation,[12] only few examples are reported in literature using these methods in the presence of acid heterocycles such as tetrazole and 1,3,4-oxadiazol-5-one. As an illustration, we will present four examples taken from the literature using tetrazole as acid heterocycle both in solution-phase and solid-phase parallel synthesis.

1.3.2. Tetrazole and solution-phase parallel synthesis in literature.

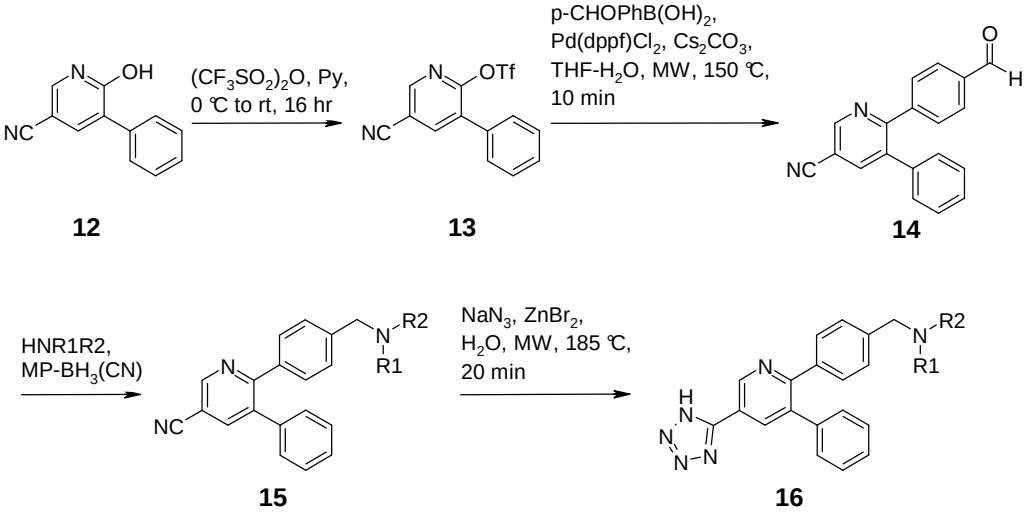
A first example for the synthesis of fused tetrazole derivatives in solution phase involved the generation of aryl radicals by diazotization and a subsequent *in situ* allylation with allylic bromide (DiazAll reaction).[13] Oxidation of the exocyclic double bond of derivatives **8**, followed by a reductive alkylation, afforded compounds **11,** which were purified by acid SPE (solid phase extraction columns). They produced a small amine library based on these novel tetrazole derivatives, where the diversification was introduced on the starting aromatic ring (R), and in the last step, on the amine HNR1R2 (*Scheme 1.2*).
Final compounds were obtained in moderate to good purity, from 65 to 97%, in yields ranging from 41 to 81%.
In this synthesis, the tetrazole formation in the second step was followed by intramolecular ring formation with allyl bromide, yielding a substituted fused tetrazole.



Scheme 1.2. Fused tetrazole derivatives synthesis.

A second example consists in the solution phase parallel synthesis of a library of 2,3,5-trisubstituted pyridine derivatives (*Scheme 1.3*).[14] Microwave assisted Suzuki coupling performed on the trifluoro-methanesulfonic acid 5-cyano-3-phenyl-pyridin-2-yl ester **13** afforded the aldehyde derivatives **14**. Further reductive aminations on these aldehydes with secondary amines HNR1R2 afforded derivatives **15**. Formation of the tetrazole was performed at the last step of this synthesis, leading to amino-acids **16**. No details on the purification process and yields were given.

In this synthesis, the diversification was introduced at the third step, on the amine HNR1R2, before the formation of the tetrazole ring at the last step. A small tetrazoylpyridine library of 32 compounds was produced following this chemical route.

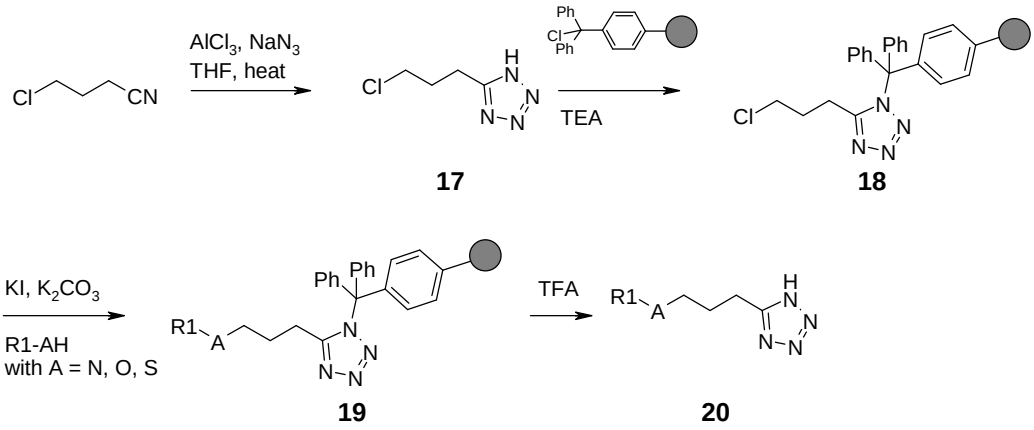


12 **13** **14** **15** **16**

Scheme 1.3. Tetrazoyl pyridine derivatives synthesis.

1.3.3. Tetrazole and solid-phase parallel synthesis in literature.

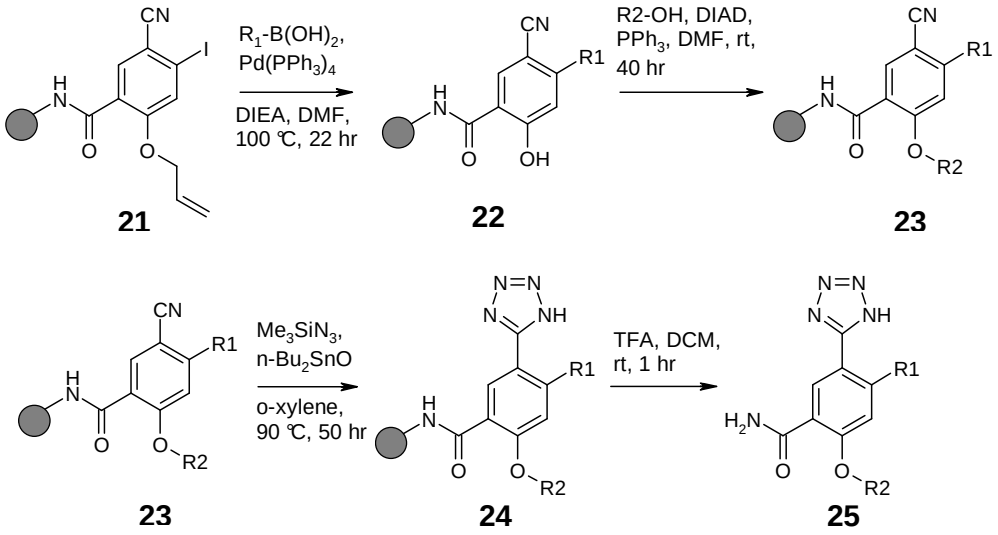
The synthesis of ω-chloroalkyl tetrazoles was described on solid phase synthesis.[15] After the tetrazole formation employing a mixture of $AlCl_3$ and NaN_3, a free NH of the heterocycle was protected with solid supported trityl chloride (derivatives **18**). Diversification was achieved by the succession of a Finkelstein reaction and a nucleophilic substitution affording compounds **20**, after cleavage of the trityl group in acidic media (*Scheme 1.4*). In this synthesis, the tetrazole was protected with a trityl group, which was also used as a linker for the solid support. A small library was produced, leading to 30 compounds with an average yield of 71% and purities above 90%, after cleavage from solid support.



17 **18** **19** **20**

Scheme 1.4. Alkyl tetrazole derivatives synthesis.

More recently, the synthesis of biphenyl tetrazole derivatives on solid-phase was described (*Scheme 1.5*).[16] Diversification was achieved by a succession of Suzuki coupling and Mitsunobu reaction. Derivative **21** was obtained by loading 2-allyloxy-5-cyano-4-iodo-benzoic acid on the amino polystyrene resin. Suzuki coupling followed by Mitsunobu reaction afforded compounds **23**. Tetrazole heterocycle **24** was then formed on solid support using trimethylsilyl azide in presence of a catalytic amount of dibutyltin oxide. The last step of this synthesis is the cleavage of the final compounds **25** in acidic conditions. Although the synthesis was performed on solid phase, final compounds were not pure enough and were further purified on preparative HPLC.



Scheme 1.5. Biphenyl tetrazole derivatives synthesis.

In these four examples, the tetrazole acid heterocycle was either formed in the last step of the synthetic process or protected, avoiding the presence of the free acidic proton during the synthesis. In the context of our work, we wanted to see if the envisioned synthesis was compatible with the presence of the free acidic proton on the heterocycle ring. For this reason, we synthesized the non-protected amino-acids building-blocks **Ax** (*Figure 2.1* - page 13). Reactions were carried out in solution, using solid-supported reagents. Solid phase extraction (SPE) was selected for the parallel purification of the final products, which can take advantage of their acid and basic properties. The demonstration of this approach in parallel synthesis is documented here through the synthesis of a set of 73 compounds.

2. Building blocks synthesis.

To study the scope of this approach, we selected ten main building blocks (**A1-A10**), six phenylamines and four benzylamines, which were substituted with either a tetrazole or an [1,3,4]oxadiazol-2-one (*Figure 2.1*). These compounds are seldomly used as building blocks, although **A1-A3** are commercially available and the synthesis of **A4-A6**, and **A10** has been reported.[17]

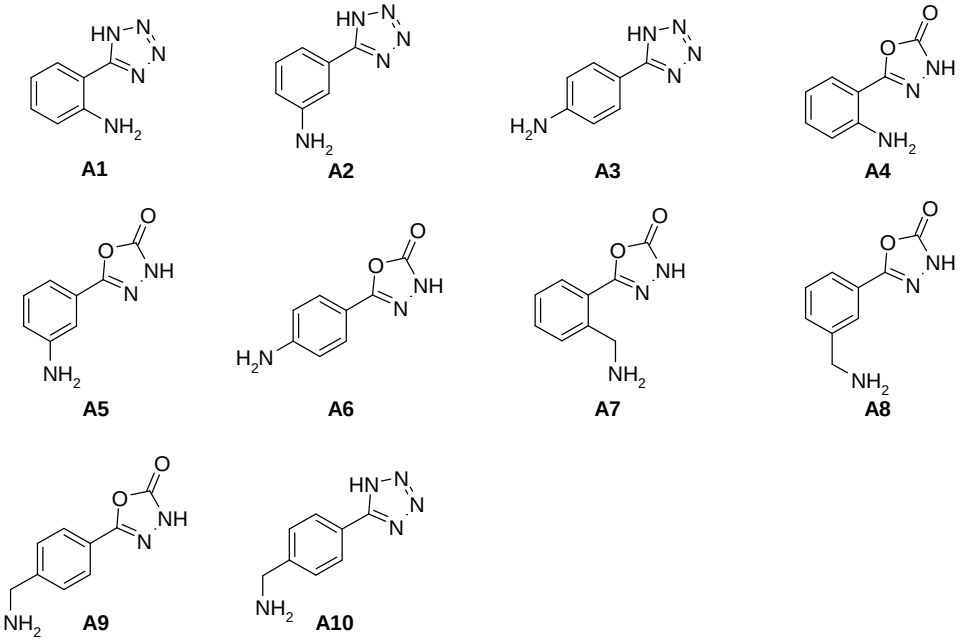
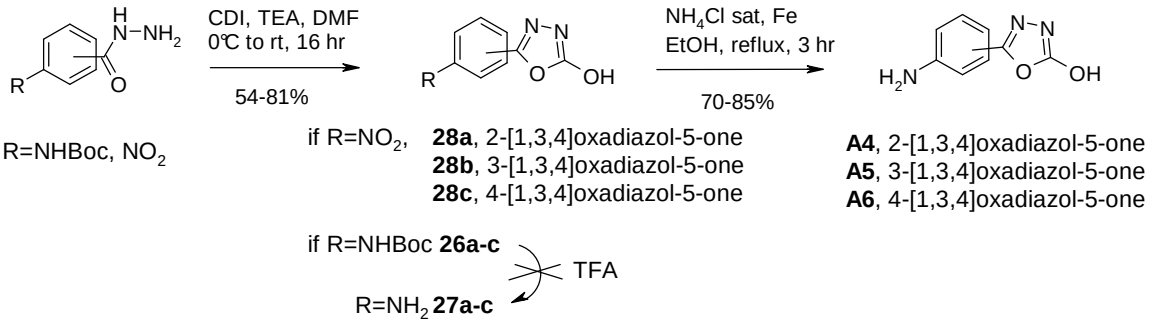


Figure 2.1. Selected phenyl- and benzyl-amines **A1** to **A10**.

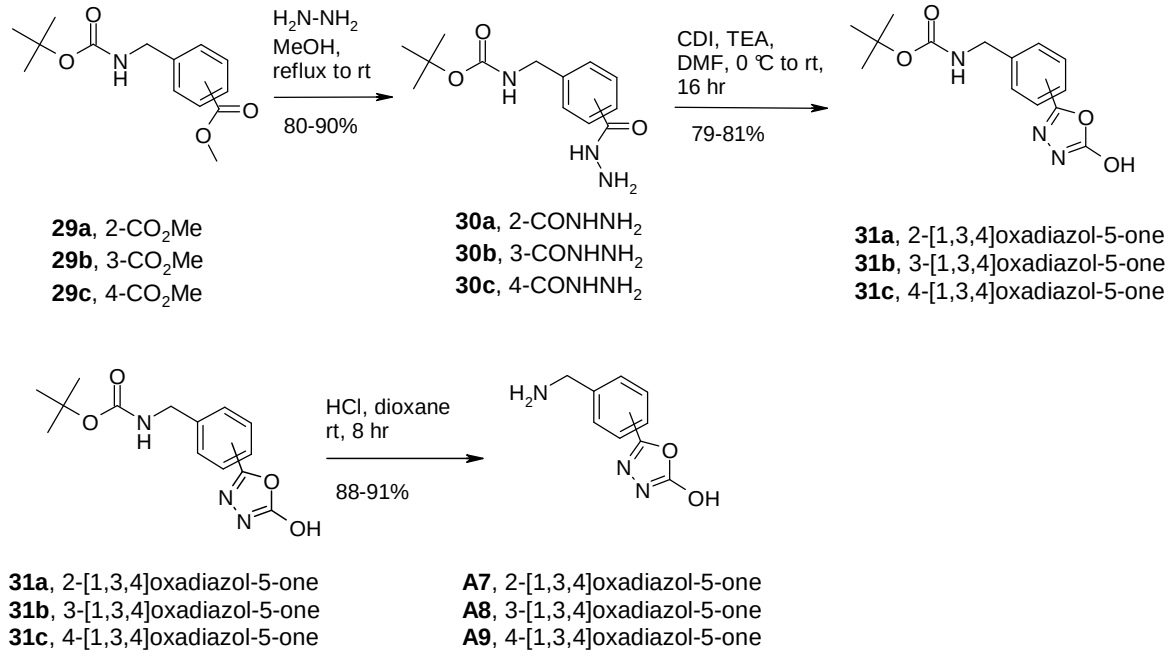
The synthesis of the 1,3,4-oxadiazol-2-one phenylamine derivatives **A4-A6** was initiated with the addition of 1,1'-carbodiimidazole to the appropriate commercially available amino-benzoic acid hydrazide.[18] In order to avoid the side-reaction of the free amino group with CDI (1,1'-carbodiimidazole), synthesis of **A4-A6** were envisaged with the protected amino-benzoic acid hydrazide. Boc was first selected as protecting group. Cyclization with CDI afforded derivatives **26a** to **26c**. Unfortunately, Boc cleavage on those derivatives, using classical deprotection conditions such as 20% of trifluoroacetic acid in dichloromethane, were not successful (*Scheme 2.1*).

Regarding these deprotection issues, a nitro group was further selected as alternative protecting group. The synthesis of three 1,3,4-oxadiazol-2-one phenylamine derivatives, **A4-A6,** was initiated with the addition of 1,1'-carbodiimidazole to the appropriate commercially available nitro-benzoic acid hydrazide to afford intermediates **28a-c**. Reduction of the nitro group with iron and ammonium chloride, provided derivatives **A4-A6** in gram scale and in good yields (*Scheme 2.1*).



Scheme 2.1. Synthesis of building blocks **A4-A6**.

The corresponding [1,3,4]oxadiazol-2-one benzylamine derivatives, **A7-A9,**[19] were obtained through a similar synthetic pathway, starting with the *N*-Boc protected aminomethyl benzoate **29a-c** (*Scheme 2.2*).[20] Hydrazine addition in MeOH afforded intermediates **30a-c** in good yields (80-90%). Cyclization with 1,1'-carbodiimidazole afforded the *N*-Boc-protected benzylamine intermediates **31a-c**. The final *N*-Boc deprotection afforded the [1,3,4]oxadiazol-2-one benzylamine building blocks, **A7-A9**, in 88 to 91% yields. In this case, contrary to the 1,3,4-oxadiazol-2-one phenylamine derivatives **A4-A6**, Boc deprotection on the benzylamine scaffold was successful. To our knowledge, this is the first synthesis of these three building blocks.



Scheme 2.2. Synthesis of building blocks **A7-A9**.

The tetrazole benzylamine building block **A10** was synthesized according to reported procedures.[7e-f]

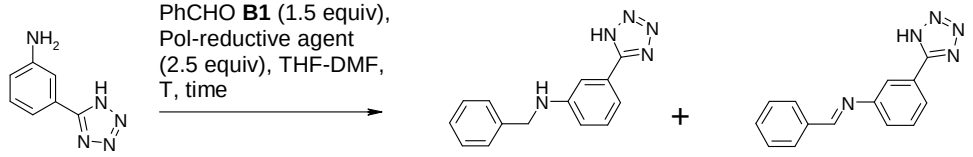
Aiming to find the best conditions suitable for the production of a library of compounds synthesized via reductive alkylations of building block **A1-A10** with diverse aldehydes, different reducing agents and SPE columns were further evaluated.

3. Optimization of reaction conditions and purification process.

3.1. Selection of solid phase supported reductive agent for reductive alkylation.

The use of reductive alkylation in solution phase parallel synthesis has been facilitated by the development of polymer supported reductive agent, such as macroporous (MP) borohydride,[21] MP-triacetoxyborohydride[21] and MP-cyanoborohydride.[21-22] MP-Borohydride is effective in a wide range of reductions similar to the ones reported for sodium borohydride. This includes carbonyl and imine reduction, reductive amination with titanium isopropoxide, with products isolation by simple filtration. MP-Triacetoxyborohydride is a versatile reducing agent for the reductive amination of carbonyl compounds.[23] It offers similar scope and reactivity to sodium triacetoxyborohydride in solution phase reductive aminations and is active under neutral conditions. MP-Cyanoborohydride is effective for a wide range of reductive aminations and offers the advantage that the toxic cyanide by-products are removed by filtration.

MP-triacetoxyborohydride and MP-cyanoborohydride were selected as solid supported reductive agents. Reductive alkylation step was optimized with 4-(*1H*-tetrazol-5-yl)-phenylamine **A2** and the benzaldehyde **B1** (*Table 3.1*).



A2 **A2B1**

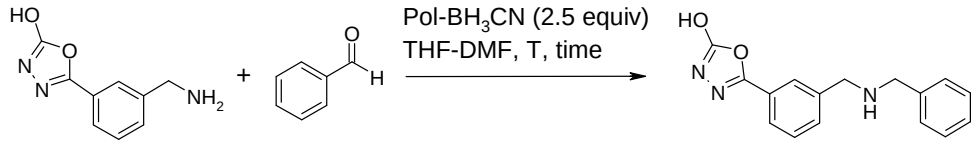
Entry	Reductive agent (equiv)	AcOH (equiv)	Reaction time (hr)	T	% conversion amine/imine	HPLC purity	Yield
1	Pol-$BH(OAc)_3$	no	24	rt	0 / 44	nd	nd
2	Pol-$BH(OAc)_3$	no	0.5	80℃ MW	0 / 33	nd	nd
3	Pol-BH_3CN	25% vol	24	rt	100 / 0	96%	46%

Table 3.1. Optimization of first reductive alkylation with phenylamine **A2**.

As described in *Table 3.1*, reaction temperatures from 25 to 80 ℃, and reaction times, from 30 min to 24 hours, have been tested. Percentages of conversion into imine with MP-triacetoxyborohdride were the same, independent to the temperature and the reaction time (*Entries 1-2*). But no reduction into secondary amine was observed.

On the other hand, MP-cyanoborohydride with 25% vol of AcOH, yielded the desired secondary amine in good purity (*Entry 3*). Optimized conditions consisted in the use of 1.5 equiv of aldehyde, 2.5 equiv of polymer supported cyanoborohydride in a mixture of THF and DMF containing AcOH (25% vol), at room temperature for 24 hours. These conditions were used for the reductive alkylation of building blocks **A1-A6** with diverse aldehydes.

When these conditions were applied to benzylamine **A8** and benzaldehyde **B1**, 58 to 75% of double reductive alkylation were observed (*Table 3.2 - Entry 1*). By decreasing the amount of aldehyde from 1.5 to 1.1 equiv, a decrease in double reductive alkylation product was observed (compare *Entry 1 and Entry 2*). Similar results were obtained with 1.5 equiv of aldehyde, performing the reaction at lower temperature, such as 0 °C for 5 hr (*Entry 3*). Optimized conditions for the reductive alkylation of building blocks **A7-A9** resulted in the use of 1.1 equiv of aldehyde, 2.5 equiv of polymer supported cyanoborohydride in a mixture of THF and DMF containing AcOH (25% vol), at 0 °C for 5 hr (*Entry 4*).



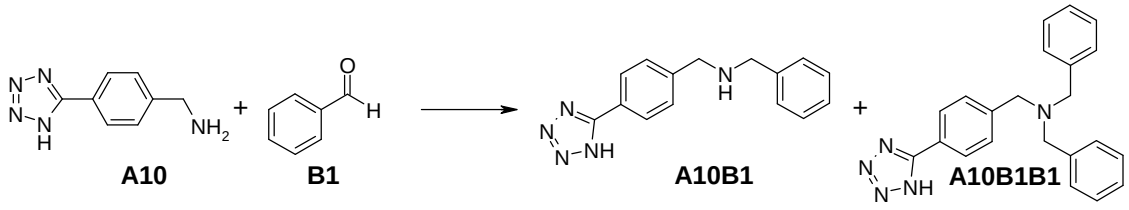
A8 **B1** **A8B1**

Conditions	Temperature	Time (hr)	Aldehyde (equiv)	% Double reductive alkylation
1[a]	rt	16	1.5	58-75
2	rt	16	1.1	22-32
3	0 °C	5	1.5	20-23
4	0 °C	5	1.1	2-4

[a]: same conditions as the one used for reductive alkylation with aminophenyl **R3**-NH2 groups

Table 3.2. Optimization of first reductive alkylation with benzylamine **A7-A9**.

When these reaction conditions were applied to tetrazole benzylamine derivatives, double reductive amination was observed. An auto-catalysis of the reaction by the acidic proton of the tetrazole could explain this result. To study this hypothesis, alternative reaction conditions were tried with 4-aminomethylphenyltetrazole **A10** and benzaldehyde **B1** as partners (*Scheme 3.1*).



A10 **B1** **A10B1** **A10B1B1**

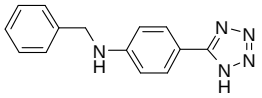
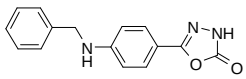
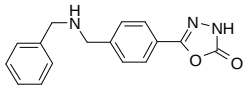
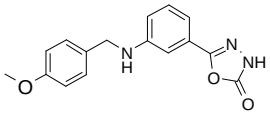
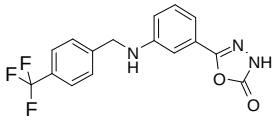
Figure 3.1. First reductive alkylation with benzylamine **A10.**

At 0 °C, when no acetic acid was added to the reaction mixture, an increase in double reductive alkylation **A10B1B1** was observed (58% vs 49%) as well as a decrease in **A10B1** (23% vs. 46%). The same reaction was performed under basic conditions, with the addition of an excess of DIEA. Only 2% of **A10B1** and 38% of **A10B1B1** were observed. In addition, 52% of an un-identified side product was formed during the reaction. A different reductive agent, Pol-$BH(OAc)_3$ was further used. However, the reaction was less clean, yielding only 2% of mono reductive alkylation. The double reductive alkylation product **A10B1B1** was not observed under these conditions. Reductive alkylation on *N*-protected tetrazole would be a way to confirm the hypothesis of auto-catalysis of the reaction by the tetrazole acidic proton. As we did not want to add protection/deprotection steps in the process, building block **A10** was removed in the library production.

3.2. Selection of Solid Phase Extraction columns for parallel purification.

Since reactions in a library synthesis give usually mixed purities, we have decided to develop a general purification strategy. One convenient purification technique used in parallel solution-phase synthesis is the catch and release method using a solid phase extraction column (SPE).[24] It consists in an extraction that uses a solid and a liquid phase to isolate one type of analyte from a solution, such as a base or an acid for respectively acid or basic SPEs. Compared to the classic liquid-liquid extraction using the separatory funnel or the preparative HPLC purification, SPE offers several advantages such as an easier manipulation and less solvent required.

Although SPE purification as work-up techniques are widely used in parallel synthesis,[25] their use has not been reported with acid heterocycles such as tetrazoles and 1,3,4-oxadiazol-2-ones. In order to select the most suitable column for solid-phase ion-exchange extraction, the pKa values of a representative number compounds were calculated (*Table 3.3*).[26] Benzyl-phenyl secondary amines **A3B1** and **A6B1** have a pKa of 2.8-2.9, whereas a pKa of 9.1 was calculated for bis-benzyl amine **A9B1.** The pKa of the acid heterocycles was also determined, and an average value of 5.0 was obtained for the tetrazolyl moiety and 7.3 for the [1,3,4]oxadiazol-2-yl moiety. Compounds with a substituted benzyl amine **A5B2**, **A5B3**, **A2B2** and **A2B3** gave similar secondary amine and acid heterocycle pKa values as the ones calculated for the compounds with unsubstituted benzyl amines **A3B1** and **A6B1**.

Compound	PKa sec amines	PKa acid heterocycle
 ***A3B1***	2.9	5.1
 ***A6B1***	2.8	8.4
 ***A9B1***	9.1	8.2
 ***A5B2***	3.1	6.7
 ***A5B3***	3.1	6.7

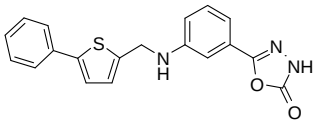
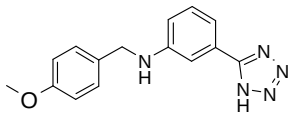
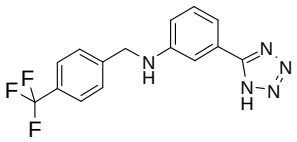
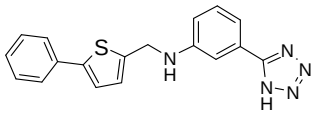
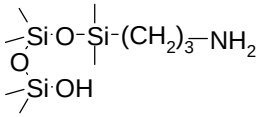
Compound	PKa sec amines	PKa acid heterocycle
 ***A5B5***	2.8	6.7
 ***A2B2***	3.2	5.0
 ***A2B3***	3.2	5.0
 ***A2B5***	2.9	5.0

Table 3.3. Calculated pKa of selected **AxBy** derivatives.

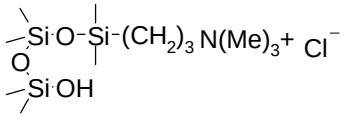
Since compounds **AxBy** contain weak acid and basic functionality, either strong anion or cation solid-phase exchange sorbents have to be used to purify them (*Figure 3.1*).

BASIC SPE:

SPE NH_2

Structure: 

SPE SAX

Structure: 

pKa estimated: 9.8

ACID SPE:

SPE SCX

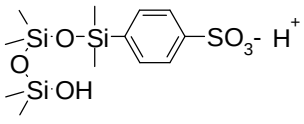
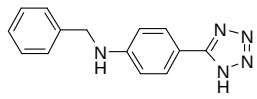
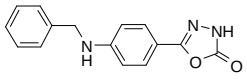
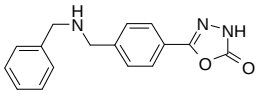
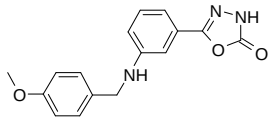
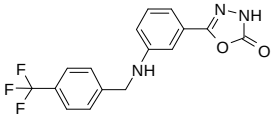
Structure: 

Figure 3.2. Basic and acid SPE used for the optimization of the purification process.

While anion exchange sorbent ISOLUTE® SPE NH_2 (an aminopropyl phase),[27] was able to retain the tetrazole derivatives, it was not basic enough to retain the [1,3,4]oxadiazol-2-one derivatives. On the other hand, the strong anion exchange sorbent ISOLUTE® SPE SAX (a quaternary amine phase with a hydroxyl counter ion) was able to retain both series of

compounds.[28] The hydroxyl counter ion on this sorbent could be easily obtained from the corresponding commercially available chlorine counter-ion by treatment with either a sodium or potassium hydroxide solution. A typical purification procedure with the strong anion exchange sorbent ISOLUTE® SPE SAX consisted of the evaporation of the reaction mixture (to avoid saturating the sorbent with acetic acid), dissolution in THF/DMF mixture, and loading of the resulting solution onto the conditioned ISOLUTE® SPE SAX sorbent. Excess aldehyde was removed by washing the column with CH_3CN, and the desired product was released with a HCl solution (0.1 to 1N) in CH_3CN/MeOH mixture. Alternatively, by taking advantage of the basic amine, a strong cation exchange sorbent ISOLUTE® SPE SCX (a benzenesulfonic acid phase) could be used to purify the final products.[29] A similar protocol was followed, except that the release step was performed with a NH_3 solution (0.1 to 0.5 N) in methanol. Yields and purities were compared with both the ISOLUTE® SPE SAX and the ISOLUTE® SPE SCX sorbents and similar results were observed (*Table 3.4*). However, when using the strong cationic exchange sorbent ISOLUTE® SPE SCX, the reaction mixtures could be directly loaded onto the column, as acetic acid is not retained on this sulphonic acid phase. Thus ISOLUTE® SPE SCX sorbent use was found more expeditious.

Compound	HPLC Purity % (Yield %)		
	Crude	SPE SAX	SPE SCX
 ***A3B1***	80	82 (78)	86 (76)
 ***A6B1***	96	100(84)	98 (85)
 ***A9B1***	91	95 (89)	98 (91)
 ***A5B2***	82	91 (80)	95 (43)
 ***A5B3***	94	98 (80)	100(65)

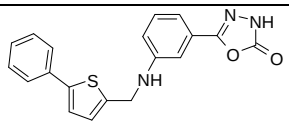
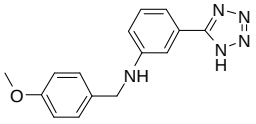
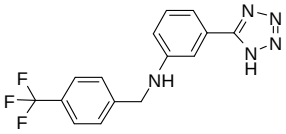
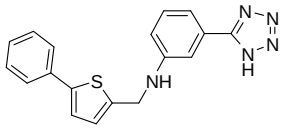
Compound	HPLC Purity % (Yield %)		
	Crude	SPE SAX	SPE SCX
 ***A5B5***	94	77 (85)	96 (85)
 ***A2B2***	77	97 (77)	97 (49)
 ***A2B3***	73	92 (62)	95 (42)
 ***A2B5***	89	96 (85)	89 (67)

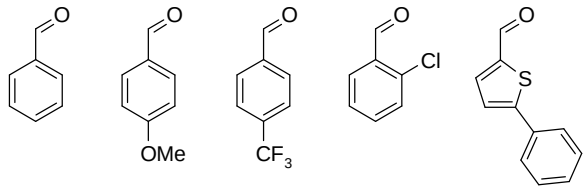
Table 3.4. Comparison of purification with SPE SAX and SPE SCX.

Optimized conditions found for reductive alkylation of phenylamine building blocks **A1-A6** and benzylamine building blocks **A7-A9** with benzyladehyde were applied to various aldehydes having diverse electronic properties. Using these conditions, a set of 73 compounds was produced by two successive reductive alkylations. Final compounds were purified using the ISOLUTE® SPE SCX sorbents.

4. Library production.

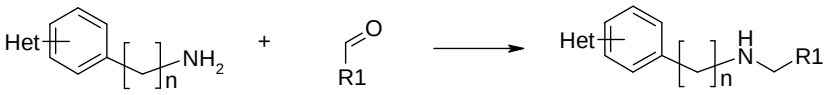
4.1. Library production.

The first step in the library production was to react the nine phenylamino and benzylamino acid derivatives, **A1-A9**, with five commercially available aromatic aldehydes that possess diverse functionality and electronic properties, **B1-B5** (*Figure 4.1*). The reactions were performed on a 0.18 mmol scale, with a reaction mixture concentration of 0.08 M, in 4 mL vials placed in a orbital shakers. The resulting secondary amines, **AxBy**, were purified by SPE using ISOLUTE® SPE SCX columns on a VacMaster®-20 manifold (*Table 4.1*). With alkyl aldehydes, double reductive alkylation could not be avoided under these conditions. For this reason, only benzaldehyde derivatives were used for the first step.



B1 **B2** **B3** **B4** **B5**

Figure 4.1. Aldehydes selected for the first reductive alkylation reaction.



A1-A9 **B1-B5** **AxBy**

Purity % (Yield %)	A1	A2	A3	A4	A5	A6	A7[d]	A8[d]	A9[d]
B1	91(80)[b]	90(92)[b]	81(98)[a]	89(97)[b]	97(84)[b]	94(52)[b]	98(70)[b]	97(32)[c]	81(76)[b]
B2	78(90)[b]	98(68)[b]	83(98)[b]	87(85)[b]	85(98)[b]	88(55)[b]	85(40)[a]	93(24)[c]	99(28)[c]
B3	92(78)[b]	95(42)[a]	84(20)[a]	95(72)[b]	99(25)[a]	96(17)[a]	68(32)[a]	85(64)[b]	99(34)[c]
B4	93(82)[b]	96(72)[b]	92(87)[b]	25(60)[b]	95(63)[b]	92(50)[b]	67(59)[b]	83(62)[b]	60(80)[b]
B5	55(31)[a]	83(44)[a]	77(30)[a]	91(74)[b]	99(44)[a]	99(40)[a]	86(73)[b]	91(31)[c]	97(33)[c]

[a]: NH_3 solution (2 x 0.1 N) in MeOH used for the release step

[b]: NH_3 solution (0.1 N + 0.5 N) in MeOH used for the release step

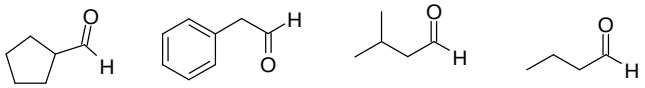
[c]: purification by ISOLUTE® SPE SCX followed by filtration of the resulting precipitate

[d]: reactions performed at 0 ℃ to avoid double reduc tive alkylation

Table 4.1. First reductive alkylation reaction.

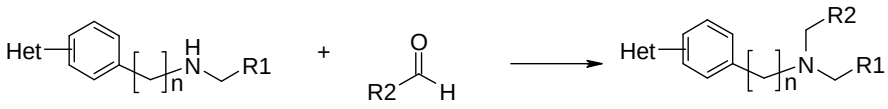
The yields were dramatically influenced by the mode of purification, and were improved with the use of a more concentrated ammonia solution for the releasing step from ISOLUTE® SPE SCX (0.5N vs. 0.1N, *Table 4.1, note b*). Interestingly, the electronic density of the aldehydes **By** had no influence on the overall yields or purity of the final products (*Table 4.1, Column 4*). In some cases, the desired product was precipitated after ISOLUTE® SPE SCX purification (*Table 4.1, note c*), which resulted in higher purity but lower yields (24 to 34% yields). In summary, under these conditions, compounds **AxBy** could be isolated with high purity (> 80% in most cases) and with moderate to excellent yields. In addition, this practical reaction procedure allowed the use of classical instruments.

Based on these promising results, the secondary amines, **AxBy**, were subjected to a second round of reductive alkylation step. Low molecular weight aldehydes were selected to provide final compounds **AxByCz** with molecular weights below 350 g mol^{-1} (*Figure 4.2*). An excess of the aldehyde (5 equiv), and a reaction mixture concentration of 0.08 M were found to be crucial for complete conversion to the final products **AxByCz**. After 24 hours at 50 ℃ and similar to the first reaction, the reaction mixtures were purified in parallel using the ISOLUTE® SPE SCX column. Under these conditions, the final tertiary amine products, **AxByCz**, were isolated in high purity (>80% in most of the cases), and modest to excellent isolated yields (27 to 98%) (*Table 4.2*). However, with benzyl-phenylamines bearing an ortho acid heterocycle **A1By** and **A4By**, the second reductive alkylation was not feasible, probably due to steric hindrance. These two secondary amines were removed in the final library production.



C1 **C2** **C3** **C4**

Figure 4.2. Aldehydes selected for the second reductive alkylation reaction.



AxBy **C1-C4** **AxByCz**

Purity % (Yield %)	A2B1	A3B1	A5B1	A6B1	A7B1	A8B1	A9B1
C1	87(98)	88(50)	92(97)	63(98)	93(85)	97(34)	84(98)
C2	85(98)	80(98)	92(98)	76(98)	92(83)	81(84)	86(98)
C3	92(96)	90(67)	95(61)	83(98)	96(83)	95(27)	83(91)
C4	87(91)	91(54)	92(97)	98(98)	96(69)	93(33)	84(81)

Table 4.2. Second reductive alkylation reaction.

4.2. Drug-like properties of the library.

The two libraries of tetrazole and [1,3,4]oxadiazol-2-one derivatives, **AxBy** and **AxByCz**, were evaluated in silico for their drug-like properties (molecular weight (MW), logP, number of hydrogen bond donors (HBDs) and acceptors (HBAs), rotating bonds and polar surface area (tPSA) - *Table 4.3*).[30] Overall, 97% of the library had no "Rule of 5" violation.[c] The majority of the tertiary amines showed a calculated logP value below 5, with an average value of 4.7. As a general observation, all parameters remained in an acceptable range for a lead-like collection of compounds as potential orally bioavailable agents.

Compound	MW	AlogP98	HBAs	HBDs	RotIbonds	tPSA
AxBy	309.23	3.3	5	2	5	71.5
AxByCz	346.11	4.7	5	1	8	61.1

Table 4.3. Molecular properties of the library members (average values).

We have developed an efficient and expeditious method to synthesize and purify drug-like amino tetrazole and [1,3,4]oxadiazol-2-one derivatives with good purities. Phenyl- and benzyl-amines, substituted with tetrazole or [1,3,4]oxadiazol-2-one carboxylic acid bioisosteres, were transformed into functionally diverse and novel compounds, with pKa values ranging from 4.9 to 8.4, by two sequential reductive alkylation reactions.

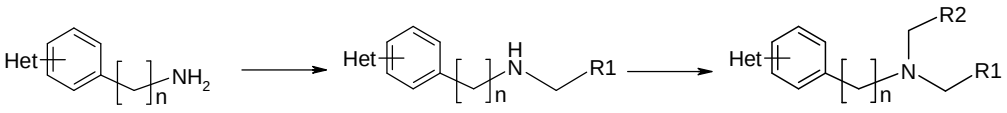
[c] Lipinski's Rule of Five is a rule of thumb to evaluate druglikeness, or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans. The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion ("ADME"). However, the rule does not predict if a compound is pharmacologically active.

Lipinski's rule says that, in general, an orally active drug has no more than one violation of the following criteria:

- Not more than 5 hydrogen bond donors
- Not more than 10 hydrogen bond acceptors
- A molecular weight under 500 daltons
- An octanol-water partition coefficient log *P* of less than 5

5. Conclusion.

The originality in the design of this library was the use of the amino acid building blocks **A1** to **A9** and the development of the synthetic route (*Scheme 5.1*). In contrast to the reported libraries in literature, we were pleased to see that no protection of the acid heterocycle was required. Moreover, the purification of final amino-acids could be done on basic and acid ISOLUTE® SPE columns, despite their wide range of pKa (from 4.9 to 8.4).



Ax **AxBy** **AxByCz**

Het: tetrazol-5-yl
[1,3,4]oxadiazol-5-one
n = 0, 1

Scheme 5.1. General structure of the library derivatives.

AxBy synthesis was successfully achieved by reductive alkylation of amino acid building blocks **A1-9** with diverse aromatic or heteroaromatic aldehydes **By**. Final secondary amines **AxBy** were obtained with HPLC purity between 81 and 100% with yields ranging from 24 to 100%. This procedure allowed us to recover 86% of the library with the desired purity.

AxByCz synthesis was successfully achieved via reductive alkylation of secondary amino acids **AxBy** with alkyl aldehydes **Cz**. Purification of the resulting tertiary amino acids **AxByCz**, achieved on ISOLUTE® SPE SCX, yielded 80% of the library having purities between 80 and 97% in yield ranging from 33 to 100%.

In conclusion, we have developed a practical and robust method to synthesize and purify drug-like amino 1*H*- tetrazole and [1,3,4]oxadiazol-2-one derivatives. Phenyl- and benzyl-amines, substituted with 1-*H*-tetrazole or [1,3,4]oxadiazol-2-one as acid bioisosteres were transformed into diverse and novel compounds, with pKa ranging from 4.9 to 8.4, by two sequential reductive alkylations. To further complete the diversity and the range of pKa of the final products, this simple procedure was applied to additional amino acid bioisosteres as building blocks. The optimized conditions of reaction and purification were used for the production of a library of 1.5 K compounds. With a charge distribution over a greater molecular surface and a greater lipophilicity character compared with the corresponding carboxylic acids, 1*H*-tetrazole and [1,3,4]oxadiazol-2-one derivatives may offer different interactions with receptors or enzymes. Biological evaluation of this collection is in progress.

6. Experimental Part.

^{1}H and ^{13}C NMR spectra were recorded with a BRUKER DPX-300 spectrometer (300 MHz and 75.47 MHz respectively). HPLC analyses were performed on a Waters 2695 instrument, equipped with a Waters 996 Photodiode Array Detector and an XTerra MSC8 3.5 μm 4.6×50 mm column. Chromatographic conditions consisted in a gradient from 95% H_2O (0.1% TFA): 5% CH_3CN (0.1% TFA) to 5% H_2O (0.1% TFA): 95% CH_3CN (0.1% TFA) over 8 minutes with a flow of 2 mL/min. Mass spectra were determined on a Micromass ZMD (electrospray, positive and negative ionisation). Elemental analyses were performed on an Erba Science 11108 CHN analyzer. Macroporous cyanoborohydride resin (macroporous triethylammonium methylpolystyrene cyanoborohydride, 0.5% inorganic antistatic agent, 655 μm, loading 2.32 mmol/g, Part no. 800406) was purchased from Argonaut. All SPE columns were purchased from Separtis. The sulfonic acid-functionalized SPE columns were ISOLUTE® SPE SCX columns (1 g: Part no. 530-0100-C, ion exchange capacity 0.29 mequiv/g; 100 mg: Part no. 530-0010-B, ion exchange capacity 0.29 mequiv/g). The aminopropyl-functionalized SPE columns were ISOLUTE® SPE NH2 column (500 mg: Part no. 470-0050-B, ion exchange capacity 0.56 mequiv/g) and the quaternary amine (chloride counter ion) functionalized SPE columns were ISOLUTE® SPE SAX columns (500 mg: Part no. 500-0050-B, ion exchange capacity 0.55 mequiv/g). 4-(1*H*-tetrazol-5-yl)-phenylamine and 2-(5-tetrazolyl)-aniline were bought from Dynamit and 3-(1*H*-tetrazol-5-yl)-phenylamine was purchased from Avocado. 4-Nitro-benzoic acid hydrazide, 3-nitro-benzoic acid hydrazide and 2-nitro-benzoic acid hydrazide were bought from Aldrich. All other reagents were bought from Aldrich or Avocado and used without purification. Anhydrous solvents were purchased, stored on activated molecular sieves, and used without prior distillation.

Starting Material Synthesis.

2-(2-aminophenyl)-1,3,4-oxadiazol-2-one (**A4**).

To a solution of 2-nitro-benzoic acid hydrazide (20 g, 0.11 mol) in dimethylformamide (200 mL), triethylamine (19 mL, 0.33 mol) was added. The reaction mixture was cooled to 0 °C for 10 minutes under nitrogen atmosphere. Then 1,1-carbonyl diimidazole (26 g, 0.16 mol) was added portionwise. The reaction mixture was stirred at room temperature for 10 hr. Completion of the reaction was confirmed by TLC. The solvents were evaporated under vacuum at 40 °C and the residue was triturated in water (150 mL). The solid obtained was filtered and washed with water to afford 12 g of **28a** (54%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 7.82-7.95 (m, 3H), 8.09-8.12 (m, 1H), 12.87 (br s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 117.2, 124.5, 130.3, 133.0, 133.4, 147.5, 150.5, 154.1; HPLC t_R = 2.43 min. ES-MS *m/z* 205.9 $(M + H)^+$. To a mixture of 5-(2-nitrophenyl)-1,3,4-oxadiazol-2-one (10 g, 0.05 mmol) and iron powder (13.3 g, 0.24 mol) in ethanol (120 mL) heated at reflux, was added dropwise a saturated aqueous solution of ammonium chloride (100 mL). The reaction

mixture was heated to 80 °C for 3 hr. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and filtered through Celite®. The filtrate was concentrated and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to afford 6 g of **A4** (70%) as a white solid.[7a-b] ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 6.30 (s, 2 H), 6.64 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 7.5 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.44 (d, J = 8 Hz, 1H), 12.50 (br s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 104.5, 115.5, 115.8, 126.7, 131.8, 146.9, 153.6, 154.6, HPLC t_R = 2.19 min, ES-MS m/z 177.9 $(M + H)^+$.

2-(3-aminophenyl)-1,3,4-oxadiazol-2-one (**A5**).

To a solution of 3-nitro-benzoic acid hydrazide (19 g, 0.10 mol, 1 equiv) in dry DMF (200 mL) at 0 °C was added TEA (29 mL, 0.21 mol, 2 equiv) and CDI (25.5 g, 0.16 mol, 1.5 equiv). The reaction mixture was stirred at room temperature under nitrogen for 18 hr and concentrated under reduced pressure. The residue was taken up in water (200 mL) and the obtained precipitate was filtered, dried under suction to afford 15 g of **28b** (71%) as a yellow solid. mp 190-192 °C. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 7.84 (d, J = 8 Hz, 1H), 8.18-8.20 (m, 1H), 8.37-8.42 (m, 2H), 12.83 (br s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 119.6, 125.5, 125.7, 131.1, 131.2, 148.1, 152.1, 154.1; HPLC t_R = 2.53 min. ES-MS m/z 205.9 $(M + H)^+$. To a solution of 5-(3-nitrophenyl)-1,3,4-oxadiazol-2-one (15 g, 0.07 mol, 1 equiv) in ethanol (400 mL) was added a saturated solution of ammonium chloride (300 mL) followed by iron powder (20 g, 0.35 mol, 5 equiv). The reaction mixture was refluxed for 3 hr, cooled down to room temperature and filtered. The filtrate was concentrated and the residue was diluted with ethyl acetate (200 mL), washed with water, brine and dried. Solvents were removed under reduced pressure to afford 10 g (77%) of **A5** as a white solid. mp 183-185 °C. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 5.45 (s, 2H), 6.70-6.72 (m, 1H), 6.89-6.91 (m, 1H), 6.98 (s, 1H), 7.15 (t, J = 8 Hz, 1H), 12.45 (s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 110.2, 112.8, 117.1, 124.7, 130.0, 149.6, 154.7, 154.9; HPLC t_R = 4.06 min. ES-MS m/z 177.9 $(M + H)^+$; Anal. calcd. for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72. Found: C, 54.46; H, 4.11; N, 23.04

2-(4-aminophenyl)-1,3,4-oxadiazol-2-one (**A6**).

To a solution of 4-nitro-benzoic acid hydrazide (19 g, 0.10 mol, 1 equiv) in dry DMF (200 mL) at 0 °C was added TEA (29 mL, 0.21 mol, 2 equiv) and CDI (25.6 g, 0.16 mol, 1.5 equiv). The reaction mixture was stirred at room temperature under nitrogen for 18 h and concentrated under reduced pressure. The residue was taken up in water (200 mL) and the resulting solid was filtered, dried under suction to afford 17 g of **28c** (81%) as a yellow solid. mp 192 °C (decomposition). ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 8.02 (d, J = 9 Hz, 2H), 8.34 (d, J = 9 Hz, 2H), 12.90 (s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 124.4, 126.5, 129.6, 148.7, 152.3, 154.2; HPLC t_R = 2.60 min; ES-MS m/z 205.9 $(M-H)^-$. To a solution of 5-(4-nitrophenyl)-1,3,4-oxadiazol-2-one (15 g, 0.07 mol, 1 equiv) in ethanol (400 mL) was added a saturated aqueous solution of ammonium chloride (300 mL) followed by iron powder (20 g, 0.35 mol, 5 equiv). The reaction mixture was refluxed for 3 hr, cooled and filtered. The filtrate was

concentrated under reduced pressure and the residue was diluted with ethyl acetate (200 mL), washed with water, brine and dried. The solvent was evaporated under reduced pressure to afford 11 g (85%) of **A6** as a white solid. mp 163-165 ℃. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H5.84 (s, 2H), 6.60-6.63 (d, J = 8.6 Hz, 2H), 7.41-7.44 (d, J = 8.3 Hz, 2H), 12.14 (s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C110.7, 113.8, 127.0, 152.2, 155.0, 155.2; HPLC t_R = 4.08 min; ES-MS m/z 177.9 $(M + H)^+$; Anal. calcd. for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72. Found: C, 53.91; H, 4.13; N, 23.39.

2-[2-(aminomethyl)phenyl]-1,3,4-oxadiazol-2-ol.hydrochloride (**A7**).

To a solution of methyl 2-{[(*tert*-butoxycarbonyl)amino]methyl}benzoate **29a**[20] (5 g, 18.00 mmol) in methanol (70 mL) was added hydrazine hydrate (1.88 g, 0.04 mol) and the mixture was refluxed for 12 hr. The solvent was removed under vacuum and the residue was triturated in water. The resulting solid was filtered and dried under suction to afford 4.2 g (84%) of the **30a** as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.40 (s, 9H), 4.24 (d, J = 6 Hz, 2H), 4.46 (s, 2H), 7.18 8t, J = 7.2 Hz, 1H), 7.25-7.45 (m, 4H), 9.52 (s, 1H), ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 28.2, 41.2, 77.9, 126.4, 127.1, 127.3, 129.7, 134.1, 138.1, 155.7, 167.9; HPLC t_R = 2.21 min; ES-MS m/z 265.9 $(M + H)^+$, Anal. calcd. for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.57; H, 7.22; N, 15.75. To a solution of *tert*-butyl [2-(hydrazinocarbonyl)benzyl]carbamate **30a** (4.0 g, 15.0 mmol) in dry DMF (100 mL) at 0 ℃ was added TEA (3.0 g, 0.03 mol) followed by CDI (3.6 g, 0.02 mol). The reaction mixture was stirred at room temperature under nitrogen for 10 hr and concentrated under reduced pressure. The residue was triturated in water (100 mL) and the resulting solid was filtered, dried under suction to afford 3.4 g (79%) of derivative **31a** as an off white solid. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 1.40 (s, 9H), 4.44 (d, J = 5 Hz, 2H), 7.33-7.74 (m, 5H), 12.59 (br s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 28.2, 41.9, 78.0, 121.6, 127.1, 127.4, 127.9, 131.1, 138.9, 153.6, 154.2, 155.8; HPLC t_R = 3.52 min; ES-MS m/z 290.0 $(M - H)^-$; Anal. calcd. for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.55; H, 5.83; N, 14.40. To a solution of *tert*-butyl [2-(5-hydroxy-1,3,4-oxadiazol-2-yl)benzyl]carbamate **31a** (4.5 g, 15.0 mmol) in dioxane (20 mL) was added a solution of HCl (4M) in dioxane (50 mL) and the reaction mixture was stirred at room temperature for 8 hr. The reaction mixture was evaporated under reduced pressure to afford 3.1 g (88%) of **A7** as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 4.37 (br s, 2H), 7.55-7.70 (m, 3H), 7.81-7.84 (m, 1H), 8.54 (br s, 3H), 12.91 (s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 40.4, 123.0, 127.9, 129.3, 131.2, 131.6, 131.9, 152.9, 154.0, HPLC t_R = 1.12 min, Anal. calcd. for $C_9H_9N_3O_2$.HCl: C, 47.48; H, 4.43; N, 18.46, Cl, 15.57. Found: C, 47.36; H, 4.32; N, 18.40, Cl, 15.35.

2-[3-(aminomethyl)phenyl]-1,3,4-oxadiazol-2-ol.hydrochloride (**A8**).

To a solution of methyl 3-{[(*tert*-butoxycarbonyl)amino]methyl}benzoate **29b**[20] (5.0 g, 0.02 mol, 1 equiv) in methanol (70 mL) was added hydrazine hydrate (2.0 g, 0.04 mol, 2 equiv) and the mixture was refluxed for 12 hr. The solvent was removed under vacuum and the residue

was triturated in water. The resulting solid was filtered and dried under suction to afford 4 g (80%) of **30b** as a white solid. mp 99.2-100.9 °C. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 1.39 (s, 9H), 4.16 (d, J = 7 Hz, 2H), 4.48 (s, 2H), 7.36-7.42 (m, 3H), 7.65-7.72 (m, 2H), 9.73 (s, 1H), ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 28.2, 43.2, 77.8, 124.9, 125.9, 128.1, 129.5, 133.3, 140.3, 155.8, 165.9; HPLC t_R = 2.18 min; ES-MS m/z 263.9 $(M-H)^-$, Anal. calcd. for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.53; H, 7.12; N, 15.78. To a solution of **30b** (8.0 g, 0.03 mol, 1 equiv) in dry DMF (150 mL) at 0 °C was added TEA (8.3 mL, 0.06 mol, 2 equiv) and CDI (4.9 g, 0.03 mol, 2 equiv). The reaction mixture was stirred at room temperature under nitrogen for 10 hr and concentrated under reduced pressure. The residue was triturated in water (100 mL) and the resulting solid was filtered, dried under suction to afford 7 g (79%) of **31b** as a white solid. mp 122-124 °C. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 1.39 (s, 9H), 4.20 (d, J = 6 Hz, 2H), 7.41-7.49 (m, 3H), 7.64-7.67 (m, 2H), 12.57 (s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 28.2, 43.0, 78.0, 123.5, 123.6, 123.9, 129.2, 130.0, 141.4, 1538, 154.4, 155.8; HPLC t_R = 3.35 min; ES-MS m/z 289.9 $(M-H)^-$. Anal. calcd. for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.89; H, 5.75; N, 14.58. To a solution of **31b** (7.0 g, 24.0 mmol, 1 equiv) in dioxane (50 mL) was added a solution of HCl (4M) in dioxane (50 mL) and reaction mixture was stirred at room temperature for 8 hr. The reaction mixture was evaporated under reduced pressure to afford 4.8 g (88%) of 5-(3-aminomethyl-phenyl)-[1,3,4]oxadiazol-2-one **A8** as a white solid. mp 253 °C (decomposition). ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 4.09 (s, 2H), 7.56-7.60 (m, 1H), 7.69-7.71 (m, 1H), 7.77-7.79 (m, 1H), 7.96 (s, 1H), 8.57 (s, 3H), 12.76 (s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 42.0, 124.5, 125.4, 126.8, 129.8, 132.4, 135.7, 153.7, 154.7; HPLC t_R = 3.89 min. ES-MS m/z 191.9 $(M + H)^+$, Anal. calcd. for $C_9H_9N_3O_2$.HCl: C, 47.48; H, 4.43; N, 18.46, Cl, 15.57. Found: C, 47.16; H, 4.33; N, 18.12, Cl, 15.29.

2-[4-(aminomethyl)phenyl]-1,3,4-oxadiazol-2-ol.hydrochloride (**A9**).

To a solution of methyl 4-{[(*tert*-butoxycarbonyl)amino]methyl}benzoate **29c**[20] (5 g, 0.02 mol, 1 equiv) in methanol (70 mL) was added hydrazine hydrate (2 g, 0.04 mol, 2 equiv) and the mixture was refluxed for 12 hr. The solvent was removed under vacuum and the residue was triturated in water. The resulting solid was filtered and dried under suction to afford 4.5 g (90%) of derivative **30c** as a solid. mp 128.8-129.9 °C. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H1.40 (s, 9H), 4.15 (d, J = 7 Hz, 2H), 4.47 (s, 2H), 7.28 (d, J = 8 Hz, 2H), 7.43 (t, J = 6 Hz, 1H), 7.76 (d, J = 8 Hz, 2H), 9.71 (s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 28.3, 43.1, 77.9, 126.7, 126.9, 131.8, 143.3, 155.8, 165.7; HPLC t_R = 2.10 min; ES-MS m/z 265.9 $(M + H)^+$; Anal. calcd. for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.89; H, 6.87; N, 15.83. To a solution of **30c** (4.5 g, 0.02 mol, 1 equiv) in dry DMF (100 mL) at 0 °C was added TEA (3.5 mL, 0.03 mol, 1.5 equiv) followed by CDI (2.7 g, 0.02 mol, 1 equiv). The reaction mixture was stirred at room temperature under nitrogen for 10 hr and concentrated under reduced pressure. The residue was triturated in water (100 mL) and the resulting solid was filtered, dried under suction to afford 4 g (81%) of **31c** as a white solid. mp 157-158 °C. ^{1}H NMR (300

MHz, DMSO-d_6), δ_H 1.39 (s, 9H), 4.18 (d, J = 6 Hz, 2H), 7.39 (d, J = 8 Hz, 2H), 7.46 (t, J = 6 Hz, 1H), 7.74 (d, J = 8 Hz, 2H), 12.54 (s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 28.2, 43.2, 77.9, 122.3, 125.2, 127.6, 143.8, 153.8, 154.4, 155.8; HPLC t_R = 3.28 min; ES-MS m/z 289.9 $(M-H)^-$. Anal. calcd. for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.75; H, 5.92; N, 14.20. To a solution of **31c** (4 g, 0.01 mol, 1 equiv) in dioxane (20 mL) was added a solution of HCl (4M) in dioxane (30 mL) and reaction mixture was stirred at room temperature for 8 hr. The reaction mixture was evaporated under reduced pressure to afford 3 g (91%) of 5-(4-aminomethyl-phenyl)-[1,3,4]oxadiazol-2-one **A9** as a white solid. mp 274 °C (decomposition). ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 4.09 (br s, 2H), 7.67 (d, J = 8 Hz, 2H), 7.82 (d, J = 8 Hz, 2H), 8.64 (br s, 3H), 12.71 (s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 42.1, 67.0, 124.2, 125.7, 130.1, 137.8, 153.7, 154.7; HPLC t_R = 3.83 min; ES-MS m/z 191.9 $(M + H)^+$; Anal. calcd. for $C_9H_9N_3O_2$.HCl: C, 47.48; H, 4.43; N, 18.46; Cl, 15.57. Found: C, 47.83; H, 4.42; N, 18.29; Cl, 16.03.

General procedure for first reductive alkylation with aniline derivatives.

In a 8 mL vial, a solution of R1-CHO (0.27 mmol, 1.50 equiv) in DMF (1 mL) was mixed with R3-NH_2 (0.18 mmol, 1 equiv) in THF (1 mL) and acetic acid (8.80 mmol; 500 µL; 44.0 equiv). MP-cyanoborohydride was added and the reaction was stirred at rt for 24 hr. After 24 hr, resine was filtered off in 8 mL vials and rinsed with THF or DMF, depending on the solubility. Purification was performed on ISOLUTE® SPE SCX 1g (Pol-SO_3H) using the following conditions:

1- SPE column was washed with 1 x 6 mL of MeOH
2- SPE column was washed with 1 x 6 mL of MeOH/DCM (1/1)
3- The reaction mixture was deposit as a solution
4- SPE column was washed with 1 x 1.5 mL of CH_3CN
5- The desired product was eluted with 1 x 3 mL of NH_3 0.1M solution in MeOH
6- The desired product was further eluted 1 x 4 mL of NH_3 0.5M solution in MeOH

Fractions 5 and 6 are combined in a 8 mL vial and solvents are evaporated with Genevac until dryness.

Compound **A1B1**. Yield = 80%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 4.56 (s, 2H), 6.71-6.76 (m, 2H), 7.23-7.50 (m, 6H), 7.81-7.85 (m, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 46.3, 106.2, 111.8, 115.5, 126.9, 127.1, 128.0, 128.3, 128.5, 129.2, 131.9, 139.3, 146.4, 155.1; HPLC t_R = 4.00 min; ES-MS m/z 251.85 $(M + H)^+$.

Compound **A1B3**. Yield = 78%. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 4.70 (br s, 2H), 6.72-6.79 (m, 2H), 7.26-7.32 (m, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.81-7.84 (m, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 45.6, 105.7, 111.9, 115.8, 124.3 (q, J = 271.7 Hz),

125.4 (q, *J* = 3.8 Hz), 127.5 (q, *J* = 31.6 Hz), 127.6, 128.5, 131.6, 132.3, 144.6, 146.2; HPLC t_R = 4.52 min; ES-MS *m*/*z* 319.86 $(M + H)^+$.

Compound **A1B4**. Yield = 82%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 4.63 (s, 2H), 6.71-6.78 (m, 2H), 7.28-7.34 (m, 3H), 7.39-7.42 (m, 1H), 7.47-7.50 (m, 1H), 7.82-7.85 (m, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 44.1, 105.7, 111.7, 115.9, 127.3, 128.5, 128.8, 128.9, 129.4, 132.3, 132.4, 136.1, 146.1, 154.6; HPLC t_R = 4.27 min; ES-MS *m*/*z* 285.86 $(M + H)^+$.

Compound **A2B1**. Yield = 92%. HPLC t_R = 4.03 min; ES-MS *m*/*z* 320.21 $(M + H)^+$.

Compound **A2B2**. Yield = 68%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 3.71 (s, 3H), 4.22 (s, 2H), 6.17 (br s, 1H), 6.46-6.50 (m, 1H), 6.86-6.90 (m, 2H), 7.01-7.07 (m, 1H), 7.10-7.16 (m, 1H), 7.24-7.37 (m, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 45.9, 55.0, 110.1, 111.3, 113.6, 113.7, 114.0, 128.3, 128.7, 132.1, 132.3, 148.6, 158.0, 160.6; HPLC t_R = 2.81 min; ES-MS *m*/*z* 281.88 $(M + H)^+$.

Compound **A2B3**. Yield = 42%. HPLC t_R = 4.03 min; ES-MS *m*/*z* 320.21 $(M + H)^+$.

Compound **A2B4**. Yield = 72%. HPLC t_R = 3.73 min; ES-MS *m*/*z* 286.18 $(M + H)^+$.

Compound **A2B5**. Yield = 44%. HPLC t_R = 3.73 min; ES-MS *m*/*z* 286.18 $(M + H)^+$.

Compound **A3B1**. Yield = 98%. HPLC t_R = 3.18 min; ES-MS *m*/*z* 252.18 $(M + H)^+$.

Compound **A3B2**. Yield = 98%. HPLC t_R = 3.07 min; ES-MS *m*/*z* 239.18 $(M + H)^+$.

Compound **A3B3**. Yield = 20%. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 4.48 (s, 2H), 6.71-6.74 (m, 2H), 7.08-7.10 (t, *J* = 6 Hz, 1H), 7.57 (d, *J* = 8 Hz, 2H), 7.69-7.74 (m, 4H), 16.22 (s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 45.4, 110.9, 112.3, 124.3 (q, *J* = 271.1 Hz), 125.2 (q, *J* = 3.8 Hz), 127.8, 128.2, 131.1 (q, *J* = 33.7 Hz), 144.7, 150.8; HPLC t_R = 3.93 min; ES-MS *m*/*z* 319.84 $(M + H)^+$.

Compound **A3B4**. Yield = 87%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 4.41 (d, *J* = 5 Hz, 2H), 6.71 (d, *J* = 9 Hz, 2H), 6.93 (t, *J* = 6 Hz, 1H), 6.27-7.33 (m, 2H), 7.37-7.40 (m, 1H), 7.45-7.49 (m, 1H), 7.73 (d, *J* = 9 Hz, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 43.8, 111.2, 112.1, 127.2, 128.2, 128.6, 128.8, 129.3, 132.3, 136.3, 150.6, 155.1; HPLC t_R = 3.61 min; ES-MS *m*/*z* 286.18 $(M + H)^+$.

Compound **A4B1**. Yield = 97%. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 4.49 (d, J = 5.6 Hz, 2H), 6.68-6.78 (m, 2H), 7.11 (t, J = 5.6 Hz, 1H), 7.22-7.39 (m, 6H), 7.47-7.61 (m, 1H), 12.58 (br s, 1H) 1; ^{13}C NMR (75.47 MHz, DMSO-d_6) δ_C 46.2, 105.4, 111.4, 115.6, 127.0, 127.1, 127.2, 128.5, 132.2, 138.9, 146.0, 153.4, 154.5; HPLC t_R = 4.28 min; ES-MS m/z 267.89 $(M + H)^+$.

Compound **A4B2**. Yield = 85%. HPLC t_R = 3.95 min; ES-MS m/z 297.91 $(M + H)^+$.

Compound **A4B3**. Yield = 72%. HPLC t_R = 4.67 min; ES-MS m/z 335.91 $(M + H)^+$.

Compound **A4B5**. Yield = 74%. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 4.72 (d, J = 5.5 Hz, 2H), 6.73-6.77 (m, 1H), 6.93-6.95 (m, 1H), 7.10-7.11 (m, 1H), 7.16 (t, J = 5.5 Hz, 1H), 7.25-7.41 (m, 5H), 7.55-7.60 (m, 3H), 12.60 (br s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 41.8, 105.7, 111.6, 116.1, 123.3, 125.1, 126.6, 127.3, 127.5, 129.1, 132.3, 133.6, 142.2, 142.5, 145.6, 153.4, 154.4; HPLC t_R = 4.96 min; ES-MS m/z 348.3 $(M-H)^-$.

Compound **A5B1**. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 4.31 (d, J = 5.8 Hz, 2H), 6.67 (t, J = 5.8 Hz, 1H), 6.74-6.77 (m, 1H), 6.93-6.99 (m, 2H), 7.16-7.25 (m, 2H), 7.30-7.38 (m, 5H), 12.46 (br s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 46.2, 108.3, 112.6, 115.1, 124.4, 126.7, 127.1, 128.3, 129.7, 139.7, 149.0, 154.3, 154.5; HPLC t_R = 3.54 min; ES-MS m/z 268.13 $(M + H)^+$; yield = 84%.

Compound **A5B2**. Yield = 98%. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 3.71 (s, 3H), 4.23 (d, J = 6 Hz, 2H), 6.57 (t, J = 6 Hz, 1H), 6.73-6.76 (m, 1H), 6.84-7.01 (m, 4H), 7.16-7.21 (m, 1H), 7.25-7.29 (m, 2H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 46.0, 55.3, 108.7, 112.9, 114.1, 115.5, 124.8, 128.7, 130.0, 131.7, 149.4, 154.7, 154.9, 158.5, 162.6; HPLC t_R = 3.29 min; ES-MS m/z 296.19 $(M - H)^-$.

Compound **A5B3**. Yield = 25%. HPLC t_R = 4.35 min; ES-MS m/z 336.13 $(M + H)^+$.

Compound **A5B4**. Yield = 63%. HPLC t_R = 4.11 min; ES-MS m/z 302.16 $(M + H)^+$.

Compound **A5B5**. Yield = 44%. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 3.41 (s, 1H), 4.51 (s, 2H), 6.83-6.86 (m, 1H), 6.97-7.00 (m, 1H), 7.06-7.07 (m, 2H), 7.21-7.29 (m, 2H), 7.35-7.40 (m, 3H), 7.57-7.59 (m, 2H), 12.47 (s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 42.3, 109.0, 113.5, 115.7, 123.6, 124.9, 125.4, 126.4, 127.8, 129.4, 134.2, 139.6, 142.2, 144.2, 149.1, 154.6, 155.0, 162.6, 184.4; HPLC t_R = 4.47 min; ES-MS m/z 348.15 $(M + H)^+$.

Compound **A6B1**. Yield = 52%. HPLC t_R = 3.61 min; ES-MS m/z 267.83 $(M + H)^+$.

Compound **A6B2**. Yield = 55%. H NMR (300 MHz, DMSO-d_6), δ_H 3.72 (s, 3H), 4.25 (d, J = 5.8 Hz, 2H), 6.66 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 6.93 (t, J = 6.3 Hz, 1H), 7.26 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 9.1 Hz, 2H), 7.68 (br s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 45.3, 55.0, 110.5, 112.0, 123.8, 121.6, 126.6, 128.4, 131.1, 135.1, 151.2, 154.6, 154.7, 158.2; HPLC t_R = 3.51 min; ES-MS m/z 297.87 $(M + H)^+$.

Compound **A6B3**. Yield = 17%. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 4.45 (d, J = 7 Hz, 2H), 6.66 (d, J = 9 Hz, 2H), 7.13 (t, J = 6 Hz, 1H), 7.47 (d, J = 9 Hz, 2H), 7.55 (d, J = 8 Hz, 2H), 7.70 (d, J = 8 Hz, 2H)12.19 (br s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 45.4, 111.0, 112.1, 124.3 (q, J = 271.7 Hz), 125.2 (q, J = 4.1 Hz), 126.7, 127.7, 131.0 (q, J = 32.2 Hz), 144.6 (q, J = 1.4 Hz), 150.9, 154.6; HPLC t_R = 4.23 min; ES-MS m/z 336.19 $(M + H)^+$.

Compound **A6B4**. Yield = 50%. HPLC t_R = 4.01 min; ES-MS m/z 302.14 $(M + H)^+$.

Compound **A6B5**. Yield = 40%. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.53 (d, J = 5.9 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 7.06-7.10 (m, 2H), 7.24-7.29 (m, 1H), 7.36-7.41 (m, 3H), 7.49-7.52 (m, 2H), 7.57-7.60 (m, 2H), 12.20 (br s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_C 41.5, 111.1, 112.3, 123.2, 125.0, 126.4, 126.6, 127.4, 129.0, 133.8, 141.9, 143.2, 150.7, 154.6; HPLC t_R = 4.46 min; ES-MS m/z 347.95 $(M-H)^-$.

General procedure for first reductive alkylation with benzylamine derivatives. In a 8 mL vial, a solution of R1-CHO (0.19 mmol, 1.10 equiv) in DMF (1 mL) was mixed with R3-NH_2 (0.18 mmol, 1 equiv) in THF (1 mL) and acetic acid (8.80 mmol; 500 µL; 44.00 equiv). MP-cyanoborohydride was added and the reaction was stirred at 0 °C for 5 hr. After 5 hr, the resine was filtered off in 8 mL vials and rinsed with THF or DMF, depending on the solubility. Purification was performed on ISOLUTE® SPE SCX 1g (Pol-SO_3H) using the following conditions:

1- SPE column was washed with 1 x 6 mL of MeOH
2- SPE column was washed with 1 x 6 mL of MeOH/DCM (1/1)
3- The reaction mixture was deposit as solution
4- SPE column was washed with 1 x 1.5 mL of CH_3CN
5- The desired product was eluted with 1 x 3 mL of NH_3 0.1M solution in MeOH
6- The desired product was further eluted 1 x 4 mL of NH_3 0.5M solution in MeOH

Fractions 5 and 6 are combined in a 8 mL vial and solvents are evaporated with Genevac until dryness.

Compound **A7B1**. Yield = 70%. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 4.19 (br s, 2H), 4.46 (br s, 2H), 7.30-7.46 (m, 4H), 7.58-7.64 (m, 3H), 7.74-7.76 (m, 1H), 7.79-7.84 (m, 1H), 10.21 (br s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6) δ_C 48.1, 50.6, 123.7, 127.8, 128.5, 128.9, 129.7, 130.1, 130.2, 131.1, 131.8, 132.9, 153.0, 154.0; HPLC t_R = 2.05 min; ES-MS *m*/*z* 280.30 $(M-H)^-$.

Compound **A7B2**. Yield = 40%. HPLC t_R = 2.46 min; ES-MS *m*/*z* 282.2 $(M + H)^+$.

Compound **A7B5**. Yield = 73%. HPLC t_R = 3.12min; ES-MS m/z 363.87 $(M + H)^+$.

Compound **A8B1**. Yield = 32%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 4.18 (s, 2H), 4.26 (s, 2H), 7.42-7.44 (m, 3H), 7.51-7.57 (m, 2H), 7.58-7.63 (m, 1H), 7.70-7.73 (m, 1H), 7.82-7.84 (m, 1H), 8.01 (m, 1H), 9.53 (br s, 1H), 12.26 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 49.9, 50.5, 124.5, 124.6, 125.9, 126.0, 127.3, 129.0, 129.3, 129.9, 130.4, 132.2, 132.3, 133.4, 153.8, 154.7; HPLC t_R = 1.62 min; ES-MS *m*/*z* 282.23 $(M + H)^+$.

Compound **A8B2**. Yield = 24%. HPLC t_R = 1.79 min; ES-MS *m*/*z* 312.28 $(M + H)^+$.

Compound **A8B3**. Yield = 64%. HPLC t_R = 2.74 min; ES-MS *m*/*z* 350.25 $(M + H)^+$.

Compound **A8B4**. Yield = 62%. HPLC t_R = 2.19 min; ES-MS *m*/*z* 316.21 $(M + H)^+$.

Compound **A8B5**. Yield = 31%. HPLC t_R = 2.68 min; ES-MS *m*/*z* 364.25 $(M + H)^+$.

Compound **A9B1**. Yield = 76%. HPLC t_R = 1.94 min; ES-MS *m*/*z* 282.22 $(M + H)^+$.

Compound **A9B2**. Yield = 28%. HPLC t_R = 1.77 min; ES-MS *m*/*z* 310.24 $(M + H)^+$.

Compound **A9B3**. Yield = 34%. HPLC t_R = 2.25 min; ES-MS *m*/*z* 350.23 $(M + H)^+$.

Compound **A9B5**. Yield = 33%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 4.25 (s, 2H), 4.41 (s, 2H), 7.31-7.49 (m, 5H), 7.64-7.66 (d, *J* = 7 Hz, 2H), 7.72-7.77 (d, *J* = 7 Hz, 2H), 7.83-7.86 (d, *J* = 9 Hz, 2H), 9.90 (br s, 1H), 12.74 (br s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 44.6, 49.4, 124.0, 124.7, 125.7, 125.8, 128.4, 129.6, 129.6, 131.3, 131.4, 132.5, 132.6, 133.6, 133.6, 135.5, 145.6, 153.8, 154.8, 162.7; HPLC t_R = 2.68 min; ES-MS m/z 364.23 $(M + H)^+$.

General procedure for second reductive alkylation.

To one of the five solutions obtained in the previous step, containing R3-NH(R_1) (0.02 mmol, 1 equiv), was added a solution of R2-CHO (0.06 mmol, 3 equiv) in THF (total volume of R_2CHO+THF = 73 µL) and acetic acid (4.40 mmol; 63 µL; 25% vol). Mp-cyanoborohydride was added and the reaction was stirred at rt for 24hr. After 24 hr, when the reaction was not complete, 3 more equiv of aldehyde R2-CHO (0.06 mmol, 3 equiv) were added and the

reaction mixture was stirred for 165 hr at rt. On the next morning, if the reaction was still not complete, 6 equiv of aldehyde R2-CHO (0.12 mmol, 6 equiv) were added and the reaction mixture was stirred at 50 °C for 2 days. When reaction was completed, resin was filtered off in 4 mL vials and rinsed with THF or DMF, depending on the solubility. Purification was performed on ISOLUTE® SPE SCX 100 mg (Pol-SO_3H) using the following conditions:

1- SPE column was washed with 1 x 3 mL of MeOH

2- SPE column was washed with 1 x 3 mL of MeOH/DCM (1/1)

3- The reaction mixture was deposit as solution

4- SPE column was washed with 1 x 750 µL of CH_3CN

5- The desired product was eluted with 1 x 2 mL of NH_3 0.1M solution in MeOH

6- The desired product was further eluted 1 x 2 mL of NH_3 0.5M solution in MeOH

Fractions 5 and 6 are combined in a 8 mL vial and solvents are evaporated with Genevac until dryness.

Compound **A2B1C1**. Yield = 98%. HPLC t_R = 4.83 min; ES-MS *m*/*z* 334.27 $(M + H)^+$.

Compound **A3B1C1**. Yield = 50%. HPLC t_R = 4.86 min; ES-MS *m*/*z* 334.26 $(M + H)^+$.

Compound **A5B1C1**. Yield = 97%. HPLC t_R = 5.23 min; ES-MS *m*/*z* 350.26 $(M + H)^+$.

Compound **A2B1C2**. Yield = 98%. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 2.91-2.94 (m, 2H), 3.64-3.70 (m, 2H), 4.58 (s, 2H), 6.78-6.79 (m, 1H), 7.19-7.34 (m, 13H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 32.7, 52.6, 53.4, 109.6, 113.0, 114.1, 126.1, 126.5, 126.7, 128.4, 128.5, 128.8, 129.7, 138.8, 139.3, 148.0, 157.9; HPLC t_R = 4.81 min; ES-MS *m*/*z* 356.29 $(M + H)^+$.

Compound **A3B1C2**. Yield = 98%. HPLC t_R = 4.72 min; ES-MS *m*/*z* 356.25 $(M + H)^+$.

Compound **A5B1C2**. Yield = 98%. HPLC t_R = 5.11 min; ES-MS *m*/*z* 372.29 $(M + H)^+$.

Compound **A2B1C3**. Yield = 96%. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 0.91 (s, 3H), 0.94 (s, 3H), 1.47-1.54 (m, 2H), 1.57-1.68 (m, 1H), 3.45-3.50 (m, 2H), 4.62 (s, 2H), 6.379-6.82 (m, 1H), 7.23-7.25 (m, 4H), 7.28-7.35 (m, 5H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 22.5, 25.6, 35.2, 49.0, 53.3, 109.6, 113.8, 114.3, 125.1, 126.5, 126.7, 128.5, 130.0, 138.7, 148.2, 155.9; HPLC t_R = 4.97 min; ES-MS *m*/*z* 338.31 $(M + H)^+$.

Compound **A3B1C3**. Yield = 67%. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 0.89 (d, *J* = 5.9 Hz, 6H), 1.5 (br s, 2H), 1.56-1.62 (m, 1H), 3.47 (br s, 2H), 4.62 (s, 2H), 6.78 (d, *J* = 8.9 Hz, 2H), 7.19-7.31 (m, 6H), 7.79 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (75.47 MHz, DMSO-d_6) δ_C 22.4, 25.6, 35.2, 49.0, 53.2, 110.2, 111.8, 126.4, 126.5, 126.7, 128.2, 128.5, 128.6, 138.4, 149.9, 154.8; HPLC t_R = 4.79 min; ES-MS *m*/*z* 322.26 $(M + H)^+$.

Compound **A5B1C3**. Yield = 61%. HPLC t_R = 4.55 min; ES-MS *m*/*z* 322.25 $(M + H)^+$.

Compound **A6B1C3**. Yield = 98%. HPLC t_R = 5.18 min; ES-MS *m*/*z* 338.24 $(M + H)^+$.

Compound **A2B1C4**. Yield = 91%. HPLC t_R = 3.58 min; ES-MS *m*/*z* 308.29 $(M + H)^+$.

Compound **A3B1C4**. Yield = 54%. HPLC t_R = 4.52 min; ES-MS *m*/*z* 308.24 $(M + H)^+$.

Compound **A5B1C4**. Yield = 97%. HPLC t_R = 3.97 min; ES-MS *m*/*z* 324.28 $(M + H)^+$.

Compound **A6B1C4**. Yield = 98%. ^{1}H NMR (300 MHz, DMSO-d_6), δ_H 0.91 (t, *J* = 7.3 Hz, 3H), 1.30-1.38 (m, 2H), 1.56-1.61 (m, 2H), 3.47 (t, *J* = 7.6 Hz, 2H), 4.64 (s, 2H), 6.74 (d, *J* = 9.6 Hz, 2H), 7.18-7.25 (m, 3H), 7.30-7.35 (m, 2H), 7.52 (d, *J* = 8.9 Hz, 2H), 12.20 (br s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 13.8, 19.6, 28.7, 50.5, 53.2, 110.3, 111.6, 126.3, 126.6, 126.7, 128.5, 138.3, 150.1, 154.5, 154.6; HPLC t_R = 4.92 min; ES-MS *m*/*z* 324.23 $(M + H)^+$.

Compound **A7B1C1**. Yield = 85%. HPLC t_R = 2.95min; ES-MS *m*/*z* 364.40 $(M + H)^+$.

Compound **A8B1C1**. Yield = 34%. HPLC t_R = 3.07 min; ES-MS *m*/*z* 364.30 $(M + H)^+$.

Compound **A9B1C1**. Yield = 98%. HPLC t_R = 3.04 min; ES-MS *m*/*z* 364.28 $(M + H)^+$.

Compound **A7B1C2**. Yield = 83%. HPLC t_R = 2.89 min; ES-MS *m*/*z* 386.40 $(M + H)^+$.

Compound **A8B1C2**. Yield = 84%. HPLC t_R = 3.15 min; ES-MS *m*/*z* 386.37 $(M + H)^+$.

Compound **A9B1C2**. Yield = 98%. HPLC t_R = 3.15 min; ES-MS *m*/*z* 386.32 $(M + H)^+$.

Compound **A7B1C3**. Yield = 83%. HPLC t_R = 3.01min; ES-MS *m*/*z* 352.30 $(M + H)^+$.

Compound **A8B1C3**. Yield = 27%. HPLC t_R = 3.03 min; ES-MS *m*/*z* 352.29 $(M + H)^+$.

Compound **A9B1C3**. Yield = 91%. HPLC t_R = 3.02 min; ES-MS *m*/*z* 352.28 $(M + H)^+$.

Compound **A7B1C4**. Yield = 69%. HPLC t_R = 2.72 min; ES-MS *m*/*z* 338.30 $(M + H)^+$.

Compound **A8B1C4**. Yield = 33%. HPLC t_R = 2.74 min; ES-MS *m*/*z* 338.27 $(M + H)^+$.

Compound **A9B1C4**. Yield = 81%. HPLC t_R = 2.72 min; ES-MS *m*/*z* 338.26 $(M + H)^+$.

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Part 2.

Synthesis and Regioselective Reactions on trichloro-pyrido[3,2-*d*]pyrimidines.

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1. Introduction.

1.1. Pyridopyrimidines syntheses.

Amongst the bioisosteres of quinazoline, pyridopyrimidines have received much attention because of their potential biological activities. Among the four regioisomers of pyridopyrimidine (*Figure 1.1*), pyrido[2,3-*d*]pyrimidine syntheses have been extensively studied.[1,2] However, a general access to other regioisomers of pyridopyrimidine and methods to further diversify them through regioselective reactions are missing. Becoming an interesting challenge, pyrido[3,2-*d*]pyrimidine scaffold has retained our attention as a central core for new chemical entities synthesis.

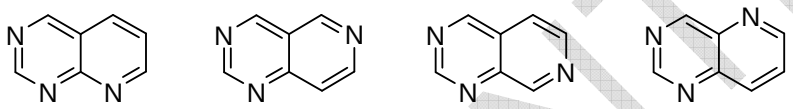


Figure 1.1. The four regioisomers of pyridopyrimidine scaffold.

Construction of functionalized pyridopyrimidines, whose synthesis is not always easy, involves cyclization of appropriately substituted pyrimidines or pyridines. In addition, pyrimidines or pyridines bearing additional substituents in useful positions are often difficult to obtain. Diverse syntheses affording mono-, di-, tri- and tetra-substituted-pyrido[3,2-*d*]pyrimidines will be reviewed in the present chapter (*Figure 1.2*).

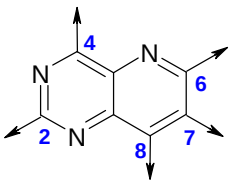
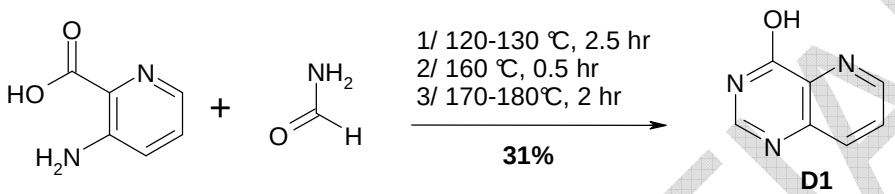


Figure 1.2. Syntheses of substituted-pyrido[3,2-*d*]pyrimidines.

1.1.1. Synthesis of mono-substituted-pyrido[3,2-d]pyrimidines.

In 1946, Price *et al.* reported the synthesis of 4-hydroxy-pyrido[3,2-*d*]pyrimidine. Condensation of 3-amino-pyridine-2-carboxylic acid with formamide between 130 and 170 °C for 5 hours afforded the desired 4-substituted-pyrido[3,2-*d*]pyrimidine **D1** in 31% yield (*Scheme 1.1*).[3,17] To the best of our knowledge, it is the only synthesis of a monosubsituted-pyrido[3,2-*d*]pyrimidine reported in literature.



Scheme 1.1. Synthesis of 4-substituted-pyrido[3,2-*d*]pyrimidine **D1.**

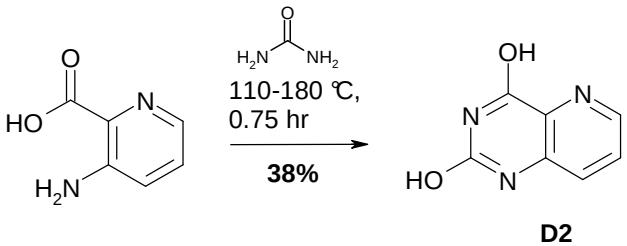
1.1.2.Syntheses of di-substituted-pyrido[3,2-d]pyrimidines.

Disubstituted pyrido[3,2-*d*]pyrimidines that have been described in literature only concern the 2,4- and 4,6-disubstituted-pyrido[3,2-*d*]pyrimidine derivatives. Their syntheses are reported below.

1.1.2.1. Syntheses of 2,4-disubstituted-pyrido[3,2-*d*]pyrimidines.

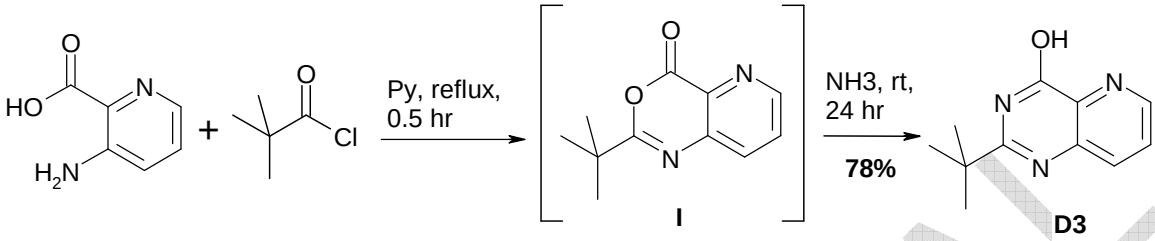
Preparation from 3-amino-pyridine-2-carboxylic acid.

The synthesis of 2,4-dihydroxy-pyrido[3,2-*d*]pyrimidine **D2** has been reported in literature via reaction of 3-amino-pyridine-2-carboxylic acid with an excess of urea. The condensation occurred by heating both starting materials between 160 and 200 °C for 1 hour, without any solvent (*Scheme 1.2*).[4] The desired 2,4-disubstituted-pyrido[3,2-*d*]pyrimidine was obtained in 38% yield.



Scheme 1.2. Synthesis of 2,4-disubstituted-pyrido[3,2-*d*]pyrimidine **D2** from 3-amino-pyridine-2-carboxylic acid.

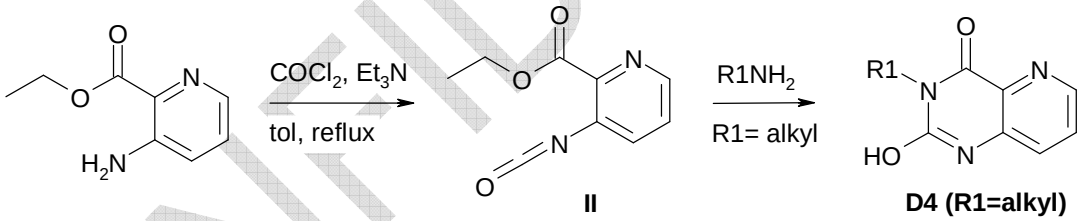
In 2004, Quéguiner *et al.* reported the synthesis of 2-*tert*-butyl-4-hydroxy-pyrido[3,2-*d*]pyrimidine **D3** via cyclization of 3-amino-pyridine-2-carboxylic acid with pivaloyl chloride leading to pyrido-oxazinone derivative **I**.[5] Further reaction with ammonia gave the expected pyrido[3,2-*d*]pyrimidine **D3** in 78% yield over the two steps (*Scheme 1.3*).



Scheme 1.3. Synthesis of 2,4-disubstituted-pyrido[3,2-*d*]pyrimidine **D3** from 3-amino-pyridine-2-carboxylic acid.

Preparation from 3-amino-pyridine-2-carboxylic acid ethyl ester.

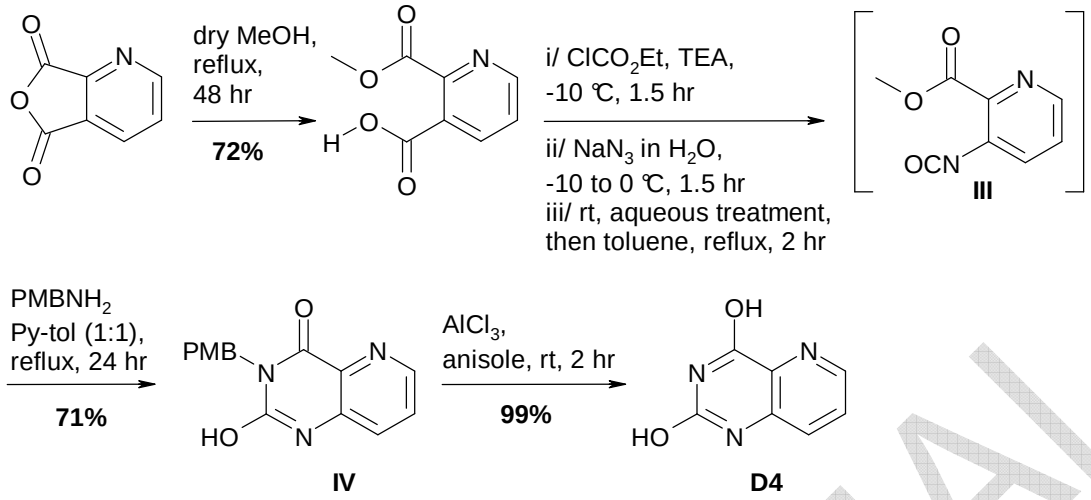
The synthesis of pyrido[3,2-*d*]pyrimidine **D4** (with R1=alkyl) was achieved in two steps via the coupling of 3-isocyanato-pyridine-2-carboxylic acid ethyl ester **II** with primary amines, followed by intramolecular cyclization (*Scheme 1.4*). The isocyanate intermediate **II** was obtained from the corresponding 3-amino-pyridine-2-carboxylic acid ethyl ester by treatment with phosgene in toluene at reflux. In certain cases, the isocyanates were not necessarly isolated but were reacted directly with the primary amines in a one pot protocol.[6]



Scheme 1.4. Synthesis of 2,4-disubstituted-pyrido[3,2-*d*]pyrimidine **D4** (R1=alkyl).

Preparation from furo[3,4-*b*]pyridine-5,7-dione.

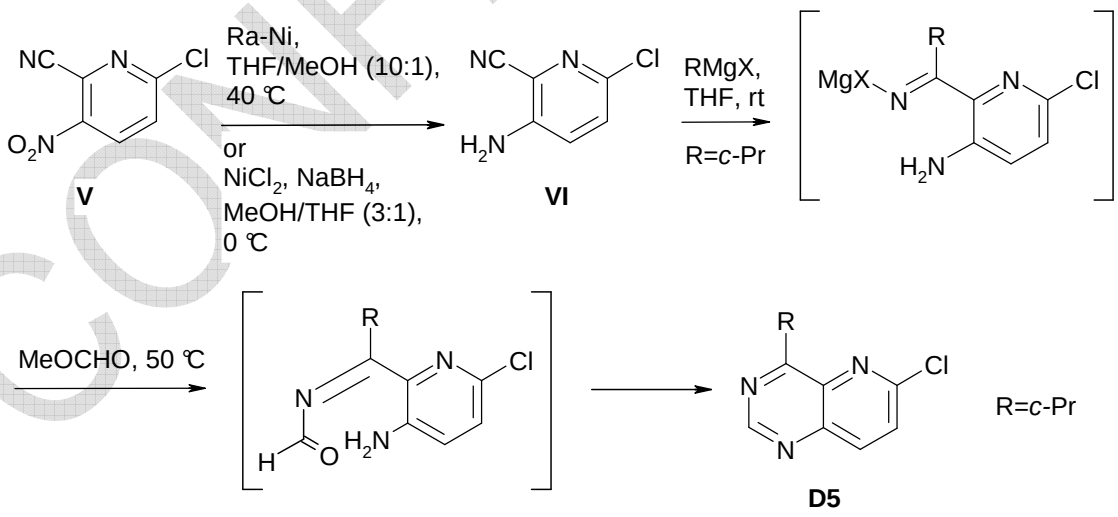
More recently, Tikad *et al.* developed a synthesis of 2,4-dihydroxy-pyrido[3,2-*d*]pyrimidine **D4** (R1=H) from furo[3,4-*b*]pyridine-5,7-dione (*Scheme 1.5*). Methanolysis followed by isocyanate formation from carboxylic acid functional group afforded the isocyanate intermediate **III** that directly reacted with *p*-methoxybenzylamine to give the *N*-protected-pyrido[3,2-*d*]pyrimidine **IV**.[7] Deprotection in anisole using an excess of $AlCl_3$ afforded 2,4-dihydro-pyrido[3,2-*d*]pyrimidine **D4** in 50% overall yield.



Scheme 1.5. Synthesis of 2,4-disubstituted-pyrido[3,2-*d*]pyrimidine **D4** (R1=H).

1.1.2.2. Syntheses of 4,6-disubstituted-pyrido[3,2-*d*]pyrimidines.

In 2007, Cox *et al.* reported the synthesis of 4,6-pyrido[3,2-*d*]pyrimidines starting from 2-cyano-3-nitro-6-chloro-pyridine **V**.[8] Reduction of the nitro group followed by the Grignard reagent addition on the cyano functionality of derivative **VI**, followed by *in-situ* trapping of the resulted imine with formic acid methyl ester afforded derivative **D5** (*Scheme 1.6*). The presence of the chloro substituent at the C-6 position offered the possibility to further diversify at this position.



Scheme 1.6. Synthesis of 4,6-disubstituted-pyrido[3,2-*d*]pyrimidine **D5**.

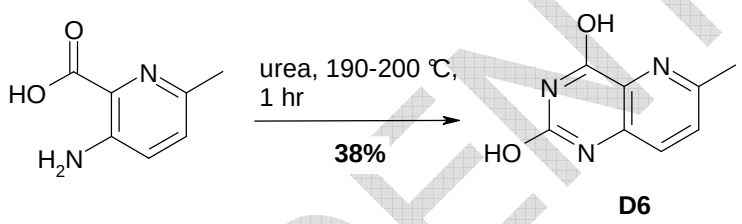
1.1.3. Syntheses of tri-substituted-pyrido[3,2-d]pyrimidines.

The below syntheses of tri-substituted-pyrido[3,2-*d*]pyrimidines reported in the literature only refer to 2,4,6-and 2,4,8-trisubstituted derivatives. Six different syntheses, starting from either pyridine or pyrimidine derivatives are detailed below.

1.1.3.1. Syntheses of 2,4,6-trisubstituted-pyrido[3,2-*d*]pyrimidines.

Preparation from 3-amino-6-methyl-pyridine-2-carboxylic acid.

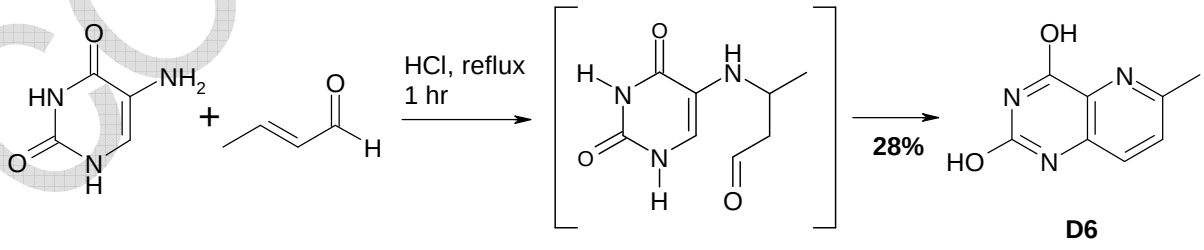
In 1956, Oakes and Rydon reported the synthesis of trisubstituted-pyrido[3,2-*d*]pyrimidine starting from 3-amino-6-methyl-pyridine-2-carboxylic acid. Its condensation with urea at 190 to 200 °C for 1 hour afforded 2,4-dihydroxy-6-methy l-pyrido[3,2-*d*]pyrimidine **D6** in 38% yield (*Scheme 1.7*).[9]



Scheme 1.7. Synthesis of 2,4,6-substituted-pyrido[3,2-*d*]pyrimidine **D6**.

Preparation from 5-aminouracil.

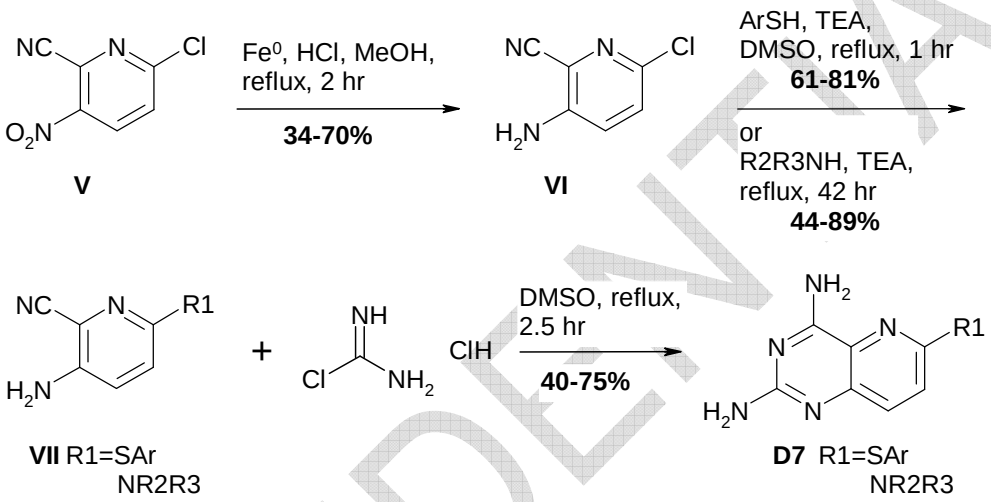
The synthesis of 2,4-dihydroxy-6-methyl-pyrido[3,2-*d*]pyrimidine **D6** has also been reported starting from a pyrimidine reagent, via the condensation of 5-aminouracil with crotonaldehyde. When these two reagents were heated at reflux for 1 hour in presence of hydrochloric acid, 2,4-dihydroxy-6-methyl-pyrido[3,2-*d*]pyrimidine **D6** was obtained in 28% yield (*Scheme 1.8*).[10]



Scheme 1.8. Synthesis of 2,4,6-substituted-pyrido[3,2-*d*]pyrimidine **D6**.

Preparation from 6-chloro-3-nitro-2-cyano-pyridine.

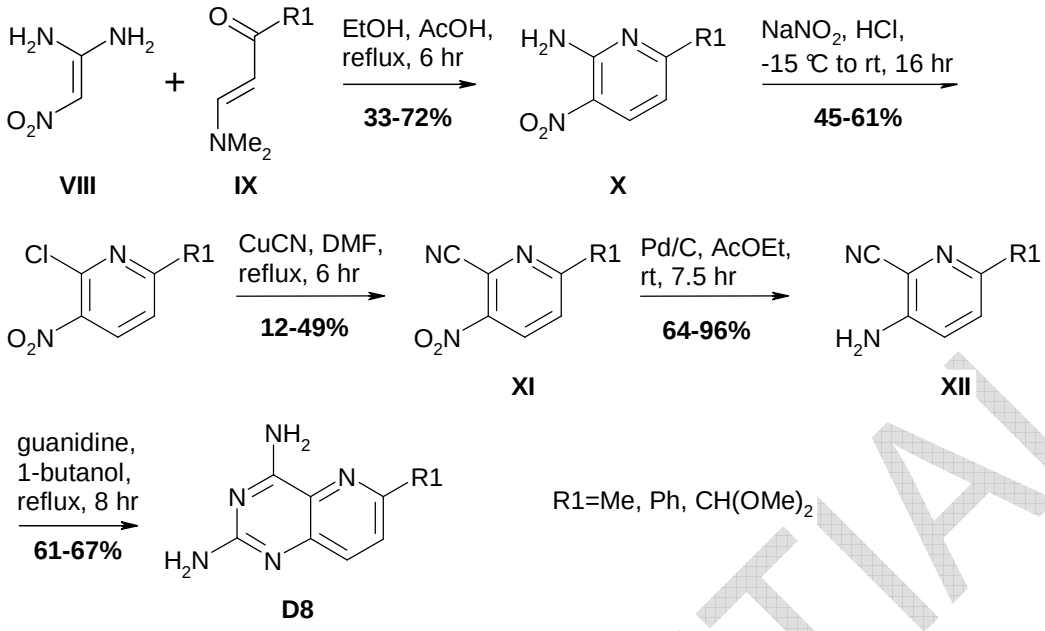
The synthesis of 2,4,6-trisubstituted-pyrido[3,2-*d*]pyrimidines starting from 6-chloro-3-nitro-2-cyano-pyridine **V** has been reported with amino groups at 2 and 4 position and amino,[11] aryl thiol,[8,12] or chloro group at C-6.[9] All three syntheses started with the reduction of the nitro group on the pyridine ring affording derivatives **VI**. C-6 chlorine on the pyridine ring was left unreacted or was further substituted with amines or aryl thiols affording derivatives **VII** with R1=Cl, NR2R3 or SAr. The last step of these syntheses consisted in the condensation of derivative **VII** with chloroformamidine hydrochloride affording 2,4,6-trisubstituted-pyrido[3,2-*d*]pyrimidines **D7** in yields ranging from 40 to 75% (*Scheme 1.9*).



Scheme 1.9. Synthesis of 2,4,6-substituted-pyrido[3,2-*d*]pyrimidine **D7**.

Preparation from 6-alkyl(aryl)-3-nitro-2-cyano-pyridine.

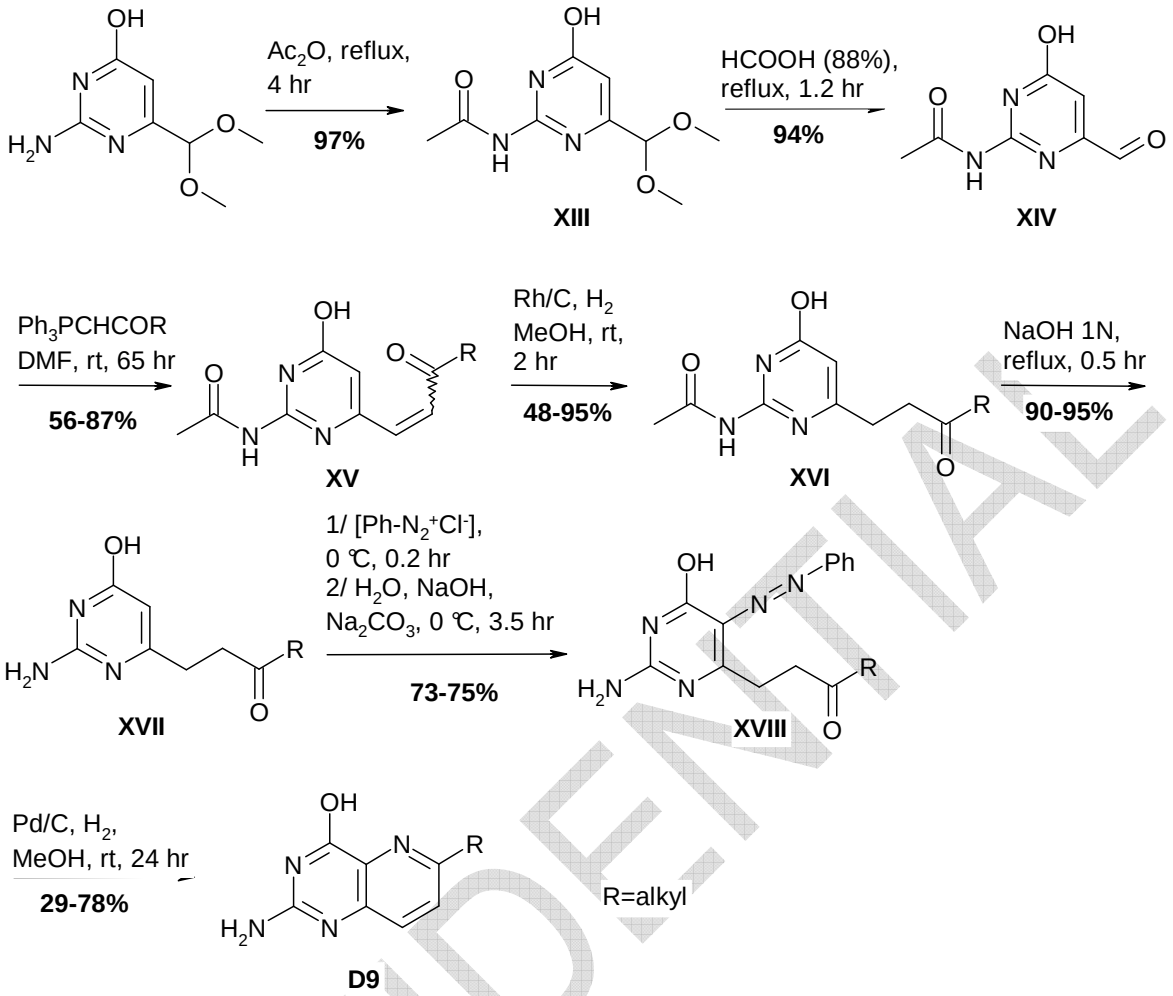
A few years later, Troschutz *et al.* reported a similar synthesis of 2,4,6-trisubstituted-pyrido[3,2-*d*]pyrimidines having alkyl and aryl groups at C-6.[13] Their synthesis started with the formation of the 6-alkyl(aryl)-3-nitro-2-cyano-pyridine reagent **XI**. Cyclocondensation of enaminone **IX** with 2-nitroethene-1,1-diamine **VIII** at reflux for 5 hours gave access to the 2-amino-3-nitro-pyridines **X**. The following steps were similar to the ones described in *Scheme 1.7*, including the reduction of the nitro group followed by the condensation of derivative **XII** with guanidine in boiling 1-butanol. Derivatives **D8** were obtained in yields ranging from 61 to 67% for the cyclization step (*Scheme 1.10*).



Scheme 1.10. Synthesis of 2,4,6-substituted-pyrido[3,2-*d*]pyrimidine **D8**.

Preparation from 2-acetamido-4-hydroxy-6-formyl-pyrimidine.

In 1976, DeGraw *et al.* reported the synthesis of 2-amino-4-hydroxy-6-alkyl-pyrido[3,2-*d*]pyrimidines **D9** starting from 2-acetamido-4-hydroxy-6-formylpyrimidine **XIV**. Wittig reaction of derivative **XIV** with an appropriate ylide afforded the pyrimidines **XV** in yields ranging from 56 to 87% yield. Reduction of the olefin, followed by deacetylation and coupling with benzene diazonium chloride afforded derivatives **XVIII** in yields ranging from 73 to 75%. Final reductive cyclization of derivatives **XVIII** gave the fully aromatic pyridopyrimidines **D9** in 29 to 78% yields (*Scheme 1.11*).[14,15] In this synthesis, the different alternatives investigated to shorten **D9** synthesis failed. For instance, reduction of the olefin moiety on derivative **XV** was necessary as direct coupling of the acetamido-enone **XV** with benzene diazonium chloride was unsuccessful.

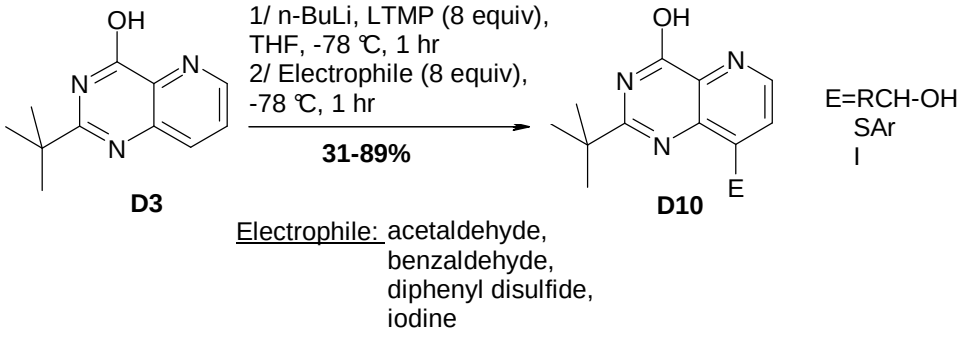


Scheme 1.11. Synthesis of 2,4,6-substituted-pyrido[3,2-*d*]pyrimidine **D9**.

1.1.3.2. Syntheses of 2,4,8-trisubstituted-pyrido[3,2-*d*]pyrimidines.

Preparation from 2-*tert*-butyl-4-hydroxy-pyrido[3,2-*d*]pyrimidine.

Starting from 2-*tert*-butyl-4-hydroxy-pyrido[3,2-*d*]pyrimidine **D3** prepared from the pyrido-oxazinone intermediate **I** (*Scheme 1.3*), Quéguiner *et al.* proposed the introduction of a third substituent via direct lithiation and functionalization of the pyridine moiety on derivative **D3**.[5] He reported a regioselective metallation on 2-*tert*-butyl-4-hydroxy-pyrido[3,2-*d*]pyrimidine **D3** at the C-8 position. Diverse electrophiles (aldehydes, diaryl disulfides and iodine) were further added on the lithiated intermediate affording pyridoyprimidines **D10** in yields ranging from 31 to 89% (*Scheme 1.12*).



Scheme 1.12. Synthesis of 2,4,8-substituted-pyrido[3,2-*d*]pyrimidine **D10**.

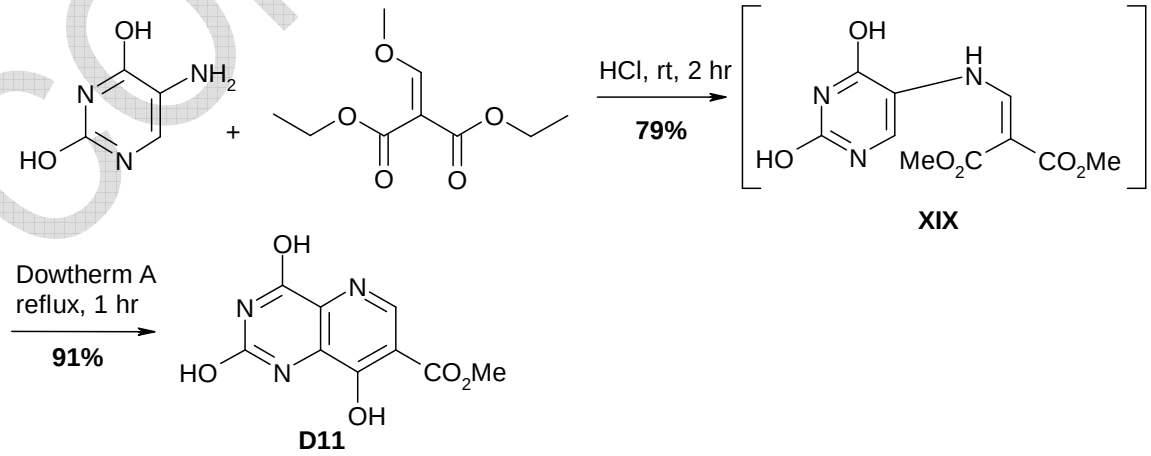
1.1.4. Syntheses of tetra-substituted-pyrido[3,2-d]pyrimidines.

Only two syntheses of tetra-substituted-pyrido[3,2-*d*]pyrimidines have been reported in literature in the 60's and the 70's.[10,16,17,18] These syntheses concern the 2,4,6,7-substituted and 2,4,6,8-substituted derivatives. Their syntheses are reviewed below.

1.1.4.1. Syntheses of 2,4,6,7-tetra-substituted-pyrido[3,2-*d*]pyrimidines.

Preparation from 5-aminouracil.

In the sixties, Irwin *et al.* and Davoll *et al.* reported that condensation of aminouracil and α,β-unsaturated aldehydes or ketones afforded 2,4-dihydro-pyrido[3,2-*d*]pyrimidines via Michael addition, after heating the reaction mixture in acidic media. [10,16.] Following these conditions and starting from diethyl ethoxymethylenemalonate and 5-aminouracil, 2,4,8-trihydroxy-pyrido[3,2-*d*]pyrimidine-7-carboxylic acid ethyl ester **D11** was synthetized in 72% overall yield after 1 hour at reflux in Dowtherm A (*Scheme 1.13*)

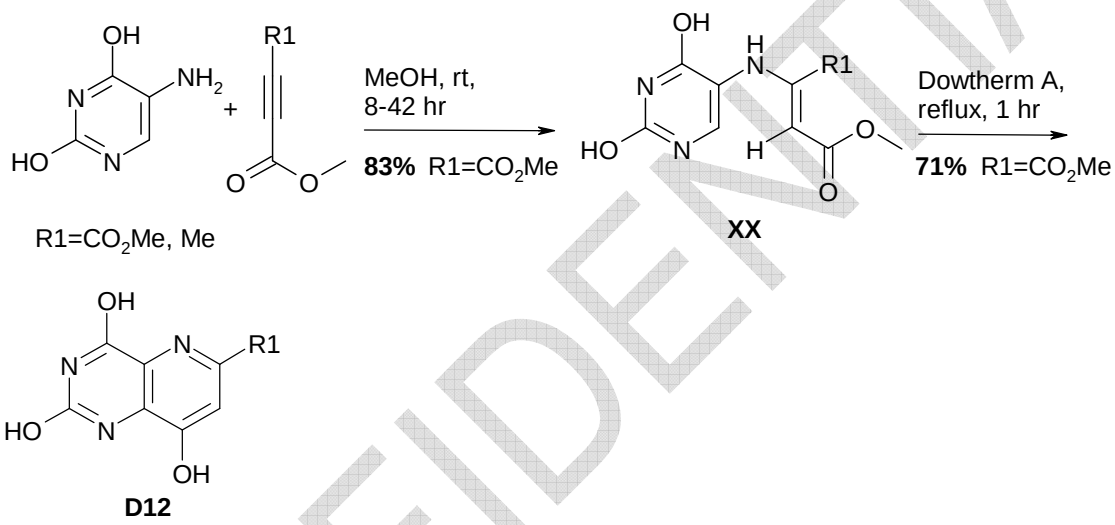


Scheme 1.13. Synthesis of 2,4,6,7-substituted-pyrido[3,2-*d*]pyrimidine **D11**.

1.1.4.2. Syntheses of 2,4,6,8-tetra-substituted-pyrido[3,2-*d*]pyrimidines.

Preparation from 5-aminouracil.

In 1979, Srinivasan *et al.* reported that the electrophilic cyclization of DMAD (R1=CO_2Me) with 5-aminouracil provided access to 2,4,8-trihydroxy-pyrido[3,2-*d*]pyrimidine **D12** (R1=CO_2Me, *Scheme 1.14*).[17,] Enamine derivative was obtained via Michael addition of 5-aminouracil to the triple bond of DMAD affording the intermediate **XX**. Subsequent cyclization was performed heating the enamine intermediate at reflux in Dowtherm A affording 2,4,8-trihydroxy-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **D12**. The same chemical pathway was used for the synthesis of trihydroxy-pyrido[3,2-*d*]pyrimidine **D12** with R1=Me starting from but-2-ynoic acid ethyl ester.[18] However no yield was given for the different steps.



Scheme 1.14. Synthesis of 2,4,6,8-substituted-pyrido[3,2-*d*]pyrimidine **D12**.

1.2. Goal of the project.

Among the diverse syntheses of pyrido[3,2-*d*]pyrimidines reported in literature, we were particularly interested in the synthesis of tetra-substituted-pyrido[3,2-*d*]pyrimidines developed by Irwin *et al.* and Srinivasan *et al.* These syntheses gave access to tri-hydroxy derivatives and could give by chlorination access to the more versatile tri-chloro analogues bearing an ester at C-6 or C-7. These intermediates appeared very interesting since the chlorines can be further transformed into diverse tetra-substituted-pyrido[3,2-*d*]pyrimidines. In addition, they bring the challenge to develop conditions that would allow the regioselective and successive transformation of these four reactive centers. Among the two tetra-substituted-pyrido[3,2-*d*]pyrimidine scaffolds reported, we selected the 2,4,6,8-tetrasubstituted-pyrido[3,2-*d*]pyrimidine as central core.

The main goals of this project were first, to find a general chemical pathway to synthesize pyrido[3,2-*d*]pyrimidines **5** having diverse substituents at C-6, and then, to explore the reactivity of the three chlorine groups on these derivatives **5**, towards S_NAr and metal-catalyzed cross-coupling reactions (*Figure 1.2*). Orthogonality of the three reactive centers via differentiation of the chlorine positions by different reaction conditions was also studied. The influence of the C-6 substituent on derivatives **5** towards the reactivity of the chlorine group was also considered.

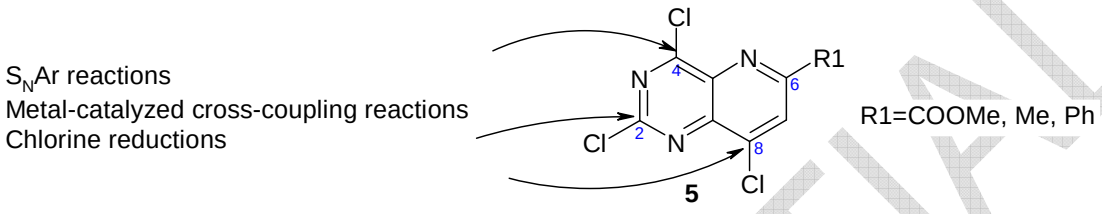
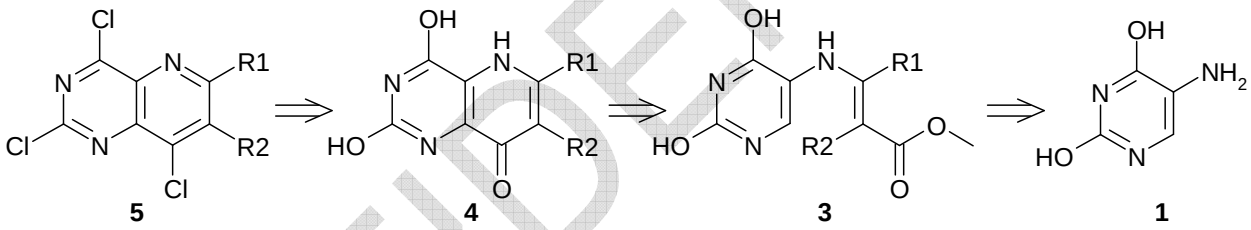


Figure 1.3. Planned reactions on trichloro-pyrido[3,2-*d*]pyrimidine derivatives **5**.

2. Synthesis of 6-substituted-2,4,8-trichloro-pyrido [3,2-*d*]pyrimidines.

2.1. Introduction.

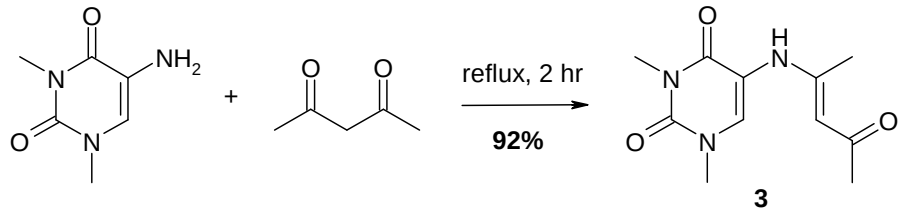
In order to have a general access to 2,4,8-trichloro-pyrido[3,2-*d*] pyrimidines **5** and inspired from the work of Irwin *et al.* and Srinivasan *et al.*, we have selected the proposed retrosynthetic pathway shown in *Scheme 2.1*. In this strategy, key intermediates are 1H-pyrido[3,2-*d*]pyrimidine-2,4,8-triones **4** and their enamine precursors **3**. Indeed, enamine **3** has two structural features which should help the ring closure to form the pyridopyrimidine **4**: a) electron-donating substituents in the 2-, 4-, and 5-positions of the pyrimidine ring, and b) a side-chain which requires no dehydrogenation to yield a fully aromatic compound on cyclization. Chlorination of **4** should give access to 2,4,8-trichloro-pyrido[3,2-*d*]pyrimidines **5** under chlorination conditions.



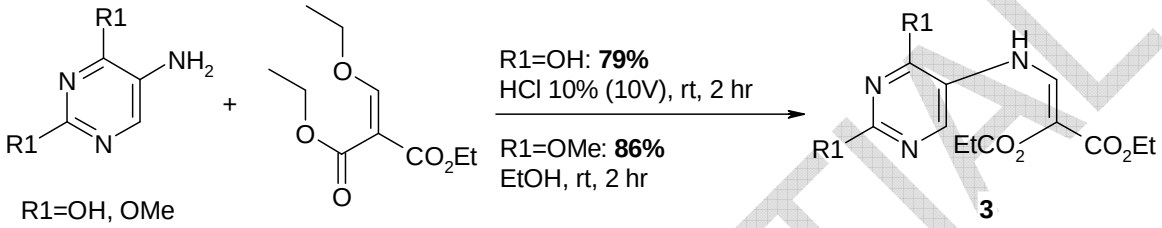
Scheme 2.1. 2,4,8-trichloro-pyrido[3,2-*d*]pyrimidine and its precursor.

Only two syntheses have been reported for the preparation of 2,4,8-trichloro-pyrido[3,2-*d*] pyrimidines **5**. One concerns the synthesis of the 6-substituted derivatives (R1≠H, R2=H),[17] and the second one concerns the synthesis of the 7-substituted derivatives (R1=H, R2≠H).[10] In both syntheses, 2,4,8-trichloro-pyrido[3,2-*d*]pyrimidines **5** were synthesized via the formation of intermediates **3** and **4**, following similar reaction conditions. Alternatively, several syntheses of enamines **3** have been reported, all starting from 5-aminouracil **1**: condensation of **1** with α,β-keto-esters, diketones or enol ethers,[10] or Michael addition of **1** on diverse alkynes.[17]

In 1967, Irwin *et al.* reported the synthesis of enamines **3** via condensation of 5-aminouracil with diketones (*Scheme 2.2*) and enol ethers (*Scheme 2.3*). Condensations were performed at room temperature or at reflux, in HCl or ethanol as solvent. Enamines **3** were obtained in yields ranging from 79 to 92% (*Schemes 2.2 and 2.3*).[10]

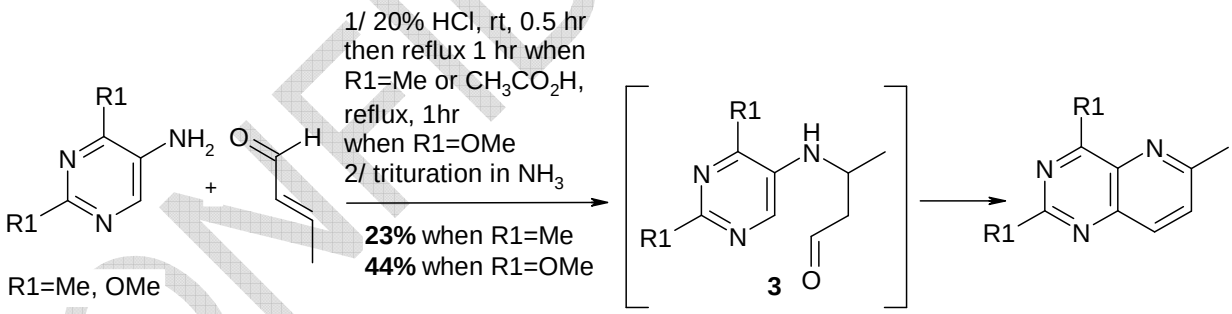


Scheme 2.2. Enamine **3** synthesis via condensation with diketone.



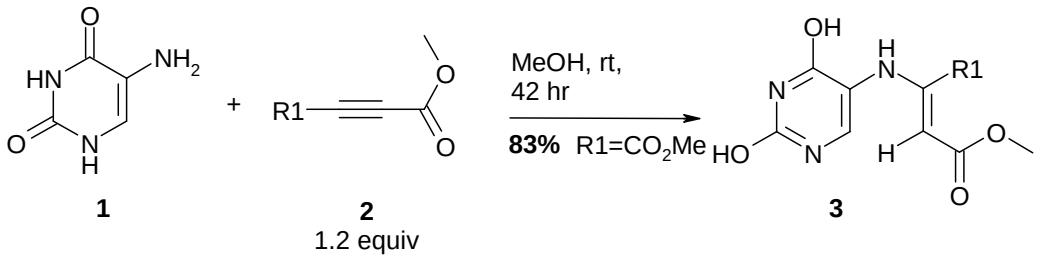
Scheme 2.3. Enamine **3** synthesis via condensation with enol ethers.

Irwin *et al.* also reported that when condensation was performed starting from α,β-unsaturated aldehydes or ketones and 5-aminouracil, final pyridopyrimidines were obtained directly after heating the reaction mixture in HCl or acetic acid (*Scheme 2.4*).[10]



Scheme 2.4. Enamine **3** synthesis via condensation with α,β-unsaturated aldehydes.

In 1979, Srinivasan *et al.* reported a different route for the synthesis of enamines **3**. They reported that the electrophilic cyclization of DMAD (derivative **2** with R1=COOMe) with 5-aminouracil **1** provided access to pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester.[17] In this synthesis, enamine derivative **3** was obtained via Michael addition of 5-aminouracil to the triple bond of DMAD (*Scheme 2.5*). The same chemical pathway was used for the synthesis of enamine **3** with R1=Me starting from but-2-ynoic acid ethyl ester.[18]

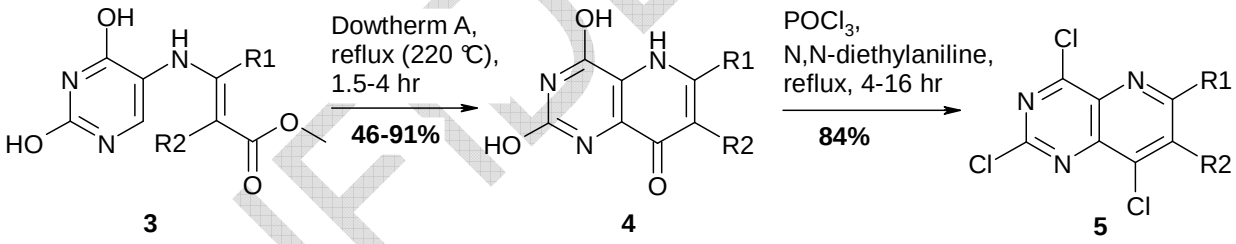


1 **2** 1.2 equiv **3**

R1=COOMe, Me

Scheme 2.5. Enamine **3** synthesis via Michael addition.

As previously mentioned, the resulting enamines **3** were transformed into 2,4,8-trichloro-pyrido[3,2-*d*]pyrimidines **5** in two steps. Cyclization was first performed by heating derivative **3** in Dowtherm A (mixture of phenoxybenzene and phenylbenzene) at reflux for 1.5 to 4 hours. Derivatives **4** were obtained in moderate to excellent yields ranging from 46 to 91%.[10,17] Trioxo derivatives **4** were finally converted into the desired 2,4,8-trichloro-pyrido[3,2-*d*]pyrimidines **5** by treatment with phosphoryl chloride in presence of N,N-diethylaniline at reflux, for 4 to 16 hours (*Scheme 2.6*).[17]



3 **4** **5**

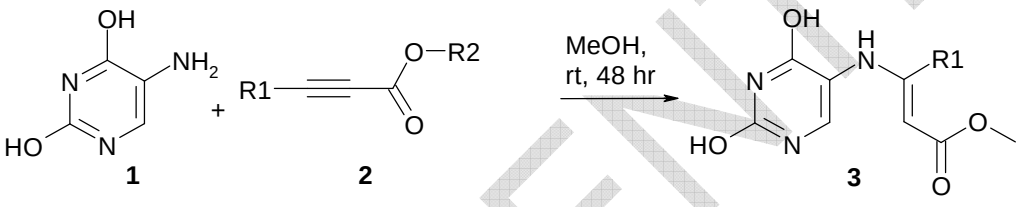
Scheme 2.6. Cyclization and chlorination of enamine **3.**

In the coming paragraph, we will investigate the different discussed routes for the preparation of enamine **3** that is needed for the synthesis of 2,4,8-trichloro-pyrido[3,2-*d*]pyrimidines **5** having diverse groups at C-6 and an hydrogen at C-7 position.

2.2. Syntheses of 2,4,8-trichloro-6-substituted-pyrido[3,2-*d*] pyrimidines **5**.

2.2.1. Route 1: Michael addition of 5-aminouracil.

Tto synthesize 2,4,8-trichloro-pyrido[3,2-*d*]pyrimidines having different R1 groups at C-6 position and an H at C-7, we first envisaged the Michael addition of 5-aminouracil on diverse activated alkynes following the chemical route described in *Scheme 2.5*. These Michael additions, performed in MeOH at room temperature, gave the desired intermediate only with R1=COOMe affording derivative **3a** (*Table 2.1 - Entry 1*). Unfortunately, no reaction was observed with the other alkynes (*Table 2.1 - Entries 2-6*). In each of these reactions, starting material could be entirely recovered. Addition of few drops of HCl 1N to activate **2** did not improve the conversion.

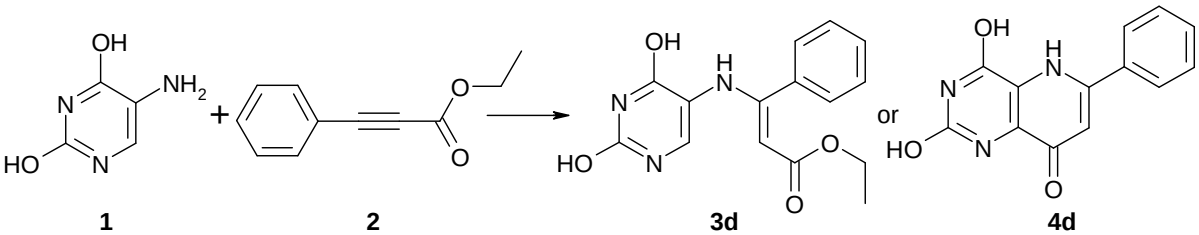


Entry	R1	R2	Product	Yield (%)
1	-COOMe	Me	**3a**	74
2	-CH_3	Me	**3b**	-
3	-Ph	Et	**3d**	-
4	-H	Me	**3e**	-
5	-$Si(CH_3)_3$	Et	**3f**	-
6	-$CH_2OSi(CH_3)_3$	Et	**3g**	-

Table 2.1. Synthesis of diverse enamines **3** via a Michael addition.

With R1=Ph, changing the solvent from MeOH to ACN and increasing the temperature from room temperature to 100 °C (under MW irradiation) did not yield any addition product (*Table 2.2 – Entries 1-3*). To further activate the Michael acceptor, different Lewis Acid were added in the reaction mixture: pTsOH[19], $Sc(OTf)_3$[20], $FeCl_3.6H_2O$,[21] $CeCl_3.7H_2O$,[21] $Zn(OAc)_2.2H_2O$,[21] $Ti(^iPrO)_4$,[21] and $ZnBr_2$.[22] Reactions were performed in ACN and were heated at 100 °C for 15 min under MW irradiation. Unfortunately, no trace of the desired compound could be observed (results not shown).

At higher temperature, in the presence of $ZnBr_2$ in dichlorobenzene (DCB), neither **3d** nor **4d** were observed (*Table 2.2 – Entries 5 to 8*).

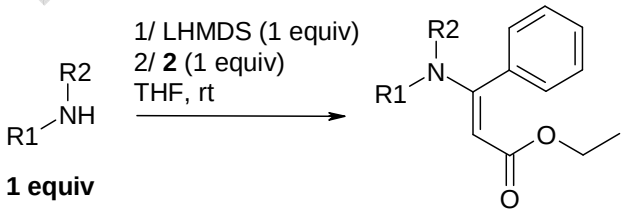


1 **2** **3d** **4d**

Entry	Additive / LA	solvent	Heating conditions	T	t	Yield (%)
1	-	MeOH	thermic	rt	48h	-
2	-	MeOH	MW	100 °C	15’	-
3	-	ACN	MW	100 °C	15’	-
4	TEA (1 equiv)	ACN	MW	100 °C	15’	-
5	$ZnBr_2$ (10% mol)	ACN	MW	100 °C	15’	-
6	$ZnBr_2$ (10% mol)	DCB	MW	100 °C	15’	-
7	$ZnBr_2$ (10% mol)	DCB	MW	200 °C	15’	-
8	$ZnBr_2$ (10% mol)	DCB	MW	250 °C	15’	-

Table 2.2. Lewis acids as catalysts for Michael addition of 5-aminouracil **1** to alkyne.

In order to enhance the reactivity of the 5-aminouracil **1**, its lithium amide was prepared and was added to ethyl phenylacetylenecarboxylate **2**. 5-aminouracil lithium amide was formed with 5-aminouracil and LHMDS in THF at room temperature. After 30 minutes, ethyl phenylacetylenecarboxylate was added and the reaction mixture was stirred at rt for 24 hours (*Table 2.3 – Entry 1*). No reaction was observed. On the other hand, the same conditions applied to imidazole gave the desired Michael adduct (*Table 2.3 – Entry 2*). This last result indicates that 5-aminouracil **1** is not nucleophilic enough to add to ethyl phenylacetylenecarboxylate **2**.



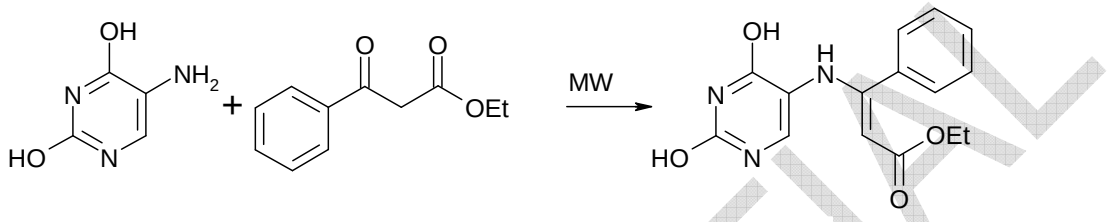
1 equiv

Entry	R1R2NH	Reaction time	Starting Material	Product Yield (%)
1	5-aminouracil	24 hr	100	-
2	imidazole	24 hr	0	100% conversion

Table 2.3. Lithium amide as activated Michael donor.

2.2.2. Route 2: Condensation of β-keto ester on 5-aminouracil.

Syntheses of enamines **3** were further envisaged via the condensation of 5-aminouracil **1** and 3-oxo-3-phenyl-propionic acid ethyl ester **6** (*Scheme 2.7*). In the literature, condensations of amines with β-diketones or β-keto esters, catalyzed by Lewis bases or acids,[20,21,22,,23] have been described to access to β-enaminones and β-enamino esters.[24]

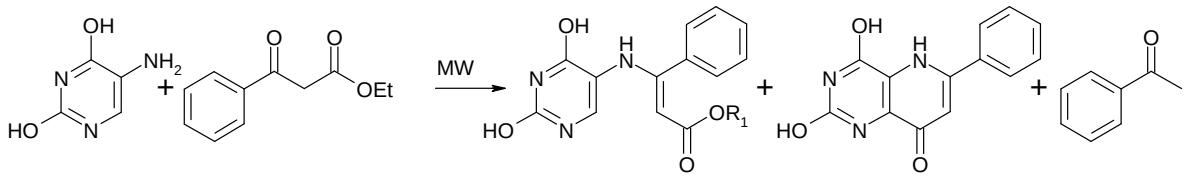


1 **6** **3d**

Scheme 2.7. Condensation of 3-oxo-3-phenyl-propionic acid ethyl ester **6** on 5-aminouracil **1**.

Reaction of 1 equiv of 5-aminouracil **1** and 1 equiv of 3-oxo-3-phenyl-propionic acid ethyl ester **6** performed in pure triethylamine[25] at 150 °C for 5 minutes under MW irradiation gave only the starting material (*Table 2.4 – Entry 1*). In order to get the desired enamine **3d**, the temperature was increased up to 250 °C. In this reaction, hydrolysis of the desired enamine as well as decarboxylation of 3-oxo-3-phenyl-propionic acid ethyl ester **6** were observed affording respectively derivative **3'd** and acetophenone **7** (*Table 2.4 – Entry 2*).

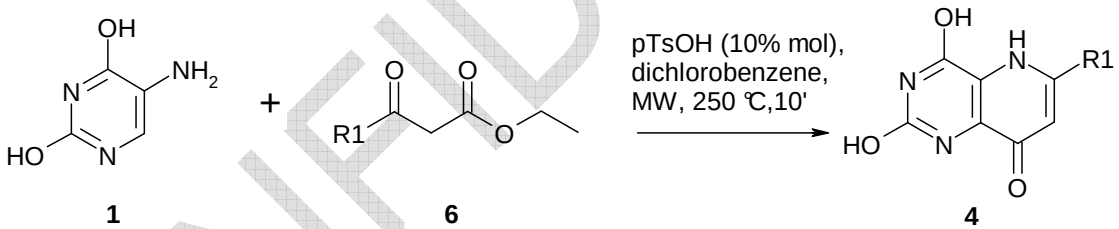
We further selected different Lewis acids to activate the Michael acceptor. Different conditions were tried with *p*-toluene sulfonic acid (pTsOH - 10% mol) (*Table 2.4*).[19] When DCB was selected as solvent, at 250 °C under MW irradiation, 50% conversion into the desired compound **4d** was observed (*Table 2.4 – Entry 3*). The same reaction mixture was further heated for another 10 minutes: conversion into the desired derivative **4d** increased up to 61% but acetophenone **7** formation was also observed (UHPLC conversion of 39%) (*Table 2.4 - Entry 4*). The use of other Lewis Acids, such as $FeCl_3.6H_2O$,[21] $CeCl_3.7H_2O$,[21] $InCl_3$,[23] and $Ti(^iPrO)_4$,[21] did not yield the formation of the desired product, even at 250 °C. Finally, the best conditions consisted in the condensation of 1 equiv of 5-aminouracil **1** with 3 equiv of 3-oxo-3-phenyl-propionic acid ethyl ester **6**, in presence of 10% mol. pTsOH with DCB as solvent (C = 0.5 M) heated under MW irradiation at 250 °C for 10 minutes (*Table 2.4 – Entry 5*).



Entry	additive	solvent	X (equiv.)	T	t	Expected compound	Compound formed	7
1	TEA (1equiv)	-	1	150 °C	5'	**3d**	no rx	-
2	TEA (1equiv)	DCB	1	250 °C	10'	**3d**	**3'd**: 28%	30%
3	pTsOH 10% mol	DCB	1	250 °C	10'	**4d**	**4d**: 50%	-
4			1	250 °C	+10'	**4d**	**4d**: 61%	39%
5	pTsOH 10% mol	DCB	3	250 °C	10'	**4d**	**4d**: 65%	28%

Table 2.4. Influence of reaction conditions on enamine formation.

Under these conditions, unfortunately, the reaction with 3-oxo-butyric acid methyl ester (R1=Me) gave many side-products (*Table 2.5 – Entry 2*).



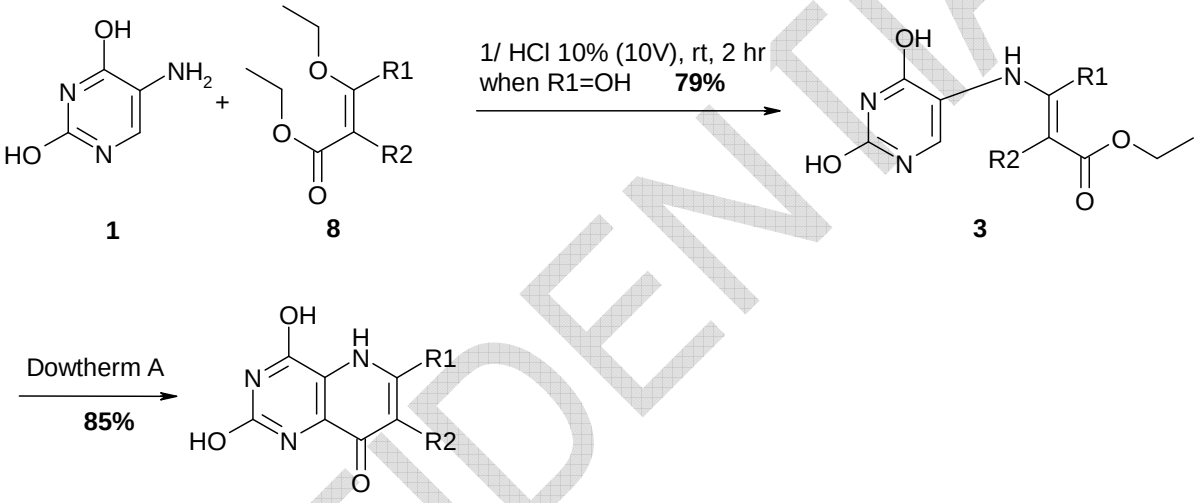
Entry	R1	C	Aminouracil 1	Compound 4	By-pdt
1	Ph	0.5M	-	55%	28% acetophenone **7**
2	Me	0.5M	46%	-	many by-pdts

Table 2.5. Influence of R1 group on β-keto ester.

To find a general procedure to synthesize diverse enamines **3**, we further envisaged their formation via condensation of enol-ethers with 5-aminouracil.

2.2.3. Route 3: Condensation of enol-ethers with 5-aminouracil.

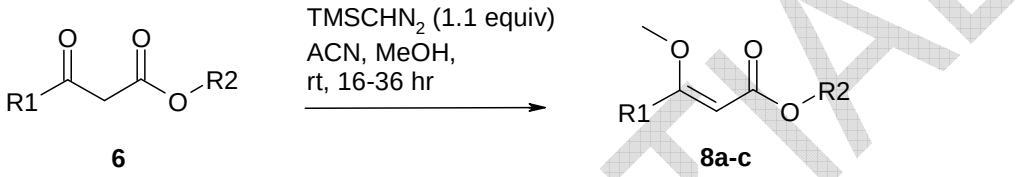
As described in the introduction of this chapter, the synthesis of 7-substituted-pyrido[3,2-*d*]pyrimidine, via the condensation of an enol ether with 5-aminouracil **1** followed by an intramolecular electrophilic cyclization, has been described only with diethyl ethoxymethylenemalonate as starting point, yielding diethyl 2,4-dihydroxypyrimidin-5-ylaminomethylenemalonate (*Scheme 2.3*).[10] To synthesize 6-substituted-2,4,8-trihydroxy-pyrido[3,2-*d*]pyrimidines **4**, without any substituent at C-7 position, we envisaged the condensation of the commercially available 5-aminouracil **1** with diverse 3-substituted-3-ethoxy-acrylic acid ethyl(methyl) ester **8** (*Scheme 2.8;* R1≠H, R2=H).



Scheme 2.8. Enamine synthesis via condensation of 5-aminouracil **1** with diverse enol ethers **8**.

2.2.3.1. Enol ethers formation.

Only few 3-substituted-3-ethoxy-acrylic acid ethyl(methyl) esters **8** are commercially available. However, they can be readily prepared via O-methylation of α,β-keto esters. Reaction of diverse α,β-keto esters with 1.1 equiv of trimethylsilyl diazomethane ($TMSCHN_2$), in a mixture of ACN and MeOH at room temperature for 16 to 36 hours, afforded the desired derivatives **8** in moderate to good yields (*Table 2.6*). Products **8** were directly used in the next step without further purification.



6 **8a-c**

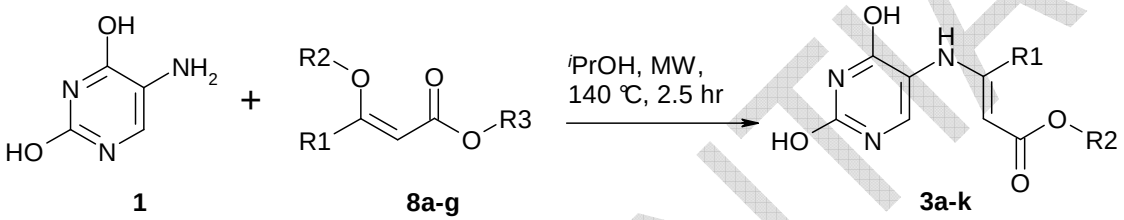
Entry	R1	R2	Scale	Product	Yield (%)
1	Ph	Et	5 g	**8a**[a]	89
2	^{i}Pr	Et	1 g	**8b**[a]	89
3	^{c}pentyl	Et	1 g	**8c**[a]	81
4	^{c}propyl	Et	1 g	**8d**	No reaction
5	3-pyridine	Me	2 g	**8e**[a]	52
6	4-pyridine	Et	2 g	**8f**	25
7	CH_2OMe	Me	2 g	**8g**[a]	84

[a]: compound used in the next step without further purification

Table 2.6. Enol ethers **8** formation via O-methylation of α,β-keto esters.

2.2.3.2. Enamine formation.

For the preparation of enamines **3**, optimized conditions consisted in the reaction of 1 equiv of 5-aminouracil **1** with 1.1 equiv of enol ether **8** in ^{i}PrOH at 140 °C under MW irradiation for 2.5 hr. Enamines **3** synthesized from enol ethers bearing R1=Me, Et (both commercially available) and R1=Ph (**8a**) were obtained in good to excellent yields following these conditions (*Table 2.7 - Entries 1-3*). In contrast, no reaction was observed with the other enol ethers (*Table 2.7 – Entries 4-9*). The lack of reactivity could be due to steric (with R1=^{i}Pr, ^{c}pentyl) and/or electronic (R1=CH_2OEt, OEt, 3- and 4-pyridine) reasons. Finally, when 3-ethoxy acrylic acid ethyl ester was used as reagent (*Table 2.7 - Entry 4*), double Michael additions was observed.



1
1 equiv

8a-g
1.1 equiv
R3=Me, Et

3a-k
R3=Me, Et

Entry	R1	R2	Product	Yield (%)
1	Me	Et	**3b**[a,d]	94
2	Et	Me	**3c**[a,d]	85
3	Ph	Me	**3d**[a]	81
4	H	Me	**3e**[b,d]	-
5	3-pyridine	Me	**3h**[c]	-
6	4-pyridine	Me	**3i**[c]	-
7	^{i}Pr	Me	**3j**[c]	-
8	^{c}pentyl	Me	**3k**[c]	-
9	OEt	Et	**3l**[c,d]	-
10	CH_2OMe	Me	**3m**[c]	-

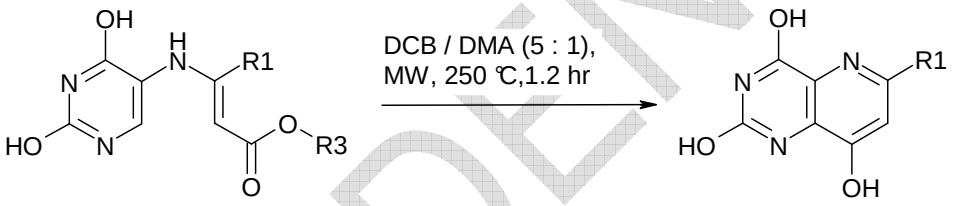
[a] Yield calculated from the mixture of ^{i}Pr-ester and R3-ester due to the transesterification
[b] double Michael additions observed
[c] No trace of desired product detected
[d] commercially available compounds

Table 2.7. Enamines **3** formation via Michael addition of 5-aminouracil and enol ethers **8**.

Enamines **3a** (obtained from Michael addition on alkyne - *Table 2.1*) and **3b-d** were further engaged for the cyclization step.

2.2.3.3. Cyclization.

Irwin *et al.* reported that the cyclization of diethyl 2,4-dihydroxypyrimidin-5-ylaminomethylene malonate was taking place by heating this compound at reflux in Dowtherm (A) (Bp=257 °C) for 1 hour.[10] While the cyclization affording the 2,4,8-trihydroxy-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **3a** occurred after 1.5 hour at reflux in Dowtherm (A) (*Scheme 2.1 – Table 2.8 – Entry 1*), first attempt of cyclization of **3b** in the same solvent did not give a good conversion after 24 hours at reflux (*Table 2.8 - Entry 2*). To increase the percentage of conversion, the same reaction was further performed under MW irradiation for 1.2 hr at 250 °C (*Table 2.8 – Entry 3*). Unfortunately, only 37% conversion was observed, probably due to a solubility problem. In order to improve the solubility of the starting material, we selected dimethylacetamide (DMA) as solubilising agent, mixed with dichlorobenzene (DCB), selected for its high boiling point (Bp=180 °C), in a 5:1 ratio. Reactions were performed in sealed MW vials for 1.2 hr at 250 °C under MW irradiation. Derivatives **4a-d** were obtained in excellent yields and purities (*Table 2.8 – Entries 4 to 7*).



3a-c **4a-c**

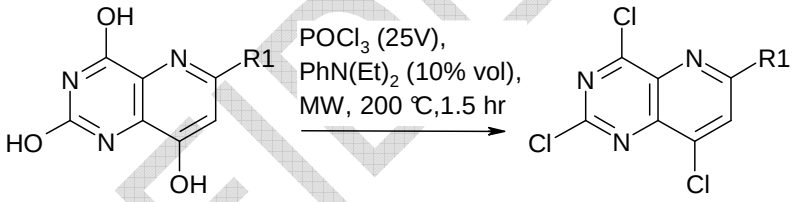
Entry	R1	Solvent	Product	Yield (%)
1	COOMe	Dowtherm (A)	**4a**[a]	46
2	Me	Dowtherm (A)	**4a**[a,b]	16% conversion
3	Me	Dowtherm (A)	**4a**[a,b]	37% conversion
4	COOMe	DCB / DMA	**4a**	88
5	Me	DCB / DMA	**4b**	84
6	Et	DCB / DMA	**4c**	67
7	Ph	DCB / DMA	**4d**	86

[a] Reaction performed at reflux under thermic conditions
[b] Determined by UHPLC ratio

Table 2.8. Cyclization of derivatives **3a-c** in a DMA / DCB mixture.

2.2.3.4. Chlorination.

Chlorination of 6-substituted-2,4,8-trihydroxy-pyrido[3,2-*d*]pyrimidine derivatives has been reported only once with an ethyl ester group at C-6 position (*Scheme 2.1 – Table 2.9- Entry 4*).[10,17] In this reaction $POCl_3$ was used in large excess in presence of 10% vol. of *N*,*N*-diethylaniline. The later was used as base to quench the proton formed during the formation of the pyridopyrimidine-phosphorous intermediate. The reaction was heated at reflux (T=106 °C) for 16 hours. Chlorinations of **5a** and **5b** were performed following these conditions, at reflux for 36 hours. After filtration of the precipitate formed during the reaction, derivative **5a** and **5b** were isolated in moderate to good yields and good purity (*Table 2.9 – Entries 1 and 2*). To decrease the reaction time, we envisaged to perform these chlorinations under MW irradiation. Unfortunately, starting from **4a** and **4b**, reaction mixtures were not clean compared to the thermic conditions. On the other hand, starting from derivatives **4c** and **4d**, the use of MW irradiation decreased the reaction time. In these two cases, optimized conditions consisted in heating at 200 °C for 1.5 hr a suspension of derivative **4** in 25V of $POCl_3$. Presence of *N*,*N*-diethylaniline in these two reaction mixtures was not necessary to reach complete conversion. After filtration of the precipitate formed during the reaction, derivatives **5c** and **5d** were obtained in moderate to good yields (*Table 2.9 – Entries 3 and 4*).



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

Entry	Heating conditions	R1	Product	Yield (%)
1	Thermic	COOMe	**5a**	84
2	Thermic	Me	**5b**	78
3	MW	Et	**5c**[a]	63
4	MW	Ph	**5d**[a]	85

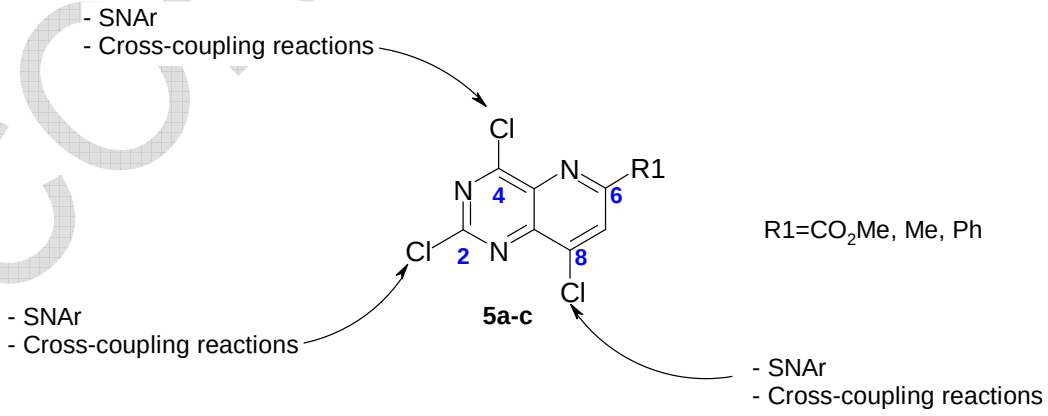
[a]: $PhN(Et)_2$ was not used

Table 2.9. Chlorination of derivative **5a-d**.

2.3. Conclusion.

A robust and straightforward synthetic route for the synthesis of 6-substituted-2,4,8-trichloro-pyrido[3,2-*d*]pyrimidines **5** has been developed. This synthetic route consisted in 3 or 4 steps: 1) the formation of enol ether **8** if not commercially available, 2) the condensation of 5-aminouracil **1** on the enol ether **8**, 3) the cyclization and finally 4) the chlorination. These four steps were perfomed under MW irradiation to complete the reactions and to reduce the reaction time. The final compounds were obtained in overall yield ranging from 30 to 52%. The scope of the second step was limited to aryl and non-branched alkyl enol ethers. No reaction was observed with pyridine and branched alkyl enol ethers, probably due to steric and/or electronic reasons. In order to have a complete conversion in the cyclization step, a mixture of DCB and DMA in a 5:1 ratio was crucial, due to a better solubilization of the reagents. Concerning the chlorination step, addition of *N*,*N*-dimethylaniline with $POCl_3$ was necessary for some of the reaction mixtures to ensure complete chlorination (with R1=Me and CO_2Me at C-6). The simplicity of the reactions and of the purification steps (precipitation and/or filtration) make this route particularly convenient for the synthesis of 6-substituted-2,4,8-trichloro-pyrido[3,2-*d*]pyrimidines with diverse aryl or alkyl groups at C-6.

The 6-substituted-2,4,8-trichloro-pyrido[3,2-*d*]pyrimidine derivatives that have been prepared, offered us scaffolds with diverse electronic properties as starting points for studying the reactivity of the three chlorines (R1=CO_2Me, Me and Ph). The goal was then to regioselectively substitute the three chlorines at position 2, 4 and 8 on 6-substituted-2,4,8-trichloro-pyrido[3,2-*d*]pyrimidines **5a-c**, via S_NAr and metal-catalyzed cross-coupling reactions.



Scheme 2.9. Regioselective chlorine substitutions on derivatives **5a-c**.

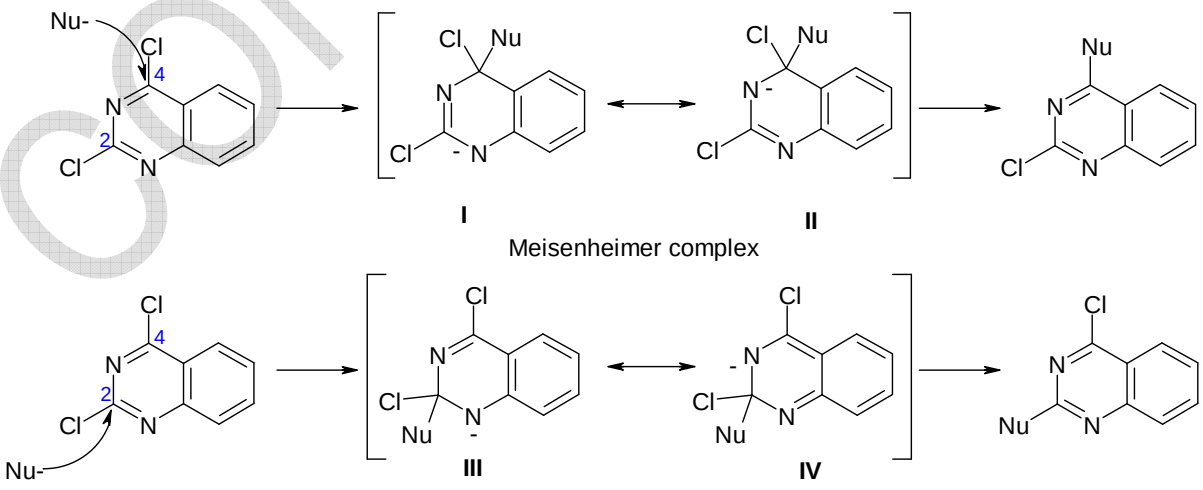
3. Reactions at C-4.

3.1. Introduction.

The regioselective diversification of the chlorines on pyridopyrimidines **5** was envisaged through aromatic nucleophilic substitutions and metal catalyzed cross-coupling reactions. Chlorines were displaced by nucleophiles through S_NAr reactions with amines and thiols. For C-C bond formation, different metal catalyzed cross-coupling reactions such as Suzuki, Stille or Negishi were firstly envisaged.

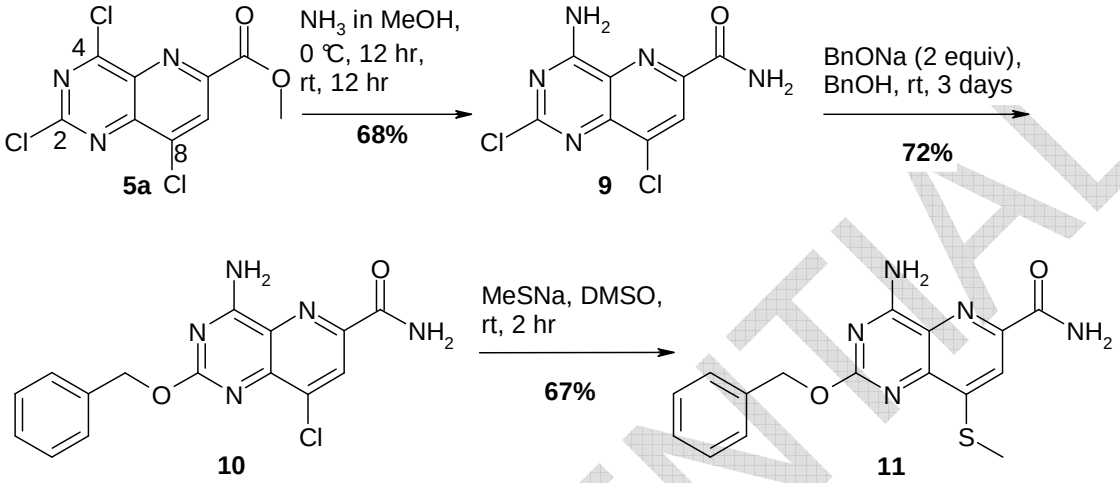
3.1.1. S_NAr reactions.

A nucleophilic aromatic substitution is a substitution reaction in which the nucleophile displaces a leaving group such as halide, on an aromatic ring. There are five nucleophilic substitution mechanisms described for aromatic systems: 1) the S_NAr (addition-elimination) mechanism,[26] 2) the SN_1 mechanism encountered with diazonium salts,[27] 3) the benzyne mechanism,[28] 4) the free radical $S_{RN}1$ mechanism[29] and 5) the ANRORC (Addition of Nucleophile, Ring Opening and Ring Closure) mechanism.[30] In the case of pyridopyrimidines-halides as well as in the case of quinazoline-halides, nucleophilic substitutions are described to occur following an addition-elimination mechanism.[10,17] When polyhalogenated-heterocycles are studied, the important factor to be controlled is the reactivity of the diverse halogens. Studies on the 4,2-dichloroquinazoline scaffold revealed that the 4-chlorine reacts 6400 times faster than the 2-chlorine atom towards piperidine.[31] The difference in reactivity between the 2- and the 4- position is explained by the stabilizing influence of the resonance forms **I** and **II** in the transition state in the 4-isomer as compared with **III** and **IV** in the 2-isomer (*Scheme 3.1*). The contribution from the canonical form **IV** is small because of the less stable *o*-quinonoid structure.



Scheme 3.1. Reactivity of 4- and 2-position of 4,2-dichloroquinazoline.

In the particular case of 2,4,8-trichloro-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **5a**, the order of reactivity of the three chlorines has been reported as C4>>C2>C8 with ammonia as nucleophile. Position 2 was further proved to react faster than C-8 with sodium benzylate. Finally, sodium methylthiolate addition took place at C-8 position as described in *Scheme 3.2*. [10,17, 32,33]

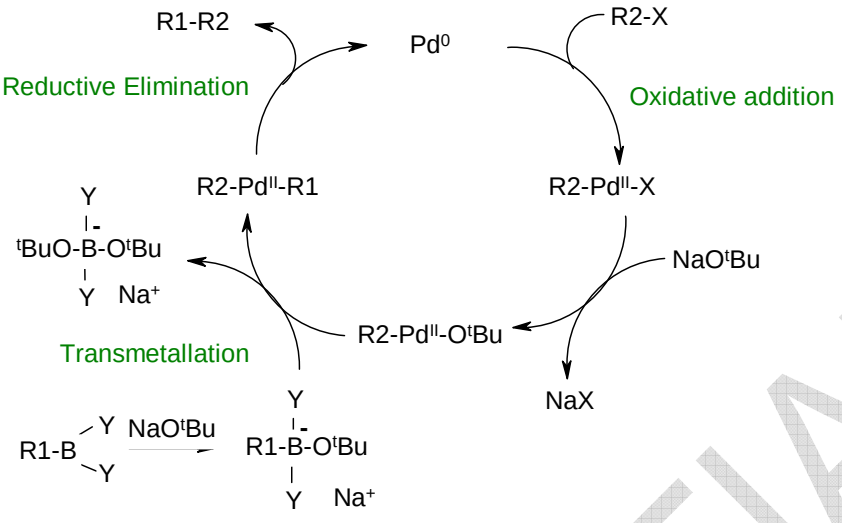


Scheme 3.2. Reported regioselectivity on derivative **5a**.

3.1.2. Metal-catalyzed cross-coupling reactions.

Cross-coupling reactions of organometallics and halides or triflates are widely used in organic chemistry for the formation of C-C bonds.[34] The general mechanism involves oxidative addition of an alkyl- or an aryl-halide to a transition metal (n) of low oxidation state (usually n=0 or 1) to form a metal (n+2) species. The rate limiting step is often the transmetallation where the nucleophile is transferred from the main group metal to the transition metal and the counterion (the halide) moves in the opposite direction. After a trans/cis isomerization, the new metal (n+2) complex with two organic ligands undergoes reductive elimination to give the coupled product and the transition metal (n) catalyst ready for another cycle. Among the cross-coupling reactions, the Suzuki and Stille reactions were selected as palladium-catalyzed cross-coupling reactions to introduce aryl groups.

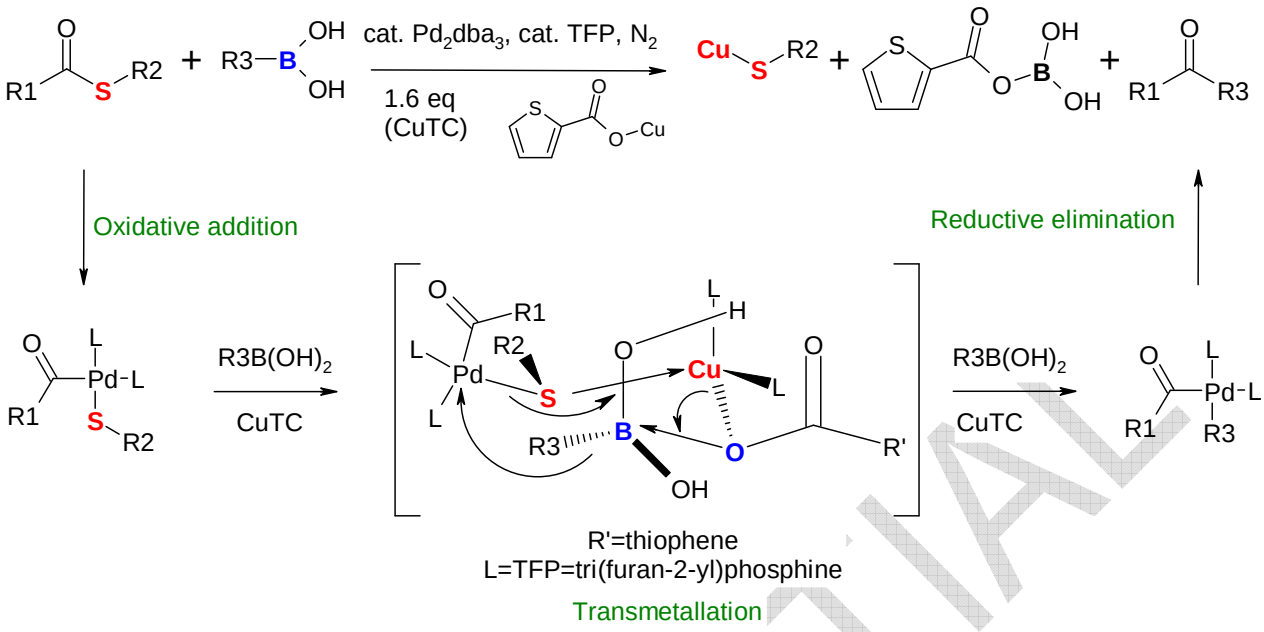
The Suzuki cross-coupling reaction, first published in 1979,[35] is the reaction of an alkyl, an aryl or vinyl boronic acid with an aryl or alkyl halide catalyzed by a palladium (0) complex. The boronic acid must be activated, for example with a base. This activation of the boron atom enhances the polarisation of the organic ligand, and facilitates transmetallation. The Suzuki cross-coupling reaction mechanism is presented in *Scheme 3.3*.



Scheme 3.3. Suzuki cross-coupling mechanism.

The Stille cross-coupling reaction is a versatile C-C bond forming reaction between stannanes and halides or pseudohalides, with very few limitations on the R-groups.[36] Moreover, due to the lower electronegativity of tin compare to boron, transmetallation of tin to transition metal is easier than the transmetallation of organoboron to transition metal. However, the main drawback of the Stille coupling is the toxicity of the tin derivatives used, and their low polarity.

In 2000, Liebeskind and Srogl have developed an extremely general palladium cross-coupling reaction that even works with base-sensitive functional groups. This base-free reaction involves the coupling of a boronic acid with a thiol ester to form ketones (*Scheme 3.4*).[37] This reaction does not only use palladium, but uses stoichiometric amount of the air stable copper(I) thiophenecarboxylate (CuTC) as a co-factor.



Scheme 3.4. Liebeskind-Srogl cross-coupling reaction of boronic acid with thiol ester.

Scheme 3.4 represents the mechanism of the Liebeskind-Srogl reaction, with the transmetallation proceeding through a six membered ring mechanism facilitated by the additive copper carboxylate. A full equivalent of Cu(I) carboxylate is required for two reasons: while the Cu(I) ion kinetically labilizes the Pd–SR2 bond of the catalytic intermediate increasing its electrophilicity, it also ends up paired with the thiolate in a thermodynamically strong Cu-SR2 bond. At the same time, a full equivalent of the borophilic carboxylate counter-ion is required to fully balance the equation and drive the $-B(OH)_2$ moiety to the formation of R'C(O)O-$B(OH)_2$ (R'=thiophene).

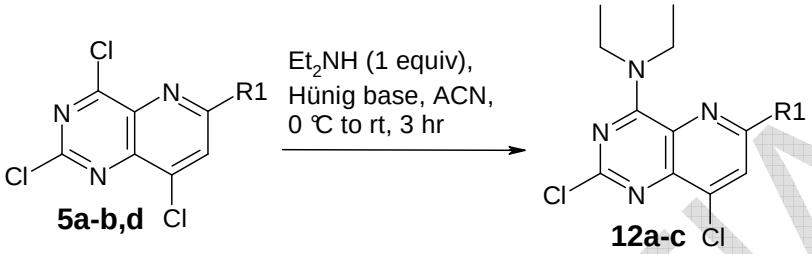
This reaction has been extended to a number of substrates: alkynes,[38] α-amino ketones,[39] heteroaromatics,[40] aryl and heteroaryl amidines,[41] functionalized pyrimidinones,[42] and cyanates.[43]

3.2. S_NAr reactions at C-4.

To confirm the reactivity order already reported towards S_NAr on 2,4,8-trichloro-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **5a** with diverse substitutents at the C-6 position (*i.e.* on derivatives **5a** to **5c**), and to study the scope of this reaction, diverse nucleophiles were selected to substitute the C-4 chlorine on 2,4,8-trichloro-6-substituted-pyrido[3,2-*d*]pyrimidine derivatives **5**.

3.2.1. S_NAr with amines.

Nucleophilic substitutions at position 4 on 2,4,8-trichloro-pyrido[3,2-*d*]pyrimidine derivatives **5** were achieved, via addition of a stoechiometric amount of diethylamine to derivatives **5** in presence of Hünig base. After 3 hours at room temperature, precipitation of desired products in methanol afforded compounds **12a** to **12c** in moderate to excellent yields (*Table 3.1*).

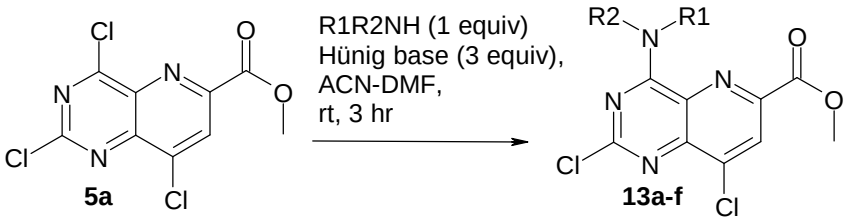


Entry	R1	Product	Yield (%)
1	COOEt	**12a**	73
2	Me	**12b**	80
3	Ph	**12c**	73

Table 3.1. S_NAr with diethylamine at C-4 on derivatives **5**.

In order to explore the scope of aromatic nucleophilic substitution of amines on derivatives **5**, diverses amines, including anilines, primary and secondary amines, were selected and added to derivative **5a** following the previous optimized conditions.

Desired compounds were obtained in good to excellent yields. As reported in *Table 3.2*, poorly reactive amines, such as anilines, could be added efficiently at C-4, indicating the high reactivity of the C4-Cl bond. In addition, only one regioisomer was formed with any of the selected amines.

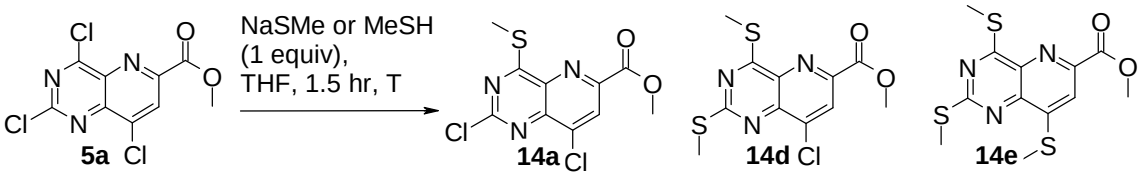


Entry	Amine	Product	Yield %
1	^{c}Hex-NH_2	**13a**	77
2	Me_2NH	**13b**	80
3	Et_2NH	**12a**	73
4	morpholine	**13c**	82
5	$PhNH_2$	**13d**	82
6	*p*-OMe-$PhNH_2$	**13e**	80
7	*p*-CF_3-$PhNH_2$	**13f**	78

Table 3.2. S_NAr with diverse amines at C-4 on derivative **5a**.

3.2.2. S_NAr with thiols.

Aromatic nucleophilic substitution on derivative **5** was further envisaged with thiol or thiolate as nucleophile. As described in *Table 3.3*, addition of 1 equiv of sodium methylthiolate to scaffold **5a**, following the same protocol as the one used for amine addition, gave a mixture of **14a**, **14d** and **14e** (*Table 3.3 - Entry 1*). By decreasing the temperature down to 0 °C, selectivity for **14a** was improved from 30 to 48% (*Table 3.3 -Entry 2*). Optimized conditions consisted in the addition of 1 equiv of sodium methylthiolate to a solution of scaffold **5a** in THF at -10 °C. After 1.5 hour, complete conversion into **14a** was obtained (*Entry 3*) with a regioselective addition at C-4.

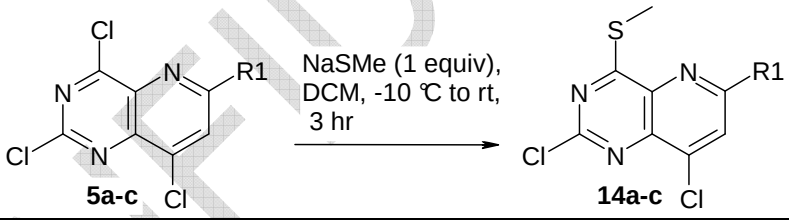


Entry	Sulfur source	T	5a %[a]	14a %[a]	14d %[a]	14e%[a]	Yield (%)
1	NaSMe	rt	19	30	6	15	-
2	NaSMe	0 °C	27	48	2	17	-
3	NaSMe	-10 °C	-	84	-	-	80

[a] percentage of conversion based on UHPLC

Table 3.3. Optimization of S_NAr with NaSMe at C-4 on derivative **5a**.

These optimized conditions, allowing the formation of derivative **14a** from derivative **5a**, were then applied to derivatives **5b** and **5c** affording respectively derivatives **14b** and **14c** in excellent yields and purities as reported in *Table 3.4*.



Entry	R1	Product	Yield (%)
1	COOEt	**14a**	84
2	Me	**14b**	84
3	Ph	**14c**	85

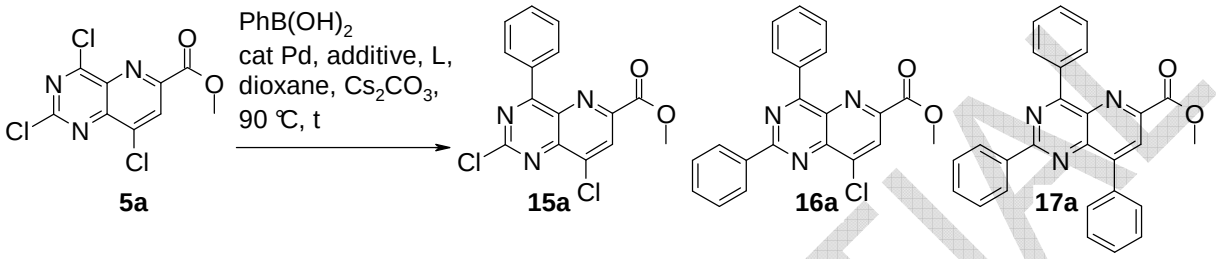
Table 3.4. S_NAr with NaSMe at C-4 on derivatives **5**.

Regioselective C-N and C-S bond formation at C-4, via S_NAr reactions, were successfully achieved on derivatives **5**. Metal-catalyzed cross-coupling reactions were further envisaged to regioselectively introduce C-C bond at C-4 on the same derivatives.

3.3. Cross-coupling reactions at C-4.

3.3.1. Suzuki cross-coupling reaction.

Suzuki cross-coupling reaction was first selected as metal-catalyzed cross-coupling reaction, using phenyl boronic acid and derivative **5a** as partners to optimize the reaction conditions (*Table 3.5*).



5a **15a** **16a** **17a**

Entry	Catalyst (4%)	Ligand (8%)	Additive	t (hr)	Conversion			
					15a[a] (%)	16a (%)	17a (%)	Yield (%)
1	$Pd(PPh_3)_4$	-	-	16	39	14	-	-
2	$Pd(PPh_3)_4$	-	$Zn(OAc)_2$	16	-	Mixture of compounds		-
3	$Pd(PPh_3)_4$		TEA AgOAc	16	24	12	-	-
4	$Pd(OAc)_2$	Carbene 1	-	16	39	10	7	-
5	Pd(OAc)2	Carbene 1	TEA	16	-	Mixture of compounds		
6	$Pd(OAc)_2$	Carbene 1	$Zn(OAc)_2$	16	22	-	-	-
7	$Pd(OAc)_2$	Carbene 1	CuI	16	18	-	-	-
8	$Pd(OAc)_2$	Carbene 1	CsF	16	-	-	-	-
9	$Pd(OAc)_2$	P^tBu_3	-	4.5	-	-	-	-
10	Pd/C	-	-	2.5	-	-	-	-
11	$Pd_2(dba)_3$	PCy_3	KF	16	10	-	-	-
12	$PdCl_2(dppf)$	Carbene 1	-	16	14	4	6	-

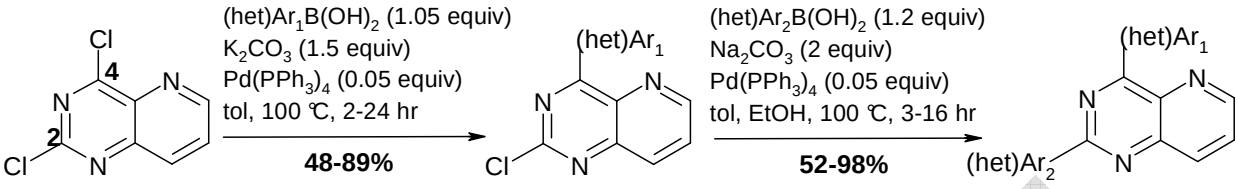
[a]: Based on HPLC (200-400 nm)

Carbene 1: 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride

Table 3.5. Optimization of Suzuki cross-coupling reaction at C-4.

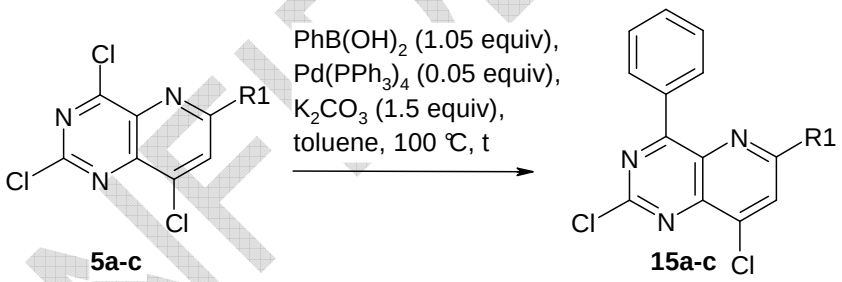
As described in *Table 3.5*, different Pd catalysts, combined with different ligands, additives and bases have been used. Percentage of conversion into the desired product never exceeded 39% (*Entries 1 to 12*). Moreover, multiple cross-coupling reactions were observed in most of the attempts (*Entries 1-5, 11 and 12*).

While we were conducting these experiments, Tikad *et al.* reported the regioselective C-C bond formation at C-4 on 4,2-dichloro-pyrido[3,2-*d*]pyrimidine via Suzuki cross-coupling reaction (Scheme 3.6).[44]



Scheme 3.5. Regioselective C-C bond formation on 4,2-dichloro-pyrido[3,2-*d*]pyrimidines.

Following the described conditions developed by Tikad *et al.*, the same conditions ($Pd(PPh_3)_4$, K_2CO_3, toluene, 100 °C) were applied on derivatives **5** with phenyl boronic acid (*Table 3.6*). Starting from **5a**, multiple cross-coupling reaction products were formed (*Table 3.6 – Entry 1*). Starting from derivatives **5b** and **5c**, only 27 to 21% conversion were respectively observed after 72 hours (*Table 3.6 – Entries 2 and 3*). Finally, starting from derivative **5c**, MW irradiation (150 °C for 0.5 hr) did not yield the d esired product, and no multiple cross-coupling products were formed (*Table 3.6 –Entry 4*).



5a-c **15a-c**

Entry	R1	t (hr)	Product	Yield (%)
1	COOMe	3	**15a**	Multiple cross-coupling reaction
2	Me	72	**15b**	27% conversion
3	Ph	72	**15c**	21% conversion
4	Ph	0.5[a]	**15c**	No reaction

[a]: Reaction performed under MW irradiation at 150 °C for 0.5 hr

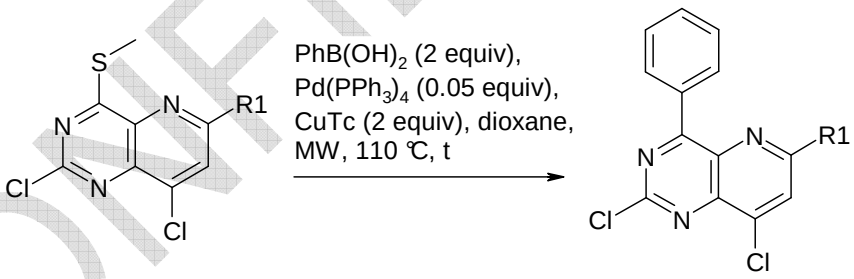
Table 3.6. Suzuki cross-coupling reaction at C-4 on derivatives **5**.

Alternative cross-coupling reactions have been investigated on compound **5a.** Unfortunately, Stille cross-coupling reactions,[36] with $PhSnBu_3$ and Negishi cross-coupling reactions,[45] with PhZnX, did not improve the percentage of conversion neither the regioselectivity. As we were able to selectively substitute the chlorine at C-4 with a methylsulfanyl group, formation of the C-C bond at C-4 was envisaged via Liebeskind-Srogl cross-coupling reaction, which would take place regioselectively at the C-S bond of derivatives **14a** to **14c**, and not at the C-Cl bonds present at C-2 and C-8 on these derivatives.

3.3.2. Liebeskind-Srogl cross-coupling reaction.

As detailed in chapter 3.1.2, the Liebeskind-Srogl cross-coupling reaction is a base-free metal-catalyzed cross-coupling reaction involving the coupling of boronic acids with thiol ethers or thiol esters to form aryl-aryl bond or ketones. On derivatives **14a-c**, the LS cross-coupling reactions were performed using phenyl boronic acid as coupling partner. First attempt was performed on derivative **14c** (with R1=Ph) with 2 equiv of phenyl boronic acid, in presence of 0.05 equiv of $Pd(PPh_3)_4$ and 2 equiv of CuTc as co-factor, in dioxane at 100 °C. Unfortunately, only 58% conversion was observed after 48 hours (*Table 3.7 – Entry 1*). Complete conversion was obtained performing the reaction with the same conditions, under MW irradiation at 110 °C for 1.5 hr. Compounds **15a-c** were obtained in moderate to good yields (*Table 3.7 – Entries 2 to 4*).

In addition, only one regioisomer was formed during this reaction, with the C-C bond formation at C-4, as disclosed by Liebeskind as orthogonal reaction.



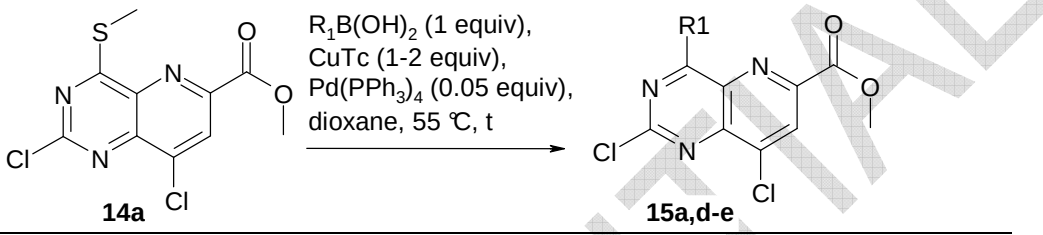
14a-c **15a-c**

Entry	R1	t (hr)	Product	Yield (%)
1	Ph	48[a]	**15c**	58% conversion
2[b]	COOMe	1	**15a**	79
3	Me	0.5	**15b**	81
4	Ph	1.5	**15c**	78

[a]: Reaction performed at 100 °C under thermic condit ions

Table 3.7. LS cross-coupling reaction at C-4 on derivatives **14**.

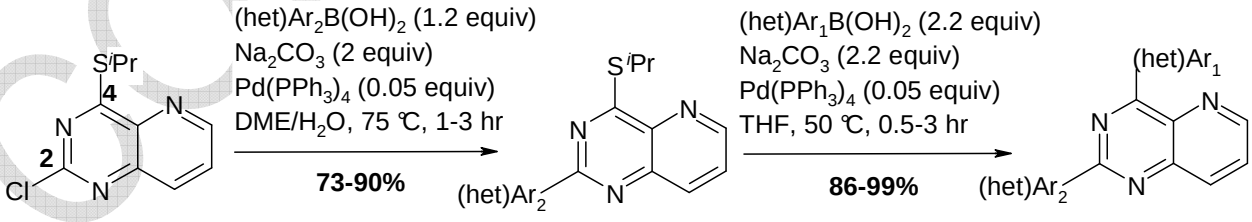
In order to investigate the scope of the LS reaction on 2,4,8-trichloro-pyrido[3,2-*d*]pyrimidines **5**, aryl boronic acids having different electronic properties (substituted with electron-donating or electron-withdrawing groups), were selected as coupling partners for LS reactions on compound **14a**. We observed that similar yields were obtained with 1 or 2 equiv of boronic acid. Optimized conditions consisted in the addition of 1 equiv of boronic acid to a solution of **14a** in dioxane, in presence of 0.05 equiv of $Pd(PPh_3)_4$ and 1 to 2 equiv of CuTc as co-factor. Reactions were performed in dioxane, at 55 °C for 0.5 to 1.5 hr. Compounds **15d-e** were obtained in good yields after precipitation in methanol (*Table 3.8 – Entries 1-3*).



Entry	R1	t (hr)	Product	Yield
1	Ph	1	**15a**	79
2	*p*-OMe-Ph	1.5	**15d**	82
3	*p*-CF_3-Ph	0.5	**15e**	77

Table 3.8. LS cross-coupling reaction at C-4 on compound **14a** with diverse boronic acids.

This alternative strategy has been also used on 2,4-dichloro-pyrido[3,2-*d*]pyrimidine by Tikad *et al.*, even though the two chlorines showed a difference in reactivity and selective Suzuki was achievable (*Scheme 3.7*).[44]



Scheme 3.6. Regioselective LS reaction on 4,2-dichloro-pyrido[3,2-*d*]pyrimidines.

3.4. Conclusion.

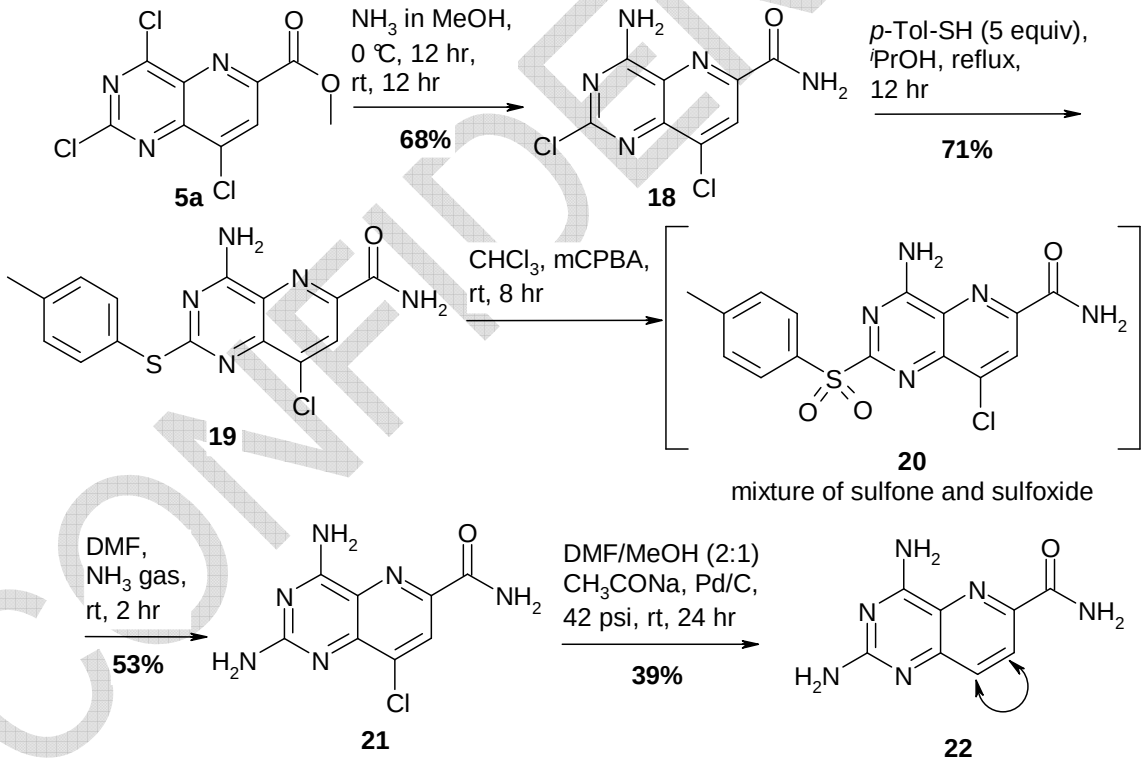
Regioselective addition of amines was successfully achieved at C-4 to derivatives **5a-c**, following what was reported in literature concerning the reactivity of the C-4 position on 6-substituted-2,4,8-trichloro-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **5a** towards S_NAr reactions. As a scope for this reaction, primary and secondary amines, but also less reactive amines such as anilines could be introduced at this position on derivatives **5**. S_NAr with sodium methylthiolate were also regioselective and took place at the same position as confirmed by the XRay structure determinations of the further diversified derivatives **38b** and **43b** (See *Crystallographic Data of compounds **38b** and **43b** in Appendix*). Classical metal-catalyzed cross-coupling reactions were not efficient or regioselective enough to form a C-C bond at C-4. We took advantage of the regioselective addition of thiol at C-4 to 2,4,8-trichloro-pyrido[3,2-*d*]pyrimidines **5** to introduce the C-C bond at this position via Liebeskind-Srogl cross-couling reaction. We showed that the LS cross-coupling reaction occurred specifically and efficiently at the C-SCH_3 bond. With this process, a C-C bond at position 4 was selectively formed and no cross-coupling side reaction was detected at the C-Cl bonds. Regioselective introduction of C-C bond at position 4 on trichloro-pyridopyrimidines (including all regioisomers) is unprecedented.

Reactivity of the two remaining chlorines on 4-substituted-2,8-trichloro-6-substituted-pyrido[3,2-*d*]pyrimidine derivatives **12** and **15** was further studied.

4. S_NAr at C-2 and C-8.

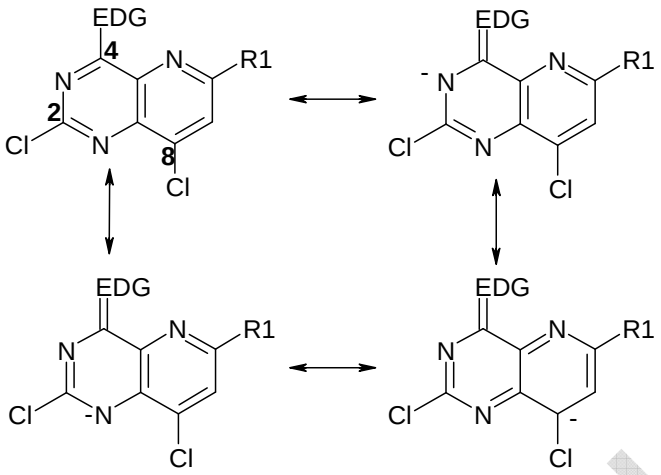
4.1. Introduction.

Synthesis and use of 2,4,8-trichloro-pyrido[3,2-*d*]pyrimidines were first reported in 1979 by Srinivasan *et al.*[17,32a,46] They were describing S_NAr on this scaffold with the regioselective addition of NH_3 at C-4 yielding 4-amino-2,8-dichloropyrido[3,2-*d*]pyrimidine-6-carboxamide **18**. Further addition of sodium benzylate, followed by sodium methyl thiolate were described to occur at 2 and 8 positions respectively (*Scheme 3.2*). Srinivasan also reported that addition of *p*-thiocresol to 4-amino-2,8-dichloropyrido[3,2-*d*]pyrimidine-6-carboxamide **18** occurred at C-2 (*Scheme 4.1*). Oxidation of the thio derivative **19**, nucleophilic substitution of the resulting sulfone **20** with ammonia, followed by reduction of the remaining chloride on derivative **21** yielded compound **22**, which structure was identified by the presence of a pair of doublet (J_{78} = 8 Hz) in the ^1H NMR spectrum. This result confirmed the regioselective addition of *p*-thiocresol to derivative **18** at position 2.



Scheme 4.1. Succesive S_NAr on carboxamide **18**.

Srinivasan *et al.* were discussing that the presence of an electron-donating group (EDG) at C-4 should, by mesomeric effect, stabilize the 8-chloro function toward nucleophilic displacement compare to the 2-chloro function, leading the 8 position the least reactive one (*Scheme 4.2*).



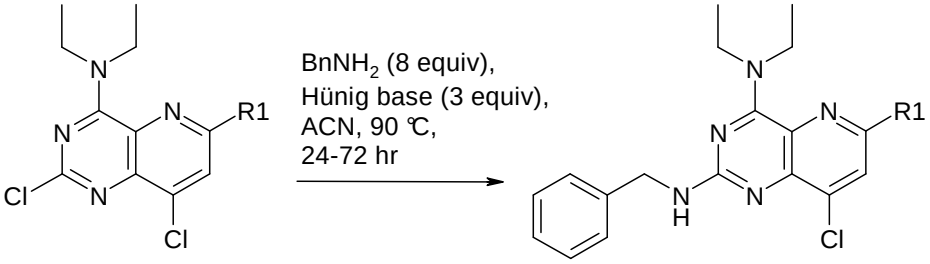
Scheme 4.2. Deactivation of position 8 with EDG at C-4.

To study the reactivity order towards S_NAr reactions on 2,8-dichloro-pyrido[3,2-*d*]pyrimidines having diverse groups at C-4 and C-6, and to study the scope of this reaction, diverse nucleophiles, such as amines and thiols, were selected to regioselectively substitute a second chlorine on derivatives **12** and **15**.

4.2. S_NAr on 2,8-dichloro-pyrido[3,2-*d*]pyrimidines **12** and **15**.

*4.2.1.S_NAr with amines on derivatives **12a-c**.*

Aromatic nucleophilic substitutions on derivatives **12a** to **12c** with benzylamine as nucleophile were performed in acetonitrile in the presence of Hünig base, with 8 equiv of benzylamine, at 90 °C for 24 to 72 hours. Derivatives **23a** to **23c** were obtained as a single product in moderate to good yield (*Table 4.1*). Even though 8 equiv of benzylamine were used, only regioselective mono-addition at C-2 was obtained, as it will be confirmed below. This result demonstrated the higher reactivity of C-2 vs. C-8 towards amine addition to scaffold **12**.



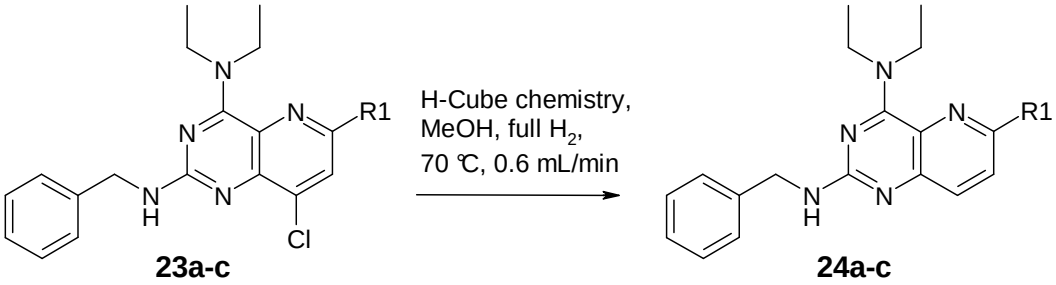
12a-c **23a-c**

Entry	R1	Product	Yield (%)
1	COOMe	**23a**	82
2	Me	**23b**	61
3	Ph	**23c**	82

Table 4.1. S_NAr of benzylamine at C-2 position on derivatives **12a-c**.

In order to confirm the regioselective addition of benzylamine to derivative **12a-c** at position 2, 2D-NMR experiments such as NOESY experiments were performed. Unfortunately, no correlation was observed that would confirm the regioselectivity of amine addition. Reduction of the remaining chlorine at C-8 on derivative **23a-c** was performed using the H-Cube™ as hydrogen reactor.[a] A solution of derivative **23** in methanol was flushed through a 10% palladium on charcoal cartridge at 70 °C with a constant hydrogen flow (full H_2 conditions corresponding to 7-10 bars). Derivatives **24a-c** were obtained in excellent yields and purities (*Table 4.2*).

[a] Reductions of chlorine groups at C-2 or C-8 positions were investigated using H-Cube™ as hydrogen reactor. In this system, a continuous-flow of substrate is combined with hydrogen, generated *in-situ* from the electrolysis of water. The substrate/hydrogen mixture is then passed through a packed catalyst cartridge (CatCart™), where the reaction takes place, and the product continuously elutes out of the cartridge into a collection vial. In such system, the hydrogen/substrate mixture can be heated up to 100 °C and the pressure can be increased up to 100 bars (1450 psi), and no filtration of catalyst is needed. In a continuous-flow system, a diluted substrate solution is usually recommended to reach a maximal conversion after the first run. Pressure, temperature, and flow rate can be modulated to optimize the reaction conversion.



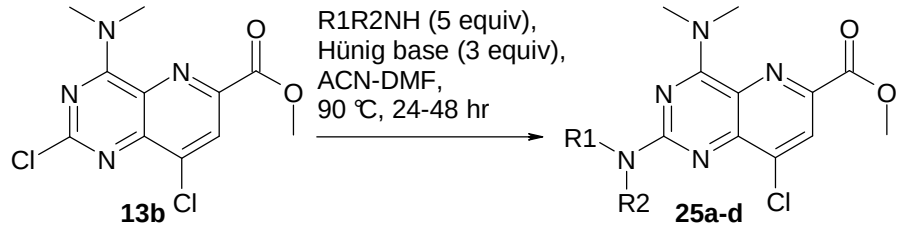
23a-c **24a-c**

Entry	R1	Product	Yield (%)
1	COOMe	**24a**	73
2	Me	**24b**	84
3	Ph	**24c**	85

Table 4.2. Reduction of C-8 chlorine on derivatives **23a-c**.

The ^{1}H NMR spectrum of derivatives **24a-c** showed a pair of doublets in the aromatic protons area, with an identical coupling constant of *J* = 8.5-8.8 Hz. For each dervivative, the aromatic proton attribution was confirmed with a COSY experiment. These results conclusively proved that benzylamine addition to **12a-c** took place regioselectively at C-2 leaving a chlorine group at position 8.

In order to have an overview of amine reactivity towards S_NAr on 4-dimethylamino-2,8-dichloro-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **13b**, four different amines were selected: butylamine and benzylamine as primary amines, diethylamine as secondary amine and aniline as aromatic amine. Aromatic nucleophilic substitutions on scaffold **13b** were performed with 5 equiv of amine, at 90 °C for 20 to 48 hours in a mixture of acetonitrile and dimethylformamide in the presence of 3 equiv of Hünig base. Derivatives **25a** and **25c** were purified by precipitation in methanol whereas compound **25b** was purified by flash chromatography. Derivatives **25a-c** were obtained in good yields (*Table 4.3 – Entries 1 to 3*). Due to its low reactivity, only 10% of conversion were obtained with aniline as amine, even after one week at 90 °C (*Table 4.3 - Entry 4*). As previously observed with benzylamine addition to derivative **12a-c** (*Table 4.1*), even though 5 equiv of amine were used, only mono-addition product was observed, with the selective addition at C-2 position.

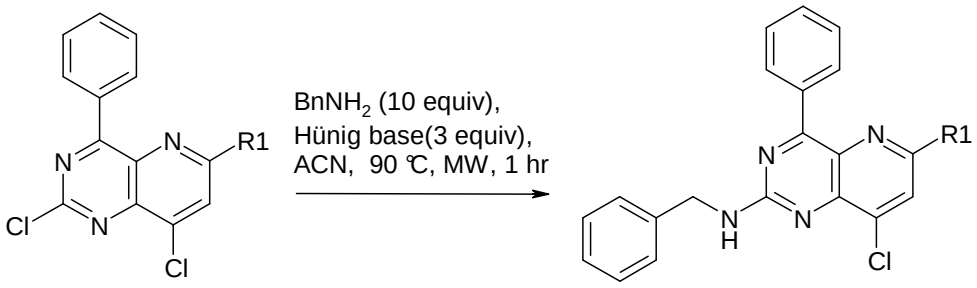


Entry	Amine	Product	Yield (%)
1	$BuNH_2$	**25a**	71
2	$BnNH_2$	**25b**	64
3	Et_2NH	**25c**	70
4	$PhNH_2$	**25d**	10% conversion

Table 4.3. S_NAr with diverse amines on derivative **13b**.

*4.2.2. S_NAr with amines on derivatives **15a-c**.*

S_NAr with benzylamine was further performed on derivatives **15**, pyridopyrimidine derivatives bearing a phenyl group at C-4 position. Optimized conditions consisted in the addition of an excess of benzylamine to a solution of derivative **15** in ACN, in presence of Hünig base. Reaction mixtures were heated under MW irradiation at 90 °C for 1 hour affording derivatives **26a** to **26c** in good yields (*Table 4.4*). As previously observed for the S_NAr of benzylamine on derivatives **12**, even though 10 equiv of benzylamine were used, only one regioisomer was obtained, with selective addition at C-2, as it will be confirmed below. Compared with the reaction conditions developed for the S_NAr of benzylamine on derivatives **12**, the reaction time has been shortened using the MW irradiation, reducing it from 24-72 to 1 hour.

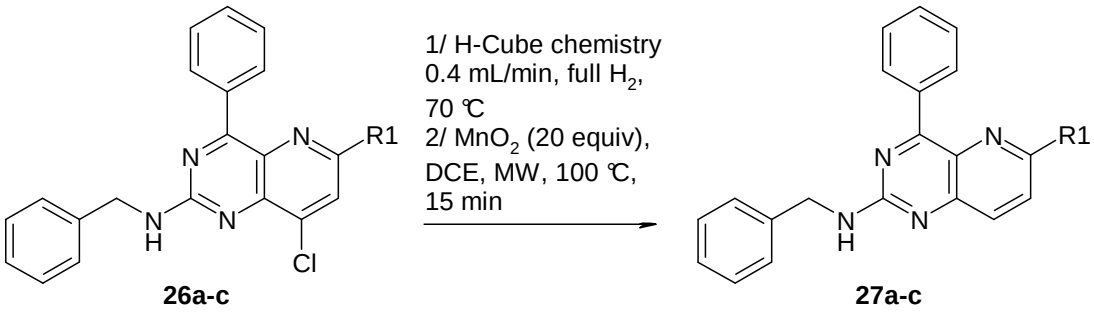


15a-c **26a-c**

Entry	R1	Product	Yield (%)
1	COOMe	**26a**	83
2	Me	**26b**	71
3	Ph	**26c**	69

Table 4.4. S_NAr with benzylamine on derivatives **15a-c**.

Similar to the results observed for derivatives **12**, NOESY experiments on derivatives **26** did not show any correlation that would indicate the regioselectivity of benzylamine addition. With this goal, reduction of the remaining chloride at C-8 on derivative **26a-c** was performed using the H-Cube™. Optimized conditions consisted in flushing a solution of derivative **26** in methanol through a 10% palladium on charcoal cartridge, at 70 °C with a constant hydrogen flow. During the chlorine reduction, another product was formed with a mass of m/z+2, corresponding to the reduction of one double bond of the pyridopyrimidine ring. After evaporation of the solvent, selective oxidation of the side product was performed with MnO_2 in DCE, under MW irradiation at 100 °C for 15 min. Derivatives **27a** to **27c** were obtained in yields ranging from 71 to 75% over the two steps (*Table 4.5*).



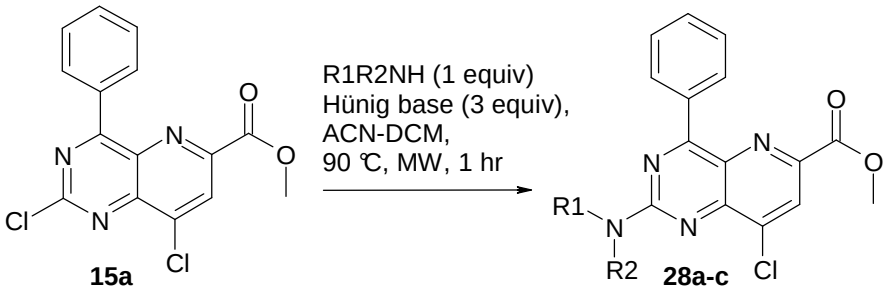
26a-c **27a-c**

Entry	R1	Product	Yield (%)
1	COOMe	**27a**	73
2	Me	**27b**	75
3	Ph	**27c**	71

Table 4.5. Reduction of C-8 chloride on derivatives **26a-c**.

The ^{1}H NMR spectrum of derivatives **27** showed a pair of doublets in the aromatic protons area, with an identical coupling constant of J = 8.8-8.9 Hz. The aromatic proton attribution was confirmed for each derivative **27** with a COSY experiment. These results conclusively proved that the chlorine atom was present at position 8 of the precursors **26**, which resulted from a C-2 regioselective addition of benzylamine to derivatives **13a-c**.

In order to have an overview of amine reactivity towards S_NAr on scaffold **15a**, three different amines were selected: butylamine and benzylamine as primary amines, and diethylamine as secondary amine. Aromatic nucleophilic substitution on 4-phenyl-2,8-dichloro-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **15a** were performed with 1 equiv of amine, at 90 °C under MW irradiation for 1.5 hr, in a mixture of acetonitrile and dimethylformamide in the presence of 3 equiv of Hünig base. Under these conditions, regioselective addition of amines at C-2 could be achieved. Derivatives **28a-b** were purified by precipitation in MeOH in yields ranging from 81 to 83% (*Table 4.6*).

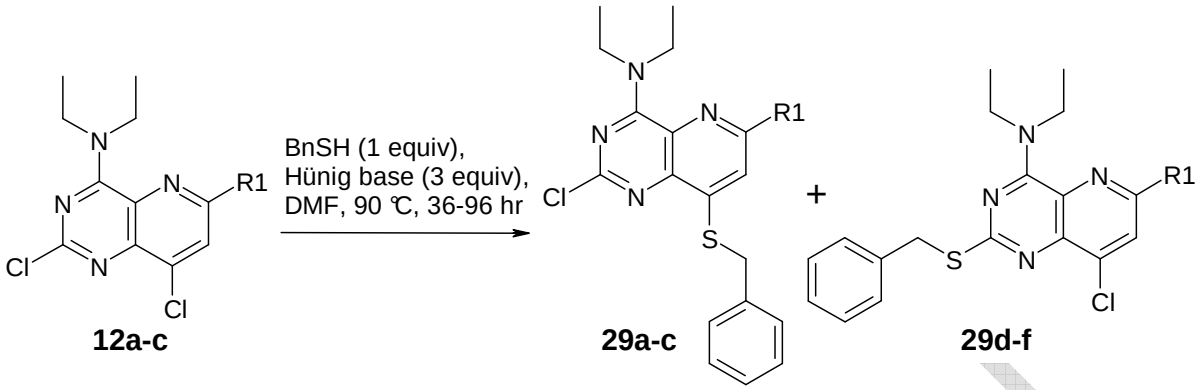


Entry	Amine	Product	Yield (%)
1	$BnNH_2$	**26a**	83
2	$BuNH_2$	**28a**	81
3	Et_2NH	**28b**	85

Table 4.6. S_NAr with diverse amines on derivative **15a**.

*4.2.3. S_NAr with thiols on derivatives **12a-c**.*

S_NAr were further performed on derivatives **12a-c** with thiols as nucleophiles. Interestingly, when benzylthiol was added to 4-diethylamino-2,8-dichloro-pyrido[3,2-*d*]pyrimidine **12a** in DMF at 90 °C, two regioisomers were formed, differe nt from the results obtained with benzylamine addition where only one regioisomer was formed (*Table 4.7 – Entry 1 vs. Table 4.1 – Entry 1*). Moreover, the major regioisomer was bearing the benzylsulfanyl group at C-8 position which was different from the regioselectivity observed with benzylamine addition to the same scaffold, and in contrary to what was reported in the literature (*i.e.* C-2 addition). To study the influence of the substituent at C-6 position on this regioselectivity, the same reaction was performed on derivatives **12b** and **12c**. This transformation could be achieved with addition of 5 equiv of benzylthiol to a solution of derivative **12** in DMF as solvent, in presence of Hünig base, at 90 °C for 36 to 96 hr (*Table 4.7 - Entries 2-3*). Derivatives **29b** and **29c** were obtained in moderate yields. In contrast to the results observed with derivative **12a** as starting material, only one regioisomer was obtained during the reaction starting with derivatives **12b-c**, even with the use of an excess of benzylthiol. This indicates that the absence of electron withdrawing group at C-6 yields a lower reactivity towards S_NAr reaction and a higher selectivity of benzylthiol addition to derivatives **12b-c**.

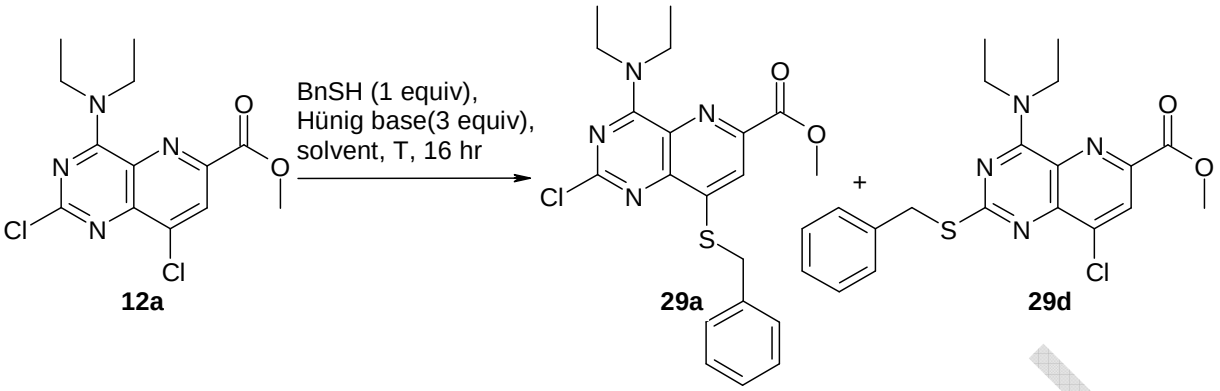


Entry	R1	Product	Yield (%)
1	COOMe	**29a / 29d**	65 / 17
2	Me	**29b / 29e**	56 / 0
3	Ph	**29c / 29f**	61 / 0

Table 4.7. S_NAr with benzylthiol on derivatives **12a-c**.

In order to confirm the regioselectivity of the benzylthiol addition to derivatives **12a-c**, NOESY experiments on derivatives **29a-c** were performed. In all three spectra, correlation between the benzylic protons of the benzylthiol and the aromatic proton of the pyridine moiety (singlet in ^{1}H NMR) was observed, confirming the C-8 regioselectivity of benzylthiol addition as the major regioisomer synthesized (See *NMR Spectra 4.1 to 4.3 in Appendix*). On the other hand, no correlation was seen for regioisomer **29d**.

In order to improve the regioselectivity observed for benzylthiol addition to derivative **12a** (COOMe at C-6) and in order to find conditions for selective regioisomer formation, different solvents were selected for this reaction: polar aprotic solvent such as THF or DMF and polar protic solvent such as ^{i}PrOH. Reactions in polar aprotic solvents could be performed at low temperature (-10 to 0 °C). As summarized in *Table 4.8*, reactions were slower when performed in THF as compared to DMF, but C-8 regioisomer was still the major regioisomer formed (*Entry 2 vs. Entry 1*). When reactions were performed in polar protic solvents, it was necessary to heat the reaction mixture at reflux to form the desired product. Even if a low conversion was obtained (only 6% of desired product observed), the use of ^{i}PrOH as solvent was favouring the C-2 regioisomer formation.

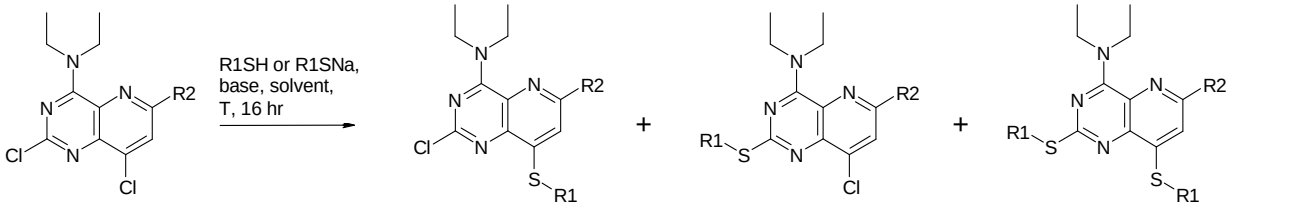


12a **29a** **29d**

Entry	Solvent (base)	T	Product	Yield (%) (UHPLC % conv. **27a** / **27d**)
1	DMF (Hünig base)	0℃ to rt	**29a / 29d**	65 / 17 (73 / 25)
2	THF (Hünig base)	-10 to rt	**29a / 29d**	15 (100 / 0)
3	^{i}PrOH (-)	Reflux	**29a / 29d**	6 (0 / 100)

Table 4.8. Improvement of selectivity by solvent modification.

In order to confirm this observation, diverse thiols were selected to be added on derivatives **12a-c** in different solvent, in presence or not of a base (*Table 4.9*). Regioisomer ratios indicated in *Table 4.9* have been determined on the reaction mixtures by UHPLC-MS. In general, we have observed that a base was necessary when the reaction was taking place in polar aprotic solvent (*Table 4.9 - Entry 2 vs. 3*), compared to reaction performed in polar protic solvent where the base was not required (*Entry 6 vs. 7*). Moreover, reactions were more regioselective with Me or Ph at C-6 than with COOMe at C-6 (*Entries 9-20 vs. 1-8*). We observed that reactions performed with sodium methylthiolate were faster and less selective than the ones performed with thiol nucleophiles such as *p*-thiocresol or benzylthiol (*Entries 11, 14 vs. 10, 13; 17, 20 vs. 16, 19*). This can be explained by the higher reactivity of thiolates compared to thiols. Interestingly, in contrary to what is observed for amine derivatives where the aniline is the less reactive nucleophile, for thiol, *p*-thiocresol showed to be more reactive than benzylthiol. When reactions were performed in polar aprotic solvent such as DMF, independently of the group at C-6, the major regioisomer obtained was the 8-thioether derivative. Interestingly, when reactions where performed in polar protic solvent such as ^{i}PrOH or MeOH, the other regioisomer, with addition of thiol at C-2, was obtained as major compound (*Table 4.9 - Entries 1-4, 9-11, 15-17 vs. 5-8, 12-14, 18-20*). As exception, with R2=Me or Ph, the same major regioisomer (*i.e.* addition at C-8) was obtained with NaSMe as nucleophile in both protic and aprotic solvent (*Table 4.9 - Entries 11 and 14; 17 and 20*). These conditions applied to compound **12a** (R2=CO_2Me) yielded addition at C-2 in MeOH and at C-8 in DMF (*Table 4.9 - Entries 4 and 8*). These differences of regioselectivity could be correlated with the higher reactivity of NaSMe combined with the difference in electronic properties of scaffolds **12a-c**.



12a-c

29a, 30a, 31a, R2=COOMe, R1
29b, 30b, 31b,R2=Me, R1
29c, 30c, 31c, R2=Ph, R1

29d, 30d, 31d, R2=COOMe, R1
29e, 30e, 31e, R2=Me, R1
29f, 30f, 31f, R2=Ph, R1

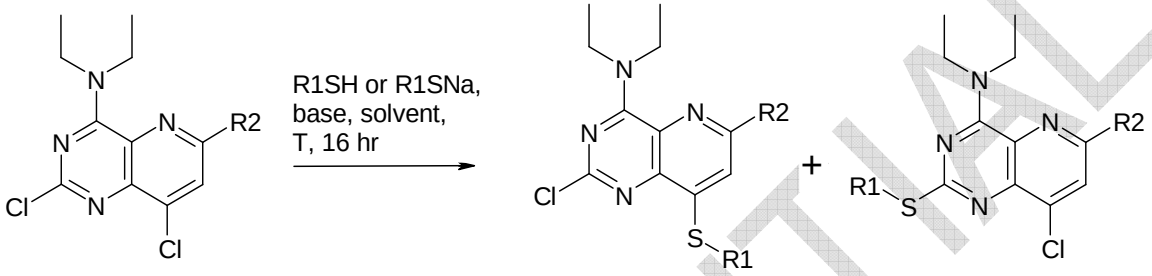
29g, 30g, 31g, R2=COOMe, R1
29h, 30h, 31h, R2=Me, R1
29i, 30i, 31i, R2=Ph, R1

Entry	R1SH	R2	Solvent (base)	T	Products	UHPLC **% conv. Products**
1	BnSH[a,c]	COOMe	DMF (Hünig base)	0℃ to rt	**29a / 29d / 29g**	73 /25 / 2
2	p-CH_3-PhSH[a,c]		DMF (Hünig base)	0℃ to rt	**30a / 30d / 30g**	68 / 32 / 0
3	p-CH_3-PhSH[a,c]		DMF (-)	0℃ to rt	**30a / 30d / 30g**	No reaction
4	MeSNa[a,c]		DMF (-)	0℃ to rt	**31a / 31d / 31g**	97 / 3 / 0
5	BnSH[b]		^{i}PrOH (-)	Reflux	**29a / 29d / 29g**	0 / 100 / 0
6	p-CH_3-PhSH[b]		^{i}PrOH (-)	Reflux	**30a / 30d / 30g**	0 / 100 / 0
7	p-CH_3-PhSH[b]		^{i}PrOH (Hünig base)	Reflux	**30a / 30d / 30g**	8 / 92 / 0
8	MeSNa[c]		MeOH (-)	Reflux	**31a / 31d / 31g**	3 / 97 / 0
9	BnSH[a,c]	Me	DMF (Hünig base)	0℃ to rt	**29b / 29e / 29h**	100 / 0 / 0
10	p-CH_3-PhSH[a,c]		DMF (Hünig base)	0℃ to rt	**30b / 30e / 30h**	97 / 3 / 0
11	MeSNa[a,c]		DMF (-)	0℃ to rt	**31b / 31e / 31h**	80 / 20 / 0
12	BnSH[b]		^{i}PrOH (-)	Reflux	**29b / 29e / 29h**	No reaction
13	p-CH_3-PhSH[b]		^{i}PrOH (-)	Reflux	**30b / 30e / 30h**	0 / 100 / 0
14	MeSNa[c]		MeOH (-)	Reflux	**31b / 31e / 31h**	100 / 0 / 0
15	BnSH[a,b]	Ph	DMF (Hünig base)	0℃ to rt	**29c / 29f / 29i**	100 / 0 / 0
16	p-CH_3-PhSH[a,b]		DMF (Hünig base)	0℃ to rt	**30c / 30f / 30i**	100 / 0 / 0
17	MeSNa[a,c]		DMF (-)	0℃ to rt	**31c / 31f / 31i**	100 / 0 / 0
18	BnSH[b]		^{i}PrOH (-)	Reflux	**29c / 29f / 29i**	No reaction
19	p-CH_3-PhSH[b]		^{i}PrOH (-)	Reflux	**30c / 30f / 30i**	0 / 100 / 0
20	MeSNa[c,d]		MeOH (-)	Reflux	**31c / 31f / 31i**	94 / 6 / 0

[a]: Reaction was performed in an ice bath
[b]: 5 equiv of thiol or thiolate was used
[c]: 1 equiv of thiol or thiolate was used
[d]: MeOH was used instead of ^{i}PrOH to avoid trans-esterification

Table 4.9. S_NAr of diverse thiols and thiolates on derivatives **12a-c**.

Conditions were optimized to maximize the regioselectivity of thiol addition to derivatives **12a-c**. To favour addition at C-8, reactions were performed in DMF in presence of a base (3 equiv of Hünig base), with 1 equiv of thiol (or thiolate), from 0 °C to room temperature for 16 hr. Formation of the other regioisomer (*i.e.* at C-2) was favoured in ^{i}PrOH or MeOH as solvent, without base, with 5 equiv of thiol (or 1 equiv of thiolate) at 90 °C for 16 hr (*Table 4.10*). Each regioisomer was isolated by MDAP® (Mass directed auto-purification fractioning).[b] Isolated yields of derivatives **29** to **31** are reported in *Table 4.10*.



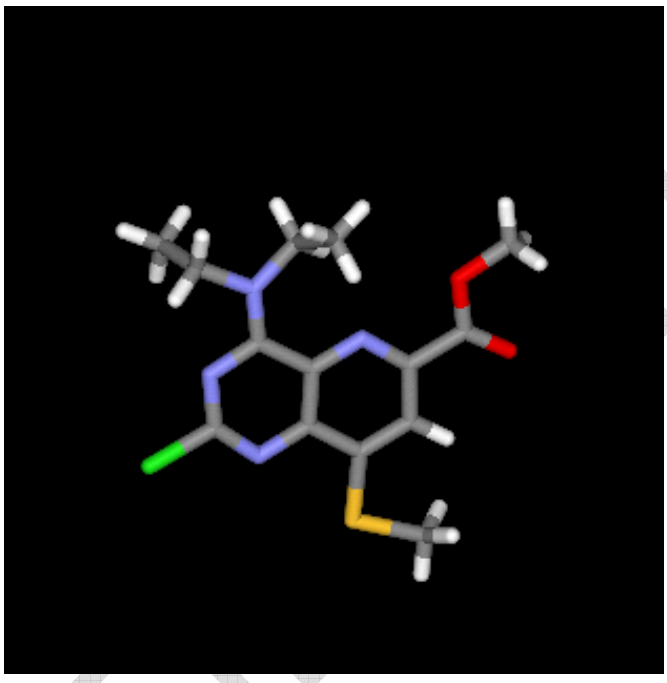
12a-c **C8** **C2**

R1 / R2	COOMe		Me		Ph	
	C8 (Yield%)	C2 (Yield%)	C8 (Yield%)	C2 (Yield%)	C8 (Yield%)	C2 (Yield%)
Bn	**29a** (42)	**29d** (17)	**29b** (76)	**-**	**29c** (61)	**-**
p-Me-Ph	**30a** (59)	**30d** (83)	**30b** (75)	**30e** (78)	**30c** (87)	**30f** (81)
Me	**31a** (77)	**31d** (73)	**31b** (68)	**31e** (13)	**31c** (86)	**-**

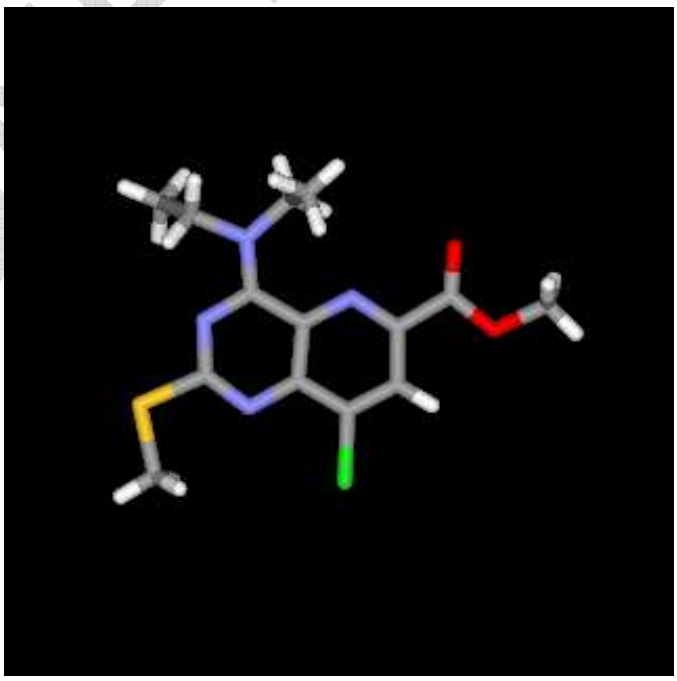
Table 4.10. Regioisomers obtained from derivatives **12a-c**.

[b] The Mass directed auto-purification fractioning system from Waters is a purification system that is capable of purifying milligrams to multiple grams, in a single system that can be configured to automatically process hundreds of samples. Different detectors can be used such as UV/Visible, evaporative light scattering (ELS), MS, and analog. The system is built around the ZQ Mass Detector, a compact, single quadrupole, atmospheric pressure ionization mass detector. The AutoPurification System, designed for mass-directed purification applications, can switch up to three columns (one analytical- and two preparative-scale) with a single command.

The regioselecitivity of thiol addition on derivatives **29a-c** and **31a-c** has been confirmed by NOESY experiments as correlations between the pyridine proton and either the benzylic protons of the benzylthiol (**29a-c**) or the methyl proton of the methyl thiol (**31a-b,d**) were observed (*NMR Spectra 4.1 to 4.6 in Appendix*). In addition to NMR experiments, structures of regioisomers **31a** and **31d** (*Table 4.9 - Entries 4 and 8*) were confirmed by X-Ray crystal structure determination confirming the results reported above (*X-Ray structure 4.1 and 4.2 – Crystallographic Data of compounds **31a** and **31d** in Appendix*).



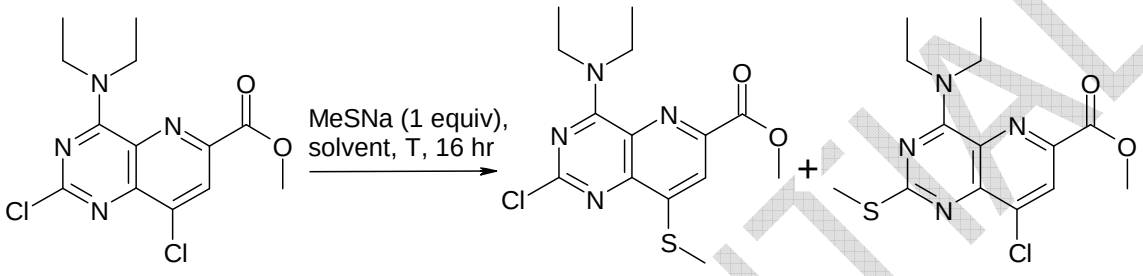
X-Ray Structure 4.1. Derivative **31a**.



X-Ray Structure 4.2. Derivative **31d**.

4.2.4. Regioselectivity study.

Following these interesting results, confirming the formation of a different regioisomer depending on the reaction's solvent, we tried to find out which other parameters could influence these results. Temperature (rt vs. reflux) and concentration (0.03M vs. 0.18M), used in the optimized conditions for the regioselective addition of NaSMe at C-2 or C-8, were significantly different (*Table 4.11*).



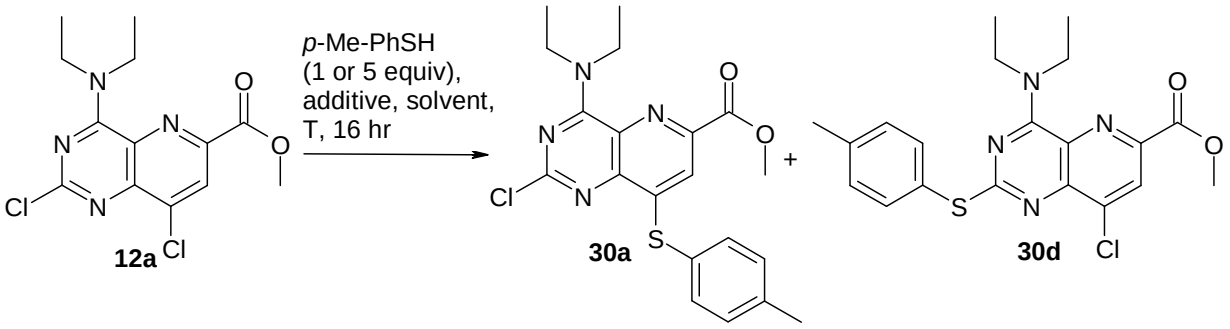
12a **31a** **31d**

Entry	Solvent	T	Conc.	Product	Yield % (UHPLC % conv. 15a/15b)
1	DMF	rt	0.18M	**31a / 31d**	**31a**: 77[a] (97 / 3)
2	^{i}PrOH	Reflux	0.03M	**31a / 31d**	**31d**: 73 (3 / 97)

[a]: Portionwise addition of MeSNa

Table 4.11. Optimized conditions for synthesis of derivatives **31a** and **31d**.

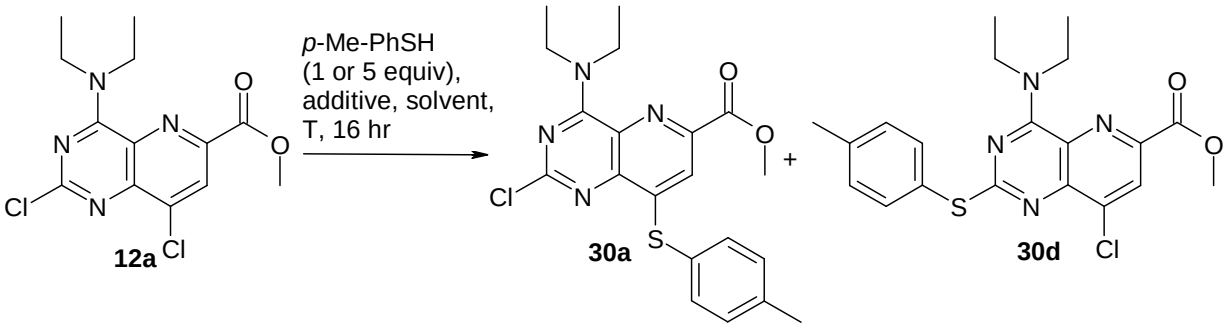
To study if the difference of regioselectivity was linked to those parameters, both reactions were performed at different temperatures and concentrations. The results, summarized in *Table 4.12*, showed that the difference of regioselectivity was independent of the reaction temperature (*Table 4.12 - Entries 3-5; 8-10*) and concentration (*Entries 1-3; 6-8*). To be sure that the regioselectivity observed was not due to the specific solvent that were selected (*i.e.* DMF and ^{i}PrOH), other polar protic solvent (*i.e.* MeOH) and polar aprotic solvent (*i.e.* THF, DCM and ACN) were further tried. Similar results were obtained with C-8 adduct as major regioisomer when reactions were performed in polar aprotic solvent, and C-2 adduct as major regioisomer when reaction were performed in polar protic solvent (results not shown). Interestingly, when a mixture of DMF and ^{i}PrOH (1:1 ratio) was used as solvent, C-8 adduct was observed as major regioisomer (*Table 4.12 - Entry 11*). These results suggested that the solvent played an important role in the control of the regioselectivity of this reaction.



Entry	Solvent (Additive)	T	Conc.	(C-8 (30a) / C-2 (30d))
1	DMF (Hünig base)	25 ℃	0.03M	C-8 major (9 / 1)
2		25 ℃	0.09M	C-8 major (9 / 1)
3		25 ℃	0.18M	C-8 major (9 / 1)
4		90 ℃	0.18M	C-8 major (9 / 1)
5		0 ℃	0.18M	C-8 major (9 / 1)
6	^{i}PrOH (-)	90 ℃	0.03M	C-2 major (1 / 0)
7		90 ℃	0.09M	C-2 major (1 / 0)
8		90 ℃	0.18M	C-2 major (1 / 0)
9		25 ℃	0.03M	C-2 major (1 / 0)
10		0 ℃	0.03M	No reaction
11	DMF+ ^{i}PrOH (Hünig base)	90 ℃	0.18M	C-8 major (9 / 1)

Table 4.12. Influence of temperature and concentration on regioisomer formation.

S_NAr reactions on chloro-pyrido[3,2-*d*]pyrimidine scaffold yields the liberation of HCl and in absence of a base to quench it, free acidic protons are liberated in the media. In order to study the influence of acidic protons on the regioselectivity of the reaction, different attempts were performed adding base (Hünig base) or acid (HCl in dioxane) to the optimized reaction conditions. Results are presented in *Table 4.13*.



Entry	T	Solvent	Additive	C-8 (30a) / C-2 (30d)
1	0 ℃	DMF	Hünig base (3 equiv)	C-8 major (9 / 1)
2			-	No reaction
3			HCl[a] (1 equiv)	C-2 major (1 / 0)
4	90 ℃	^{i}PrOH	Hünig base (3 equiv)	C-2 major (1 / 0)
5			-	C-2 major (1 / 0)
6		CF_3CH_2OH	-	C-2 major (1 / 0)

[a] a 4M solution of HCl in dioxane was used

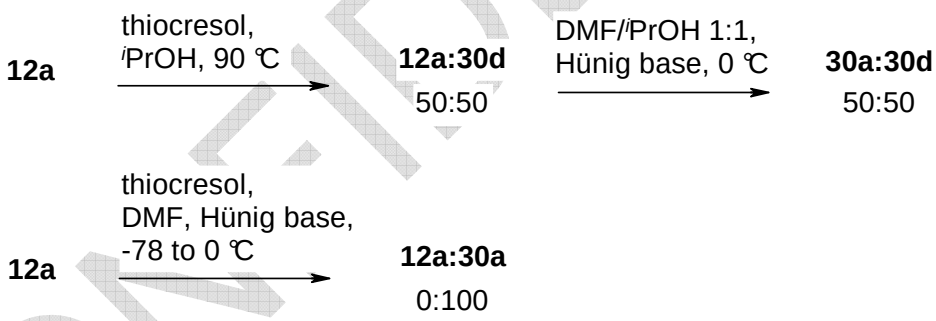
Table 4.13. Influence of basic or acidic media on regioisomer formation.

As previously mentioned (*Table 4.9)*, presence of a base was required when the reaction was performed in DMF as solvent, yielding the formation of the C-8 adduct as major regioisomer (*Table 4.13 - Entries 1 vs. 2*). Interestingly, when 1 equiv of HCl was added to the reaction mixture, the regioselectivity was reversed and the C-2 adduct was formed as major regioisomer (*Table 4.13 - Entry 3*). When reactions were performed in ^{i}PrOH, the presence or the absence of a base did not influence the regioselectivity and yielded the formation of the C-2 adduct as major regioisomer (*Table 4.13 – Entries 4 and 5*). Similar results were observed when reaction was performed in CF_3CH_2OH as solvent (*Entry 6*). These results would suggest that the regioselectivity was dependent on the ability of the scaffold to be or not protonated and on the ability of the solvent to form or not hydrogen bond.

We further envisaged a radical mechanism for the formation of one of the two regioisomers. In order to confirm this hypothesis, reactions with radical quenchers such as TEMPO or PBN (phenyl n-*tert*-butylnitrone) were performed. Reaction conditions consisted in doing the reaction in THF, with 0.2 to 1 equiv of radical quencher, in presence of Hünig base, at -10 ℃ for 16 hr. Following these experimental conditions, no difference in the regioisomers ratio was observed.

Finally, stability of the two regioisomers and reversibility of their formation were studied. C-8 regioisomer **30a** (obtained in DMF at 0 °C) was dissolved in ^{i}PrOH at 90 °C, reaction conditions used to obtain **30d**. After 16 hr in ^{i}PrOH at 90 °C, unchanged **30a** was recovered, without any trace of its regioisomer **30d**. Same reaction was performed, placing **30d** in DMF at 0 °C for 16 hr. After this time, unchanged **30d** was recovered without any trace of **30a**. These results suggested that both regioisomers **30a** and **30d** were stable.

For the reversibility study, the goal was to investigate if one regioisomer would be transformed into the other by changing the reaction conditions during the reaction. These experiments were performed by stopping the reaction after 50% conversion into one of the regioisomer, removing the solvent and adding the reagents and solvent needed for the other regioisomer formation as shown in *Scheme 4.3*. The reaction was first started in ^{i}PrOH, and stopped after 50% conversion; DMF and Hünig base were further added. In this reaction, ^{i}PrOH was not removed as it was shown previously that in a mixture of ^{i}PrOH and DMF, the regioisomer formed in DMF was obtained (*i.e.* C-8 regioisomer - *Table 4.11 – Entry 11*). After few hours, a 50:50 mixture of both regioisomers was observed in the reaction media, demonstrating that the formation of each regioisomer is not reversible. On the other hand, when the reaction was performed in DMF, the reaction could not be stopped at 50% conversion as the reaction was too fast. Decreasing the temperature down to -78 °C did not change this result.

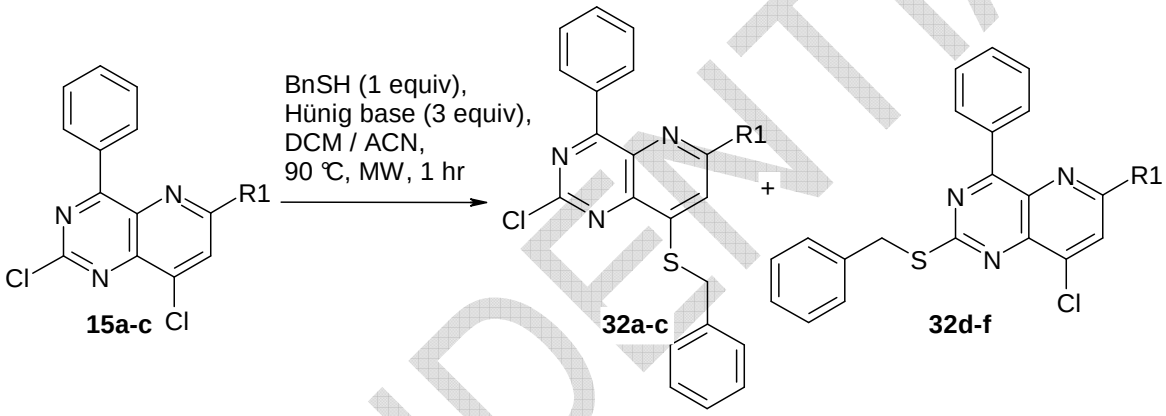


Scheme 4.3. Reversibility study of regioisomers **30a** and **30d**.

From these experiments, no clear conclusion can be formulated to explain the difference in regioselectivity observed with the nature of the solvent, protic or aprotic polar solvent. The regioselectivity was independent of the reaction temperature and the reaction concentration, and both regioisomers were stable and their formation was not reversible. On the other hand, regioselectivity seemed to be dependent on the ability of the solvent to form H bond as well as the ability of the scaffold to be protonated.

*4.2.5. S_NAr with thiols on derivatives **15a-c**.*

The regioselectivity of thiol addition to 2,8-dichloro-4-phenyl-pyrido[3,2-*d*]pyrimidine derivatives **15a-c** was then studied. Optimized conditions consisted in the addition of 1 equiv of benzylthiol to a solution of derivative **15** in a mixture of ACN and DCM, in presence of Hünig base. Reactions were performed at room temperature for 1 hour starting from derivative **15a** (R1=COOMe), and under MW irradiation at 90 °C for 1 hour starting from derivatives **15b** and **15c** (*Table 4.14 - Entries 1 to 3*). After purification, derivatives **32a-f** were isolated and characterized. Interestingly, different from the results of thiol addition to derivatives **12**, C-2 addition products were the major regioisomers formed during these reactions. This illustrates that the regiochemistry of thiol addition not only depends on the solvent, but also on the substrate at C-4.



Entry	R1	Product	Yield (%)
1[a]	COOMe	**32a / 32d**	12 / 73
2	Me	**32b / 32e**	20 / 60
3	Ph	**32c / 32f**	18 / 60

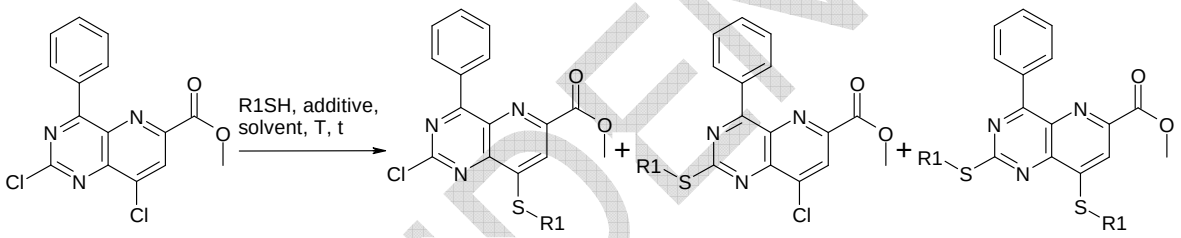
[a]: reaction performed at rt for 1 hour

Table 4.14. S_NAr with benzylthiol on derivatives **15a-c**.

In order to confirm the structure of the major and the minor regioisomers obtained in these reactions, NOESY experiments of derivatives **32** were performed. In the NOESY spectrum of derivative **32a**, correlation observed between the benzylic protons and the aromatic proton of the pyridine moiety confirmed that the minor regioisomer resulted from a C-8 addition of benzylthiol to derivative **15a**. Moreover, a correlation was also observed on derivative **32d**, between the aromatic protons of the phenyl group at C-4 and the benzylic protons of the benzylthiol. This observation confirmed that the major regioisomer formed during addition of benzylthiol to derivative **15a**, resulted from addition at C-2 (*NMR Spectra 4.7 of compound **32a** in Appendix*).

In the NOESY spectrum of derivatives **32e** and **32f**, the major regioisomers formed from the addition of benzylthiol to derivative **15b** and **15c** respectively, no correlation could be observed between the benzylic protons and the aromatic protons of the phenyl group at C-4 (*NMR Spectra 4.11 and 4.12 in Appendix* respectively). On the other hand, in the NOESY spectrum of **32b** and **32c**, the minor regioisomers formed during those reactions, correlation was observed between the benzylic protons and the aromatic proton of the pyridine moiety (*NMR Spectra 4.8* and *4.9 in Appendix*). These results confirmed that the minor regioisomers resulted from a C-8 addition of benzylthiol to derivative **15b** and **15c** respectively.

In order to study the influence of the solvent and the nature of the thiol on the regioselectivity of this reaction, diverse thiols were added to derivative **15a** (benzylthiol, *p*-thiocresol and sodium methylthiolate). With the goal to have a simpler protocol, DCM/ACN mixture was replaced by either DMF or THF. To maximize the regioselectivity, reactions were performed at low temperature: 0 °C in DMF, and - 10 °C in THF. Results are presented in *Table 4.15*.



15a **32a, 33a, 34a** **32d, 33b, 34b** **32g, 33c, 34c**

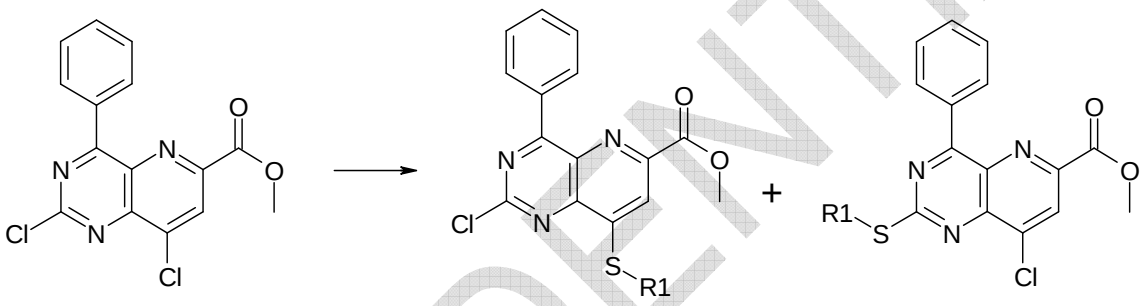
Entry	R1SH	Solvent (base)	T	Products	UHPLC **% conv. Products**
1[a,b]	BnSH	DMF(Hünig base)	0°C to rt	**32a / 32d / 32g**	12 / 61 / 23
2[a,b]	p-CH_3-PhSH	DMF(Hünig base)	0°C to rt	**33a / 33b / 33c**	4 / 49 / 54
3[b]	MeSNa	DMF	0°C to rt	**34a / 34b / 34c**	3 / 15 / 36
4[c]	BnSH	THF(Hünig base)	-10°C to rt	**32a / 32d / 32g**	6 / 73 / 21
5[c]	p-CH_3-PhSH	THF(Hünig base)	-10°C to rt	**33a / 33b / 33c**	3 / 76 / 14
7[b]	MeSNa	THF	-10°C to rt	**34a / 34b / 34c**	6 / 66 / 3
8[b]	BnSH	^{i}PrOH (-)	90 °C	**32a / 32d / 32g**	No reaction
9[b]	p-CH_3-PhSH	^{i}PrOH (-)	90 °C	**33a / 33b / 33c**	2 / 69 / 25
10[b]	MeSNa	MeOH (-)	90 °C	**34a / 34b / 34c**	9 / 74 / 17

[a]: Reaction was performed in an ice bath
[b]: 1 equiv of thiol was used
[c]: 5 equiv of thiol was used

Table 4.15. Influence of thiol and solvent on regioselectivity.

When reactions were performed in DMF, with both thiols and thiolate, the major regioisomer resulted from a C-2 addition. Due to the high reactivity of the starting material under these reaction conditions, from 23 to 54% of double-addition products were also observed (*Table 4.15 – Entries 1-3*). Amount of double-addition products was reduced by performing the reaction in THF at -10 °C (*Table 4.15 – Entries 7-9*). When reactions were performed in ^{i}PrOH, C-2 addition products were the major regioisomers, similar to the major regioisomers formed in DMF or THF (*Table 4.15 – Entries 4-7*).

Derivatives **32a,d**, **33a-b** and **34a-b** were isolated from the previous reactions after purification by MDAP® system (Mass directed auto-purification fractioning). Isolated yield of each regioisomer are reported in *Table 4.16*.

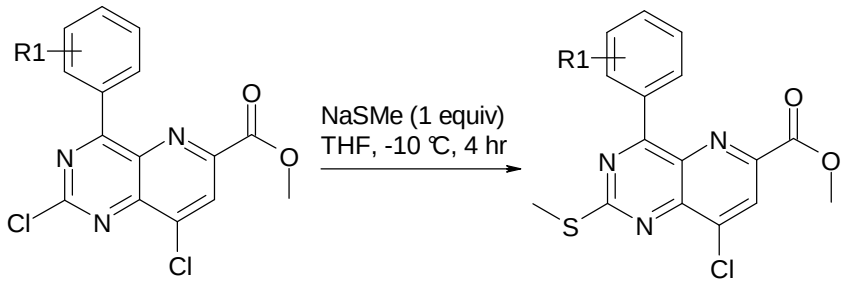


15a **C8** **C2**

R1	C8 (Yield %)	C2 (Yield %)
Bn	**32a** (12)	**32d** (73)
p-Me-Ph	**33a** (-)	**33b** (63)
Me	**34a** (-)	**34b** (60)

Table 4.16. Regioisomers obtained from derivatives **15a**.

In order to study the scope of this reaction towards diverse aryl groups at C-4, sodium methylthiolate was added on scaffold **15d** and **15e**, having 4-OMe-Ph and 1-F-Ph groups at C-4 respectively (*Table 4.14*). Reaction conditions giving the highest regioselectivity were selected for these reactions. Addition of sodium methylthiolate to a suspension of derivatives **15d-e** in THF at -10 °C afforded the desired compounds in 4 hours. After purification by precipitation in MeOH, derivative **35a** and **35b** were obtained in yield ranging from 57 to 76% (*Table 4.14 - Entries 2 and 3*). These results indicated that regioselectivity of thiol addition to derivatives **15** was independent of the substituent on the aryl group at C-4, *i.e.* R1=4-OMe, 1-F and H.



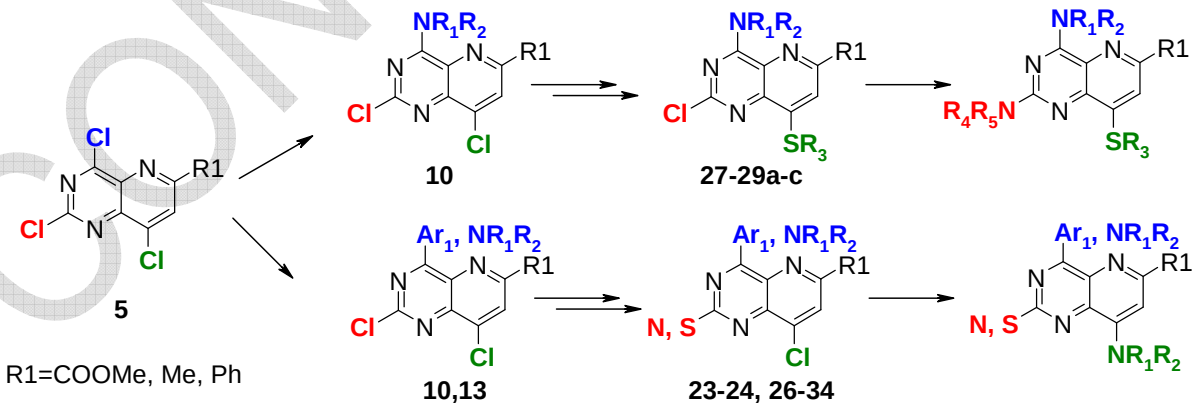
15a,d-e **34b,35a-b**

Entry	R1	Product	Yield (%)
1	H	**34b**	60
2	4-OMe	**35a**	57
3	1-F	**35b**	76

Table 4.17. S_NAr with sodium methylthiolate on derivative **15a,d-e**.

4.3. S_NAr on monochloro-pyrido[3,2-*d*]pyrimidines **28c**, **31a** and **34b**.

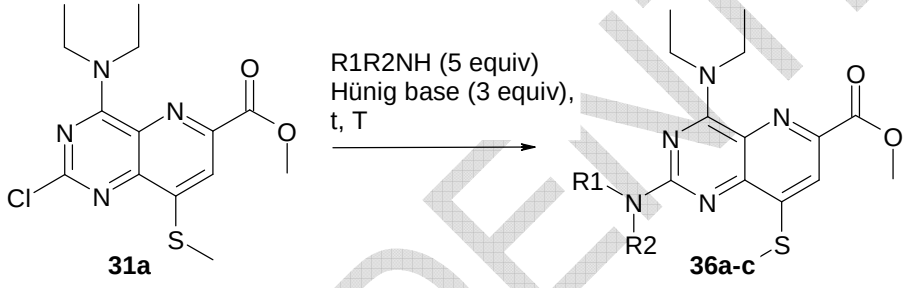
Starting from 2,4,8-trichloro-pyrido[3,2-*d*]pyrimidine derivatives **5**, C-4 and C-2 or C-8 chlorines were substituted by S_NAr reactions with amines or sodium thiolate and subsequently by metal-catalyzed cross-coupling reactions. Substitution of the remaining chlorine at C-8 or C-2 on such derivatives was further investigated via S_NAr reactions with amines as nucleophiles (*Scheme 4.4*). Derivatives with R1=CO_2Me (*i.e.* derivatives **28c**, **31a** and **34b**) were selected as starting material for this study.



Scheme 4.4. Chemistry previously described starting from derivative **5**.

*4.3.1. S_NAr with amines on derivatives **31a**.*

In order to have an overview of C-2 chlorine reactivity towards S_NAr with amines on scaffold **31**, three different amines were selected: butylamine and benzylamine as primary amines, and diethylamine as secondary amine (*Table 4.18*). Previously described conditions used for the C-2 addition of amine to derivatives **12a-c** (*Table 4.1*) did not give a complete conversion, even after 33 hr at 90 °C (*Table 4.18 – Entry 1*). In order to heat at higher temperature for a shorter time, amines additions to **31a** were performed under MW irradiation at 180 °C for 20 min in ACN (*Table 4.18 – Entries 2,3 and 4*). Complete conversion into **36a** to **36c** was reached. After purification by precipitation in MeOH, both compounds were obtained in good yields (*Table 4.18*). Introduction of anilines were not successful regarding the poor reactivity of those amines as nucleophiles.



31a **36a-c**

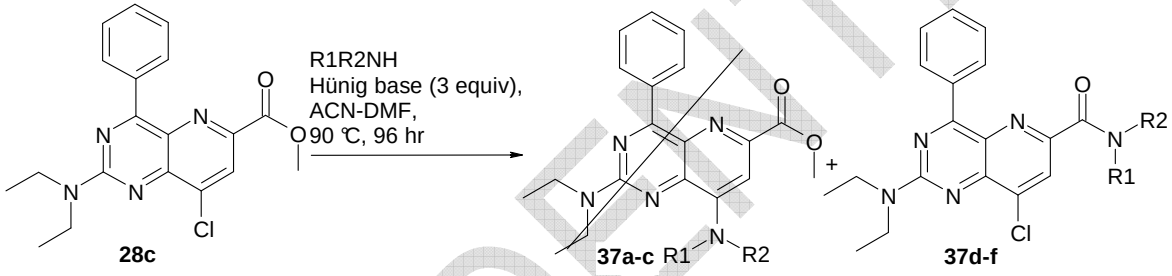
Entry	Amine	Solvent	t (hr)	T	Product	Yield (%)
1	$BnNH_2$	DCM/ACN	33	90 °C	**36a**	81% conv.
2	$BnNH_2$	ACN	20’	180 °C MW	**36a**	74
3	$BuNH_2$	ACN	20’	180 °C MW	**36b**	71
4	Et_2NH	ACN	20’	180 °C MW	**36c**	72

Table 4.18. S_NAr with amines on derivative **31a**.

Comparing the reaction conditions used for the addition of amines to derivative **12a** (*Table 4.1* and *Table 18 – Entry 1*) and to derivative **31a** (*Table 4.18 – Entries 2-4*), one can notice that the presence of the methylsulfanyl group at C-8 decreased the reactivity of the 2-chloro group towards amine addition, compared with a chloro group at C-8. This could be explained by the electron-donating character of the sulfanyl group (leading a negative partial charge at C-2 via mesomeric forms) compared to the electron-withdrawing character of the chlorine group (leading a positive partial charge at C-2).

*4.3.2. S_NAr with amines on derivatives **28c**.*

The three same amines were selected for S_NAr reactions on derivative **28c** (*Table 4.19*). These reactions were performed with 1 equiv of amine, in presence of 3 equiv of Hünig base at 90 °C, using thermic conditions. Unfortunately, the desired product was not formed (*Table 4.19 – Entries 1 to 3*). Amide bond at C-6 ester was formed. In addition, these conversions were low (16% with benzylamine and 20% with butylamine) and compounds **37d** and **37e** were not isolated. No reaction occurred with diethylamine as nucleophile, probably due to its steric hindrance (*Table 4.19 - Entry 3*). As an alternative, Buchwald cross-coupling reaction was investigated (using Pd_2dba_3 as catalyst, ^{t}BuOK as base and 1,3-bis-(2,6-diisopropyl-phenyl)-3*H*-imidazol-1-ium chloride as ligand) but did not yield the formation of the desired products.

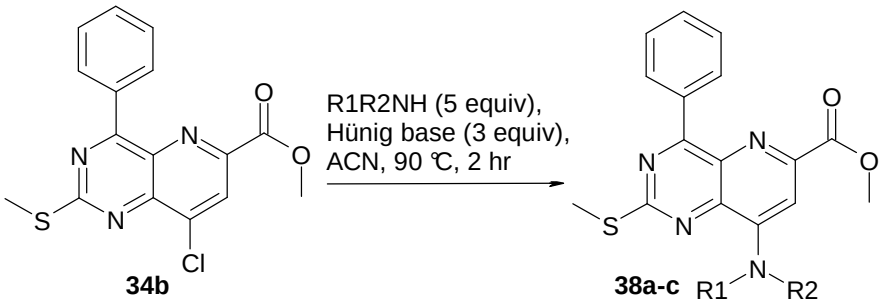


Entry	Amine	Product	Amide	% conversion
1	$BnNH_2$	**37a**	**37d**	**37d** 16%
2	$BuNH_2$	**37b**	**37e**	**37e** 20%
3	Et_2NH	**37c**	**37f**	No reaction

Table 4.19. S_NAr with amines on derivative **28c**.

*4.3.3.S_NAr with amines on derivatives **34b**.*

Derivative **34b** was submitted to S_NAr reaction with diverse amines. As previously, butylamine and benzylamine were selected as primary amines and diethylamine as secondary amine (*Table 4.20*). Optimized conditions consisted in the addition of 5 equiv of amine to a solution of derivative **34b** in ACN in the presence of Hünig base for 2 hours at 90 °C (*Table 4.20*). After purification, derivatives **38a** to **38c** were obtained in good yields (*Table 4.20 – Entries 1-3*).

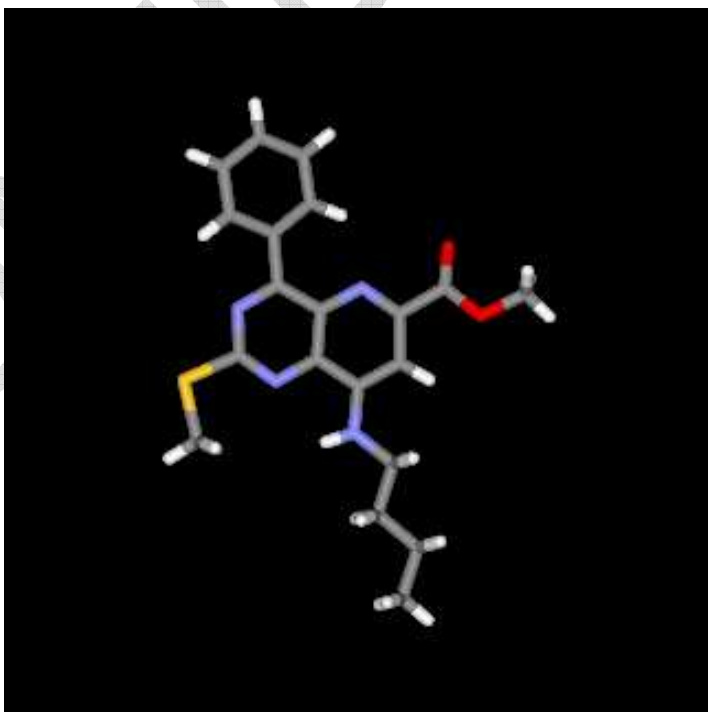


Entry	Amine	Product	Yield (%)
1	$BnNH_2$	**38a**	73[a]
2	$BuNH_2$	**38b**	83
3	Et_2NH	**38c**	84

[a]: purification performed using Mass Directed Auto-Purification system

Table 4.20. S_NAr with amines on derivative **34b**.

X-ray structure determination was obtained for derivative **38b** confirming the regioselectivity of thiol addition at C-2 and amine addition at C-8 (*X-Ray Structure 4.3* and *Crystallographic Data of compounds **38b** in Appendix*).



X-Ray Structure 4.3. Derivative 38b.

4.4. Conclusion.

Regioselective nucleophilic additions of primary and secondary amines to 4-substituted-2,8-dichloro-pyrido[3,2-*d*]pyrimidines were successfully achieved at C-2, independently of the C-4 substituent as shown in *Figure 4.1* (*i.e.* amine or aryl). However, reactivity of chlorine at C-2 towards amine addition was influenced by the nature of the substituent at C-8, being less reactive when a methylsulfanyl group was present at C-8 (derivative **31**) compare to a chloro group (derivative **12a**). Regioselective C-2 addition of amine to derivatives **12** (with an amino group at C-4) and **15** (with a phenyl group at C-4) was confirmed by 2D-NMR analyses.

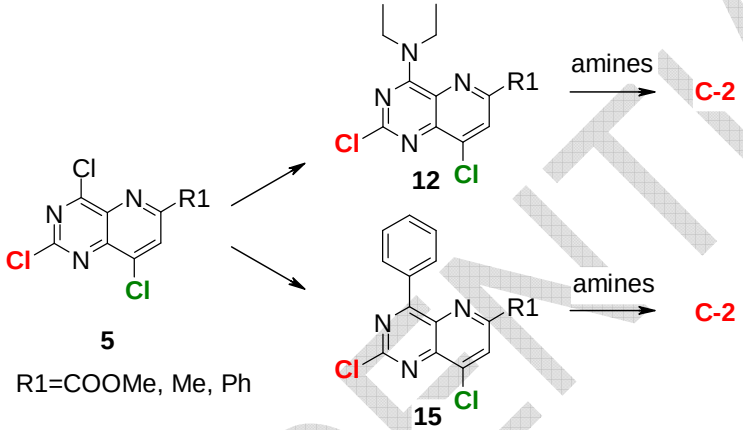


Figure 4.1. Amines additions to derivatives **12** and **15.**

Nucleophilic addition of thiols and thiolates to derivatives **12** and **15** were giving mixture of two regioisomers (*i.e.* addition at 2 or 8 position). Reaction conditions were optimized on derivatives **12** in order to favour one or the other regioisomer. This was achieved by modifying the reaction solvent. Portionwise addition of the sodium methyl thiolate at 0 °C in DMF for 16 hr yielded majoritarly the addition at C-8 (9:1 ratio), as confirmed by X-ray structure determination of the major regioisomer **31a**. When additions were performed in ^{i}PrOH or MeOH at 90 °C for 16 hr, C-2 addition product was o btained as the only compound in a 1:0 ratio (X-ray structure determination of **31d**). On the other hand, the regioselectivity of thiols addition was also influenced by the C-4 substituent when the reaction was performed in DMF. Addition of thiols and sodium thiolates occurred predominantly at the 8 position for derivative **12** (having an amino group at C-4) and at the 2 position for derivative **15** (having a phenyl group at C-4) (X-ray structure determination of **38b**). These results are summarized in *Figure 4.2*.

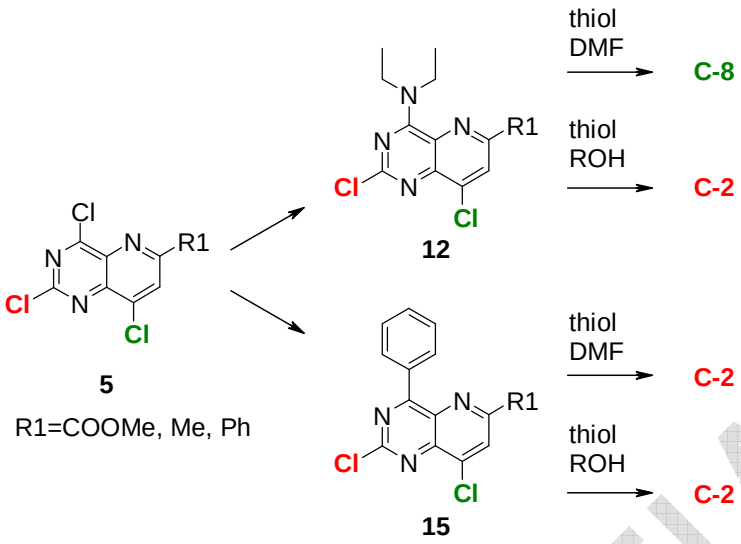


Figure 4.2. Thiol additions to derivatives **12** and **15.**

Concerning the regioselectivity study, no clear explanation can be formulated to rationalize the difference of regioselectivity observed when reactions are performed in polar protic or polar aprotic solvent. The regioselectivity is independent of the reaction temperature and the reaction concentration. In addition, both regioisomers are stable and their formation is not reversible. On the other hand, regioselectivity seems to be dependent on the ability of the solvent to form H bond as well as the ability of the scaffold to be protonated.

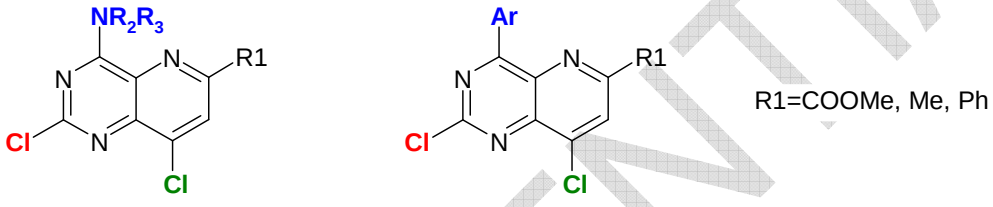
For the substitution of the last chlorine, S_NAr with amines at C-8 on 4-phenyl-2-diethylamino-8-chloro-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **28c** were not achieved and competition with amide-bond formation was observed. On the other hand, S_NAr on 4-phenyl-2-methylsulfanyl-8-chloro-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **34b** gave the desired products in good yields (X-ray structure determination of derivative **38b**).

After having reviewed S_NAr reactions on 2,8-dichloro-pyrido[3,2-*d*]pyrimidines **12** and **15**, and on monochloro-pyrido[3,2-*d*]pyrimidines **28c**, **31a** and **34b**, C-C bond formations, through Suzuki and Liebeskind-Srogl cross-coupling reactions were further studied on the same scaffolds.

5. Cross-coupling reactions at C-2 and C-8.

5.1. Introduction.

Regioselective chlorine substitution on derivatives **12** and **15** was further studied via metal-catalyzed cross-coupling reactions. In addition to the implementation of the reaction conditions, the reactivity difference of the two remaining reactive centers at 2 and 8 positions was investigated. Derivatives with R1=COOMe were selected as starting material for this study. Metal-catalyzed cross-coupling reactions on 4-amino-2,8-dichloro-pyrido[3,2-*d*]pyrimidines **12** and 4-aryl-2,8-dichloro-pyrido[3,2-*d*]pyrimidines **15** have never been reported in literature (*Figure 5.1*).



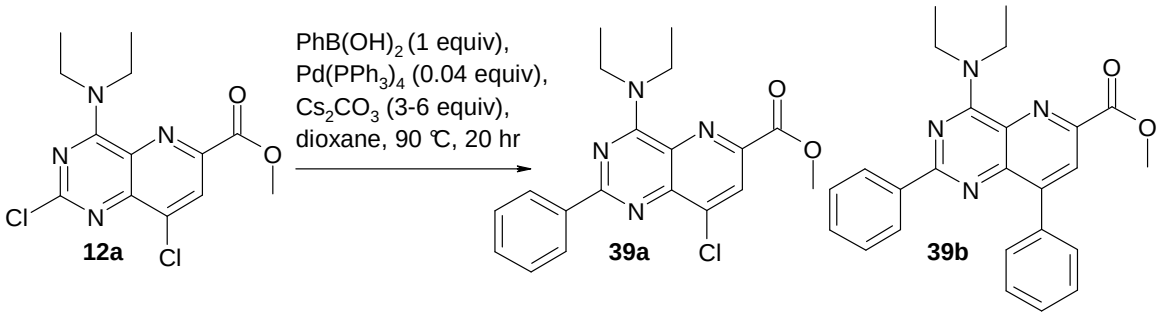
12 **15**

Figure 5.1. Starting material for metal-catalyzed cross-coupling reactions at C-2 and/or C-8.

5.2. Suzuki cross-coupling reactions.

*5.2.1. Suzuki cross-coupling reactions on derivatives **12a** and **15a**.*

Suzuki cross-coupling reactions on derivative **12a** were first investigated. Different reaction conditions were selected for this reaction, including the ones developed by Tikad *et al.* for the regioselective Suzuki cross-coupling reaction on 2,4-dichloro-pyrido[3,2-*d*]pyrimidine scaffold.[7] Reactions were performed in dioxane with 1 equiv of phenyl boronic acid, using $Pd(PPh_3)_4$ as catalyst, in presence of Cs_2CO_3 as base. Reactions were heated at 90 °C for 20 hours. Single Suzuki cross-coupling reaction was not achieved even with 1 equiv of boronic acid (*Table 5.1*). The ratio between **39a** and **39b**, respectively product of mono- and bis-Suzuki cross-coupling reaction was of 60 to 40 (*Table 5.1 - Entry 1*). A ratio of 15 to 85 was obtained when 2 equiv of boronic acid were used (*Table 5.1 - Entry 2*).



Entry	$PhB(OH)_2$	% conversion	Ratio 39a/39b	Yield (%)
1	1 equiv	54	60/40	-
2	2 equiv	93	15/85	-

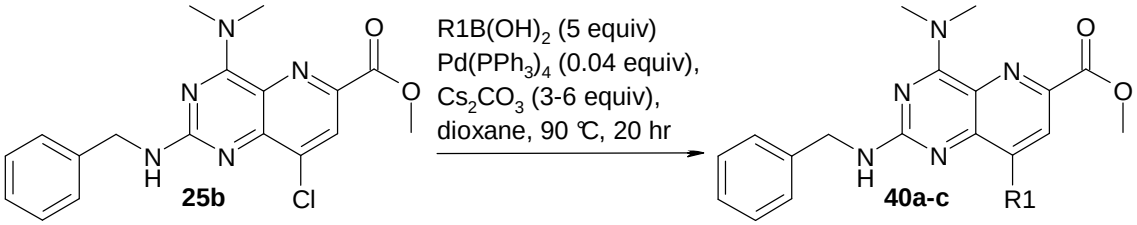
Table 5.1. Suzuki cross-coupling of phenyl boronic acid and compound **12a**.

As Suzuki cross-coupling reactions were not selective on 4-diethylamino-2,8-dichloro-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **12a**, differenciation of the two reactive centers (*i.e*. chlorine groups at 2 and 8 positions) was envisaged, via selective addition of amine or thiol. Suzuki cross-coupling reactions were further performed on 4-methylamino-2-benzylamino-8-chloro-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **25b** and 4-diethylamino-2-chloro-8-methylsulfanyl-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **31a**. Following the same strategy, and in order to avoid double Suzuki cross-coupling reactions on 4-phenyl-2,8-dichloro-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **15a**, metal-catalyzed cross-coupling reactions were performed on 4-phenyl-2-diethylamino-8-chloro-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **28c** and 4-aryl-2-methylsulfanyl-8-chloro-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **34b** and **35a-b**.

*5.2.2.Suzuki cross-coupling reactions on derivatives **25b**, **31a**, **28c**, **34b** and **35a-b**.*

5.2.2.1. Suzuki cross-coupling reactions on derivative **25b**.

To overview the reactivity of C-8 chlorine towards C-C bond formation on derivative **25**, three different boronic acids were selected: phenyl boronic acid, p-methoxyphenylboronic acid as electron-donating aryl and p-trifluoromethylphenylboronic acid as electron-withdrawing aryl group. Same reaction conditions as the one previously used in *Table 5.1* were selected for the Suzuki cross-coupling reaction on derivative **25b** except that, to reduce the reaction time, an excess of boronic acid was used (*Table 5.2 – Entries 1, 2 and 3*). Compounds **40a** and **40c** were purified by precipitation in MeOH whereas compound **40b** was purified by flash chromatography (*Table 5.2 – Entry 2*). Final compounds **40a** to **40c** were obtained in yields ranging from 78 to 82%.

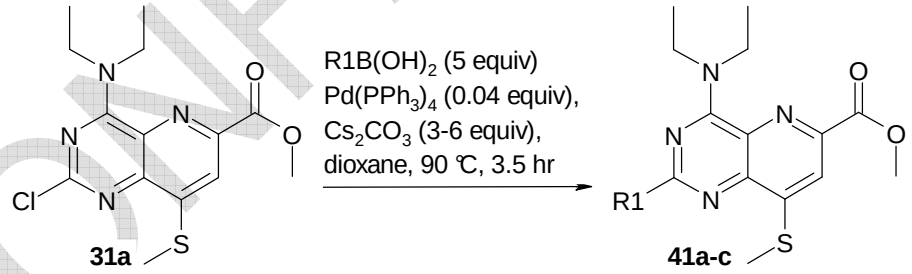


Entry	$R_1B(OH)_2$ (eq)	Product	Yield (%)
1	$PhB(OH)_2$	**40a**	82
2	*p*-OMe-$PhB(OH)_2$	**40b**	82
3	*p*-CF_3-$PhB(OH)_2$	**40c**	78

Table 5.2. Suzuki cross-coupling reactions on derivative **25b**.

5.2.2.2. Suzuki cross-coupling reactions on derivative **31a**.

Suzuki cross-coupling reactions were further performed on derivative **31a** under the same reaction conditions. After 3.5 hours at 90 °C, desired products were precipitated in MeOH affording derivatives **41a** to **41c** in yields ranging from 79 to 88% (*Table 5.2 - Entries 1, 2 and 3*). Diversification was achieved with the use of boronic acids bearing different electronic properties.

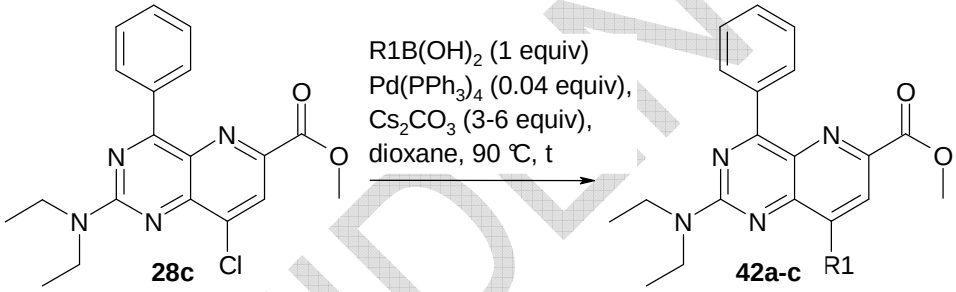


Entry	$R1B(OH)_2$	Product	Yield (%)
1	$PhB(OH)_2$	**41a**	88
2	*p*-OMe-$PhB(OH)_2$	**41b**	79
3	*p*-CF_3-$PhB(OH)_2$	**41c**	84

Table 5.3. Suzuki cross-coupling reaction on derivative **31a**.

5.2.2.3. Suzuki cross-coupling reactions on derivative **28c**.

Suzuki cross-coupling reactions on derivative **28c** were performed using the same reaction conditions as previously, except that only 1 equiv of boronic acid was used. Indeed, the reaction times were similar when 1 or 5 equiv of boronic acids were used. Reactions were performed in dioxane at 90 °C for 3.5 to 16 hr (*Table 5.4 – Entries 1, 2 and 3*). A complete conversion was obtained for compounds **42a** and **42c**, that were purified by precipitation in MeOH (*Table 5.4 – Entries 1 and 3*). On the other hand, reaction with *p*-OMe-PhB(OH)$_2$ was less clean as two other products were formed during the reaction: 23% of the carboxylic acid derivative of **42b** and 20% of a by-product that could not be identified (*Table 5.4– Entry 2*). The reaction mixture of **42b** was filtered through a NH2-SPE, affording the desired product as single product, with purity above 98%. Due to the formation of these two by-products during the reaction, a moderate yield (51%) was obtained for this reaction. Final products **42a** to **42c** were obtained in yield ranging from 51 to 82%.

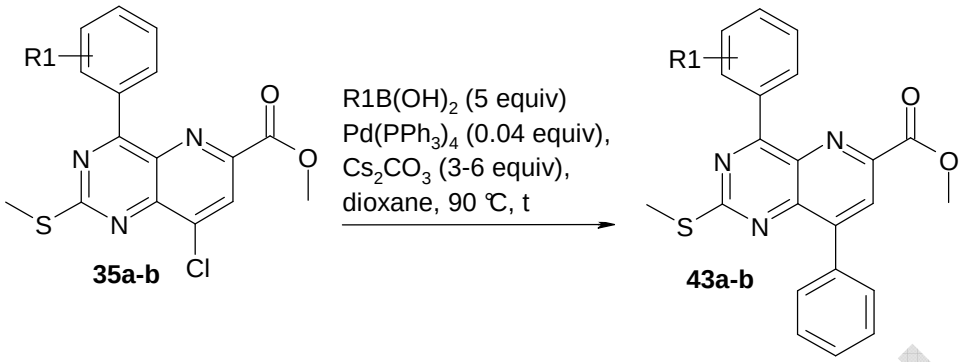


Entry	$R_1B(OH)_2$	t (hr)	Product	Yield (%)
1	PhB(OH)$_2$	7	**42a**	80
2	*p*-OMe-PhB(OH)$_2$	16	**42b**	51
3	*p*-CF$_3$-PhB(OH)$_2$	3.5	**42c**	82

Table 5.4. Suzuki cross-coupling reaction on derivative **28c**.

5.2.2.4. Suzuki cross-coupling reactions on derivatives **34b**, **35a-b**.

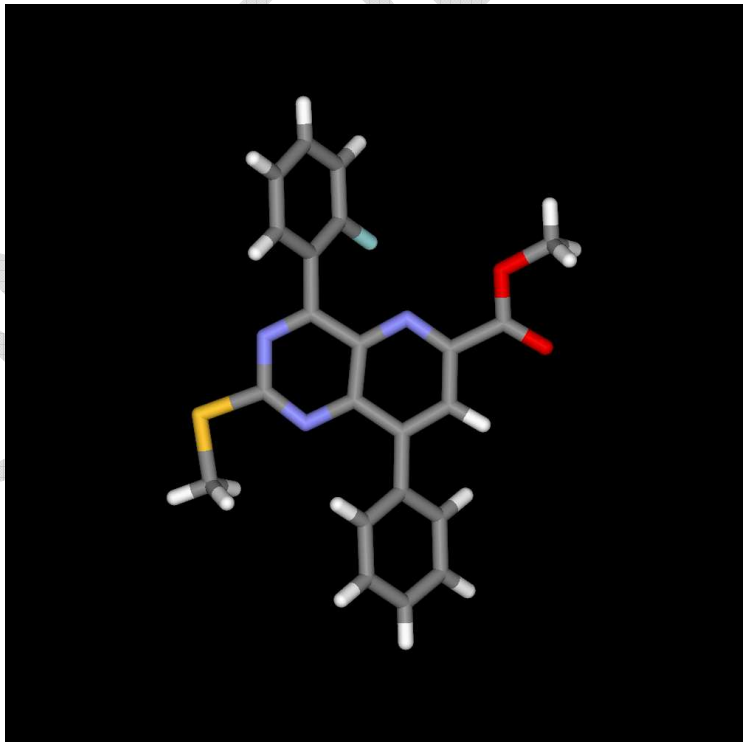
Reaction conditions selected for Suzuki cross-coupling reaction on derivatives **34b** and **35a-b** were the same as the ones previously used for the Suzuki cross-coupling reactions on derivative **31a**. Purification with MDAP® afforded derivatives **43a** and **43b** in yields ranging from 71 to 82% (*Table 5.5 - Entries 1and 2*).



Entry	R1	Product	Yield (%)
1	4-OMe	**43a**	82
2	2-F	**43b**	71

Table 5.5. Suzuki cross-coupling reaction on derivatives **35a-b**.

X-ray structure determination on derivative **43b** confirmed the regioselectivity attributed to the thiol addition to derivative **33b** (at C-2) and to the Suzuki cross-coupling reaction (at C-8) (*X-Ray Structure 5.1* and *Crystallographic Data of compounds **43b** in Appendix*).



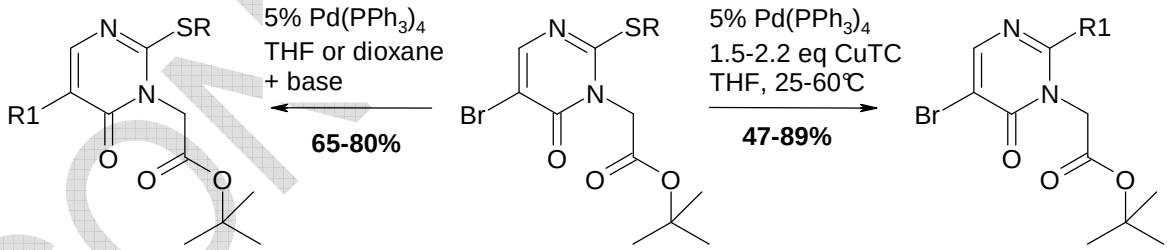
X-Ray Structure 5.1. Derivative **43b**.

Selective metal-catalyzed cross-coupling reactions were feasible only on mono-chloro pyridopyrimidines derivatives such as **25b**, **31a**, **28c**, **34b** and **35a-b**. Introduction of an amino group at C-2 or a methylsulfanyl group at C-2 or C-8, leaving only one chlorine on the molecule, offered the possibility to differentiate the reactivity of positions 2 and 8 substituted with orthogonal groups, amine or methylsulfanyl group and chlorine.
Liebeskind-Srogl cross-coupling reactions were further performed on compounds bearing a methylsulfanyl group at C-2 or C-8 position such as derivatives **31a**, **41a** and **36a**.

5.3. LS cross-coupling reactions on derivatives **31a**, **41a**, **36a**.

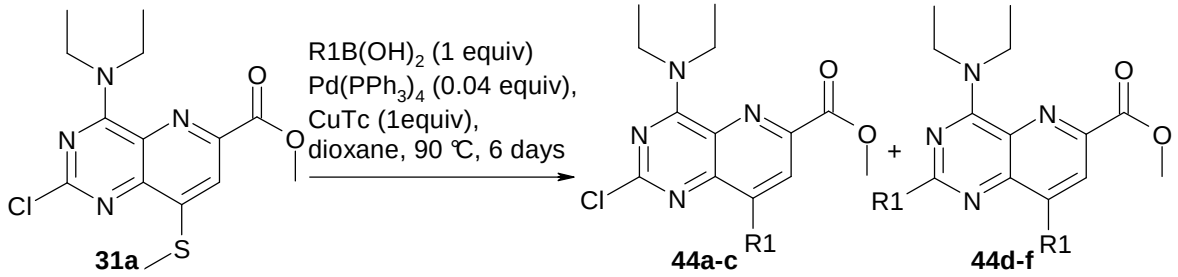
*5.3.1. Liebeskind-Srogl cross-coupling reactions on derivative **31a**.*

Suzuki cross-coupling reactions on 4-diethylamino-2-chloro-8-methylsulfanyl-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **31a** were selective as cross-coupling reaction occurred only at the 2-chlorine position (*Table 5.3*). With the goal to study the selectivity of the Liebeskind-Srogl cross-coupling reactions on such derivatives, bearing both chloro and methylsulfanyl groups at C-2 and C-8 positions, LS cross-coupling reactions were envisaged on derivative **31a**. Liebeskind *et al.* reported the orthogonal selectivity of the Liebeskind-Srogl cross-coupling versus the Suzuki cross-coupling reaction on 5-bromo-2-methylthiouracil (*Scheme 5.1*). Their optimized conditions consisted in using a stoeichiometric amount of boronic acid, in presence of 0.04 equiv of $Pd(PPh_3)_4$ and 1.5-2.2 equiv of CuTc as co-factor. Reactions were performed in THF or dioxane between 25 and 60 °C.



Scheme 5.1. Liebeskind-Srogl cross-coupling reaction vs. Suzuki cross-coupling reaction.

Liebeskind-Srogl cross-coupling reactions on derivative **31a** were performed using the reaction conditions optimized by Liebeskind *et al.*, heating the reaction mixture in dioxane at 90 °C for 6 days (*Table 5.6*). Unfortunately, even with long reaction times, less than 50% of conversion was obtained. Moreover, between 4 to 13% of cross-coupling reactions at the C-Cl bond was observed, yielding formation of compounds **44d-f** (*Table 5.6 – Entries 1 to 3*).



Entry	R1B(OH)$_2$	Product	By-Product	Conversion %
1	PhB(OH)$_2$	**44a**	**44d**	**44a**: 47; **44d**: 4
2	*p*-OMe-PhB(OH)$_2$	**44b**	**44e**	**44b**: 42; **44e**: 13
3	*p*-CF$_3$-PhB(OH)$_2$	**44c**	**44f**	**44c**: 48; **44f**: 9

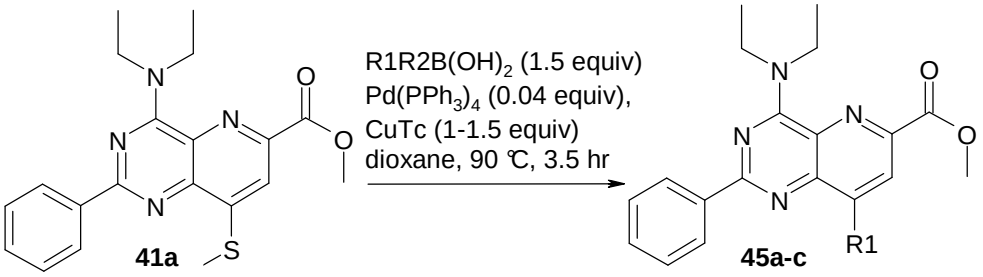
Table 5.6. LS cross-coupling reaction on derivative **31a**.

Regioselective cross-coupling reaction on the methylsulfanyl group without reacting on the chlorine could not be achieved on derivative **31a**. Introduction of a phenyl group or an amino group at the chlorine position (C-2) was achievable as discussed earlier, and offered the possibility to differenciate the reactivity of position 2 and 8, allowing the LS cross-coupling reaction selectively at position 8.

*5.3.2. Liebeskind-Srogl cross-coupling reactions on derivative **41a**.*

Liebeskind-Srogl cross-coupling reaction conditions used on derivative **31a** were applied on derivative **41a**. After 3.5 hours at 90 °C, compounds **45a** and **45b** were formed with a complete conversion (*Table 5.7 – Entries 1 and 2*). On the other hand, only 60% of conversion was obtained for scaffold **45c** after 3.5 hr. The reaction was stopped and relaunched after work-up following the same conditions. After this second run, complete reaction was reached. Compounds **45a** to **45c** were obtained in yields ranging from 84 to 88% (*Table 5.7*).

Electron density of *p*-trifluoromethylphenylboronic acid can explain the difference of reactivity compared to phenyl boronic acid and *p*-methoxyphenylboronic acid. In *p*-trifluoromethylphenylboronic acid, boron is electron-poor due to the electron withdrawing property of CF$_3$ group, making it less reactive towards Suzuki or LS cross-coupling reactions compare to the two other boronic acids selected.



Entry	R2	Product	Yield (%)
1	$PhB(OH)_2$	**45a**	84
2	*p*-OMe-$PhB(OH)_2$	**45b**	88
3	*p*-CF_3-$PhB(OH)_2$	**45c**	87[a]

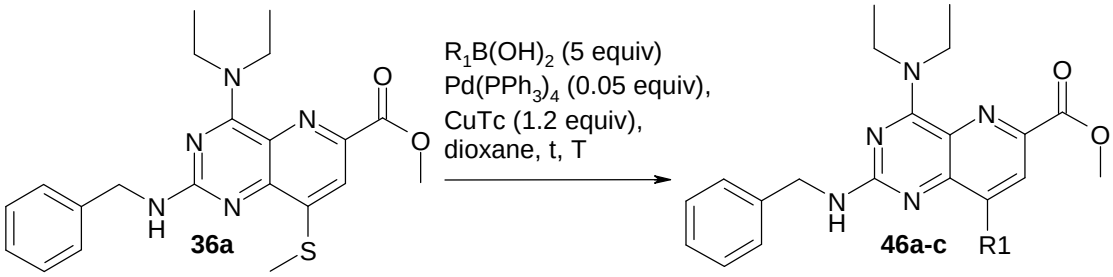
[a]: reaction was relaunched with another equiv of boronic acid for completion

Table 5.7. LS cross-coupling reaction on derivative **41a.**

*5.3.3. Liebeskind-Srogl cross-coupling reactions on derivative **36a**.*

Liebeskind-Srogl cross-coupling reactions were further performed on derivative **36a** following the same reaction conditions. Unfortunately, after 48 hours at 90 °C, no reaction took place (*Table 5.8 – Entry 1*). Liebeskind has reported that $Zn(OAc)_2$ was an essential additive in some cases, presumably by tying up basic nitrogen atoms that potentially interfere with the reaction system (coordination of Cu or deprotonation of the boronic acid).[40] This strategy was further applied to derivative **36a**. LS cross-coupling reaction of phenyl boronic acid with derivative **36a**, performed in presence of 5 equiv of $Zn(OAc)_2$ at 90 °C for 20 hours, afforded derivative **46a** in 80% yield (*Table 5.8 – Entry 2*). In order to decrease the reaction time, same reaction was performed under MW irradiation at 180 °C. After a 50 min run under MW irradiation, complete conversion was reached and the isolated yield was similar (*Table 5.8 – Entry 3*).

These optimized conditions were selected for LS cross-coupling reactions of diverse substituted phenylboronic acids on derivative **36a**. Following this procedure, final products **46a** to **46c** were obtained in yields ranging from 71 to 80% (*Table 5.8- Entries 3 to 5*).



Entry	R1B(OH)$_2$	Additive 5 equiv	Heating conditions	T	t (hr)	Product	Yield %
1	PhB(OH)$_2$	-	Thermic	90 °C	48	**46a**	-
2	PhB(OH)$_2$	Zn(OAc)$_2$	Thermic	90 °C	20	**46a**	80
3	PhB(OH)$_2$	Zn(OAc)$_2$	MW	180 °C	50’	**46a**	80
4	*p*-OMe-PhB(OH)$_2$	Zn(OAc)$_2$	MW	180 °C	50’	**46b**	71
5	*p*-CF$_3$-PhB(OH)$_2$	Zn(OAc)$_2$	MW	180 °C	50’	**46c**	76

Table 5.8. LS cross-coupling reaction on derivative **36a**.

5.4. Conclusion.

Regioselective C-C bond formation at 2 or 8 positions via Suzuki cross-coupling reactions was not achieved on 4-amino-2,8-dichloro-pyrido[3,2-*d*]pyrimidine derivatives **12**. In this derivative, the two chloro positions had to be the first differentiated by regioselective S_NAr addition with amine or sodium methylthiolate. With the presence of two differentiated substituents, regioselective C-C bond formation could be achieved via Suzuki cross-coupling reactions on derivatives **25b**, **31a**, **28c**, **34b** and **35a-b**. On the other hand, selective LS cross-coupling reaction was not achieved on 4-diethylamino-2-chloro-8-methylsulfanyl-pyrido[3,2-*d*]pyrimidine **31a** as C-C bond formation not only occurred at C-S (C-8) but also at C-Cl (C-2). As previously, differentiation of the two reactive centers (*i.e.* chlorine and methylsulfanyl groups), by substitution of the remaining chlorine via S_NAr or Suzuki cross-coupling reaction, allowed the selective reaction at the methylsulfanyl group at C-8. This stategy was applied to derivatives **31a**, **41a** and **36a**.

In this work, unprecedented regioselective C-C bond formation at C-2 and C-8 positions on the pyrido[3,2-*d*]pyrimidine derivatives was successfully achieved via differentiation of two reactive centers after regioselective addition of methylsulfanyl group at C-2 or C-8.

6. Conclusion.

In the present work, pyrido[3,2-*d*]pyrimidine central core was selected for the challenges it offer in heterocyclic chemistry and for its potential biological activity. Different from its regioisomers, it has not been much explored. In particular, 2,4,8-trichloro-pyrido[3,2-*d*]pyrimidine derivatives were chosen as they offer a convergent way to get access to diverse substituted pyridopyrimidines, via the regioselective and successive transformations of the three chlorines, a challenging goal that has been explored in this work (*Figure 6.1*).

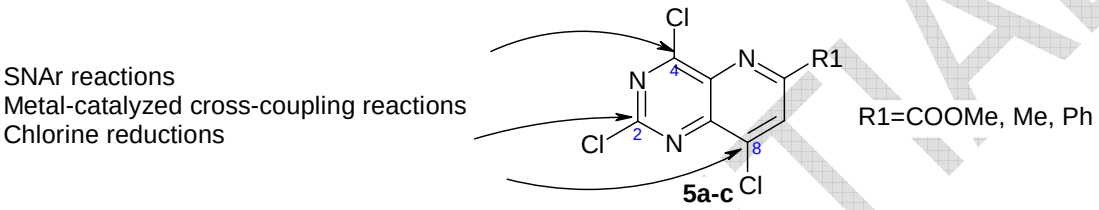


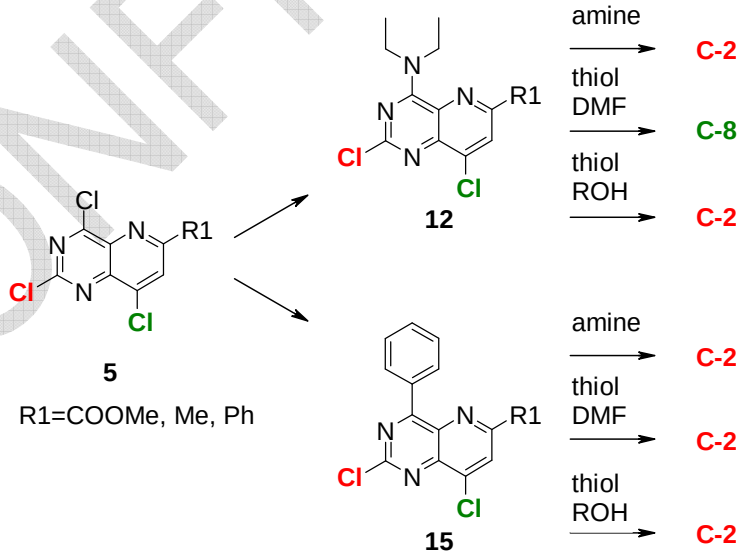
Figure 6.1. Chemistry developed on trichloro-pyrido[3,2-*d*]pyrimidine derivatives **5**.

We have developed a new synthetic route for the synthesis of 6-substituted-2,4,8-trichloro-pyrido[3,2-*d*]pyrimidines **5**. To the best of our knowledge, it is the first report of a general synthetic pathway for the synthesis of such compounds. The synthetic route consisted in 3 or 4 steps: 1) formation of enol ether **8** if not commercially available, 2) condensation of 5-aminouracil **1**, 3) cyclization, and 4) chlorination. Trichloro- derivatives were obtained in overall yield ranging from 30 to 52%. The simplicity of the reactions and of the purification steps make this route particularly convenient for synthesis of 6-substituted-2,4,8-trichloro-pyrido[3,2-*d*]pyrimidines with aryl or alkyl group at C-6.

We have then studied the regioselective substitutions of the three chlorines at positions 2, 4 and 8 on derivatives **5a-c**. Additions of primary and secondary amines and of anilines to derivatives **5** were regioselective at C-4. S_NAr with sodium methylthiolate were also regioselective and took place at the same position. Furthermore, we have selectively formed a C-C bond from the C-S bond at C-4 via Liebeskind-Srogl cross-coupling reaction, as classical metal-catalyzed cross-coupling reactions on the trichloro-pyrido[3,2-*d*]pyrimidines, such as Suzuki, Stille and Negishi couplings, yielded non selective reactions. We showed that the LS cross-coupling reaction occurred specifically and efficiently at the C-SCH_3 bond, and that no cross-coupling side reaction was detected at the other C-Cl bonds. With this process, a C-C bond at position 4 was selectively formed. Regioselective introduction of C-C bond at position 4 on 2,4,(6,7 or 8)-trichloro-pyridopyrimidines (including all regioisomers) is unprecedented.

The reactivity of the two remaining chlorines on 4-substituted-2,8-dichloro-6-substituted-pyrido[3,2-*d*]pyrimidine derivatives **12** and **15** has further been studied. Addition of primary and secondary amines, via S_NAr reactions, took place regioselectively at C-2, independently of the C-4 substituent (*i.e.* amine or aryl). Only one regioisomer was obtained in yields ranging from 69 to 85%. On the other hand, nucleophilic substitutions with thiols and thiolates on derivatives **12** and **15** were giving mixture of two regioisomers (*i.e.* addition at 2 or 8 position). Reaction conditions could be optimized on derivatives **12** in order to regioselectively synthezise one or the other regioisomer. In DMF, C-8 addition was favoured while in ^{i}PrOH, addition took place majoritarly at C-2. Interestingly, the regioselectivity in DMF was dependant on the C-4 substituent (*i.e.* amine or aryl group) giving a C-8 addition with derivatives **12** (bearing an amino group at C-4), and a C-2 addition with derivatives **15** (bearing an aryl group at C-4). On the other hand, regioselectivity in ^{i}PrOH was independent of the C-4 substituent giving for both starting material (*i.e.* derivatives **12** and **15**), addition at C-2. As a summary on S_NAr reactions on dichloro-pyrido[3,2-*d*]pyrimidine derivatives, and more precisely on thiol addition to derivatives bearing an amino group at C-4, different regioselectivities were observed when reactions were preformed in polar protic or polar aprotic solvent. We have shown that regioselectivity was independent of the reaction temperature and the reaction concentration, but seemed to be dependant on the ability of the solvent to form H bond as well as the ability of the scaffold to be protonated. In addition, both regioisomers were stable and their formation was not reversible.

Regioselectivities observed for S_NAr reactions on dichloro-pyrido[3,2-*d*]pyrimidines **12** and **15** are summarized in *Scheme 6.1*.



Scheme 6.1. Summary of regioselectivities observed for S_NAr reactions on derivatives **12** and **15**.

Regioselective C-C bond formation at 2 and 8 positions on 4-amino(aryl)-pyrido[3,2-*d*]pyrimidine derivatives could be achieved after having differenciate the two chloro positions by regioselective S_NAr addition of sodium methylthiolate. With the presence of two orthogonal substituents, regioselective C-C bond formation could be achieved via Suzuki cross-coupling reactions on the C-Cl bond. On the other hand, selective Liebeskind-Srogl cross-coupling reaction was not achievable on 4-diethylamino-2-chloro-8-methylsulfanyl-pyrido[3,2-*d*]pyrimidine **31a** as, under the LS conditions, C-C bond was also formed at C-2. First substitution of 2-chlorine via S_NAr or Suzuki cross-coupling reaction, allowed the selective cross-coupling reaction on the methylsulfanyl group at C-8 in a second step. In this work, unprecedented regioselective C-C bond formation at C-2 and C-8 positions in the pyrido[3,2-*d*]pyrimidine derivatives was successfully achieved.

The chemistry described in this work can give access to many diverse substituted pyrido[3,2-*d*]pyrimidines starting from one common precursor, 2,4,8-trichloro-pyrido[3,2-*d*]pyrimidine **5**, as it has been demonstrated in this work and as depicted in *Figure 6.2*.

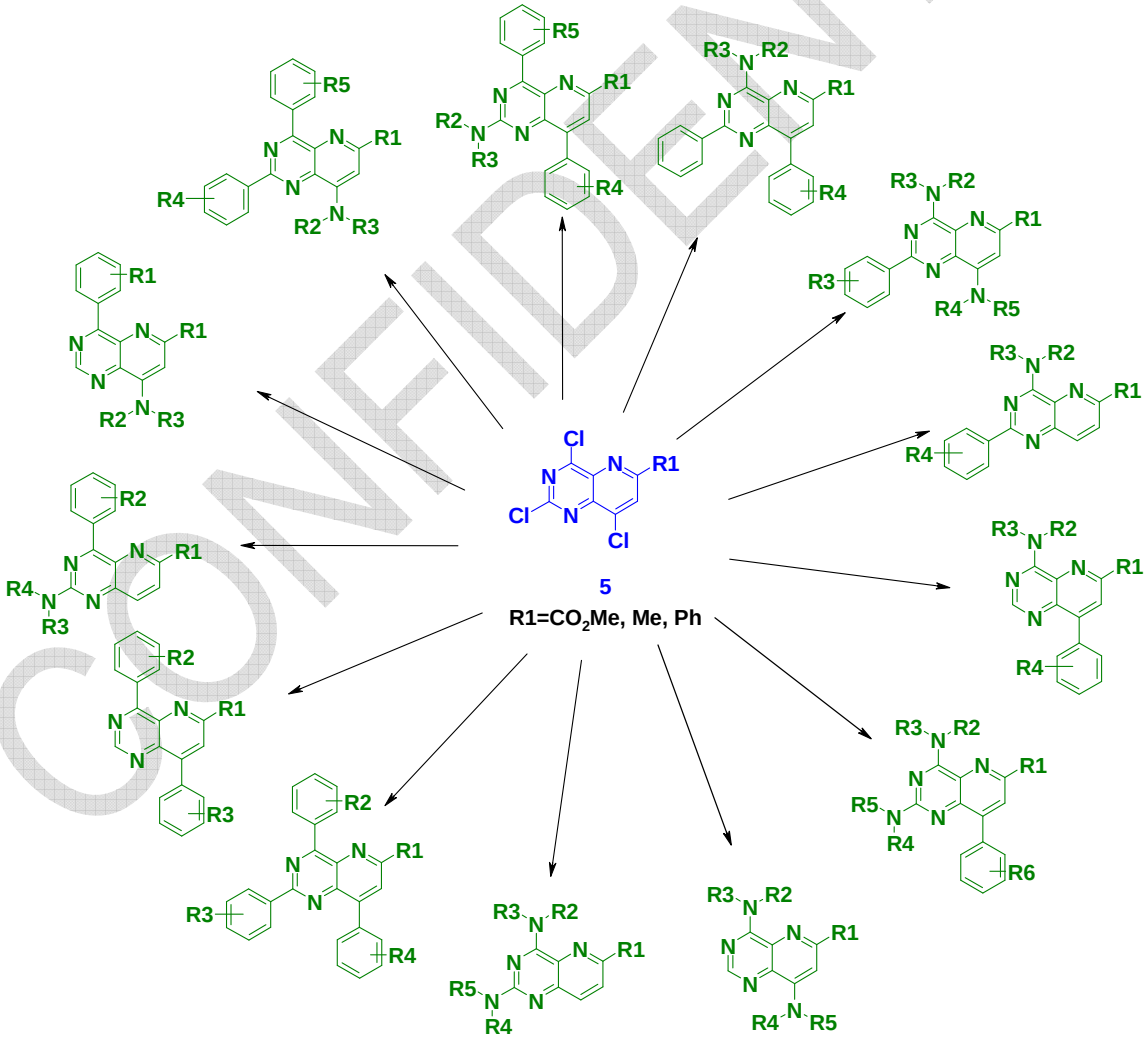


Figure 6.2. Diverse compounds that can be synthesized from derivative **5.**

The methodology and optimized reaction conditions reported in this work were transferred for the production of compound libraries, where a wider diversity of nucleophilic amines and boronic acids in the LS and Suzuki cross-coupling reactions were used. To date, more than 2K compounds have been synthesised following the protocol described. The methodology developed here has already demonstrated its robustness and potential for future applications in the synthesis of polysubstituted heterocycles.

7. Experimental Part.

The commercially available starting materials used in the following experimental description were purchased from Aldrich, Fluka or Acros unless otherwise reported.

^{1}H and ^{13}C NMR spectra were recorded with a BRUKER DPX-300 spectrometer (300 MHz and 75.47 MHz respectively). HPLC analyses were performed on a Waters 2695 instrument, equipped with a Waters 996 Photodiode Array Detector and an X-Bridge column C8 50 x 4.6 mm 3.5 µm. Chromatographic conditions consisted in a gradient from 95% H_2O (0.1% TFA): 5% CH_3CN (0.1% TFA) to 5% H_2O (0.1% TFA): 95% CH_3CN (0.1% TFA) over 8 minutes with a flow of 2 mL/min. LCMS analyses spectra were determined on a Waters Alliance 2795 coupled with ZMD (ES) equipped with Waters X-Bridge column C8 30 x 2.1 mm 3.5 µm. UHPLC/MS analyses were performed on a Waters Acquity coupled with Waters Acquity S70QD (ES) equipped with Waters Acquity BEH column C18 50 x 2.1 mm 1.7 µm, using the following conditions: MeCN /H_2O (NH_4OAc 10mM), 5 to 100% (2-3 min), max plot 230-400 nm. Elemental analyses were performed on an Erba Science 11108 CHN analyzer. Melting points were determined on Buchi Melting Point B-545 apparatus.

The preparative HPLC purifications are performed with a mass directed autopurification Fractionlynx from Waters equipped with a sunfire prep C18 OBD column 19x100 mm 5 µm, unless otherwise reported. All HPLC purifications were performed with a gradient of ACN/H_2O.

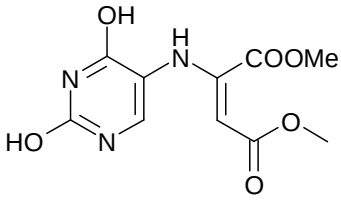
The microwave chemistry is performed on a single-mode microwave reactor Emrys™ Optimiser from Personal Chemistry or a single-mode microwave reactor Initiator 60™ from Biotage.

General procedure for enol ether 8 formation.

To a solution of β-keto ester (2.00 g; 10.41 mmol; 1.00 equiv) in a mixture of ACN (36.00 mL) and MeOH (9.00 mL) was added (trimethylsilyl)diazomethane (10.41 mL; 2.00 M; 20.81 mmol; 2.00 equiv) 2M in Et_2O. The solution was stirred at rt for 15 to 36 hr. No purification was performed on the product formed (derivative **8**) which were directly used for the next step.

General procedure for enamine 3a formation.

To a suspension of 5-aminouracil (275 g, 2.16 mol, 1 equiv) in dry methanol (5.5 L) was added dimethyl acetylene dicarboxylate (344 g, 2.42 mol, 1.1 equiv) dropwise at room temperature under nitrogen atmosphere. The mixture was stirred at room temperature for 24 hr. The precipitate formed during the reaction was filtered, washed twice with methanol, and dried under suction affording derivative **3a** in 74% yield as a yellow solid.



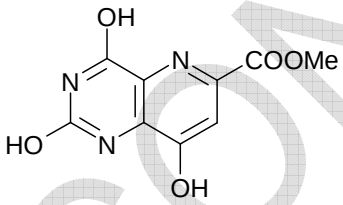
3-(2,4-Dioxo-1,2,3,4-tetrahydro-pyrimidin-5-ylamino)-but-2-enoic acid ethyl ester **3a**. mp 239-240 °C; IR *v*max 1658, 1223 cm-1; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 3.63 (s, 3H), 3.65 (s, 3H), 5.21 (s, 1H), 7.42 (s, 1H), 9.07 (s, 1H), 10.82 (br s, 1H), 11.33 (br s, 1H); ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 50.9, 52.6, 89.4, 114.6, 132.4, 148.6, 150.2, 161.9, 163.2, 169.0; HPLC t_R = 1.56 min; ES-MS *m*/*z* 269.83 (M + H)+.

General procedure for enamine 3 formation.

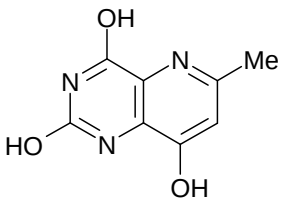
5-aminouracil (1.00 g; 7.87 mmol; 1.00 equiv) and derivative **8** (1.10 equiv) were heated at 140 °C in ^{i}PrOH (5.00 mL) for 2.5 hr under microwave irradiation. The yellow precipitate obtained was filtrated off, washed twice with MeOH and dried under succion with diethyl ether affording the enamine **3** derivatives. Mixture of methyl ester and isopropyl ester (product from transesterification) were obtained. Derivatives **3b-d** were used without further purification for the next step.

General procedure for cyclization of derivatives 3.

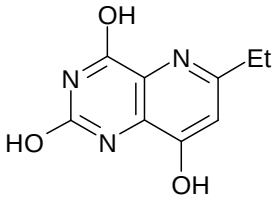
A suspension of derivative **3** (4.18 mmol; 1.00 equiv) in a mixture of DMA (1.00 mL) and 1,2-dichlorobenzene (9.00 mL) was heated at 250 °C for 1.2 hr under MW irradiation. The precipitate formed during the reaction was filtered, and washed with MeOH and Et_2O affording the title compound as coloured powder. Tautomers were observed in ^{1}H NMR.



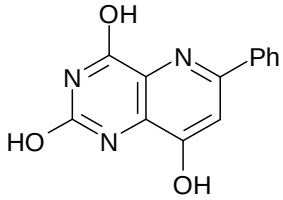
2,4,8-Trioxo-1,2,3,4,5,8-hexahydro-pyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester **4a**. Brown powder. Yield=88%. mp 255 °C (decomp.); IR *v*max 1682, 1295 cm-1; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 3.86 (s, 3H), 7.57 (s, 1H), 10.91 (br s, 1H,), 11.57 (br s, 1H), 12.05 (br s, 1H); ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 52.4, 113.1, 113.3, 129.8, 131.4, 142.4, 149.4, 160.9, 164.5; HPLC t_R = 0.79 min; ES-MS *m*/*z* 237.8 $(M + H)^+$.



6-Methyl-1,5-dihydro-pyrido[3,2-d]pyrimidine-2,4,8-trione **4b**. Pale brown powder. Yield = 84%. mp 300 °C (decomp.); IR *v*max 3195, 1684, 1633, 1552, 1417 cm-1; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 2.30 (s, 3H), 6.13 (s, 1H), 8.26 (s, 1H), 10.52 (br s, 1H), 11.7 (br s, 1H), ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 18.6, 113.2, 114.2, 125.3, 148.9, 149.4, 152.7, 160.7; HPLC t_R = 0.41 min; ES-MS *m*/*z* 194.0 $(M + H)^+$; Anal. calcd. for $C_8H_7N_3O_3$: C, 49.75; H, 3.65; N, 21.75. Found: C, 49.66; H, 3.49; N, 21.96.



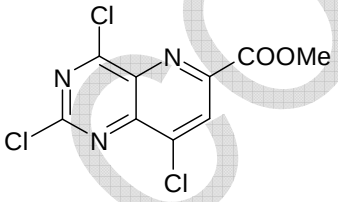
6-Ethyl-1,5-dihydro-pyrido[3,2-d]pyrimidine-2,4,8-trione **4c**. Dark brown powder. Yield = 67%. mp 300 °C (decomp.); IR *v*max 3204, 1681, 1555, 1415 cm-1; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 1.15 (t, *J* = 7.5 Hz, 3H), 2.62 (q, *J* = 7.5 Hz, 2H), 6.17 (s, 1H), 10.51 (br s, 1H), 11.70 (br s, 1H), 11.84 (br s, 1H), ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 13.6, 25.3, 111.7, 114.2, 148.9, 149.4, 153.3, 160.0, 160.7; HPLC t_R = 0.79 min; ES-MS *m*/*z* 208.0 $(M + H)^+$; Anal. calcd. for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.47; H, 4.18; N, 20.30.



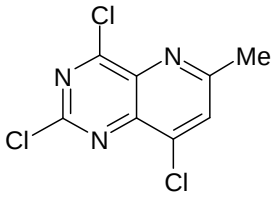
6-Phenyl-1,5-dihydro-pyrido[3,2-d]pyrimidine-2,4,8-trione **4d**. Pale pink powder. Yield = 86%. mp 300 °C (decomp.); IR *v*max 3010, 2843, 1681, 1479 cm-1; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 7.48-7.88 (m, 6H), 10.66 (s, 1H), 11.55 (br s, 1H), 11.85 (br s, 1H), ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 126.8, 127.0, 128.6, 129.4, 141.8, 143.0, 149.2, 169.3; HPLC t_R = 1.51 min; ES-MS *m*/*z* 254 $(M - H)^-$; Anal. calcd. for $C_{13}H_9N_3O_3$: C, 61.18; H, 3.55; N, 16.46. Found: C, 60.44; H, 3.48; N, 16.47.

General procedure for chlorination of derivatives 4.

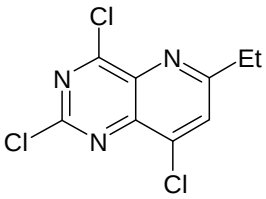
A suspension of derivative **4** (3.11 mmol; 1.00 equiv) in a mixture of phosphorus oxide chloride (15.00 mL) and *N*,*N*-diethylaniline (600.0 µl; 1.00 V) was refluxed for 16 hr . After 16 hr, the mixture was cooled down to room temperature and $POCl_3$ was removed under vacuo at 40 °C. The reaction mixture was then cooled down to 0 °C and ice was added. The precipitate formed was filtered, washed once with MeOH and dried under succion with diethyl ether. The residue was taken off with MeOH affording derivative **5** in moderate to good yield.



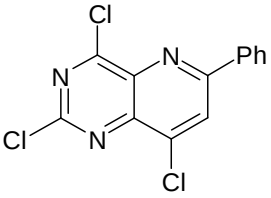
2,4,8-Trichloro-6-methyl-pyrido[3,2-*d*]pyrimidine **5a**. Brown powder. Yield=84%. mp 181-182 °C; IR *v*max 1724, 1249 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 4.12 (s, 3H), 8.69 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 52.9, 128.9, 139.2, 141.2, 143.9, 145.8, 147.1, 159.4, 163.5; HPLC t_R = 3.49 min; ES-MS *m*/*z* 292.81 $(M + H)^+$.



2,4,8-Trichloro-6-methyl-pyrido[3,2-*d*]pyrimidine **5b**. Pink powder. Yield = 78%. %. mp = 219 °C (decomp.); IR *v*max 1545, 1454, 1388, 1145, 795 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.83 (s, 3H), 7.85 (s, 1H), ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 25.5, 130.6, 137.2, 142.7, 145.2, 155.3, 162.7, 165.5, HPLC t_R = 3.55 min, ES-MS *m*/*z* 248.0 $(M + H)^+$; Anal. calcd. for $C_8H_4Cl_3N_3$: C, 38.67; H, 1.62; N, 16.91; Cl, 42.8. Found: C, 38.29; H, 1.70; N, 16.62; Cl, 42.52.



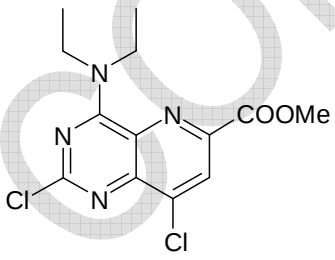
2,4,8-Trichloro-6-ethyl-pyrido[3,2-*d*]pyrimidine **5c**. Purple-brown powder. Yield = 63%. mp 113.5-114.5 °C; IR *v*max 1548, 1359, 794 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δH 1.46 (t, *J* = 7.4 Hz, 3H), 3.10 (q, *J* = 7.5 Hz, 2H), 7.88 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δC 10.1, 32.1, 129.7, 137.2, 142.7, 145.3, 155.2, 165.8, 167.4, HPLC t_R = 4.65 min, ES-MS *m*/*z* 263.8 $(M + H)^+$; Anal. calcd. for $C_9H_6Cl_3N_3$: C, 41.18; H, 2.30; N, 16.01; Cl, 40.51. Found: C, 41.33; H, 2.32; N, 15.82; Cl, 40.90.



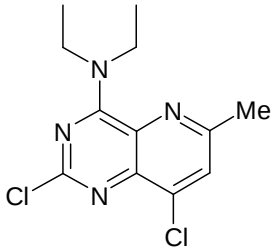
2,4,8-Trichloro-6-phenyl-pyrido[3,2-*d*]pyrimidine **5d**. Pale brown powder. Yield = 85%. mp > 300 °C; IR *v*max 3012, 2843, 1681, 1479, 1420 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 7.59-7.61 (m, 3H), 8.22-8.25 (m, 2H), 8.46 (s, 1H), ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 126.6, 127.2, 128.7, 130.9, 135.6, 137.0, 142.8, 144.8, 154.8, 158.8, 165.7, HPLC t_R = 5.13 min, ES-MS *m*/*z* 310.00 $(M + H)^+$; Anal. calcd. for $C_{13}H_6Cl_3N_3$: C, 50.28; H, 1.95; N, 13.53; Cl, 34.25. Found: C, 49.74; H, 2.07; N, 13.85; Cl, 34.12.

General procedure for S_NAr with diethylamine on derivatives 5.

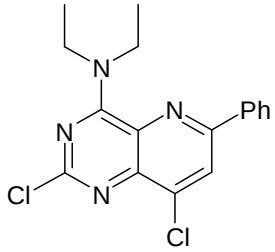
To a suspension of derivative **5** (1.61 mmol; 1.00 equiv) in ACN (20.00 mL) was added diethylamine (167.3 µl; 1.61 mmol; 1.00 equiv) in presence of Hünig base (832.3 µl; 4.83 mmol; 3.00 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 3 hr. Precipitates formed during the reaction were filtered and washed twice with MeOH and once with Et_2O affording derivatives **12** in yield ranging from 73 to 80%.



2,8-Dichloro-4-diethylamino-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **12a**. Brown powder. Yield = 73%. mp 128-129 °C; IR *v*max 2932, 1742, 1254 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.33 (t, *J* = 7 Hz, 3H), 1.44 (t, *J* = 7 Hz, 3H), 3.89 (q, *J* = 7 Hz, 2H), 4.01 (s, 3H), 4.34 (q, *J* = 7 Hz, 2H), 8.38 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 12.1, 14.2, 47.2, 47.4, 53.4, 127.9, 132.8, 142.3, 143.3, 148.0, 159.6, 160.4, 164.4; HPLC t_R = 4.83 min; ES-MS *m*/*z* 328.99 $(M + H)^+$; Anal. calcd. for $C_{13}H_{14}Cl_2N_4O_2$: C, 47.43; H, 4.29; N, 17.02. Found: C, 47.18; H, 4.29; N, 16.89.



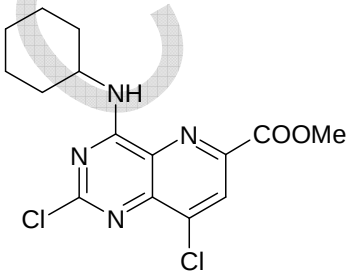
(2,8-Dichloro-6-methyl-pyrido[3,2-*d*]pyrimidin-4-yl)-diethyl-amine **12b**. Pale orange powder. Yield = 80%. mp 105.1-105.5 °C; IR *v*max 1487, 1337, 1146 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.35 (br s, 6H), 2.60 (s, 3H), 3.80 (br s, 2H), 4.29 (br s, 2H), 7.54 (s, 1H), ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 17.4, 18.7, 24.6, 46.4, 127.4, 132.6, 141.1, 144.5, 154.7, 157.2, 159.1, HPLC t_R = 5.04 min, ES-MS *m*/*z* 285.10 $(M + H)^+$; Anal. calcd. for $C_{12}H_{14}Cl_2N_4$: C, 50.54; H, 4.95; N, 19.65; Cl, 24.86. Found: C, 50..19; H, 4.69; N, 19.45; Cl, 24.99.



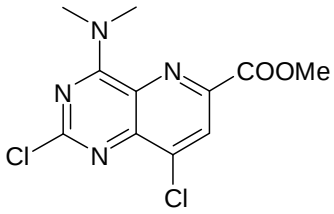
(2,8-Dichloro-6-phenyl-pyrido[3,2-*d*]pyrimidin-4-yl)-diethyl-amine **12c**. Pale yellow powder. Yield = 73%. mp 141.8-142.8 °C; IR *v*max 2361, 1531, 1475, 1436, 1336, 1149, 768 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.35 (br s, 3H), 1.47 (br s, 3H), 3.85 (br s, 2H), 4.48 (br s, 2H), 7.47-7.54 (m, 3H), 7.94-7.97 (m, 2H), 8.15 (s, 1H),^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 11.9, 14.4, 46.5, 124.5, 126.9, 129.1, 129.9, 133.1, 137.7, 142.1, 145.3, 153.4, 157.7, 159.2, HPLC t_R = 5.82 min, ES-MS *m*/*z* 347.1 $(M + H)^+$; Anal. calcd. for $C_{17}H_{16}Cl_2N_4$: C, 58.80; H, 4.64; N, 16.13; Cl, 20.42. Found: C, 58.84; H, 4.42; N, 15.87; Cl, 20.23.

General procedure for S_NAr with amines on 5a.

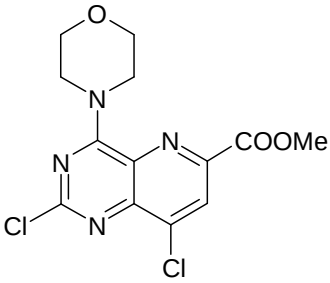
To a solution of methyl 2,4,8-trichloropyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester **5a** (0.17 mmol; 1.00 equiv) in ACN (250.0 µl) was added the amine dissolved in ACN (250.0 µl) in presence of Hünig base (88.4 µl; 0.51 mmol; 3.00 equiv) at 0 °C. Reaction mixture was stirred at 0 °C for 2 hr. ACN was removed under reduced pressure at 40 °C. The solid obtained was suspended in MeOH, filtered and dried under suction affording compounds **13a** to **13g**.



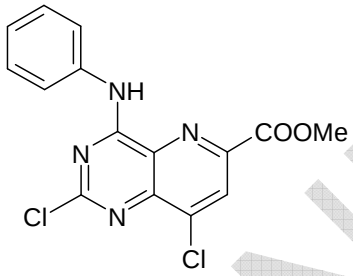
2,8-Dichloro-4-cyclohexylamino-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **13a**. Purple powder. Yield 77%. mp 205-206 °C (decomp.); IR *v*max 3548, 1725, 1231 cm-1; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 1.27 (m, 1H), 1.47 (m, 2H), 1.74 (m, 3H), 1.82 (m, 4H), 3.96 (s, 3H), 4.10 (m, 1H), 8.42 (s, 1H), 8.71 (d, *J* = 8Hz, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 25.2, 25.8, 32.8, 50.8, 53.7, 129.0, 131.4, 143.0, 145.1, 145.2, 160.3, 161.9, 164.2; HPLC t_R = 4.77 min; ES-MS *m*/*z* 355.27 $(M + H)^+$; Anal. calcd. for $C_{15}H_{16}Cl_2N_4O_2$: C, 50.72; H, 4.54; N, 15.77. Found: C, 50.38; H, 4.21; N, 15.39.



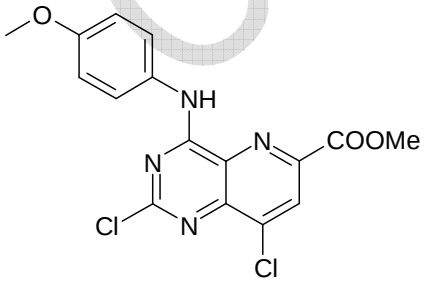
2,8-Dichloro-4-dimethylamino-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **13b**. Pink powder. Yield = 80%. mp 216-217 °C (decomp.); IR *v*max 1716, 1208 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 3.45 (s, 6H), 4.01 (s, 3H), 8.40 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 42.3, 43.3, 53.5, 128.0, 133.3, 142.5, 143.2, 147.9, 160.1, 160.7, 164.3; HPLC t_R = 3.81 min; ES-MS *m*/*z* 301.00 $(M + H)^+$; Anal. calcd. for $C_{11}H_{10}Cl_2N_4O_2$: C, 43.87; H, 3.35; N, 18.61. Found: C, 43.71; H, 3.34; N, 18.93.



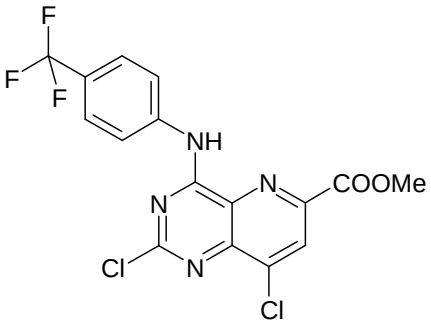
2,8-Dichloro-4-morpholin-4-yl-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **13c**. Purple powder. Yield = 82%. mp 212-213 °C (decomp.); IR *v*max 1738, 1246 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 3.88 (t, *J* = 5 Hz, 6H), 4.01 (s, 3H), 4.20 (br s, 2H), 5.09 (br s, 2H), 8.41 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 47.6, 50.6, 53.6, 67.5, 128.3, 132.2, 143.2, 143.3, 148.2, 159.7, 160.2, 164.0; HPLC t_R = 3.79 min; ES-MS *m*/*z* 343.23 $(M + H)^+$; Anal. calcd. for $C_{13}H_{12}Cl_2N_4O_3$: C, 45.50; H, 3.52; N, 16.33. Found: C, 45.24; H, 3.66; N, 16.13.



2,8-Dichloro-4-phenylamino-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **13d**. Brown powder. Yield = 82%. mp 223-224 °C (decomp.); IR *v*max 3338, 1731, 1574 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 4.07 (s, 3H), 7.24 (m, 1H), 7.45 (m , 2H), 7.90 (d, *J* = 8 Hz, 2H), 8.49 (s, 1H), 9.45 (br s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 53.8, 121.6, 126.0, 129.3, 129.6, 131.3, 137.0, 143.7, 145.3, 145.8, 158.5, 161.4, 163.9; HPLC t_R = 4.48 min; ES-MS *m*/*z* 349.19 $(M + H)^+$; Anal. calcd. for $C_{15}H_{10}Cl_2N_4O_2$: C, 51.60; H, 2.89; N, 16.05; Cl, 20.31. Found: C, 51.24; H, 2.76; N, 15.82; Cl, 19.95.



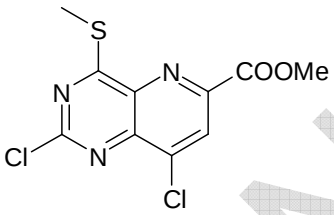
2,8-Dichloro-4-(4-methoxy-phenylamino)-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **13e**. Yellow powder. Yield = 80%. mp 231-232 °C (decomp.); IR *v*max 3333, 1729, 1574, 1248 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 3.85 (s, 3H), 4.07 (s, 3H), 6.98 (m, 2H), 7.79 (m, 2H), 8.48 (s, 1H), 9.36 (br s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 53.8, 55.9, 114.7, 123.3, 129.2, 130.1, 131.4, 143.5, 145.3, 145.6, 157.8, 158.2, 161.6, 164.0 ; HPLC t_R = 4.42 min; ES-MS *m*/*z* 379.22 $(M + H)^+$; Anal. calcd. for $C_{16}H_{12}Cl_2N_4O_3$: C, 50.68; H, 3.19; N, 14.77. Found: C, 51.03; H, 3.52; N, 14.48.



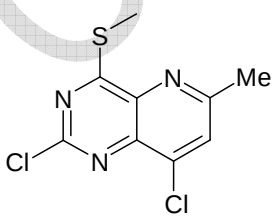
2,8-Dichloro-4-(4-trifluoromethyl-phenylamino)-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **13f**. Brown powder. Yield = 78%. mp 192-193 °C (decomp.); IR *v*max 1723, 1572, 1316, 1106 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 4.09 (s, 3H), 7.72 (d, *J* = 8.5 Hz, 2H), 8.08 (d, *J* = 8.5 Hz, 2H), 8.53 (s, 1H), 9.61 (br s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 53.9, 121.3, 124.2 (q, *J = 267.2 Hz*), 126.9 (q, *J = 3.7 Hz*), 127.5 (q, *J = 32 Hz*), 129.5, 131.1, 140.1, 144.1, 145.4, 146.2, 158.6, 161.1, 163.8; HPLC t_R = 5.23 min; ES-MS *m*/*z* 417.20 $(M + H)^+$; Anal. calcd. for $C_{16}H_9Cl_2F_3N_4O_2$: C, 46.07; H, 2.17; N, 13.43. Found: C, 45.72; H, 2.47; N, 13.34.

General procedure for S_NAr with NaSMe on derivatives 5.

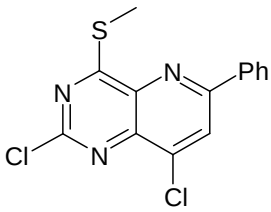
To a suspension of derivative **5** (0.32 mmol; 1.00 equiv) in DCM (2.00 mL) was added sodium thiomethoxide (0.32 mmol; 1.00 equiv) at -10 °C. Th e reaction was stirred at -10 °C for 3 hr. The precipitate formed during the reaction was then filtered and washed twice with MeOH and once with Et_2O affording derivatives **14** in good to excellent yields.



2,8-Dichloro-4-methylsulfanyl-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **14a**. Grey powder. Yield = 84%. mp 229-230 °C; IR *v*max 1720, 1248 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.64 (s, 3H), 4.00 (s, 3H), 8.50 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 13.7, 54.0, 129.5, 138.4, 144.0, 144.3, 147.7, 159.3, 164.0, 180.9; HPLC t_R = 4.10 min; ES-MS *m*/*z* 303.93 $(M + H)^+$; Anal. calcd. for $C_{10}H_7Cl_2N_3O_2S$: C, 39.49; H, 2.32; N, 13.82. Found: C, 39.19; H, 2.37; N, 13.71.



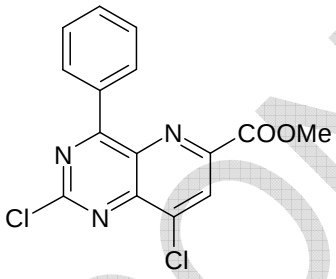
2,8-Dichloro-6-methyl-4-methylsulfanyl-pyrido[3,2-*d*]pyrimidine **14b**. White off powder. Yield = 84%. mp 145.5-146.5 °C; IR *v*max 1534, 1382, 1152, 799 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.67 (s, 3H), 2.75 (s, 3H), 7.72 (s, 1H),^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 13.2, 25.1, 129.7, 138.1, 141.1, 142.1, 156.4, 160.1, 178.1, HPLC t_R = 4.20 min, ES-MS *m*/*z* 260.00 $(M + H)^+$; Anal. calcd. for $C_9H_7Cl_2N_3S$: C, 41.55; H, 2.71; N, 16.15; Cl, 27.26. Found: C, 41.67; H, 2.82; N, 16.11; Cl, 27.10.



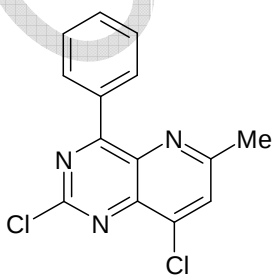
2,8-Dichloro-6-phenyl-4-methylsulfanyl-pyrido[3,2-*d*]pyrimidine **14c**.
Pale yellow powder. Yield = 85%. mp 186.6-187.6 °C; IR *v*max 1510, 1447, 1172, 803, 679 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δH 2.72 (s, 3H), 7.55-7.59 (m, 3H), 8.16-8.19 (m, 2H), 8.33 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 13.2, 126.2, 127.6, 129.2, 130.9, 136.5, 138.4, 141.5, 142.9, 156.7, 157.1, 179.0, HPLC t_R = 5.40 min, ES-MS *m*/*z* 322.0 $(M + H)^+$; Anal. calcd. for $C_{14}H_9N_2O_3S$: C, 52.19; H, 2.82; N, 13.04; Cl, 22.01. Found: C, 52.25; H, 2.78; N, 13.42; Cl, 21.97.

General procedure for Liebeskind-Sgrol cross-coupling reaction on derivatives 14.

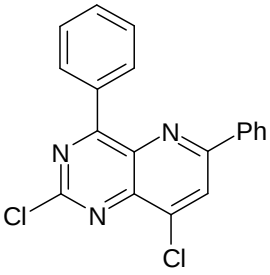
In a degassed solution of derivative **14** (0.78 mmol; 1.00 equiv) in dioxane (4.00 mL) was added a boronic acid (1.55 mmol; 2.00 equiv), copper(I) thiophene-2-carboxylate (1.55 mmol; 2.00 equiv) and tetrakis(triphenylphosphine)palladium (0) (0.04 mmol; 0.05 equiv). The reaction was heated under MW irradiation at 100 °C for 1.5 hr. After filtration through Celite®, the residue was extracted with DCM and $NaHCO_3$. Combined organic layers were washing with brine, and dried over Na_2SO_4. After having removed solvents under vacuum at 40 °C, the solid obtained was suspended in MeOH, filtered and dried under suction to afford derivatives **15a-c** in good yields.



2,8-Dichloro-4-phenyl-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **15a**. Brown powder. Yield = 79%. mp 230-231 °C; IR *v*max 1712, 1524, 1246 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 4.08 (s, 3H), 7.57-7.65 (m, 3H), 8.59-8.62 (m, 2H), 8.64 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 53.8, 128.5, 128.7, 132.8, 132.7, 134.2, 137.8, 144.6, 147.8, 148.5, 160.2, 164.0, 170.6; HPLC t_R = 4.75 min; ES-MS *m*/*z* 333.94 $(M + H)^+$; Anal. calcd. for $C_{15}H_9Cl_2N_3O_2$: C, 53.92; H, 2.71; N, 12.57. Found: C, 53.65; H, 2.93; N, 12.23.

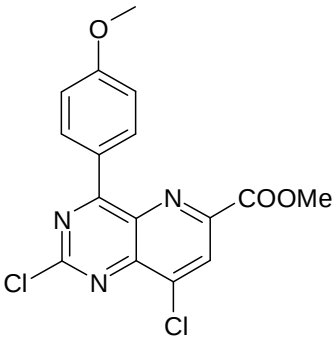


2,8-Dichloro-6-methyl-4-phenyl-pyrido[3,2-*d*]pyrimidine **15b**.
Pale yellow powder. Yield = 81%. mp 158.5-159.5 °C; IR *v*max 1524, 1329, 1150 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.78 (s, 3H), 7.55-7.60 (m, 3H), 7.79 (s, 1H), 8.42-8.45 (m, 2H),^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 25.5, 128.3, 129.1, 131.8, 132.3, 134.7, 137.8, 142.5, 145.9, 157.3, 160.8, 169.1, HPLC t_R = 4.75 min, ES-MS *m*/*z* 290.00 $(M + H)^+$; $)^+$; Anal. calcd. for $C_{14}H_9Cl_2N_3$: C, 57.95; H, 3.13; N, 14.48; Cl, 24.44. Found: C, 56.58; H, 3.11; N, 14.23; Cl, 24.09.

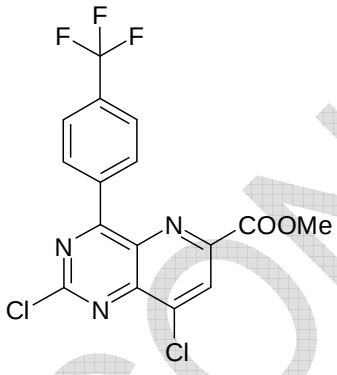


2,8-Dichloro-6-phenyl-4-phenyl-pyrido[3,2-*d*]pyrimidine **15c.** Pale beige

powder. Yield = 78%. mp 158 °C (decomp.); IR *v*max 2361, 2341, 1461, 774, 686 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δH 7.54-7.62 (m, 6H), 8.13 (br s, 2H), 8.41 (s, 1H), 8.50 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 125.7, 127.7, 128.3, 129.3, 131.0, 131.8, 132.4, 134.8, 136.8, 138.1, 143.4, 146.2, 157.6, 158.0, 169.8, HPLC t_R = 5.56 min, ES-MS *m*/*z* 352.0 $(M + H)^+$. Anal. calcd. for $C_{19}H_{11}Cl_2N_3$: C, 64.79; H, 3.15; N, 11.93; Cl, 20.13. Found: C, 64.34; H, 3.15; N, 11.85; Cl, 19.92.



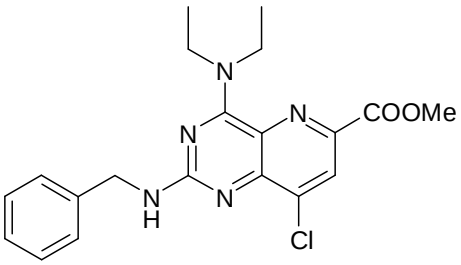
2,8-Dichloro-4-(4-methoxy-phenyl)-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **15d**. Brown powder. Yield = 82%. mp 247-248 °C; IR *v*max 1723, 1251 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 3.94 (s, 3H), 4.09 (s, 3H), 7.09 (d, *J* = 9 Hz, 2H), 8.60 (s, 1H), 8.79 (d, *J* = 9 Hz, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 54.0, 55.9, 114.5, 127.1, 128.5, 135.4, 138.0, 144.6, 148.0, 148.1, 160.4, 164.1, 164.3, 169.4; HPLC t_R = 4.87 min; ES-MS *m*/*z* 363.93 $(M + H)^+$; Anal. calcd. for $C_{16}H_{11}Cl_2N_3O_3$: C, 52.77; H, 3.04; N, 11.54. Found: C, 52.38; H, 3.16; N, 11.19.



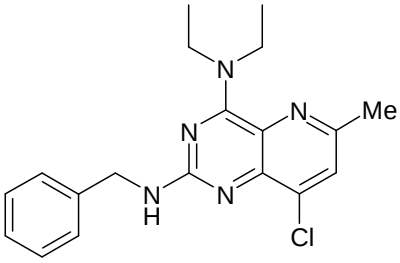
2,8-Dichloro-4-(4-trifluoromethyl-phenyl)-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **15e**. Pink powder. Yield = 77%. mp 183-184 °C; IR *v*max 1731, 1320 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 4.09 (s, 3H), 7.79 (d, *J* = 8 Hz, 2H), 8.60 (s, 1H), 8.65 (d, *J* = 8 Hz, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 53.9, 124.0 (q, *J* = *31.2 Hz*), 125.5 (q, *J* = *3.6 Hz*), 128.8, 133.0, 133.9 (q, *J* = *278.9 Hz*), 137.3, 137.6, 145.0, 148.0, 148.9, 160.2, 163.8, 169.2; HPLC t_R = 5.31 min; ES-MS *m*/*z* 401.94 $(M + H)^+$; Anal. calcd. for $C_{16}H_8Cl_2F_3N_3O_2$: C, 47.79; H, 2.00; N, 10.45. Found: C, 47.94; H, 2.24; N, 10.13.

General procedure for S_NAr with benzylamine on derivative 12.

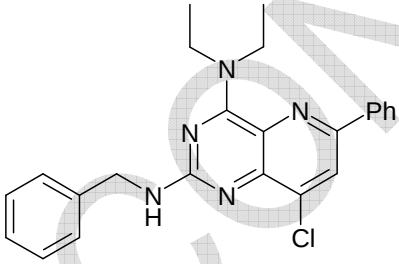
In a suspension of derivative **12** (0.29 mmol; 1.00 equiv) in ACN (1.00 mL) was added benzylamine (2.32 mmol; 8.00 equiv) followed by Hünig base (98.6 µl; 0.58 mmol; 2.00 equiv). The reaction mixture was stirred at 90 °C for 24 to 72 hr. After having removed solvents, the solid obtained was suspended in Et_2O, filtered and dried under suction to afford derivatives **23a-c**.



2-Benzylamino-8-chloro-4-diethylamino-pyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester **23a**. Pale yellow powder. Yield = 82%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.18 (t, *J* = *6.2 Hz*, 3H), 1.45 (t, *J* = *6.5 Hz*, 3H), 3.73 (q, *J* = *6.6 Hz*, 2H), 3.97 (s, 3H), 4.39 (q, *J* = *6.8 Hz*, 2H), 4.68 (br s, 2H), 7.24-7.33 (m, 5H), 8.23 (s, 1H), 8.77 (br s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 11.8, 14.2, 45.7, 46.3, 52.5, 127.0, 127.1, 127.7, 128.0, 128.4, 128.8, 137.3, 139.5, 148.9, 159.2, 160.1, 165.0, HPLC t_R = 3.90 min, ES-MS *m*/*z* 366.30 $(M + H)^+$; Anal. calcd. for $C_{20}H_{22}ClN_5O_2$: C, 60.07; H, 5.55; N, 17.51; Cl, 8.87. Found: C, 59.73; H, 5.39; N, 17.19; Cl, 8.68.



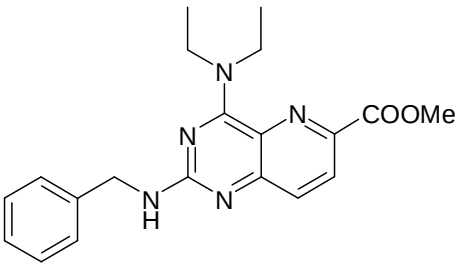
2-Benzyl-8-chloro-4-diethyl-6-methyl-pyrido[3,2-*d*]pyrimidine-2,4-diamine **23b**. Pale yellow powder. Yield = 61%. mp 88.8-88.9 °C. IR *v*max 1633, 1535, 1353, 698 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.29 (t, *J* = 6.8 Hz, 6H), 2.54 (s, 3H), 3.98 (br s, 4H), 4.71 (d, *J* = 4.7 Hz, 2H), 5.53 (br s, 1H), 7.28-7.34 (m, 3H), 7.40 (s, 1H), 7.43 (m, 2H), ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 13.2, 24.1, 45.8, 126.5, 126.9, 127.5, 128.4, 130,9, 138.3, 140.2, 145.2, 148.7, 158.8, 159.0, HPLC t_R = 3.98 min, ES-MS *m*/*z* 356.2 $(M + H)^+$; Anal. calcd. for $C_{19}H_{22}ClN_5$: C, 64.13; H, 6.23; N, 19.68; Cl, 9.96. Found: C, 63.96; H, 6.27; N, 19.57; Cl, 10.05.



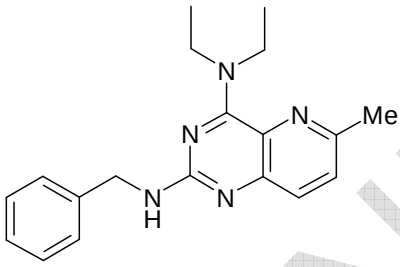
2-Benzyl-8-chloro-4-diethyl-6-phenyl-pyrido[3,2-*d*]pyrimidine-2,4-diamine **23c**. Yellow powder. Yield = 82%. mp 69.2-70.2 °C; IR *v*max 1531, 1433, 1335, 797, 691 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δH 1.26 (br s, 3H), 1.39 (br s, 3H), 3.76 (br s, 2H), 4.41 (br s, 2H), 4.71 (d, *J* = 5.9 Hz, 2H), 7.30-7.35 (m, 3H), 7.39-7.51 (m, 5H), 7.88-7.91 (m, 2H), 8.04 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 17.2, 45.3, 45.9, 46.7, 47.2, 126.6, 126.8, 126.9, 127.0, 127.4, 127.8, 127.9, 128.3, 128.4, 128.5, 128.6, 128.7, 128.9, 129.2, 129.3, 134.9, 135.2, 136.1, 163.6, HPLC t_R = 4.45 min, ES-MS *m*/*z* 418.2 $(M + H)^+$; Anal. calcd. for $C_{24}H_{24}ClN_5$: C, 68.97; H, 5.79; N, 16.76; Cl, 8.48. Found: C, 68.82; H, 5.69; N, 16.60; Cl, 8.57.

General procedure for chlorine reduction on derivatives 23.

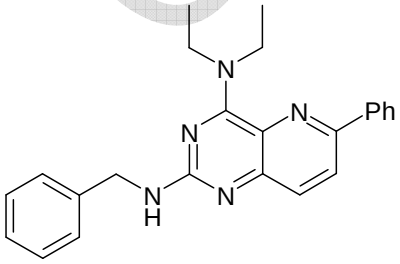
A solution of derivative **23** (1.00 equiv) in AcOEt (C=0.007 to 0.013M) or MeOH (C=0.02M) was passed through the 10% Pd/C cartridge at 70 °C with a flow of 0.7 mL/min at 7-10 bars. Complete conversion was observed after one run. After having removed solvents, the solid obtained was suspended in MeOH, filtered and dried under suction to afford derivatives **24a** to **24c**.



2-Benzylamino-4-diethylamino-pyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester **24a**. Yellow powder. Yield = 73%. mp 102.5-103.5 °C; IR *v*max 1535, 1337 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.18 (t, *J* = *6.2 Hz*, 3H), 1.45 (t, *J* = *6.5 Hz*, 3H), 3.73 (q, *J* = *6.6 Hz*, 2H), 3.97 (s, 3H), 4.39 (q, *J* = *6.8 Hz*, 2H), 4.68 (br s, 2H), 7.24-7.33 (m, 5H), 8.00 (d, *J* = *8.1 Hz*, 1H), 8.28 (d, *J* = *8.2 Hz*, 1H), 8.77 (br s, 1H), ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 11.4, 43.9, 44.4, 15.2, 45.6, 52.4, 126.5, 126.7, 127.9, 128.1, 128.2, 136.2, 140.7, 147.7, 148.6, 158.4, 159.7, 164.1; HPLC t_R = 3.90 min, ES-MS *m*/*z* 366.30 $(M + H)^+$.



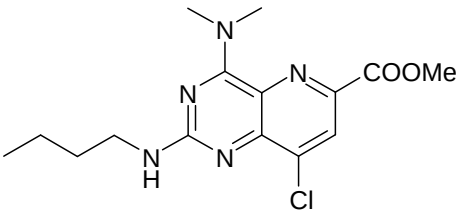
2-Benzyl-4-diethyl-6-methyl-pyrido[3,2-*d*]pyrimidine-2,4-diamine **24b**. Pale yellow powder. Yield = 84%. mp 176.0-177.0 °C; IR *v*max 3297, 2927, 1633, 1551, 1353, 694 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.08 (br s, 3H), 1.34 (br s, 3H), 2.56 (s, 3H), 3.69 (br s, 2H), 4.31 (br s, 2H), 4.64 (br s, 2H), 7.27-7.28 (m, 1H), 7.32-7.37 (m, 4H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 8.60 (br s, 1H), ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 11.4, 13.9, 23.9, 44.2, 46.3, 46.5, 125.7, 126.8, 127.0, 127.2, 128.4, 128.9, 135.6, 138.7, 150.9, 153.6, 157.2, HPLC t_R = 3.98 min, ES-MS *m*/*z* 322.20 $(M + H)^+$; Anal. calcd. for $C_{19}H_{23}N_5$: C, 71.00; H, 7.21; N, 21.79. Found: C, 70.87; H, 7.25; N, 21.42.



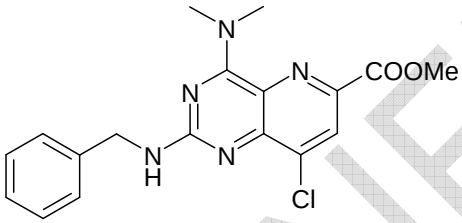
2-Benzyl-4-diethyl-6-phenyl-pyrido[3,2-d]pyrimidine-2,4-diamine **24c**. Pale yellow powder. Yield = 85%. mp 268.9-269.9 °C; IR *v*max 3245, 1638, 1555, 1020, 699 cm-1; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 1.11 (t, *J* = 7.3 Hz, 3H), 1.42 (t, *J* = 6.2 Hz, 3H), 3.75 (q, *J* = 6.7 Hz, 2H), 4.47 (q, *J* = 6.0 Hz, 2H), 4.69 (br s, 2H), 7.30-7.34 (m, 3H), 7.42-7.56 (m, 3H), 7.88-7.92 (m, 2H), 8.01-8.07 (m, 2H), 8.04 (d, *J* = 8.3 Hz, 1H), 8.39 (d, *J* = 8.7 Hz, 1H), 8.72 (br s, 1H), ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 11.8, 14.4, 45.3, 46.9, 47.5, 125.9, 126.8, 127.0, 127.5, 128.1, 128.4, 128.8, 129.1, 129.7, 129.8, 130.1, 133.3, 136.5, 137.7, 137.8, 151.9, 153.1, 157.9, 169.8; HPLC t_R = 4.49 min, ES-MS *m*/*z* 384.3 $(M + H)^+$.

General procedure for S_NAr with amines on scaffold 13b.

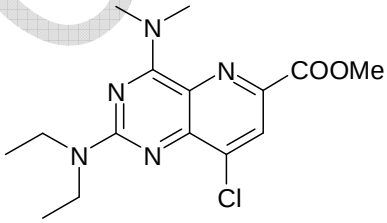
To a solution of derivative **13b** (1.00 equiv) in a mixture of ACN (1.00 mL) and DMF (1.00 mL) was added an amine (1.00 equiv) in presence of Hünig base (3.00 equiv). The reaction mixture was stirred at 90 °C for 3 hr. Solvents wer e further removed under vacuum at 40 °C. The solid obtained was suspended in MeOH, filtered and dried under suction to afford derivatives **25a**-**c** in good yields.



2-Butylamino-8-chloro-4-dimethylamino-pyrido[3,2-*d*] pyrimidine-6-carboxylic acid methyl ester **25a**.Yellow powder. Yield = 71%. IR *v*max 3400, 1697, 1537 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 0.96 (t, *J* = 7, 3H), 1.43 (q, *J* = 7, 2H), 1.59 (br m, 2H), 3.51 (br s, 8H), 3.96 (s, 3H), 5.30 (br s, 1H), 8.23 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 14.2, 20.5, 32.3, 41.8, 42.3, 53.0, 127.6, 137.3, 142.9, 143.4, 149.2, 160.3, 160.8, 165.3; HPLC t_R = 3.08 min; ES-MS *m*/*z* 338.38 $(M + H)^+$; Anal. calcd. for $C_{15}H_{20}ClN_5O_2$: C, 53.33; H, 5.97; N, 20.73. Found: C, 53.64 H, 5.59; N, 20.51.



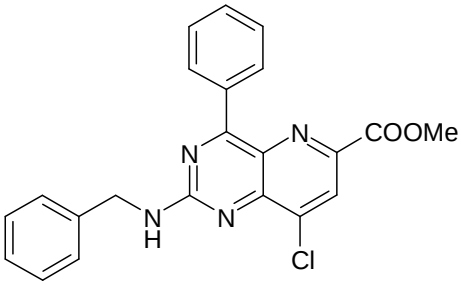
2-Benzylamino-8-chloro-4-dimethylamino-pyrido[3,2-*d*] pyrimidine-6-carboxylic acid methyl ester **25b**. Yellow powder. Yield = 64%. mp 157-158 °C; IR *v*max 3381, 1699, 1534 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 3.33-3.84 (br s, 6H), 3.96 (s, 3H), 4.71 (br s, 2H), 5.77 (br s, 1H), 7.25-7.38 (m, 5H), 8.24 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 42.1, 46.8, 53.3, 124.1, 127.7, 127.9, 129.1, 131.6, 133.5, 137.8, 139.6, 156.9, 159.9, 160.7, 168.5;HPLC t_R = 3.05 min; ES-MS *m*/*z* 372.04 $(M + H)^+$; Anal. calcd. for $C_{18}H_{18}ClN_5O_2$: C, 58.15; H, 4.88; N, 18.83. Found: C, 57.70; H, 5.05; N, 18.90.



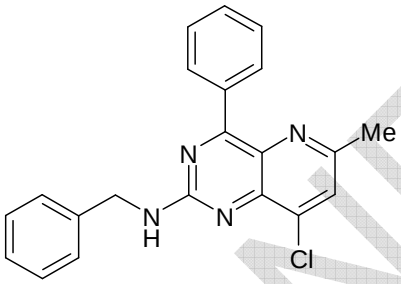
2-Diethylamino-8-chloro-4-dimethylamino-pyrido[3,2-*d*] pyrimidine-6-carboxylic acid methyl ester **25c**. Yellow powder. Yield = 47%. mp 119-120 °C; IR *v*max 1711, 1537 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.24 (s, 6H), 3.71-3.95 (br m, 13H), 8.20 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 13.62, 41.93, 42.50, 52.93, 127.33, 130.96, 136.58, 138.75, 149.39, 158.67, 160.54, 165.47; HPLC t_R = 3.07 min; ES-MS *m*/*z* 338.39 $(M + H)^+$; Anal. calcd. for $C_{15}H_{20}ClN_5O_2$: C, 53.33; H, 5.97; N, 20.73. Found: C, 53.25; H, 5.93; N, 20.47.

General procedure for S_NAr with benzylamine on derivatives 15.

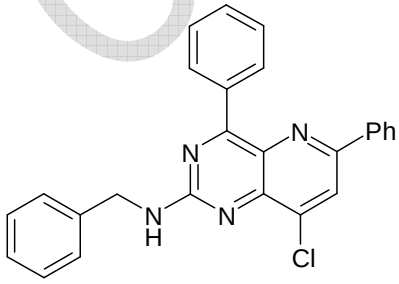
To a solution of derivative **15** (0.21 mmol; 1.00 equiv) in ACN (1.00 mL) was added benzylamine (2.1 mmol; 10.00 equiv) in presence of Hünig base (106.9 µl; 0.62 mmol; 3.00 equiv). The reaction mixture was heated at 90 °C for 0.5 hr under MW irradiation. After having removed solvents under vacuum at 40 °C, the solid obtained was suspended in MeOH, filtered and dried under suction to afford derivatives **26a** to **26c** in good yields.



2-Benzylamino-8-chloro-4-phenyl-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **26a**. Yellow powder. Yield = 83%. mp 200-201 °C; IR *v*max 3374, 1706, 1551 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 3.99 (s, 3H), 4.85 (br s, 2H), 6.10 (br s, 1H), 7.24-7.53 (m, 8H), 8.38-8.41 (m, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 46.5, 53.5, 128.0, 128.2, 128.6, 128.7, 129.1, 131.7, 132.1, 132.5, 135.7, 138.7, 141.6, 142.5, 148.4, 159.9, 165.1, 169.6; HPLC t_R = 5.34 min; ES-MS *m*/*z* 405.03 $(M + H)^+$; Anal. calcd. for $C_{22}H_{17}ClN_4O_2$: C, 65.27; H, 4.23; N, 13.84. Found: C, 65.29; H, 4.27; N, 13.46.



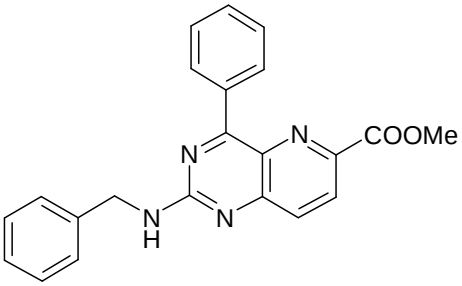
Benzyl-(8-chloro-6-methyl-4-phenyl-pyrido[3,2-d]pyrimidin-2-yl)-amine **26b**. White off powder. Yield = 71%. mp 127.2-128.2 °C; IR *v*max 1556, 1450, 1355 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.63 (s, 3H), 4.82 (d, *J* = 5.70 Hz, 2H), 5.86 (br s, 1H), 7.28-7.39 (m, 3H), 7.46-7.52 (m, 5H), 7.58 (s, 1H), 8.29 (br s, 2H), ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 24.8, 46.0, 127.4, 127.9, 128.0, 128.1, 128.6, 130.6, 131.6, 131.7, 134.2, 135.4, 136.2, 139.0, 154.0, 158.6, 167.8, HPLC t_R = 5.82 min, ES-MS *m*/*z* 361.10 $(M + H)^+$; Anal. calcd. for $C_{21}H_{17}ClN_4$: C, 69.90; H, 4.75; N, 15.53; Cl, 9.82. Found: C, 69.83; H, 4.78; N, 15.47; Cl, 9.77.



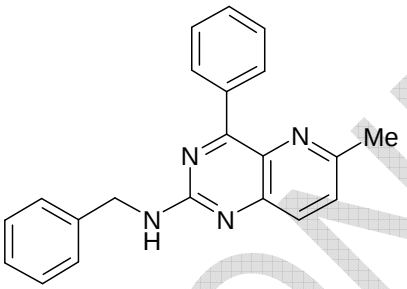
Benzyl-(8-chloro-6-phenyl-4-phenyl-pyrido[3,2-d]pyrimidin-2-yl)-amine **26c**. White off powder. Yield = 69%. mp 126.2-127.2 °C; IR *v*max 1556, 1450, 1355 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 4.87 (d, J = 5.1 Hz, 2H), 5.94 (br s, 1H), 7.26-7.39 (m, 5H), 7.47-7.49 (m, 3H), 7.56 (m, 3H), 8.05 (d, *J* = 8.9 Hz, 2H), 8.20 (s, 1H), 8.34 (br s, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 46.1, 124.7, 126.9, 127.4, 127.9, 128.2, 128.6, 129.0, 129.5, 130.0, 130.6, 131.7, 131.8, 134.3, 136.3, 137.9, 138.9, 151.9, 160.4, 166.1, HPLC t_R = 6.01 min, ES-MS *m*/*z* 423.230 $(M + H)^+$; Anal. calcd. for $C_{26}H_{19}ClN_4$: C, 73.84; H, 4.53; N, 13.25; Cl, 8.38. Found: C, 73.43; H, 4.56; N, 12.96; Cl, 8.32.

General procedure for chlorine reduction on derivatives 26.

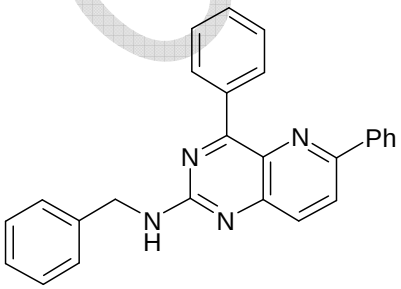
A solution of derivative **26** (1.00 equiv) in a mixture of MeOH and AcOEt (1:1) (C=0.022M) was passed through the 10% Pd/C cartridge at 70 °C with a flow of 0.4 mL/min at 7-10 bars. A mixture of desired derivative **27** and over-reduced compound was obtained. After evaporation of the solvents, the residue was dissolved in DCE (3 mL) and MnO_2 (20 equiv) was added. The reaction mixture was heated under MW irradiation at 100 °C for 15 min. After evaporation of the solvent under vacuum at 40 °C, the residue was dissolved in a minimum mixture of ACN/DMSO (1:1) and purified by MDAP® system affording derivatives **27a** to **27c** in good yields.



2-Benzylamino-4-phenyl-pyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester **27a**. Pale yellow powder. Yield = 73%. mp 151.4-152.4 °C; IR *v*max 1715, 1591, 1291; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 3.89 (s, 3H), 4.69 (d, *J* = 6.1 Hz, 2H), 7.21-7.44 (m, 5H), 7.56-7.60 (m, 3H), 8.00 (d, *J* = 8.9 Hz, 1H), 8.23 (d, *J* = 8.9 Hz, 1H), 8.30-8.32 (m, 2H), 8.67 (t, *J* = 6.0 Hz, 1H); ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 44.1, 52.5, 126.7, 127.2, 127.3, 127.8, 127.9, 128.3, 130.7, 131.2, 132.8, 134.4, 139.5, 142.0, 159.5, 164.6; HPLC t_R = 4.75 min, ES-MS *m*/*z* 371.0 $(M + H)^+$.



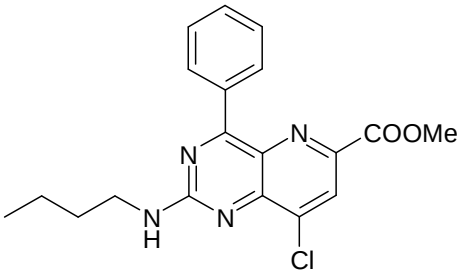
Benzyl-(6-methyl-4-phenyl-pyrido[3,2-*d*]pyrimidin-2-yl)-amine **27b**. Pale yellow powder. Yield = 75%. IR *v*max 3253, 1591, 1352, 685 cm-1; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 2.56 (s, 3H), 4.64 (d, *J* = 6.2 Hz, 2H), 7.19-7.24 (m, 1H), 7.28-7.34 (m, 2H), 7.39-7.41 (m, 2H), 7.52-7.56 (m, 3H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 1H), 8.10 (br s, 1H), 8.19-8.22 (m, 2H), ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 24.4, 44.2, 126.5, 127.2, 127.6, 128.2, 128.9, 130.0, 131.0, 133.6, 133.8, 136.4, 140.2, 152.6, 154.0, 158.6; HPLC t_R = 4.37 min, ES-MS *m*/*z* 327.09 $(M + H)^+$.



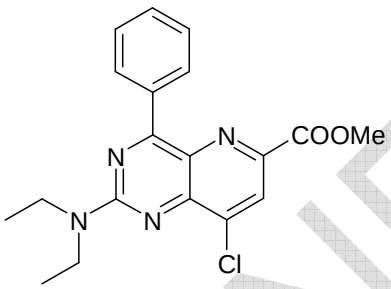
Benzyl-(4,6-diphenyl-pyrido[3,2-*d*]pyrimidin-2-yl)-amine **27c**. Pale yellow powder. Yield = 71%. mp 119.0-120.0 °C; IR *v*max 3255, 1592, 1537, 1454, 693 cm-1; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 4.69 (d, *J* = 6.1 Hz, 2H), 7.22-7.25 (m, 1H), 7.30-7.35 (m, 2H), 7.41-7.54 (m, 5H), 7.58-7.60 (m, 3H), 7.99 (d, *J* = 8.9 Hz, 1H), 8.12-8.15 (m, 2H), 8.26-8.30 (m, 3H), 8.33 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C125.3, 126.6, 127.3, 127.7, 127.8, 128.2, 128.9, 129.2, 130.2, 130.3, 131.1, 134.3, 134.6, 136.2, 138.1, 138.2, 148.7, 151.2, 160.3; HPLC t_R = 4.62 min, ES-MS *m*/*z* 389.20 $(M + H)^+$.

General procedure for S_NAr with amines on derivative 15a.

To a solution of derivative **15a** (1.00 equiv) in ACN (40 V) was added an amine (1.00 equiv) in presence of Hünig base (3.00 equiv). The reaction was heated at 90 °C for 1.5 hr. After having removed solvents under vacuum at 40 °C, the solid obtained was suspended in MeOH, filtered and dried under suction to afford derivatives **28a** and **28b**.



2-Butylamino-8-chloro-4-phenyl-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **28a**. Yellow powder. Yield = 81%. mp 183-184 °C; IR *v*max 3382, 1704, 1556 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 0.99 (t, *J* = 7 Hz, 3H), 1.48 (q, *J* = 7 Hz, 2H), 1.71 (m, 2H), 3.68 (m, 2H), 3.99 (s, 3H), 7.55 (m, 3H), 8.45 (m, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 14.0, 20.3, 31.5, 41.8, 53.2, 128.0, 128.3, 129.6, 131.4, 132.0, 135.6, 141.2, 141.9, 148.2, 159.9, 164.9, 169.2; HPLC t_R = 5.60 min; ES-MS *m*/*z* 370.93 $(M + H)^+$; Anal. calcd. for $C_{19}H_{19}ClN_4O_2$: C, 61.54; H, 5.16; N, 15.11; Cl, 9.56. Found: C, 61.57; H, 5.00; N, 14.72; Cl, 9.58.



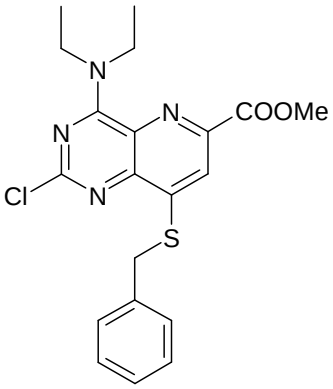
2-Diethylamino-8-chloro-4-phenyl-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **28b**. Yellow powder. Yield = 85%. mp 123-124 °C; IR *v*max 1717, 1520, 1335 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.33 (br s, 6H), 3.88 (q, *J* = 7 Hz, 4H), 4.08 (s, 3H), 7.53 (d, *J* = 2 Hz, 3H), 8.38 (s, 1H), 7.53 (d, *J* = 2 Hz, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 12.9, 14.0, 43.1, 53.3, 127.8, 128.5, 131.4, 132.2, 134.7, 136.5, 141.0, 141.3, 148.9, 158.8, 165.3, 168.2; HPLC t_R = 6.10 min; ES-MS *m*/*z* 371.07 $(M + H)^+$; Anal. calcd. for $C_{19}H_{19}ClN_4O_2$: C, 61.54; H, 5.16; N, 15.11. Found: C, 61.25; H, 5.18; N, 14.76.

General procedure for S_NAr of thiols and thiolates on derivative 12a-c in DMF.

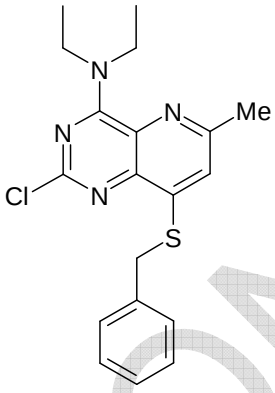
To a solution of methyl 2,8-dichloro-4-(diethylamino)pyrido[3,2-*d*]pyrimidines **12** (0.46 mmol; 1.00 equiv) in DMF (4.00 mL) was added benzylthiol (1.00 equiv) in presence of Hünig base (1.37 mmol; 3.00 equiv) at 0 °C for 16 hr. The precipitate formed during the reaction was filtered and purified using MDAP® to isolate the regioisomers. Derivatives **29a-d** were obtained in yield ranging from 17 to 61%.

General procedure for S_NAr of thiols and thiolates on derivative 12a in ^{i}PrOH.

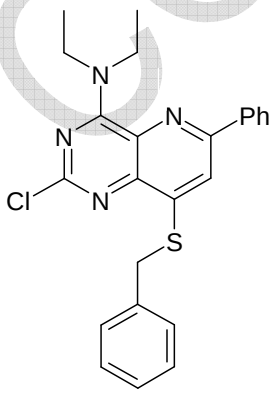
To a solution of 2,8-dichloro-N,N-diethylamine-pyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester **12a** (0.18 mmol; 1.00 equiv) in ^{i}PrOH (5.4 mL) was added the thiol (0.18 mmol; 1.00 equiv) at 90 °C. After 16 hr at reflux, solven t were removed under vacuo at 40 °C and the resulted residue was dissolved in a mixture of ACN and DMSO in order to be purified MDAP®. Derivatives **29**, **30** and **31** were obtained in moderate to good yields.



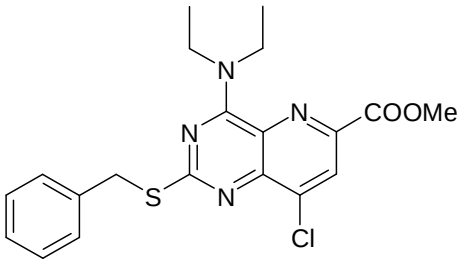
8-Benzylsulfanyl-2-chloro-4-diethylamino-pyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester **29a**. White off powder. Yield = 65 %. mp 101.4-102.4 °C; IR *v*max 1504, 1346, 1248, 1128 cm-1; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 1.26 (m, 3H), 1.36 (m, 3H), 3.74 (m, 2H), 3.91 (s, 3H), 4.32 (m, 2H), 4.42 (s, 2H), 7.29-7.39 (m, 3H), 7.50-7.52 (m, 2H), 8.13 (s, 1H), ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 11.6, 13.9, 33.9, 45.9, 46.3, 52.9, 120.7, 127.6, 128.7, 129.0, 129.4, 135.6, 142.6, 146.5, 148.8, 156.8, 158.9, 164.3, HPLC t_R = 6.17 min, ES-MS *m*/*z* 417.3 $(M + H)^+$. Anal. calcd. for $C_{20}H_{21}ClN_4O_2S$: C, 57.62; H, 5.08; N, 13.44; Cl, 8.50. Found: C, 57.42; H, 5.17; N, 13.34; Cl, 8.46.



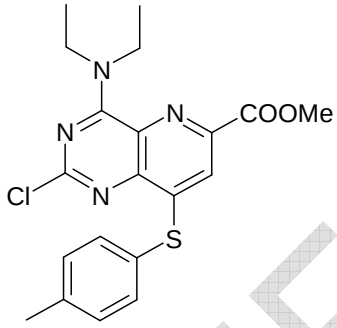
(8-Benzylsulfanyl-2-chloro-6-methyl-pyrido[3,2-d]pyrimidin-4-yl)-diethyl-amine **29b**. White off powder. Yield = 76%. mp 183.4-184.4 °C; IR *v*max 2927, 1651, 1453, 731 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.32 (t, *J* = 6.8 Hz, 6H), 2.53 (s, 3H), 3.95 (br s, 4H), 4.18 (s, 2H), 7.15 (s, 1H), 7.26-7.35 (m, 3H), 7.42-7.46 (m, 2H),^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 13,5, 25.0, 35.4, 46.1, 120.6, 127.6, 128.7, 129.0, 130.1, 135.3, 144.7, 147.8, 154.2, 155.5, 159.2, HPLC t_R = 5.99 min, ES-MS *m*/*z* 373.10 $(M + H)^+$; Anal. calcd. for $C_{19}H_{21}ClN_4S$: C, 61.20; H, 5.68; N, 15.02; Cl, 9.51. Found: C, 60.91; H, 5.79; N, 14.87; Cl, 9.69.



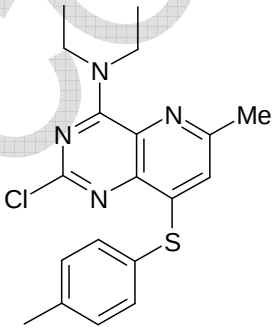
(8-Benzylsulfanyl-2-chloro-6-phenyl-pyrido[3,2-d]pyrimidin-4-yl)-diethyl-amine **29c**. Pale yellow powder. Yield = 61%. mp 175.2-176.2 °C; IR *v*max 1495, 1470, 1154, 693 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δH 1.39 (br s, 6H), 3.83 (br s, 2H), 4.30 (s, 2H), 4.48 (br s, 2H), 7.29-7.39 (m, 3H), 7.43-7.53 (m, 5H), 7.74 (s, 1H), 7.83-7.85 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 12.0, 14.2, 35.5, 46.2, 118.1, 127.0, 127.7, 128.8, 128.9, 129.0, 129.3, 130.5, 135.3, 139.0, 145.5, 148.5, 152.9, 156.0, 159.3, HPLC t_R = 6.37 min, ES-MS *m*/*z* 435.10 $(M + H)^+$; Anal. calcd. for $C_{24}H_{23}ClN_4S$: C, 66.27; H, 5.33; N, 12.88; Cl, 8.15. Found: C, 65.99; H, 5.12; N, 12.55; Cl, 7.90.



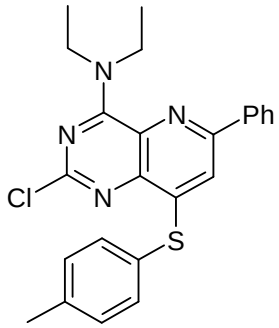
2-Benzylsulfanyl-8-chloro-4-diethylamino-pyrido[3,2-d] pyrimidine-6-carboxylic acid methyl ester **29d**. White off powder. Yield = 17%. mp 118.3-119.3 °C; IR *v*max 1713, 1440, 1352 cm-1; ^{1}H NMR (300 MHz, DMSO-*d6*), δH 1.22 (m, 3H), 1.36 (m, 3H), 3.75 (m, 2H), 3.92 (s, 3H), 4.27 (m, 2H), 4.48 (m, 2H), 7.23-7.34 (m, 3H), 7.48-7.51 (m, 2H), 8.36 (s, 1H); ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 11.6, 13.9, 34.6, 45.7, 46.3, 52.8, 126.9, 127.1, 128.4, 128.8, 131.6, 138.3, 139.7, 141.2, 145.7, 156.9, 163.6, 169.4, HPLC t_R = 6.13 min, ES-MS *m*/*z* 417.3 $(M + H)^+$. Anal. calcd. for $C_{20}H_{21}ClN_4O_2S$: C, 57.62; H, 5.08; N, 13.44; Cl, 8.50. Found: C, 57.85; H, 5.09; N, 13.43; Cl, 8.48.



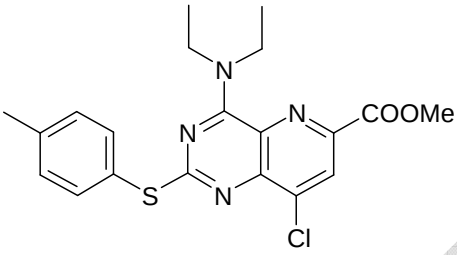
2-Chloro-4-diethylamino-8-p-tolylsulfanyl-pyrido[3,2-d] pyrimidine-6-carboxylic acid methyl ester **30a**. Pale yellow powder. Yield = 59%. mp 195.2-196.2 °C; IR *v*max 2940, 2356, 1716, 1347, 1129 cm-1; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 1.23-1.27 (m, 3H), 1.31-1.37 (m, 3H), 2.43 (s, 3H), 3.80 (m, 5H), 4.30-4.33 (m, 2H), 7.35 (s, 1H), 7.44 (d, *J* = 7.9 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 11.6, 13.8, 20.9, 45.9, 46.3, 52.8, 120.4, 124.2, 126.7, 131.3, 135.6, 140.6, 141.1, 142.7, 150.6, 158.8, 164.2, 165.9 , HPLC t_R = 6.06 min, ES-MS *m*/*z* 417.1 $(M + H)^+$; Anal. calcd. for $C_{20}H_{21}ClN_4O_2S$: C, 57.62; H, 5.08; N, 13.44; Cl, 8.50. Found: C, 57.62; H, 4.85; N, 13.70; Cl, 8.10.



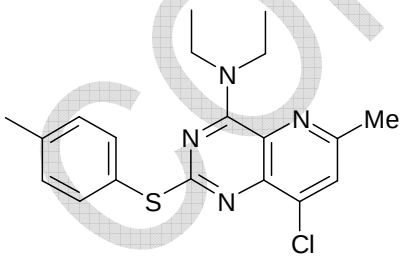
(2-Chloro-6-methyl-8-p-tolylsulfanyl-pyrido[3,2-d]pyrimidin-4-yl)-diethyl-amine **30b**. White off powder. Yield = 75%. mp 200.4-201.4 °C; IR *v*max 1545, 1505, 1478, 1433, 1341, 1149; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.35 (t, *J* = 6.9 Hz, 6H), 2.42 (s, 3H), 2.47 (s, 3H), 4.08 (br s, 4H), 6.59 (s, 1H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 13.1, 18.7, 21.4, 24.9, 46.1, 121.0, 125.8, 130.2, 130.9, 136.0, 140.2, 144.0, 150.0, 154.4, 155.5, 159.2, HPLC t_R = 6.59 min, ES-MS *m*/*z* 373.2 $(M + H)^+$; Anal. calcd. for $C_{19}H_{21}ClN_4S$: C, 61.20; H, 5.68; N, 15.02; Cl,.9.51. Found: C, 61.46; H, 5.92; N, 14.84; Cl, 9.56.



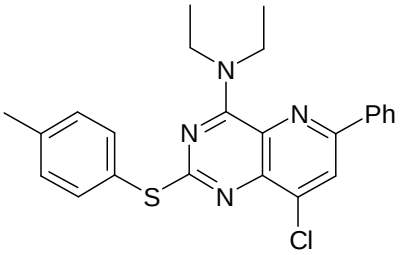
(2-Chloro-6-phenyl-8-p-tolylsulfanyl-pyrido[3,2-d]pyrimidin-4-yl)-diethyl-amine **30c**. White off powder. Yield = 87%. mp 184.5-185.5 °C; IR *v*max 1547, 1470, 1345; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.39 (br s, 6H), 2.46 (s, 3H), 3.87 (br s, 2H), 4.50 (br s, 2H), 7.22 (s, 1H), 7.32-7.39 (m, 5H); 7.52-7.55 (m, 2H), 7.67-7.69 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 12.3, 14.1, 21.5, 46.2, 118.3, 124.7, 125.7, 126.9, 128.8, 129.2, 130.7, 131.0, 136.0, 139.0, 140.4, 144.8, 151.1, 152.0, 159.3; HPLC t_R = 6.83 min, ES-MS *m*/*z* 435.09 $(M + H)^+$; Anal. calcd. for $C_{24}H_{23}ClN_4S$: C, 66.27; H, 5.33; N, 12.88; Cl, 8.15. Found: C, 65.85; H, 5.42; N, 12.82; Cl, 8.15.



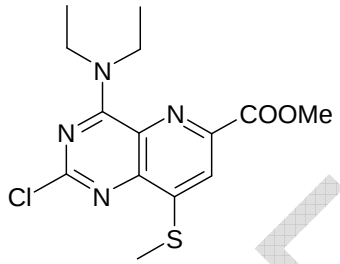
8-Chloro-4-diethylamino-2-p-tolylsulfanyl-pyrido[3,2-*d*] pyrimidine-6-carboxylic acid methyl ester **30d**. Pale orange powder. Yield = 83%. mp 137.8-138.8 °C; IR *v*max 1713, 1532, 1504, 1435, 1345, 1245, 1129 cm-1; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 0.82 (m, 3H), 1.29 (m, 3H), 2.37 (s, 3H), 3.90 (s, 3H), 4.18 (m, 4H), 7.29 (d, *J* = 7.7 Hz, 2H), 7.52 (d, *J* = 7.8 Hz, 2H), 8.31 (s, 1H); ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 11.4, 13.7, 20.8, 45.7, 46.1, 52.8, 126.1, 127.0, 129.5, 131.6, 135.4, 138.9, 139.8, 141.2, 146.1, 156.8, 163.6, 170.2, HPLC t_R = 5.69 min, ES-MS *m*/*z* 417.1 $(M + H)^+$; Anal. calcd. for $C_{20}H_{21}ClN_4O_2S$: C, 57.62; H, 5.08; N, 13.44; Cl, 8.50. Found: C, 57.21; H, 4.99; N, 13.08; Cl, 8.12.



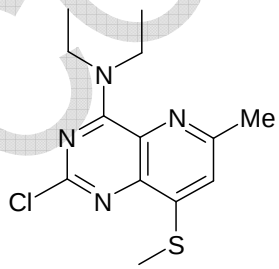
(8-Chloro-6-methyl-2-p-tolylsulfanyl-pyrido[3,2-d]pyrimidin-4-yl)-diethyl-amine **30e**. Yellow oil. Yield = 78%. IR *v*max 1538, 1508, 1355, 1153; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.09 (br s, 6H), 2.38 (s, 3H), 2.54 (s, 3H), 3.50 (br s, 2H), 4.08 (br s, 2H), 7.17-1.79 (m, 2H), 7.44 (s, 1H), 7.55-7.56 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 12.4, 13.6, 21.3, 24.4, 46.0, 126.9, 127.7, 129.3, 132.1, 135.9, 138.6, 140.5, 144.1, 152.8, 157.2, 168.1, HPLC t_R = 4.97 min, ES-MS *m*/*z* 373.2 $(M + H)^+$; Anal. calcd. for $C_{19}H_{21}ClN_4S$: C, 61.20; H, 5.68; N, 15.02; Cl, 9.51. Found: C, 59.56; H, 5.98; N, 14.87; Cl, 9.56.



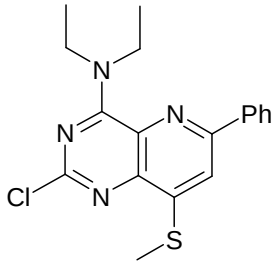
(8-Chloro-6-phenyl-2-p-tolylsulfanyl-pyrido[3,2-*d*]pyrimidin-4-yl)-diethyl-amine **30f**. White off powder. Yield = 81%. mp 116.8-117.8 °C; IR *v*max 1488, 1337; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 0.90 (br s, 3H), 1.40 (br s, 3H), 2.41 (s, 3H), 3.42 (br s, 2H), 4.37 (br s, 2H), 7.20-7.26 (m, 2H), 7.40-7.51 (m, 3H), 7.56-7.58 (m, 2H), 7.91-7.95 (m, 2H), 8.09 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 11.7, 14.4, 21.3, 46.1, 124.1, 126.7, 127.5, 128.9, 129.4, 132.6, 135.9, 138.1, 138.7, 141.4, 144.8, 151.6, 157.3, 168.9; HPLC t_R = 5.92 min, ES-MS *m*/*z* 435.11 $(M + H)^+$; Anal. calcd. for $C_{24}H_{23}ClN_4S$: C, 66.27; H, 5.33; N, 12.88; Cl, 8.15. Found: C, 66.02; H, 5.31; N, 12.77; Cl, 8.11.



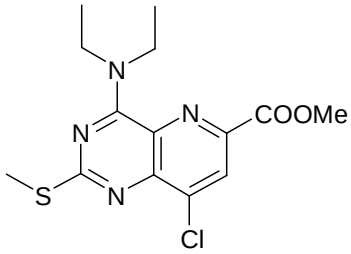
2-Chloro-4-diethylamino-8-methylsulfanyl-pyrido[3,2-d] pyrimidine-6-carboxylic acid methyl ester **31a**. Pale yellow powder. Yield = 77%. mp 153-154 °C; IR *v*max 1716, 1251 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.30 (br t, *J* n/a, 3H), 1.41 (br t, *J* n/a, 3H), 2.53 (s, 3H), 3.81 (br d, *J* n/a, 2H), 3.97 (s, 3H), 4.36 (br d, *J* n/a, 2H), 7.97 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 12.25, 14.25, 14.40, 46.82, 47.16, 53.21, 120.07, 129.96, 143.17, 147.86, 151.03, 158.52, 159.80, 165.63; HPLC t_R = 5.05 min; ES-MS *m*/*z* 341.32 $(M + H)^+$; Anal. calcd. for $C_{14}H_{17}ClN_4O_2S$: C, 49.34; H, 5.03; N, 16.44. Found: C, 49.07; H, 5.03; N, 16.29.



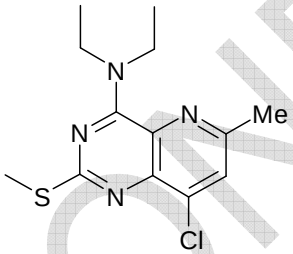
(2-Chloro-6-methyl-8-methylsulfanyl-pyrido[3,2-d]pyrimidin-4-yl)-diethyl-amine **31b**. Whitte off powder. Yield = 68%. mp 109.5-110.5 °C; IR *v*max 1515, 1478, 1429, 1343, 1149; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.33 (t, *J* = 6.9 Hz, 6H), 2.46 (s, 3H), 2.56 (s, 3H), 4.08 (br s, 4H), 7.07 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 13.7, 25.1, 46.1, 119.7, 129.9, 144.8, 149.0, 154.2, 155.5, 159.3, HPLC t_R = 5.36 min, ES-MS *m*/*z* 297.2 $(M + H)^+$; Anal. calcd. for $C_{13}H_{17}ClN_4S$: C, 52.61; H, 5.77; N, 18.88; Cl, 11.94. Found: C, 52.24; H, 5.56; N, 18.70; Cl, 11.87.



(2-Chloro-6-phenyl-8-methylsulfanyl-pyrido[3,2-d]pyrimidin-4-yl)-diethyl-amine **31c**. Pale yellow powder. Yield = 86%. mp 152.5-153.5 °C; IR *v*max 1496, 1470, 1349; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.39 (br s, 6H), 2.56 (s, 3H), 3.84 (br s, 2H), 4.48 (br s, 2H), 7.43-7.54 (m, 3H), 7.66 (s, 1H), 7.94-7.99 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 11.9, 13.9, 14.3, 46.2, 116.8, 127.0, 128.9, 129.3, 130.3, 139.1, 145.6, 150.0, 153.0, 156.0, 159.3; HPLC t_R = 5.92 min, ES-MS *m*/*z* 359.00 $(M + H)^+$; Anal. calcd. for $C_{18}H_{19}ClN_4S$: C, 60.24; H, 5.34; N, 15.61; Cl, 9.88. Found: C, 60.07; H, 5.35; N, 15.54; Cl, 9.89.



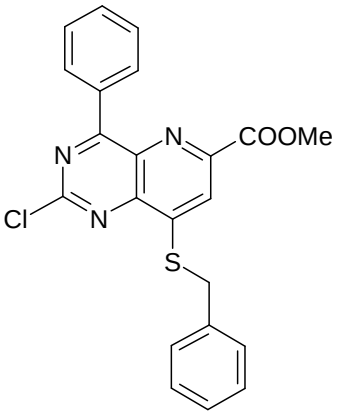
8-Chloro-4-diethylamino-2-methylsulfanyl-pyrido[3,2-d] pyrimidine-6-carboxylic acid methyl ester **31d**. Orange powder. Yield = 73%. mp 122.5-123.5 °C; IR *v*max 2359, 1737, 1435, 1244, 1130 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.25-1.41 (m, 6H), 2.61 (s, 3H), 3.84 (br s, 2H), 3.91 (s, 3H), 4.33 (br s, 2H), 8.33 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 11.9, 14.0, 14.6, 46.3, 46.8, 52.8, 127.3, 132.0, 140.8, 140.9, 146.6, 157.3, 164.5, 171.5, HPLC t_R = 4.31 min; ES-MS *m*/*z* 341.1 $(M + H)^+$; Xray data available in Appendix.



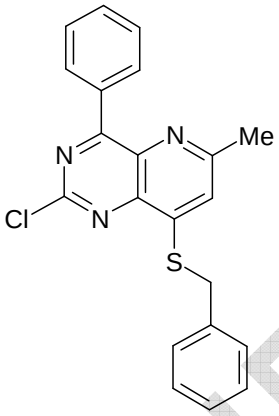
(8-Chloro-6-methyl-2-methylsulfanyl-pyrido[3,2-d]pyrimidin-4-yl)-diethyl-amine **31e**. White off powder. Yield = 13%. mp 82.3-83.3 °C; IR *v*max 1540, 1509, 1311, 1155, 928; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.33 (t, *J* = 6.9 Hz, 6H), 2.57 (s, 3H), 2.60 (s, 3H), 4.06 (br s, 4H), 7.48 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 14.4, 14.5, 24.4, 46.1, 126.9, 132.1, 143.7, 148.9, 152.6, 153.2, 157.4; HPLC t_R = 3.33 min; ES-MS *m*/*z* 297.2 $(M + H)^+$.

General procedure for S_NAr with benzylthiol on derivatives 15.

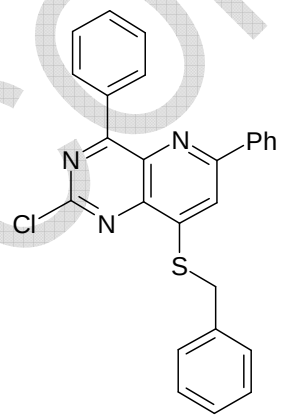
To a solution of derivative **15** (0.21 mmol; 1.00 equiv) in ACN (1.00 mL) and DCM (1.00 mL) was added benzylthiol (1.05 mmol; 5.00 equiv) in presence of Hünig base (106.9 µl; 0.62 mmol; 3.00 equiv). The reaction mixture was heated at 90 °C for 1 hr under MW irradiation. As two regioisomers were formed during the reaction, the reaction mixture was purified by MDAP® system using an apolar method. Derivatives **32a-f** were obtained in yields ranging from 12 to 73%.



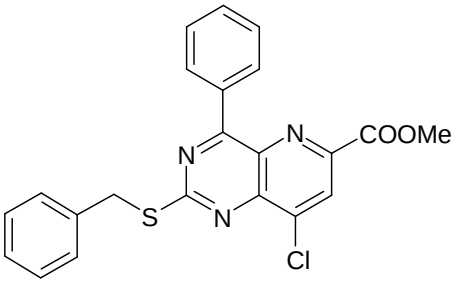
8-Chloro-4-phenyl-2-p-tolylsulfanyl-pyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester **32a**. Pale yellow powder. Yield = 12%. mp 150.8-151.8 °C; IR *v*max 1719, 1430, 1244, 1139; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 2.41 (s, 3H), 3.94 (s, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.50-7.57 (m, 3H), 7.60-7.66 (m, 3H), 8.30 (d, *J* = 8.5 Hz, 2H), 8.52 (s, 1H); ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 20.9, 53.2, 125.2, 127.8, 128.1, 129.9, 131.7, 131.9, 134.5, 136.7, 139.4, 142.0, 145.7, 146.4, 163.5, 166.5, 170.3, HPLC t_R = 5.87 min, ES-MS *m/z* 422.1 $(M + H)^+$; Anal. calcd. for $C_{22}H_{16}ClN_3O_2S$: C, 62.63; H, 3.82; N, 9.96; Cl, 8.40. Found: C, 62.55; H, 3.83; N, 10.00; Cl, 8.39.



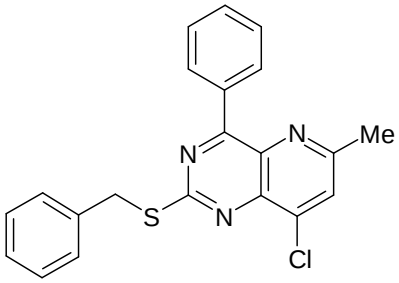
8-Benzylsulfanyl-2-chloro-6-methyl-4-phenyl-pyrido[3,2-*d*] pyrimidine **32b**. Pale orange powder. Yield = 20%. mp 172.3-173.3 °C; IR *v*max 1521, 1448, 1332, 1153, 689, 639 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.70 (s, 3H), 4.29 (s, 2H), 7.34-77.35 (m, 2H), 7.37 (s, 1H), 7.38-7.40 (m , 1H), 7.46-7.51 (m, 2H), 7.52-7.56 (m, 3H), 8.42-8.46 (m, 2H),^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 25.8, 35.5, 122.3, 128.0, 128.2, 128.9, 129.0, 131.4, 132.2, 134.6, 135.2, 135.8, 144.1, 146.6, 149.6, 160.0, 168.6, HPLC t_R = 5.62 min, ES-MS *m/z* 378.10 $(M + H)^+$; Anal. calcd. for $C_{21}H_{16}ClN_3S$: C, 66.75; H, 4.27; N, 11.12; Cl, 9.38. Found: C, 66.95; H, 4.32; N, 10.72; Cl, 9.45.



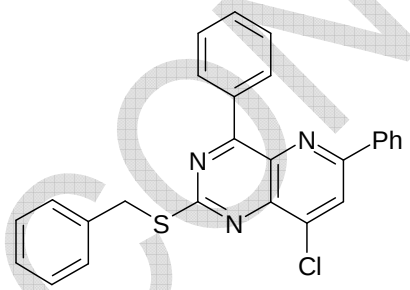
8-Benzylsulfanyl-2-chloro-4,6-diphenyl-pyrido[3,2-*d*]pyrimidine **32c**. White off powder. Yield = 18 mp 180.5-181.5 °C; I R *v*max 1524, 1455, 684 cm-1; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 4.68 (s, 2H), 7.29-7.34 (m, 1H), 7.38-7.43 (m, 2H), 7.58-7.60 (m, 4H), 7.62-7.66 (m, 4H), 8.21-8.23 (m, 2H), 8.33 (s, 1H), 8.37-8.39 (m, 2H),^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 41.9, 119.9, 126.1, 127.6, 127.7, 128.0, 128.1, 128.7, 129.1, 130.6, 131.5, 131.9, 134.8, 135.8, 137.4, 146.5, 149.9, 154.5, 156.6, 168.9, HPLC t_R = 6.20 min, ES-MS *m/z* 440.1 $(M + H)^+$; Anal. calcd. for $C_{26}H_{18}ClN_3S$: C, 70.98; H, 4.12; N, 9.55; Cl, 8.06. Found: C, 70.56; H, 4.38; N, 9.39; Cl, 7.90.



2-Benzylsulfanyl-8-chloro-4-phenyl-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **32d**. Pale orange powder. Yield = 73%. mp 135.4-136.4 °C; IR *v*max 1724, 1531, 1314, 1244, 1108; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 3.95 (s, 3H), 4.63 (s, 2H), 7.23-7.36 (m, 3H), 7.56-7.68 (m, 5H), 8.33-8.34 (m, 2H), 8.35 (s, 1H), ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 35.0, 53.2, 127.2, 128.0, 128.1, 128.4, 129.1, 131.6, 131.9, 134.65, 136.7, 137.7, 141.8, 145.5, 146.2, 163.5, 166.9, 170.1, HPLC t_R = 5.91 min, ES-MS *m*/*z* 422.20 $(M + H)^+$. Anal. calcd. for $C_{22}H_{16}ClN_3O_2S$: C, 62.63; H, 3.82; N, 9.96; Cl, 8.40. Found: C, 62.30; H, 3.72; N, 9.84; Cl, 8.49.



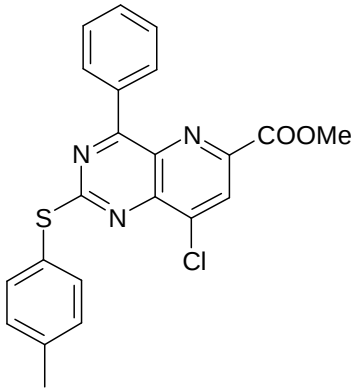
2-Benzylsulfanyl-8-chloro-6-methyl-4-phenyl-pyrido[3,2-d] pyrimidine **32e**. Pale yellow powder. Yield = 60%. mp 121.5-122.5 °C; IR *v*max 1529, 1455, 1147, 690 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.67 (s, 3H), 4.57 (s, 2H), 7.21-7.31 (m, 3H), 7.48-7.50 (m, 3H), 7.55-7.58 (m, 2H), 7.65 (s, 1H), 8.30-8.33 (m, 2H),^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 25.2, 35.9, 127.2, 128.0, 128.4, 129.3, 131.0, 132.0, 135.5, 137.1, 138.0, 141.9, 144.4, 158.2, 166.0, 168.0, HPLC t_R = 5.90 min, ES-MS *m*/*z* 378.10 $(M + H)^+$; Anal. calcd. for $C_{21}H_{16}ClN_3S$: C, 66.75; H, 4.26; N, 11.05; Cl, 9.38. Found: C, 66.73; H, 4.26; N, 11.05; Cl, 9.36.



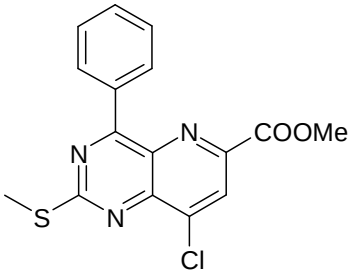
2-Benzylsulfanyl-8-chloro-6-phenyl-4-phenyl-pyrido[3,2-d] pyrimidine **32f**. Pale yellow powder. Yield = 60%. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 4.63 (s, 2H), 7.30-7.32 (m, 3H), 7.50-7.62 (m, 8H), 8.08-8.11 (m, 2H), 8.32 (s, 1H), 8.38-8.42 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 36.0, 125.1, 127.2, 127.4, 128.0, 128.5, 129.0, 129.1, 129.3, 130.3, 131.0, 132.1, 135.5, 137.3, 137.4, 138.0, 142.8, 144.7, 155.7, 166.7, HPLC t_R = 6.47 min, ES-MS *m*/*z* 440.10 $(M + H)^+$.

General procedure for S_NAr with thiols on derivative 15a.

To a solution of derivative **15a** (0.21 mmol; 1.00 equiv) in DMF (2.00 mL) was added a thiol (1.00 equiv) in presence of Hünig base (106.9 µl; 0.62 mmol; 3.00 equiv). The reaction mixture was heated at 0 °C for 16 hr. As two regioi somers were formed during the reaction, the reaction mixture was purified by MDAP® system. Derivatives **33** and **34** were obtained in yields ranging from 12 to 73%.



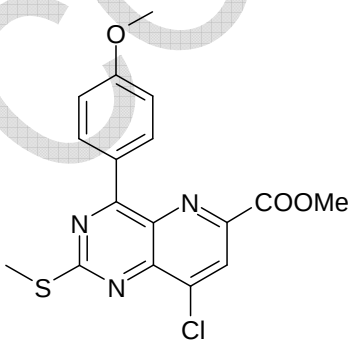
8-Chloro-4-phenyl-2-p-tolylsulfanyl-pyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester **33b**. Pale yellow powder. Yield = 63%. mp 193.5-194.5 °C; IR *v*max 1719, 1430, 1244, 1139; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 2.41 (s, 3H), 3.94 (s, 3H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.50-7.57 (m, 2H), 7.60-7.66 (m, 3H), 8.30 (d, *J* = 8.5 Hz, 2H), 8.52 (s, 1H); ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 20.9, 53.2, 125.2, 127.8, 128.1, 129.9, 131.7, 131.9, 134.5, 136.7, 139.4, 142.0, 145.7, 146.4, 163.5, 166.5, 170.3, HPLC t_R = 5.87 min, ES-MS *m*/*z* 422.1 $(M + H)^+$; Anal. calcd. for $C_{22}H_{16}ClN_3O_2S$: C, 62.63; H, 3.82; N, 9.96; Cl, 8.40. Found: C, 62.76; H, 3.82; N, 9.72; Cl, 8.17.



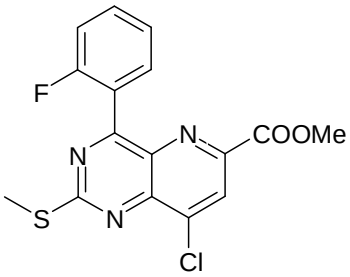
8-Chloro-2-methylsulfanyl-4-phenyl-pyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester **34b**. Beige powder. Yield = 60%. mp 165-166 °C; IR *v*max 1721, 1531, 1251 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.78 (s, 3H), 4.05 (s, 3H), 7.56-7.58 (m, 3H), 8.52-8.55 (m, 3H), ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C15.32, 53.77, 128.30, 128.71, 132.16, 132.72, 135.20, 137.21, 143.73, 146.20, 146.58, 164.68, 167.21, 172.98, HPLC t_R = 5.16 min, ES-MS *m*/*z* 345.99 $(M + H)^+$; Anal. calcd. for $C_{16}H_{12}ClN_3O_2S$: C, 55.57; H, 3.50; N, 12.15. Found: C, 55.15; H, 3.57; N, 11.85.

General procedure for S_NAr with MeSNa on derivatives 15d-e.

To a solution of derivative **15** (0.21 mmol; 1.00 equiv) in THF (2.00 mL) was added a sodium methylthiolate (1.00 equiv). The reaction mixture was heated at -10 °C for 4 hr. As two regioisomers were formed during the reaction, the reaction mixture was purified by MDAP® system. Derivatives **35a** and **35b** were obtained in yields ranging from 57 to 76%.



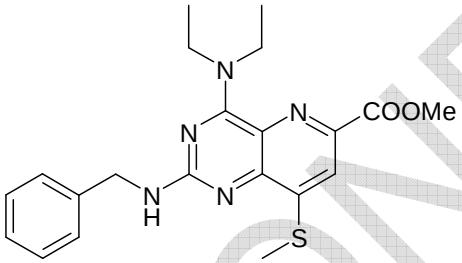
8-Chloro-4-(4-methoxy-phenyl)-2-methylsulfanyl-pyrido[3,2-*d*] pyrimidine-6-carboxylic acid methyl ester **35a**. Yellow powder. Yield = 57%. mp 197-198; °C; IR *v*max 2821, 1722, 1525 cm-1; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 2.71 (s, 3H), 3.89 (s, 3H), 3.96 (s, 3H), 7.13-7.15 (d, 2H), 8.53 (s, 1H), 8.58-8.66 (d, 2H); ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 14.9, 53.4, 55.5, 113.9, 127.4, 127.7, 134.5, 136.9, 143.2, 145.3, 146.2, 162.9, 164.3, 165.4, 172.4, HPLC t_R = 5.15 min, ES-MS *m*/*z* 376.0 $(M + H)^+$; Anal. calcd. for $C_{17}H_{14}ClN_3O_3S$: C, 54.33; H, 3.75; N, 11.18; Cl, 9.43. Found: C, 53.93; H, 3.75; N, 10.64; Cl, 9.59.



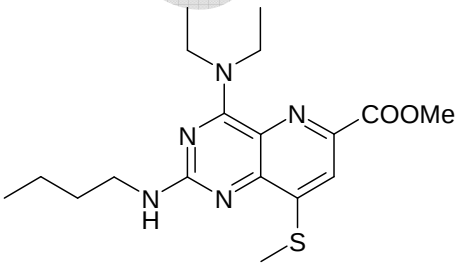
8-Chloro-4-(4-trifluoromethyl-phenyl)-2-methylsulfanyl-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **35b**. White powder. Yield = 76%. mp 197.5-198.5; °C; IR *v*max 1719, 1536, 1255 cm-1; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 2.72 (s, 3H), 3.90 (s, 3H), 7.39-7.44 (m, 2H), 7.71-7.75 (m, 2H), 8.58 (s, 1H), ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 15.0, 53.3, 116.1 (d, *J = 22.4 Hz*), 123.4 (d, *J = 14.4 Hz*), 124.1 (d, *J = 3.9 Hz*), 128.3, 132.3, 132.7 (d, *J = 8.3 Hz*), 136.9, 143.0, 145.5, 146.4, 160.9 (d, *J = 253.5 Hz*), 164.2, 166.7, 172.6; HPLC t_R = 4.67 min, ES-MS *m/z* 364.0 $(M + H)^+$; Anal. calcd. for $C_{16}H_{11}ClFN_3O_2S$: C, 52.83; H, 3.05; N, 11.55; Cl, 9.75. Found: C, 52.45; H, 3.09; N, 11.48; Cl, 10.13.

General procedure for S_NAr with amines on 31a.

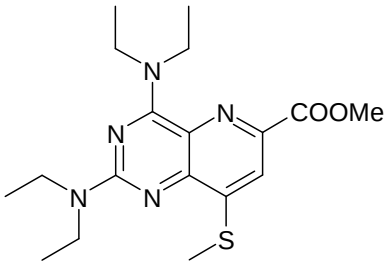
To a solution of **31a** (100 mg, 1.00 equiv) in ACN (40 V) was added an amine (5.00 equiv) in presence of Hünig base (3.00 equiv). The reaction was heated at 180 °C under MW irradiation for 20 min. Solvent were removed under vacuum at 40 °C and the solid obtained was suspended in MeOH, filtered and dried under suction to afford derivatives **36a** to **36c**.



2-Benzylamino-4-diethylamino-8-methylsulfanyl-pyrido[3,2-*d*] pyrimidine-6-carboxylic acid methyl ester **36a**. Yellow powder. Yield = 74%. mp 121-122 °C; IR *v*max 3548, 1725, 1231 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.30 (br s, 6H), 2.50 (s, 3H), 3.70 (br s, 2H), 3.95 (s, 3H), 4.19 (br s, 2H), 4.68 (m, 2H), 5.58 (br s, 1H), 7.29 (m, 5H), 7.86 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 12.5, 13.5, 14.2, 46.1, 52.8, 119.7, 127.4, 127.9, 128.3, 128.8, 138.4, 140.1, 148,9, 159.4, 159.7, 166.4; HPLC t_R = 3.90 min; ES-MS *m/z* 412.52 $(M + H)^+$; Anal. calcd. for $C_{21}H_{25}N_5O_2S$: C, 61.29; H, 6.12; N, 17.02. Found: C, 61.17; H, 6.12; N, 16.95.



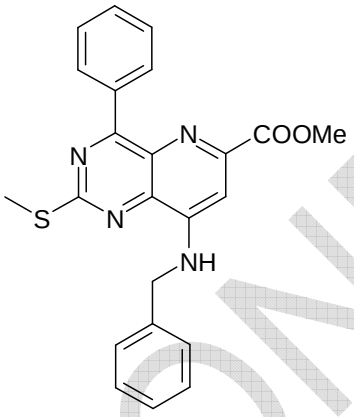
2-Butylamino-4-diethylamino-8-methylsulfanyl-pyrido[3,2-*d*] pyrimidine-6-carboxylic acid methyl ester **36b**. Yellow oil. Yield = 71%. IR *v*max 1712, 1530 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 0.93 (t, *J* = 7 Hz, 3H), 1.32 (br s, 6H), 1.41 (m, 2H), 1.59 (m, 2H), 2.49 (s, 3H), 3.45 (d, *J* = 6 Hz, 2H), 3.60-3.86 (br s, 1H), 3.93 (s, 3H), 3.95-4.02 (br s, 1H), 4.04-4.54 (br s, 2H), 5.16 (br s, 1H), 7.83 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 12.7, 12.8, 19.2, 25.9, 28.7, 29.1, 31.0, 40.3, 44.8, 51.3, 118.2, 126.0, 136.6, 144.3, 147.7, 158.2, 165.0; HPLC t_R = 3.91 min; ES-MS *m/z* 378.07$(M + H)^+$.



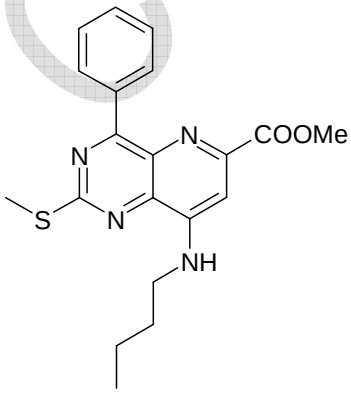
2-Diethylamino-4-diethylamino-8-methylsulfanyl-pyrido[3,2-*d*] pyrimidine-6-carboxylic acid methyl ester **36c**. Yellow powder. Yield = 72%. mp 127-128 °C; IR *v*max 1706, 1527 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.23 (br t, *J* n/a, 6H), 1.33 (br t, *J* n/a, 6H), 2.49 (s, 3H), 3.70 (m, 11H), 7.83 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 13.71, 14.11, 29.25, 42.44, 46.23, 52.68, 119.45, 127.02, 137.51, 146.41, 149.12, 158.05, 159.28, 166.64; HPLC t_R = 3.97 min; ES-MS *m/z* 378.10 $(M + H)^+$; Anal. calcd. for $C_{18}H_{27}N_5O_2S$: C, 57.27; H, 7.21; N, 18.55. Found: C, 56.94; H, 7.01; N, 18.21.

General procedure for S_NAr with amines on derivative 34b.

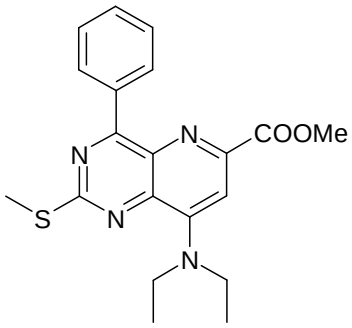
To a solution of **34b** (100 mg, 1.00 equiv) in ACN (40 V) was added the amine (5.00 equiv) in presence of Hünig base (3.00 equiv). The reaction was heated at 180 °C under MW irradiation for 20 min. Solvent were removed under vacuum at 40 °C and the solid obtained was suspended in MeOH, filtered and dried under suction. Derivative **38a** was further purified using MDAP® system as the precipitate firstly obtained was not pure. Derivatives **38a** to **38c** were isolated in yields ranging from 73 to 84%.



8-Benzylamino-2-methylsulfanyl-4-phenyl-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **38a**. Yellow powder. Yield = 73%. mp 150.0-151.0 °C; IR *v*max 1720, 1528, 1266, 1112 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.69 (s, 3H), 3.98 (s, 3H), 4.63 (d, *J* = 5.8 Hz, 2H), 6.70 (t, *J* = 5.6 Hz, 1H), 7.33-7.41 (m, 5H), 7.43 (s, 1H), 7.53-7.55 (m, 3H), 8.61-8.64 (m, 2H), ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 14.9, 46.8, 53.0, 102.7, 127.3, 127.9, 128.2, 129.0, 131.2, 132.2, 135.0, 135.8, 137.0, 140.2, 147.5, 149.2, 165.9, 166.2, 167.7; HPLC t_R = 0.42 min; ES-MS *m/z* 417.30 $(M + H)^+$; Anal. calcd. for $C_{23}H_{20}N_4O_2S$: C, 66.33; H, 4.84; N, 13.45. Found: C, 66.15; H, 4.80; N, 13.34.



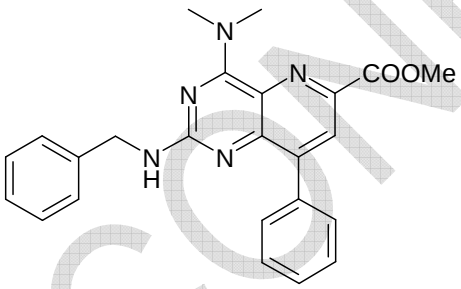
8-Butylamino-2-methylsulfanyl-4-phenyl-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **38b**. Yellow-orange powder. Yield = 83%. mp 124.5-125.5 °C; IR *v*max 1527, 1253, 1017 cm-1; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 0.95 (t, *J = 7.3 Hz*, 3H), 1.41 (sx, *J = 7.3 Hz*, 2H), 1.65 (qt, *J = 7.2 Hz*, 2H), 2.73 (s, 3H), 3.40 (q, *J = 6.8 Hz*, 2H), 3.89 (s, 3H), 7.29 (s, 1H), 7.53-7.6 (m, 3H), 8.44-8.47 (m, 2H), ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 13.8, 14.8, 20.3, 30.9, 42.5, 53.0, 102.1, 128.1, 131.1, 132.2, 135.0, 135.9, 140.2, 147.5, 149.3, 165.8, 166.4, 167.3, HPLC t_R = 5.81 min; ES-MS *m/z* 383.3 $(M + H)^+$; XRay data in Appendix.



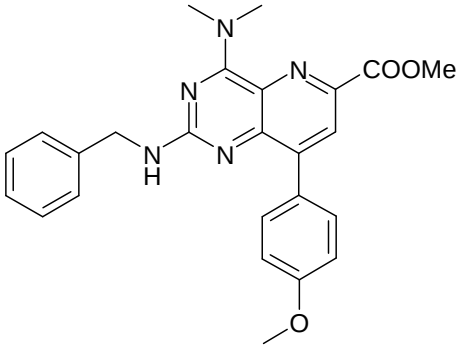
8-Diethylamino-2-methylsulfanyl-4-phenyl-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **38c**. Yellow powder. Yield = 84%. mp 110.5-111.0 °C; IR *v*max 1736, 1530, 1236 cm-1; ^{1}H NMR (300 MHz, DMSO-*d6*), δ_H 1.28 (t, *J = 6.9 Hz*, 6H), 2.63 (s, 3H), 3.87 (s, 3H), 3.91 (q, *J = 6.4 Hz*, 4H), 7.42 (s, 1H), 7.51-7.63 (m, 3H), 8.28-8.31 (m, 2H), ^{13}C NMR (75.47 MHz, DMSO-*d6*), δ_C 12.7, 13.9, 46.4, 52.6, 107.7, 127.7, 130.6, 131.6, 136.0, 137.0, 141.7, 146.4, 149.4, 164.4, 165.5, 166.3, HPLC t_R = 4.64 min; ES-MS *m*/*z* 383.3 $(M + H)^+$; Anal. calcd. for $C_{20}H_{22}N_4O_2S$: C, 62.81; H, 5.80; N, 14.65. Found: C, 62.68; H, 5.47; N, 14.81.

General procedure for Suzuki cross-coupling on derivative 25b.

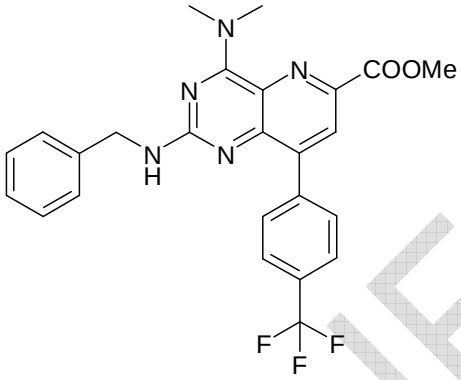
To a suspension of boronic acid (1.80 mmol, 5.00 equiv) and derivative **25b** (0.30 mmol, 1.00 equiv) were added cesium carbonate (0.30 mmol; 3.00 equiv) and tetrakis(triphenylphosphine)palladium(0) (0.01 mmol; 0.05 equiv) in degassed dioxane (2.00 mL). The reaction mixture was heated at 90 °C for 5 to 7 hr. After complete conversion, the desired product was extracted with water and DCM. The combined organic layers were were dried on anhydrous Na_2SO_3 and filtered on Celite®. After purification using MDAP® system, derivatives **40** were obtained in good yields.



2-Benzylamino-4-dimethylamino-8-phenyl-pyrido[3,2-*d*] pyrimidine-6-carboxylic acid methyl ester **40a**. Yellow powder. Yield = 82%. mp 118-119 °C; IR *v*max 2922, 1713, 1533, 1243 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.25 (br s, 6H), 3.98 (s, 3H), 4.62 (br s, 2H), 5.39 (br s, 1H), 7.24-7.39 (m, 8H), 7.75-7.78 (m, 2H), 8.20 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 30.1, 42.0, 46.0, 52.9, 127.1, 127.2, 127.4, 128.0, 128.2, 128.6, 128.8, 130.6, 137.4, 140.2, 143.6, 159.5, 161.6, 166.2; HPLC t_R = 3.73 min; ES-MS *m*/*z* 414.05 $(M + H)^+$; Anal. calcd. for $C_{24}H_{23}N_5O_2$: C, 69.72; H, 5.61; N, 16.94. Found: C, 69.29; H, 6.02; N, 16.63.



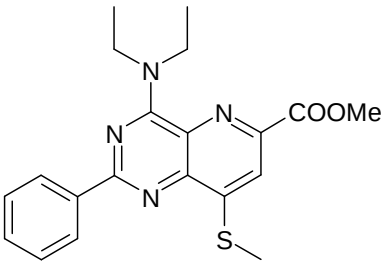
2-Benzylamino-4-dimethylamino-8-(4-methoxy-phenyl)-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **40b**. Yellow powder. Yield = 82%. mp 151-152 °C; IR *v*max 3392, 1698, 1532, 1247 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 3.56 (br s, 6H), 3.80 (s, 3H), 3.92 (s, 3H), 4.57 (d, *J = 6 Hz*, 2H), 5.38 (br s, 1H), 6.88 (d, *J = 8 Hz*, 2H), 7.26-7.28 (m, 5H), 7.70-7.73 (m, 2H), 8.13 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 29.7, 41.7, 45.6, 52.5, 55.3, 113.3, 126.1, 127.0, 127.6, 128.1, 128.4, 129.1, 129.3, 131.5, 135.9, 138.0, 139.9, 159.2, 159.7, 161.3, 165.9; HPLC t_R = 3.42 min; ES-MS *m*/*z* 444.19 $(M + H)^+$; Anal. calcd. for $C_{25}H_{25}N_5O_3$: C, 67.71; H, 5.68; N, 15.79. Found: C, 67.41; H, 5.94; N, 15.59.



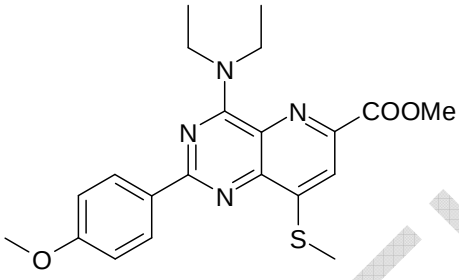
2-Benzylamino-4-dimethylamino-8-(4-trifluoromethyl-phenyl)-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **40c**. Yellow powder. Yield = 78%. mp 176-177 °C; IR *v*max 3411, 1700, 1522, 1251 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.25 (s, 6H), 3.99 (s, 3H), 4.59 (br s, 2H), 5.44 (br s, 1H), 7.28-7.32 (m, 5H), 7.65-7.72 (m, 2H), 7.82-7.85 (m, 2H), 8.18 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 30.1, 42.1, 46.0, 53.0, 124.3 (q, *J = 272.0 Hz*), 124.9 (q, *J = 4.1 Hz*), 127.2, 127.6, 127.8, 128.6, 130.6, 130.7 (q, *J = 34.8 Hz*), 138.0, 138.7, 139.7, 140.2, 140.6, 148.2, 159.3, 165.7, 169.1; HPLC t_R = 4.23 min; ES-MS *m*/*z* 482.16 $(M + H)^+$; Anal. calcd. for $C_{25}H_{22}F_3N_5O_2$: C, 62.37; H, 4.61; N, 14.55. Found: C, 61.98; H, 5.01; N, 14.82.

General procedure for Suzuki cross-coupling on scaffold 31a.

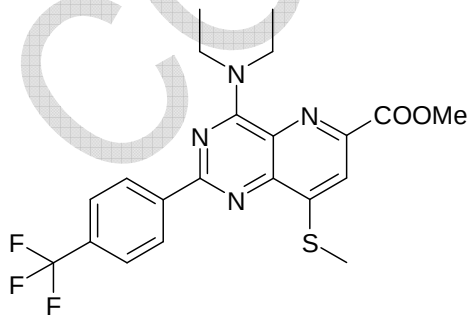
A solution of boronic acid (1.20 mmol; 5.00 equiv), **31a** (0.24 mmol; 1.00 equiv), cesium carbonate (0.73 mmo; 3.00 equiv) and tetrakis(triphenylphosphine)palladium(0) (0.01 mmol; 0.05 equiv) in degassed dioxane (2.00 mL) was heated at 90 °C for 3.5 hr. Water and DCM were added in the reaction mixture and the organic phase were extracted. Combined organic layers were washed with brine, dried over Na_2SO_4 and solvents were removed under vacuum. The obtained residue was dissolved in DCM and filtered on Celite®. After having removed solvents under vacuum at 40 °C, the solid obtained was suspended in MeOH, filtered and dried under suction to afford derivatives **41a** to **41c**.



4-Diethylamino-8-methylsulfanyl-2-phenyl-pyrido[3,2-*d*] pyrimidine-6-carboxylic acid methyl ester **41a**. Yellow powder. Yield = 88%. mp 167-168 °C; IR *v*max 1718, 1519 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.44 (t, *J* = 7 Hz, 6H), 2.58 (s, 3H), 4.00 (s, 3H), 4.38 (br s, 4H), 7.46-7.70 (m, 3H), 8.01 (s, 1H), 8.56-8.59 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 14.3, 14.6, 46.7, 53.1, 67.4, 119.6, 128.5, 128.6, 130.0, 135.5, 138.7, 142.4, 147.3, 151.7, 159.2, 160.7, 166.1; HPLC t_R = 5.77 min; ES-MS *m*/*z* 383.40 $(M + H)^+$; Anal. calcd. for $C_{20}H_{22}N_4O_2S$: C, 62.81; H, 5.80; N, 14.65. Found: C, 62.47; H, 5.88; N, 14.74.



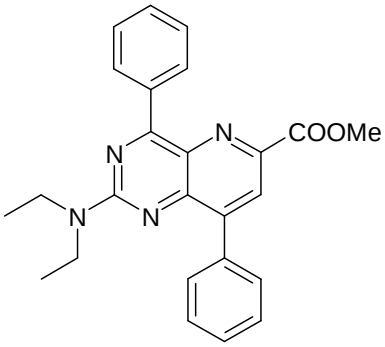
4-Diethylamino-2-(4-methoxy-phenyl)-8-methylsulfanyl-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **41b**. Yellow powder. Yield = 79%. mp 147-148 °C; IR *v*max 1733, 1519, 1240 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.43 (t, *J* = 7 Hz, 6H), 2.57 (s, 3H), 3.88 (s, 3H), 3.99 (s, 3H), 4.36 (br s, 4H), 6.98 (d, *J* = 9 Hz, 2H), 7.99 (s, 1H), 8.52 (d, *J* = 9 Hz, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 12.6, 13.3, 14.0, 46.4, 52.8, 55.5, 113.7, 119.3, 129.6, 130.6, 131.2, 141.8, 147.01, 150.9, 158.9, 160.3, 161.9, 165.9; HPLC t_R = 5.40 min; ES-MS *m*/*z* 413.40 $(M + H)^+$; Anal. calcd. for $C_{21}H_{24}N_4O_3S$: C, 61.15; H, 5.86; N, 13.58. Found: C, 61.13; H, 5.54; N, 13.44.



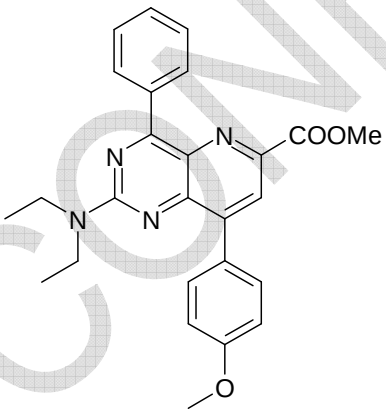
4-Diethylamino-2-(4-trifluoromethyl-phenyl)-8-methylsulfanyl-pyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester **41c**. Yellow powder. Yield = 84%. mp 148-149 °C; IR *v*max 1721, 1521, 1321 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.45 (br s, 6H), 2.59 (s, 3H), 4.01 (br s, 5H), 4.42 (br s, 2H), 7.72 (d, *J* = 8 Hz, 2H), 8.03 (s, 1H), 8.67 (d, *J* = 8 Hz, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 12.1, 14.1, 14.2, 46.6, 46.7, 52.9, 119.5, 124.6 (q, *J* = *272.5 Hz*), 125.3 (q, *J = 3.4 Hz*), 129.1, 130.0, 132.1 (q, *J* = *31.2 Hz*), 141.8, 142.7, 146.9, 151.8, 159.0, 159.1, 165.8; HPLC t_R = 6.54 min; ES-MS *m*/*z* 451.41 $(M + H)^+$; Anal. calcd. for $C_{21}H_{21}F_3N_4O_2S$: C, 55.99; H, 4.70; N, 12.44. Found: C, 55.61; H, 4.53; N, 12.24.

General procedure for Suzuki cross-coupling on derivative 28c

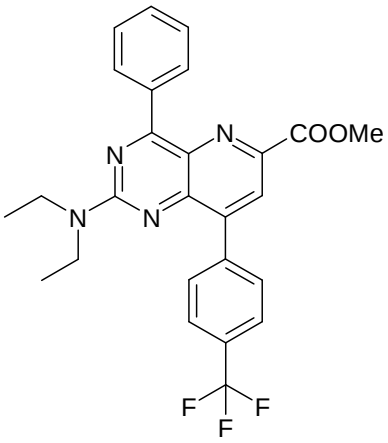
A solution of boronic acid (0.24 mmol; 1.00 equiv), **28c** (0.24 mmol; 1.00 equiv), cesium carbonate (0.73 mmol; 3.00 equiv) and tetrakis(triphenylphosphine)palladium(0) (0.01 mmol; 0.05 equiv) in degassed dioxane (2.00 mL) was heated at 90 °C. After 7 hr, DCM was added to the reaction mixture and the solution was filtrate on celite®. After having removed solvents under vacuum at 40 °C, the solid obtained was suspe nded in MeOH, filtered and dried under suction to afford derivatives **42a** to **42c**.



2-Diethylamino-4,8-diphenyl-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **42a**. Yellow powder. Yield = 80%. mp 133-134 °C; IR *v*max 1555, 1240 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.26 (m, 6H), 3.76 (br s, 4H), 4.01 (s, 3H), 7.45-7.52 (m, 3H), 7.56-7.58 (m, 3H), 7.90-7.93 (m, 2H), 8.36 (s, 1H),. 8.52-8.55 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 13.4, 14.2, 42.9, 53.2, 127.2, 128.2, 128.4, 128.9, 130.7, 131.1, 132.3, 134.8, 136.8, 137.1, 142.0, 145.0, 149.9, 158.5, 166.3, 168.2; HPLC t_R = 5.16 min, ES-MS *m*/*z* 345.99 $(M + H)^+$; Anal. calcd. for $C_{25}H_{24}N_4O_2$: C, 72.80; H, 5.86; N, 13.58. Found: C, 72.40; H, 5.82; N, 13.35.



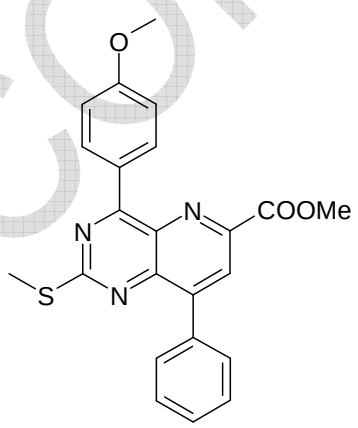
2-Diethylamino-8-(4-methoxy-phenyl)-4-phenyl-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **42b**. Yellow powder. Yield = 51%. mp 129-130 °C; IR *v*max 1721, 1557, 1248 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.28 (t, *J* = 7 Hz, 6H), 3.79 (br s, 4H), 3.91 (s, 3H), 4.01 (s, 3H), 7.03 (d, *J* = 9 Hz, 2H), 7.55 (m, 3H), 7.93 (d, *J* = 9 Hz, 2H), 8.34 (s, 1H), 8.51-8.54 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 13.7, 13.9, 42.9, 53.2, 55.7, 113.7, 114.5, 126.5, 128.1, 128.3, 129.2, 131.0, 132.3, 134.8, 137.2, 142.0, 144.5, 158.4, 160.4, 166.4, 168.2; HPLC t_R = 6.43 min; ES-MS *m*/*z* 443.56 $(M + H)^+$; Anal. calcd. for $C_{26}H_{26}N_4O_3$: C, 70.57; H, 5.92; N, 12.66. Found: C, 70.27; H, 5.96; N, 12.28.



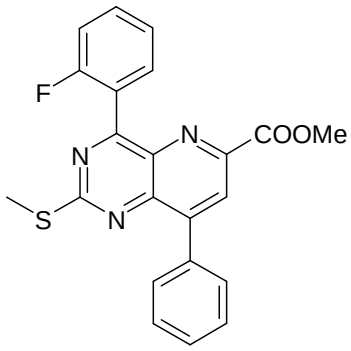
2-Diethylamino-8-(4-methoxy-phenyl)-4-phenyl-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **42c**. Yellow powder. Yield = 82%. mp 165-166 °C; IR *v*max 1711, 1558, 1321 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.27 (m, 6H), 3.77 (br s, 4H), 4.02 (s, 3H), 7.56 (m, 3H), 7.75 (d, *J* = 8 Hz, 2H), 8.02 (d, *J* = 8 Hz, 2H), 8.35 (s, 1H), 8.53 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 13.3, 13.8, 42.8, 53.0, 124.3 (q, *J = 277.8 Hz*), 124.8 (q, *J = 3.6 Hz*), 127.0, 128.2, 130.4 (q, *J = 30.0 Hz*), 130.7, 131.0, 132.0, 134.7, 136.6, 140.2, 141.6, 143.1, 148.9, 158.3, 165.8, 168.1, HPLC t_R = 6.94 min; ES-MS *m*/*z* 481.36 $(M + H)^+$; Anal. calcd. for $C_{26}H_{23}F_3N_4O_2$: C, 64.99; H, 4.82; N, 11.66. Found: C, 64.65; H, 4.82; N, 11.45.

General procedure for Suzuki cross-coupling on derivatives 35a-b.

A solution of boronic acid (1.20 mmol; 5.00 equiv), derivative **35** (0.24 mmol; 1.00 equiv), cesium carbonate (0.72 mmol; 3.00 equiv) and tetrakis(triphenylphosphine)palladium(0) (0.01 mmol; 0.04 equiv) in degassed dioxane (2.00 mL) was heated at 90 °C for 3.5 hr. Water and DCM were added in the reaction mixture and the organic phase were extracted. Combined organic layers were washed with brine, dried over Na_2SO_4 and solvents were removed under vacuum. The obtained residue was dissolved in DCM and filtered on Celite®. After having removed solvents under vacuum at 40 °C, the solid obtained was suspended in MeOH, filtered and dried under suction to afford compounds **43a** and **43b**.



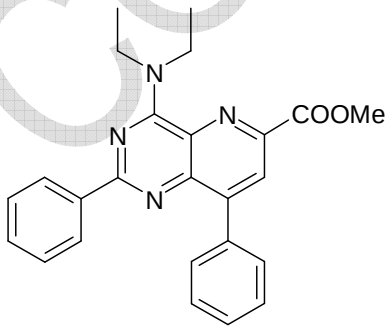
4-(4-Methoxy-phenyl)-2-methylsulfanyl-8-phenyl-pyrido [3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **43a**. Yellow powder. Yield = 82%. mp 226.0-227.0 °C; IR *v*max 1118, 1242, 1439, 1527, 1714, 2361 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.56 (s, 3H), 3.90 (s, 3H), 3.98 (s, 3H), 7.15 (d, *J = 8.9 Hz*, 2H), 7.56-7.58 (m, 3H), 7.91-7.93 (m, 2H), 8.38 (s, 1H), 8.58 (d, *J = 8.9 Hz*, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 14.7, 53.2, 55.5, 113.8, 127.1, 128.0, 128.1, 129.2, 130.6, 134.4, 135.4, 137.0, 145.8, 146.6, 147.0, 162.6, 165.3, 165.8, 170.8; HPLC t_R = 5.77 min; ES-MS *m*/*z* 418.30 $(M + H)^+$; Anal. calcd. for $C_{23}H_{19}N_3O_3S$: C, 66.17; H, 4.59; N, 10.06. Found: C, 65.89; H, 4.49; N, 9.80.



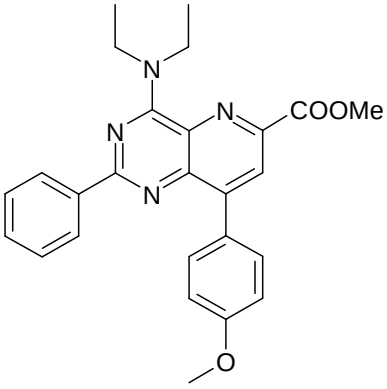
4-(2-Fluoro-phenyl)-2-methylsulfanyl-8-phenyl-pyrido[3,2-*d*] pyrimidine-6-carboxylic acid methyl ester **43b**. Pale yellow powder. Yield = 71%. mp 201-202 °C; IR *v*max 1716, 1537, 1115 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 2.61 (s, 3H), 3.98 (s, 3H), 7.36 (dt, *J_1 = 1.19 Hz*, *J_2 = 7.63 Hz*, 1H), 7.22-7.27 (m, 1H), 7.53-7.57 (m, 4H), 7.80 (dt, *J_1 = 1.87 Hz*, *J_2 = 7.36 Hz*, 1H), 7.90-7.93 (m, 2H), 8.52 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 14.9, 53.2, 116.04 (d, *J = 22 Hz*), 124.04 (d, *J = 3.3 Hz*), 127.7, 128.2, 129.4, 130.6, 132.4 (d, *J = 3.1 Hz*), 132.4 (d, *J = 7.7 Hz*), 135.0, 137.0, 146.0, 146.8, 146.9, 161.0 (d, *J = 252.8 Hz*), 165.6, 166.8, 166.9, 171.0; HPLC t_R = 5.27 min; ES-MS *m/z* 406.20 $(M + H)^+$; Anal. calcd. for $C_{22}H_{16}FN_3O_2S$: C, 65.17; H, 3.98; N, 10.36. Found: C, 65.05; H, 3.96; N, 10.25.

General procedure for Liebeskind-Srogl cross-coupling on derivative 41a

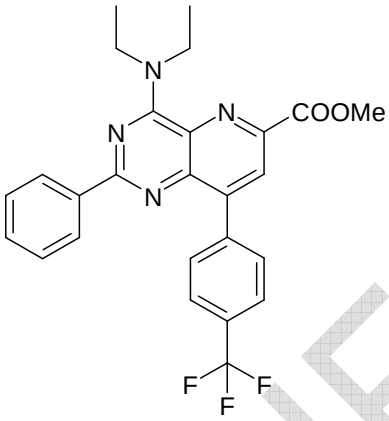
Boronic acid (0.21 mmol; 1.50 equiv), derivative **41a** (0.14 mmol, 1.00 equiv), copper(i) thiophene-2-carboxylate (0.21 mmol; 1.50 equiv), zinc acetate (0.117 mmol; 1.20 equiv) and tetrakis(triphenylphosphine)palladium(0) (0.07mmol; 0.05 equiv) were placed in a flask with dioxane (3.00 mL). The reaction was stirred at 50 °C and monitored by LCMS. After 3.5 hr, $NaHCO_3$ was added in the reaction mixture and extraction was performed with DCM. Combined organic layers were washed with brine, dried over Na_2SO_4 and solvents were removed under vacuum. The obtained residue was dissolved in DCM and filtered on Celite®. After having removed solvents under vacuum at 40 °C , the solid obtained was suspended in MeOH, filtered and dried under suction to afford derivatives **45a** to **45c**.



4-Diethylamino-2,8-diphenyl-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **45a**. Yellow powder. Yield = 84%. mp 147-147 °C; IR *v*max 2921, 1737, 1524, 1231 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.49 (s, 6H), 4.02 (s, 3H), 4.36 (br s, 4H), 7.43-7.45 (m, 3H), 7.49-7.58 (m, 3H), 7.91-7.94 (m, 2H), 8.38 (s, 1H), 8.45-8.49 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 10.9, 13.0, 52.6, 126.6, 128.1, 128.2, 128.7, 128.9, 130.6, 130.7, 136.3, 136.6, 139.2, 142.5, 146.7, 150.2, 151.4, 159.2, 160.8; HPLC t_R = 5.09 min; ES-MS *m/z* 428.99 $(M + H)^+$; Anal. calcd. for $C_{25}H_{24}N_4O_2$: C, 72.80; H, 5.86; N, 13.58. Found: C, 72.58; H, 5.46; N, 13.83.



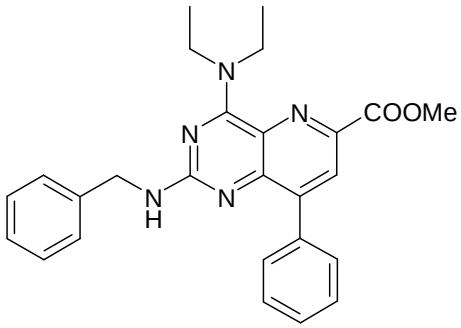
4-Diethylamino-8-(4-methoxy-phenyl)-2-phenyl-pyrido[3,2-*d*] pyrimidine-6-carboxylic acid methyl ester **45b**. Yellow powder. Yield = 88%. mp 165-166 °C; IR *v*max 1715, 1511, 1242 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.49 (s, 6H), 3.93 (s, 3H), 4.02 (s, 3H), 4.33 (s, 4H), 7.10 (d, *J = 8 Hz*, 2H), 7.47 (m, 3H), 7.92 (d, *J = 8 Hz*, 2H), 8.36 (s, 1H), 8.47-8.49 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 13.7, 14.3, 41.1, 46.6, 52.7, 55.4, 113.6, 125.9, 128.2, 128.8, 129.0, 130.4, 132.2, 133.0, 138.7, 142.4, 146.3, 147.1, 159.3, 160.2, 160.7, 165.7; HPLC t_R = 4.93 min; ES-MS *m/z* 443.09 $(M + H)^+$; Anal. calcd. for $C_{26}H_{26}N_4O_3$: C, 70.57; H, 5.92; N, 12.66. Found: C, 70.38; H, 6.05; N, 12.48.



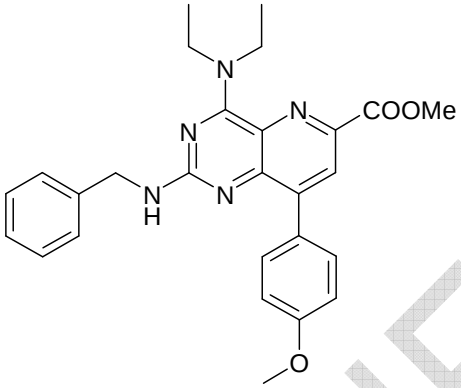
4-Diethylamino-8-(4-trifluoromethyl-phenyl)-2-phenyl-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **45c**. Yellow powder. Yield = 87%. mp 193-194 °C; IR *v*max 1712, 1521, 1320 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.49 (br s, 6H), 4.03 (s, 3H), 4.43 (br s, 4H), 7.45-7.47 (m, 3H), 7.80 (d, *J = 8 Hz*, 2H), 7.98 (d, *J = 8 Hz*, 2H), 8.37 (s, 1H), 8.44-8.46 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 12.1, 14.4, 46.7, 52.8, 124.2 (q, *J = 272.2 Hz*), 125.0 (q, *J = 3.6 Hz*), 126.6, 128.5, 128.9, 130.6 (q, *J = 32.6 Hz*), 130.8, 131.2, 133.2, 138.6, 140.5, 142.5, 145.3, 147.2, 159.2, 161.4, 165.5; HPLC t_R = 6.23 min; ES-MS *m/z* 481.16 $(M + H)^+$.

General procedure for Liebesking-srogl cross-coupling on derivative 34a.

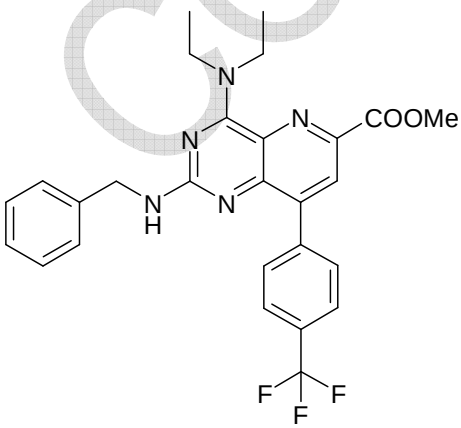
Boronic acid (1.20 mmol; 5.00 equiv), derivative **34a** (0.24 mmol; 1.00 equiv), copper(i) thiophene-2-carboxylate (0.30 mmol; 1.2 equiv), zinc acetate (1.20 mmol; 5.00 equiv) and tetrakis(triphenylphosphine)palladium(0) (0.05 mmol; 0.20 equiv) were placed in a flask with dioxane (1.50 mL). The reaction was stirred 180 °C under MW irradiation for 50 min. After completion of the reaction, an extraction was performed with $NaHCO_3$ and DCM. Combined organic layers were washed with brine, dried over Na_2SO_4 and solvents were removed under vacuum. The obtained residue was dissolved in DCM and filtered on Celite®. After having removed solvents under vacuum at 40 °C, the solid obtained was suspended in MeOH, filtered and dried under suction to afford derivatives **46a** to **46c**.



2-Benzylamino-4-diethylamino-8-phenyl-pyrido[3,2-*d*] pyrimidine-6-carboxylic acid methyl ester **46a**. Yellow powder. Yield = 80%. mp 114-115 °C; IR *v*max 1712, 1530, 1235 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.35 (br s, 6H), 3.96 (br s, 7H), 4.61 (br d, *J* = 6 Hz, 2H), 5.38 (br s, 1H), 7.28 (m, 8H), 7.75 (m, 2H), 8.18 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 13.4, 14.2, 46.0, 52.7, 127.1, 127.3, 127.9, 128.3, 128.5, 128.8, 130.5, 137.6, 138.3, 138.4, 140.5, 143.3, 159.9, 160.1, 166.4, 168.6; HPLC t_R = 4.32 min; ES-MS *m*/*z* 442.17 $(M + H)^+$; Anal. calcd. for $C_{26}H_{27}N_5O_2$: C, 70.73; H, 6.16; N, 15.86. Found: C, 70.56; H, 6.10; N, 15.50.



2-Benzylamino-4-diethylamino-8-(4-methoxy-phenyl)-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **46b**. Orange powder. Yield = 71%. mp 124-125 °C; IR *v*max 1704, 1529, 1232 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.35 (br s, 6H), 3.79 (br s, 2H), 3.86 (s, 3H), 3.96 (s, 3H), 4.09 (br s, 2H), 4.62 (d, *J = 6 Hz*, 2H), 5.30 (s, 1H), 6.93-6.96 (m, 2H), 7.26-7.33 (m, 5H), 7.74-7.76 (m, 2H), 8.16 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 45.6, 46.1, 52.3, 53.4, 55.3, 113.4, 126.2, 126.9, 127.4, 128.4, 129.4, 130.2, 131.5, 138.2, 140.0, 158.9, 159.0, 159.2, 159.3, 159.7, 166.0; HPLC t_R = 4.35 min; ES-MS *m*/*z* 472.32 $(M + H)^+$; Anal. calcd. for $C_{27}H_{29}N_5O_3$: C, 68.77; H, 6.20; N, 14.85. Found: C, 68.53; H, 6.20; N, 14.68;



2-Benzylamino-4-diethylamino-8-(4-trifluoromethyl-phenyl)-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **46c**. Yellow powder. Yield = 76%. mp 134-135 °C; IR *v*max 1696, 1531 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.36 (br s, 6H), 3.33-4.39 (br s, 7H), 4.59 (br s, 2H), 5.40 (br s, 1H), 7.25-7.32 (m, 5H), 7.65 (br s, 2H), 7.83-7.85 (m, 2H), 8.17 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$), δ_C 13.4, 14.1, 29.9, 45.7, 46.2, 52.5, 117.9, 120.7, 124.4 (q, *J = 272.0 Hz*), 124.9 (q, *J = 4.3 Hz*), 126.8, 127.2, 127.5, 128.5, 128.6, 130.0 (q, *J = 31.7 Hz*), 130.6, 138.1, 140.0, 140.9, 159.7, 159.8, 165.9; HPLC t_R = 4.64 min; ES-MS *m*/*z* 510.26 $(M + H)^+$; Anal. calcd. for $C_{27}H_{26}F_3N_5O_2$: C, 63.65; H, 5.14; N, 13.74. Found: C, 63.28; H, 5.25; N, 13.42; Yield = 76%.

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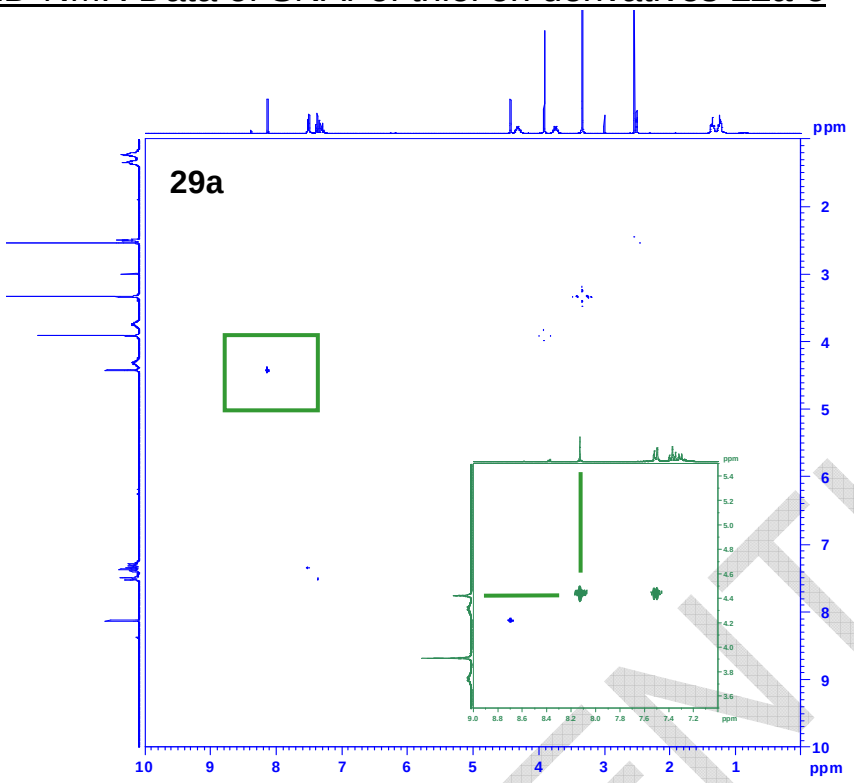
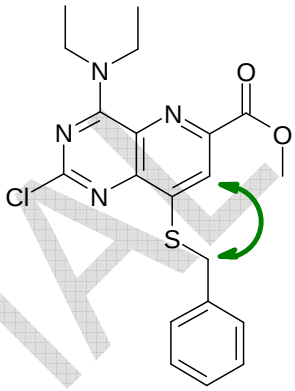
Appendix.

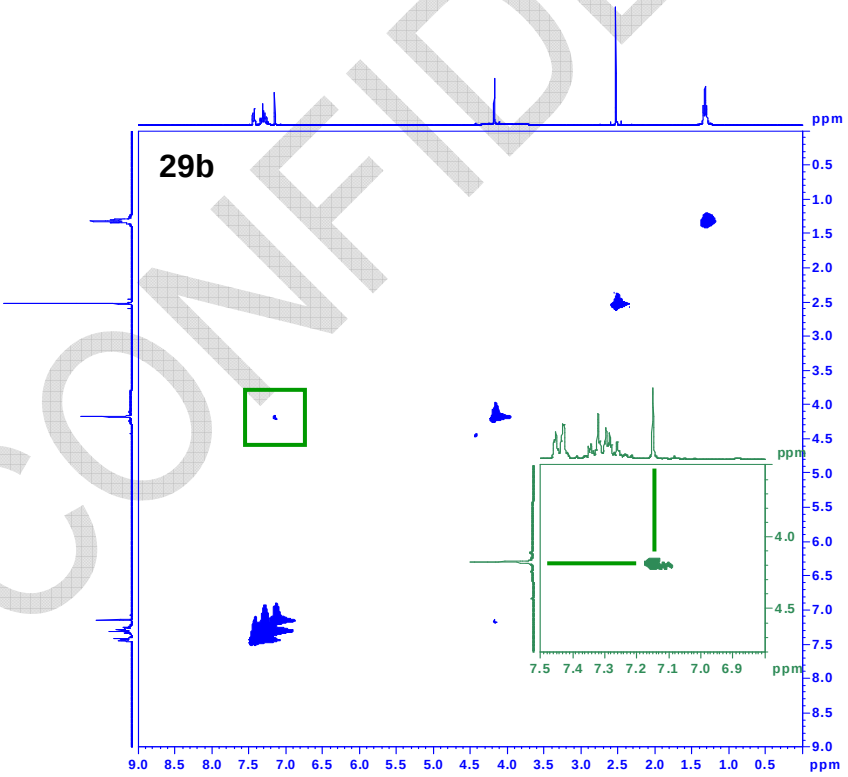
2D-NMR Data of SNAr of thiol on derivatives **12a-c**

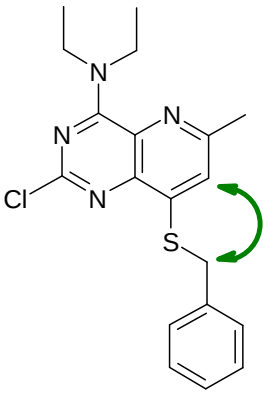




Exact Mass =416

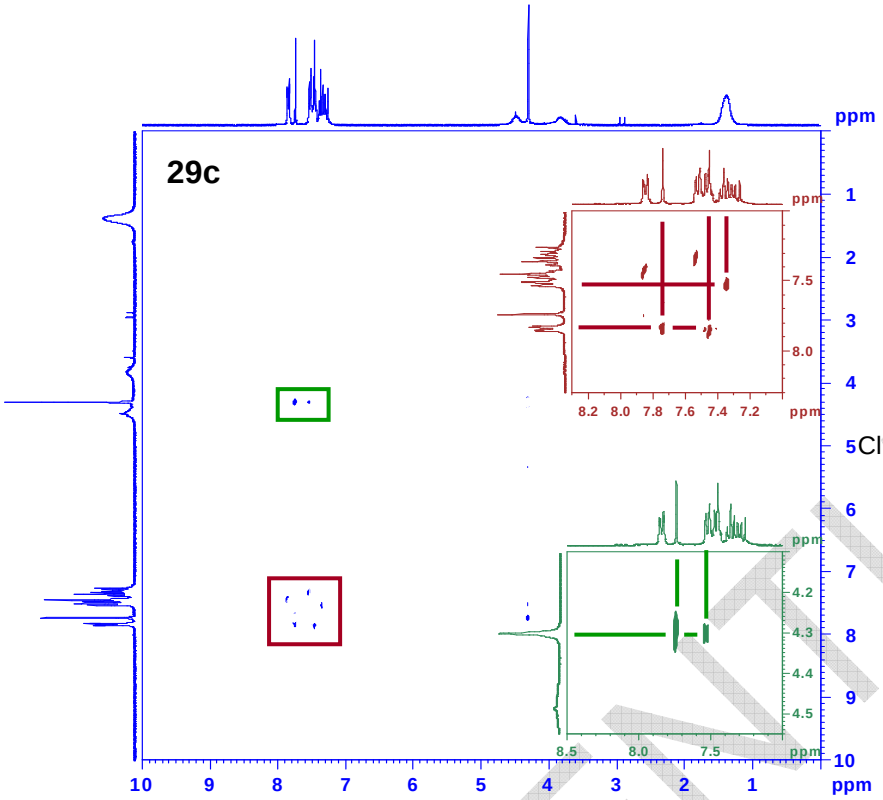
NMR Spectra 4.1. NOESY experiment of derivative **29a.**

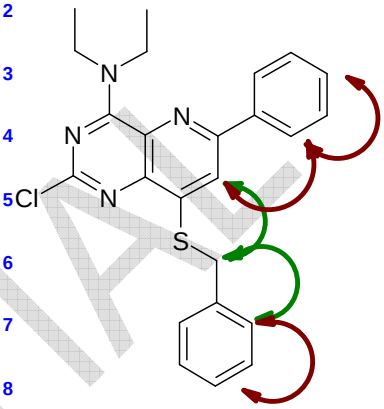




Exact Mass =372

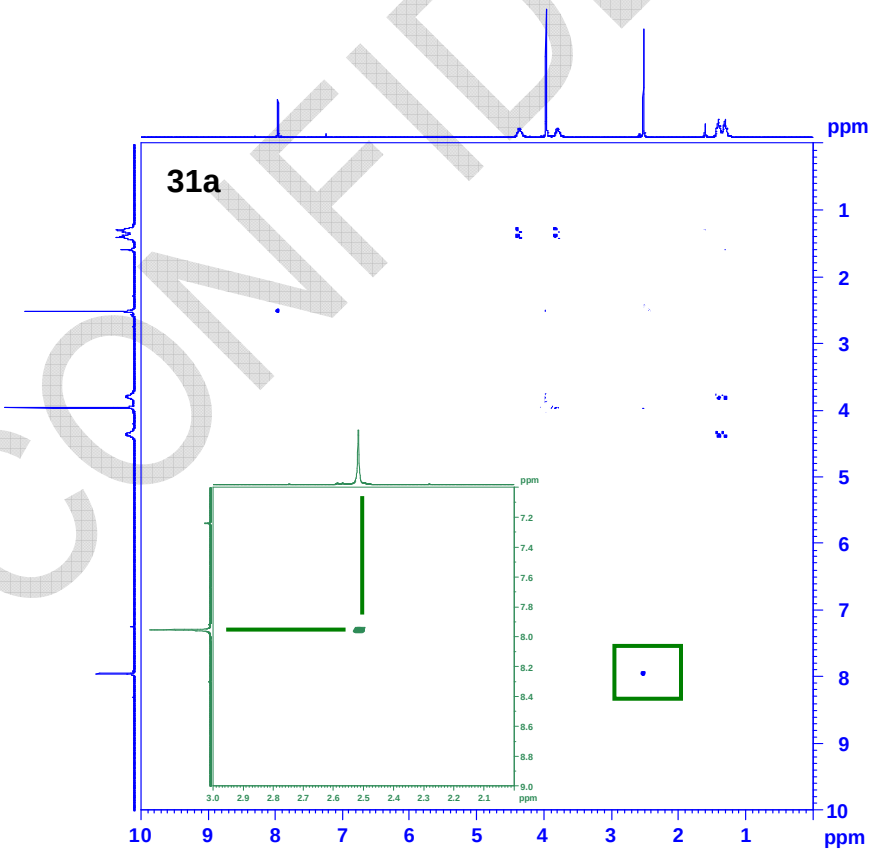
NMR Spectra 4.2.NOESY experiment of derivative **29b.**

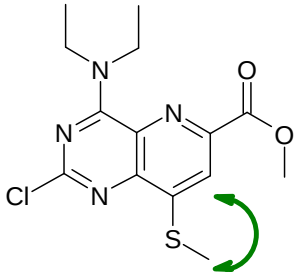




Exact Mass =434

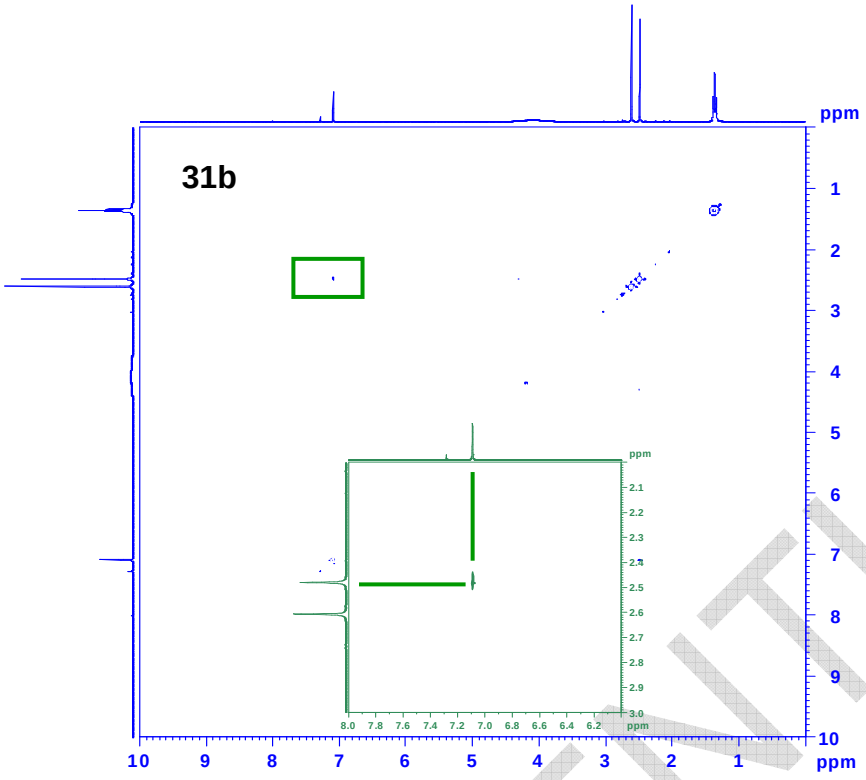
NMR Spectra 4.3. NOESY experiment of derivative **29c.**

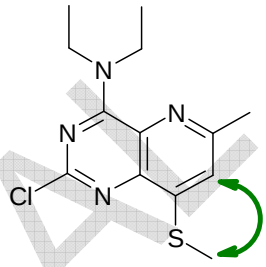




Exact Mass =340

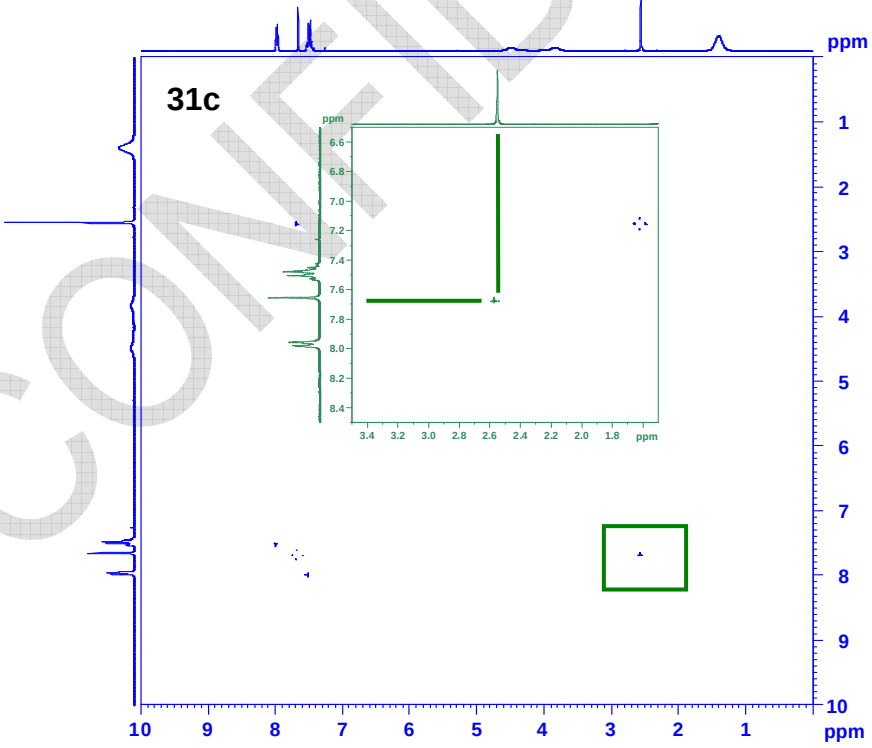
NMR Spectra 4.4. NOESY experiment of derivative **31a.**

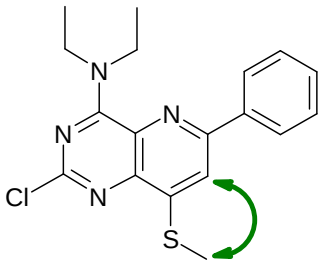




Exact Mass =296

NMR Spectra 4.5. NOESY experiment of derivative **31b.**

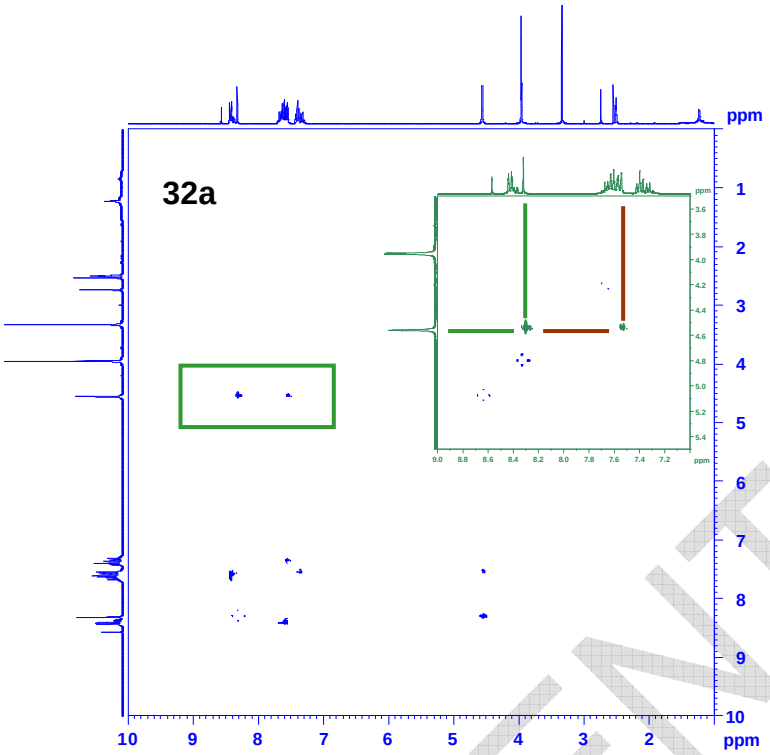


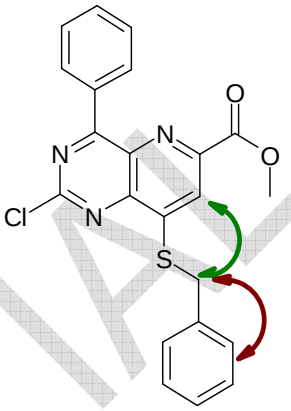


Exact Mass =358

NMR Spectra 4.6. NOESY experiment of derivative 31c.

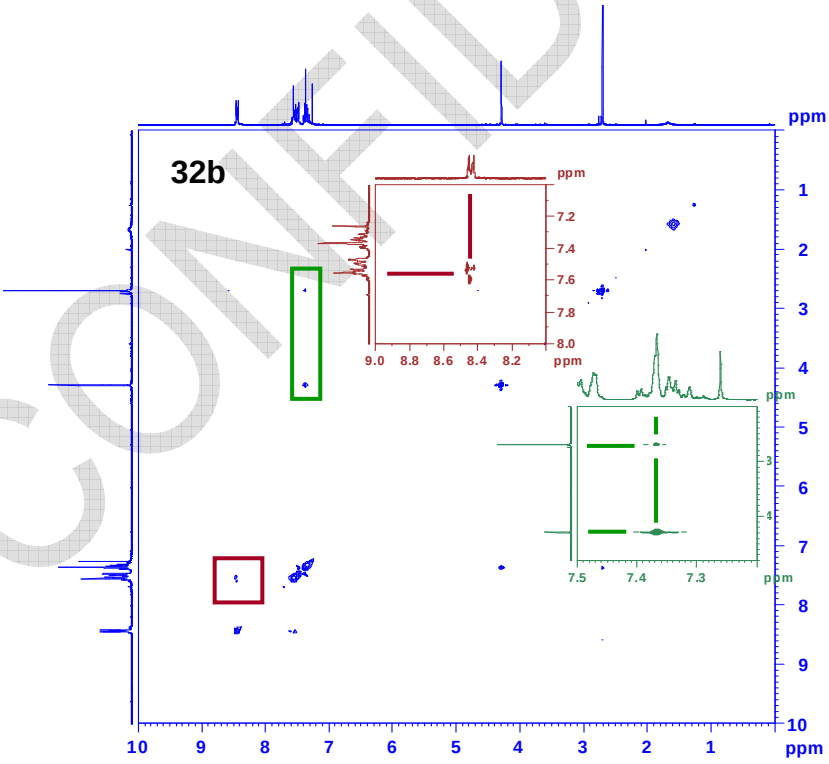
2D-NMR Data of SNAr of thiol on derivatives 15a-c

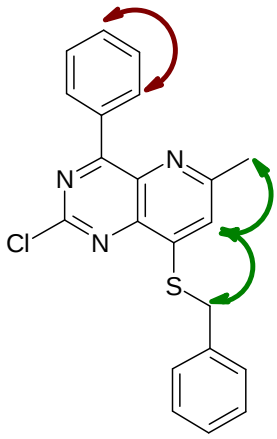




Exact Mass =421
MINOR REGIOISOMER

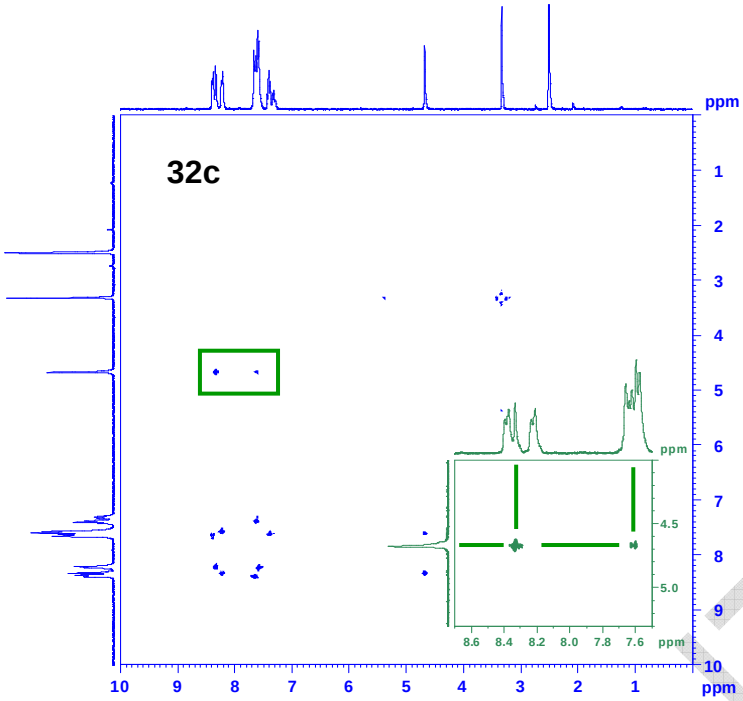
NMR Spectra 4.7. NOESY experiment of derivative **32a**.

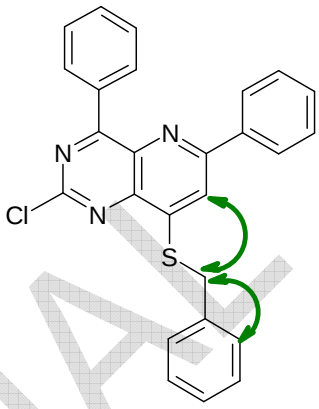




Exact Mass =377
MINOR REGIOISOMER

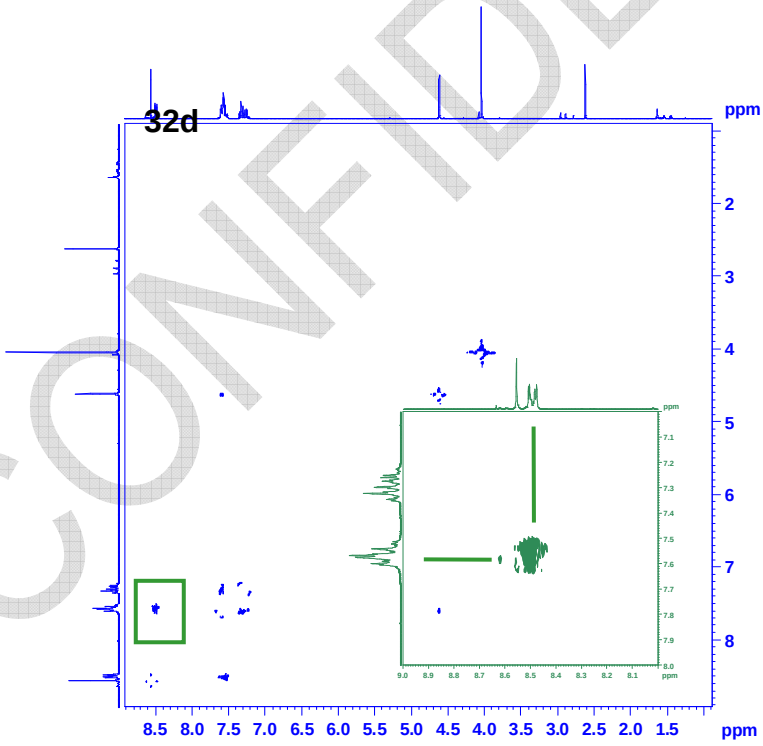
NMR Spectra 4.8. NOESY experiment of derivative **32b**.

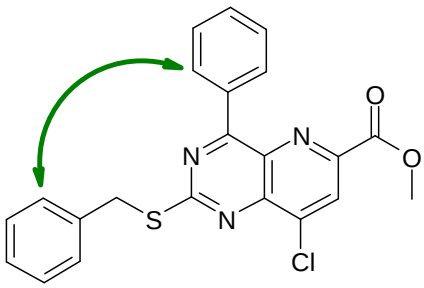




Exact Mass =439
MINOR REGIOISOMER

NMR Spectra 4.9. NOESY experiment of derivative **32c**.

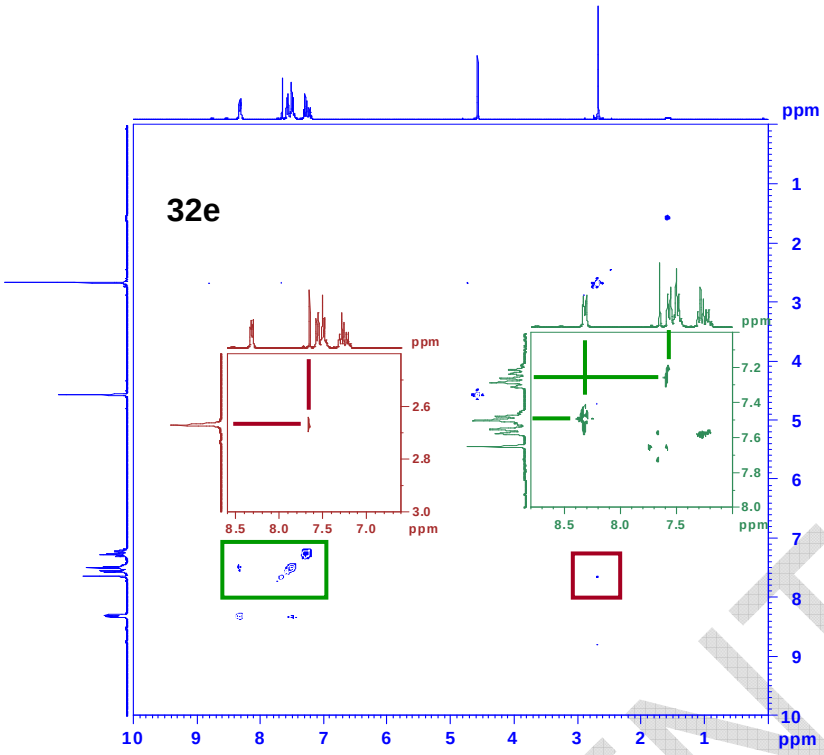


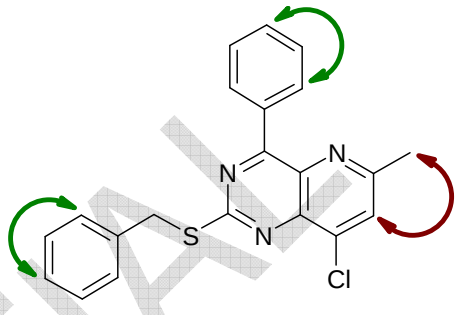


Exact Mass =421

MAJOR REGIOISOMER

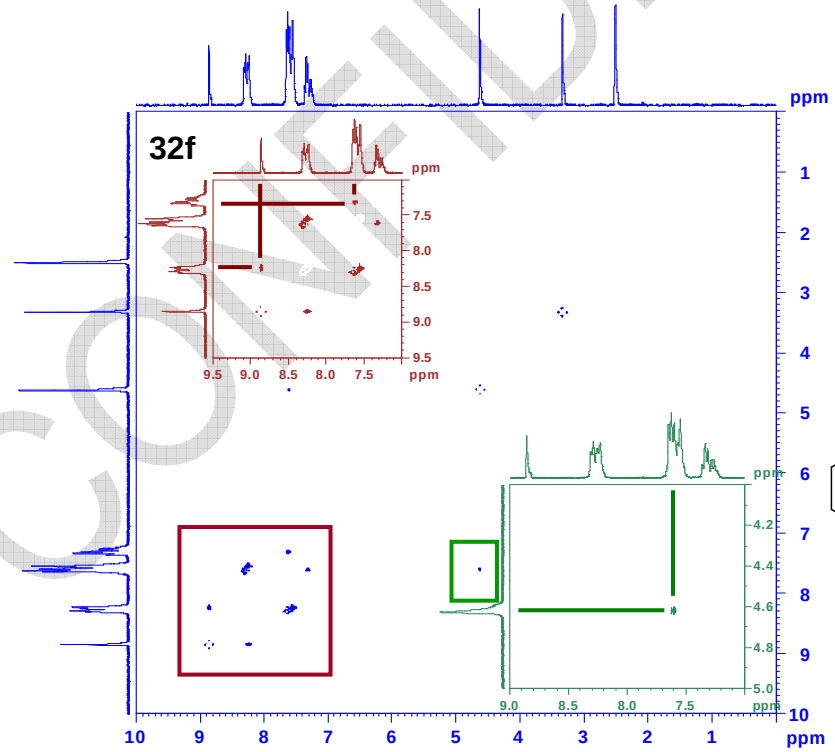
NMR Spectra 4.10. NOESY experiment of derivative **32d**.

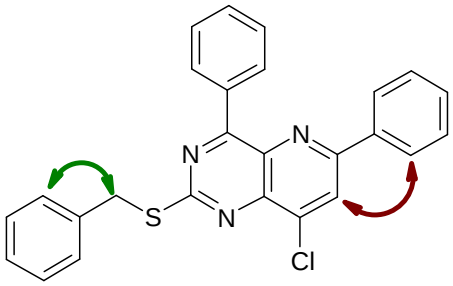




Exact Mass =377
MAJOR REGIOISOMER

NMR Spectra 4.11. NOESY experiment of derivative **32e.**





Exact Mass =439
MAJOR REGIOISOMER

NMR Spectra 4.12. NOESY experiment of derivative **32f**.

Crytallographic Data

Compound **31a**

Formule brute:	$C_{14}H_{17}N_4O_2SCl$
Poids moléculaire:	340.9
Coefficient d'absorption linéaire	μ = 0.382 mm^{-1} (Mo (Kα))
Solvant de recristallisation	?
Densité Do = ?	Dx = 1.419 ($gr.cm^{-3}$)
Diffractomètre	STOE IPDS

Géométrie de la maille

Système cristallin: Monoclinique	Groupe d'espace: $P\,2_1/c$
a = 10.7148 (6) (Å)	α = 90°
b = 20.2974 (8)(Å)	β = 104.928 (7)°
c = 7.5927 (4)(Å)	γ = 90°
V = 1595.6 (1)($Å^3$)	Z = 4
Nombre de réflexions pour l'affinement des paramètres:	8000 (7.8° < 2 θ < 56.0°)

Forme et dimensions du cristal

Forme: prisme; Couleur: transparent
Dimensions: 0.053 x 0.085 x 0.339 mm
Mode de fixation: RS3000

Conditions expérimentales pour la collection des intensités

Température:	220 K	Longueur d'onde	0.7107(Å)
Mode de balayage	φ-scan	$\Delta\varphi$ / image	1.0 (°)
T Irradiation / image	4 (min)	φ min, max =	0 - 300 (°)
Distance cristal / IP	60 (mm)	Nombre d'images	300
EMS	0.008	Moyenne (I/σ(I))	6.5
Limites angulaires	5.7° < 2 θ < 56.0°		
Limites d'indices	-14 < h < 14 ; -26 < k < 26 ; -9 < ℓ < 10		

Nombre de réflexions mesurées: 23'431

Réduction des données

Corrections :	LP	☒	
	Disp. anomale	☒	
	Absorption	☒	T min. , max. = 0.9442 , 0.9831

Nombre de réflexions observables	1710	|Fo|> 4σ(Fo)
Nombre de réflexions non-observables	2027	
Nombre de réflexions uniques	3737	R_{int} pour 19'360 réfl. équivalentes = 0.082

Statistique des réflexions

Facteur de température global	2.64 ($Å^2$)
Distribution des $<E^2>$: centrique	$<E^2-1> = 1.01$

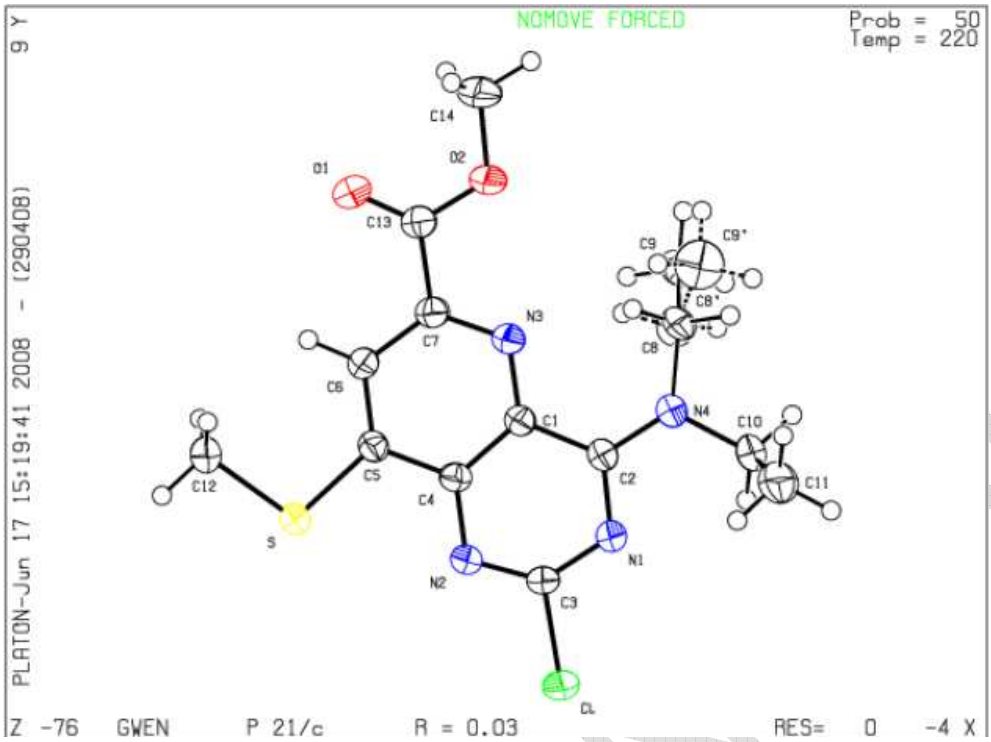
Résolution et affinement de la structure

Résolution:	Méthodes directes (SIR97)
Fonction minimisée :	$\Sigma (\omega (Fo-Fc)^2)$
Fonction de poids :	$\omega = 1/[\sigma^2(Fo) + 0.00015 (Fo^2)]$
Nombre d'atomes affinés "iso" :	2 (C8' , C9')
Nombre d'atomes affinés "aniso":	22
Coordonnées des atomes d'hydrogène:	calculées
Programme	XTAL 3.2

Valeurs obtenues en fin d'affinement

Nombre de variables:	207
Nombre de réflexions :	1915
Nbe reflexions / Nbe de variables	9.3
Affinement par moindres carrés:	Full matrix
"shift/error":	moyen : 0.35 10^{-4} , Maximum : 0.64 10^{-3}
Résidus (delta F) ($eÅ^{-3}$):	-0.54 , 0.46
Configuration absolue: x =	
"Goodness of fit": S =	1.13(1)

Facteur résiduel final	**R = 0.031**
Facteur résiduel pondéré	**ωR = 0.031**



$C_{14}H_{17}N_4O_2SCl$ EX/90 *P* $2_1/c$ 200K IPDS

Bond Distances (Angstroms)

Cl-C3	1.758(3)	S-C5	1.751(3)
S-C12	1.807(3)	O1-C13	1.203(3)
O2-C13	1.327(3)	O2-C14	1.451(4)
N1-C2	1.350(3)	N1-C3	1.332(3)
N2-C3	1.301(3)	N2-C4	1.371(3)
N3-C1	1.356(3)	N3-C7	1.322(3)
N4-C2	1.341(3)	N4-C8	1.494(4)
N4-C10	1.473(3)	C1-C2	1.463(3)
C1-C4	1.409(3)	C4-C5	1.435(3)
C5-C6	1.373(4)	C6-C7	1.406(3)
C7-C13	1.503(4)	C8-C9	1.512(6)
C10-C11	1.503(5)		

Bond Angles (degrees)

C5-S-C12	101.6(1)	C13-O2-C14	115.7(2)
C2-N1-C3	116.9(2)	C3-N2-C4	112.9(2)
C1-N3-C7	117.4(2)	C2-N4-C8	126.5(2)
C2-N4-C10	119.4(2)	C8-N4-C10	112.9(2)
N3-C1-C2	120.8(2)	N3-C1-C4	123.1(2)
C2-C1-C4	116.1(2)	N1-C2-N4	116.6(2)
N1-C2-C1	118.7(2)	N4-C2-C1	124.7(2)
Cl-C3-N1	113.3(2)	Cl-C3-N2	115.0(2)
N1-C3-N2	131.7(2)	N2-C4-C1	123.6(2)

N2-C4-C5	118.4(2)	C1-C4-C5	118.0(2)
S-C5-C4	116.6(2)	S-C5-C6	125.6(2)
C4-C5-C6	117.8(2)	C5-C6-C7	119.5(2)
N3-C7-C6	124.2(2)	N3-C7-C13	117.8(2)
C6-C7-C13	118.0(2)	N4-C8-C9	110.8(3)
N4-C10-C11	111.9(2)	O1-C13-O2	124.2(3)
O1-C13-C7	122.9(2)	O2-C13-C7	112.9(2)

Dihedral Angles (degrees)

C12-S-C5-C4	178.4(2)	C12-S-C5-C6	.0(3)
C14-O2-C13-O1	1.4(5)	C14-O2-C13-C7	-178.2(3)
C3-N1-C2-N4	-179.9(2)	C3-N1-C2-C1	-.4(4)
C2-N1-C3-Cl	178.5(2)	C2-N1-C3-N2	-1.9(4)
C4-N2-C3-Cl	-178.5(2)	C4-N2-C3-N1	1.9(4)
C3-N2-C4-C1	.5(4)	C3-N2-C4-C5	179.6(2)
C7-N3-C1-C2	179.8(2)	C7-N3-C1-C4	-1.2(4)
C1-N3-C7-C6	1.2(4)	C1-N3-C7-C13	178.9(2)
C8-N4-C2-N1	-167.0(3)	C8-N4-C2-C1	13.6(5)
C10-N4-C2-N1	-.6(4)	C10-N4-C2-C1	180.0(3)
C2-N4-C8-C9	-95.5(4)	C10-N4-C8-C9	97.3(3)
C2-N4-C10-C11	-84.8(3)	C8-N4-C10-C11	83.3(3)
N3-C1-C2-N1	-178.6(2)	N3-C1-C2-N4	. 8(4)
C4-C1-C2-N1	2.3(4)	C4-C1-C2-N4	-178.3(3)
N3-C1-C4-N2	178.5(2)	N3-C1-C4-C5	-.6(4)
C2-C1-C4-N2	-2.4(4)	C2-C1-C4-C5	178.5(2)
N2-C4-C5-S	4.7(3)	N2-C4-C5-C6	-176.8(2)
C1-C4-C5-S	-176.2(2)	C1-C4-C5-C6	2.4(4)
S-C5-C6-C7	176.0(2)	C4-C5-C6-C7	-2.3(4)
C5-C6-C7-N3	.5(4)	C5-C6-C7-C13	-177.1(2)
N3-C7-C13-O1	-177.5(3)	N3-C7-C13-O2	2.1(4)
C6-C7-C13-O1	.2(4)	C6-C7-C13-O2	179.9(3)

Compound **31d**.

Formule brute:	$C_{14}H_{17}N_4O_2SCl$
Poids moléculaire:	340.9
Coefficient d'absorption linéaire	μ = 0.390 mm^{-1} (Mo (Kα))
Solvant de recristallisation	$CDCl_3$
Densité Do = ?	Dx = 1.450 ($gr.cm^{-3}$)
Diffractomètre	STOE IPDS

Géométrie de la maille

Système cristallin: Monoclinique	Groupe d'espace: $P2_1/n$
a = 7.4207 (5) (Å)	α = 90°
b = 17.8547 (9)(Å)	β = 100.761 (8)°
c = 11.9918 (9)(Å)	γ = 90°
V = 1560.91) (18)($Å^3$)	Z = 4
Nombre de réflexions pour l'affinement des paramètres:	8000 (8.6°< 2 θ < 51.6°)

Forme et dimensions du cristal

Forme: prisme; Couleur: transparent
Dimensions: 0.136 x 0.19 x 0.21 mm
Mode de fixation: RS3000

Conditions expérimentales pour la collection des intensités

Température: (Å)	150 K	Longueur d'onde	0.7107
Mode de balayage	φ-scan	$\Delta\varphi$ / image	1.3 (°)
T Irradiation / image (°)	4 (min)	φ min, max =	0 - 202.2
Distance cristal / IP	70 (mm)	Nombre d'images	156
EMS	0.009	Moyenne (I/σ(I))	13.6
Limites angulaires	5.7°< 2 θ < 51.6°		
Limites d'indices	-9 < h < 9 ; -21 < k < 21 ; -14 < ℓ < 14		

Nombre de réflexions mesurées: 12'479

Réduction des données

Corrections :	LP	☒	
	Disp. anomale	☒	
	Absorption	☒	T min. , max. = 0.9623 , 0.9556

Nombre de réflexions observables	2112	**|Fo| > 3σ(Fo)**
Nombre de réflexions non-observables	885	
Nombre de réflexions uniques	2997	R_{int} pour 9241 réfl. équivalentes = 0.040

Statistique des réflexions

Facteur de température global	2.8 ($Å^2$)
Distribution des $<E^2>$: centrique	$<E^2-1> = 1.004$

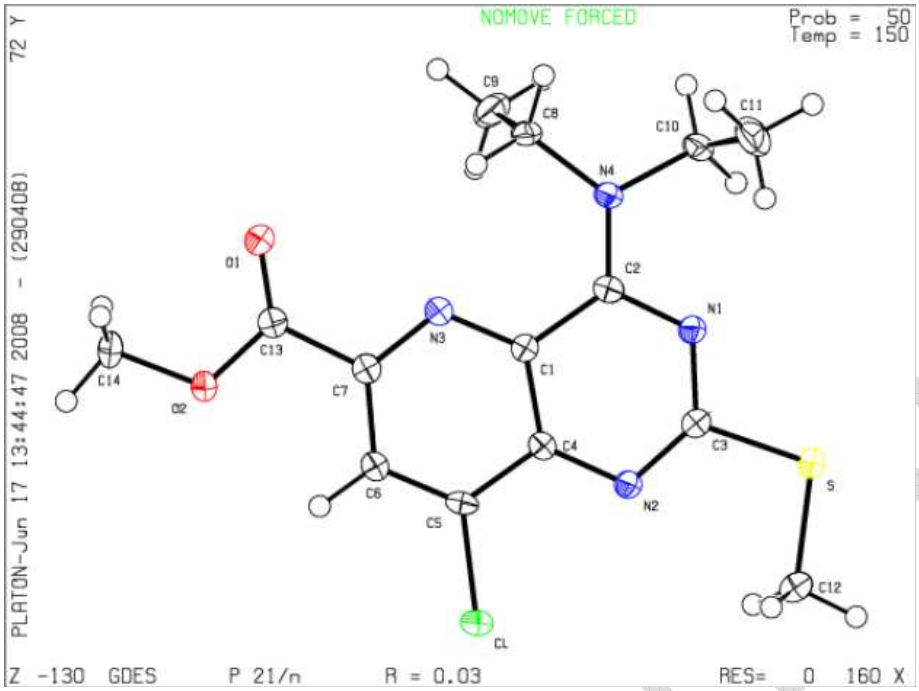
Résolution et affinement de la structure

Résolution:	Méthodes directes (SIR97)
Fonction minimisée :	$\Sigma (\omega (Fo-Fc)^2)$
Fonction de poids :	$\omega = 1/[\sigma^2(Fo) + 0.00015 (Fo^2)]$
Nombre d'atomes affinés "iso" :	-
Nombre d'atomes affinés "aniso":	22
Coordonnées des atomes d'hydrogène:	calculées
Programme	XTAL 3.2

Valeurs obtenues en fin d'affinement

Nombre de variables:	199
Nombre de réflexions :	2166
Nbe reflexions / Nbe de variables	10.9
Affinement par moindres carrés:	Full matrix
"shift/error":	moyen : 0.38 10^{-4} , Maximum : 0.40 10^{-3}
Résidus (delta F) ($eÅ^{-3}$):	-0.60 , 0.48
"Goodness of fit": S =	1.28(2)

Facteur résiduel final	**R = 0.030**
Facteur résiduel pondéré	**ωR = 0.030**



$C_{14}H_{17}N_4O_2SCl$ EX/98 $P2_1/n$ 150K IPDS

Bond Distances (Angstroms)

Cl-C5	1.736(2)	S-C3	1.762(2)
S-C12	1.796(2)	O1-C13	1.207(2)
O2-C13	1.348(2)	O2-C14	1.447(2)
N1-C2	1.338(2)	N1-C3	1.349(2)
N2-C3	1.318(3)	N2-C4	1.358(2)
N3-C1	1.346(2)	N3-C7	1.328(3)
N4-C2	1.352(2)	N4-C8	1.478(2)
N4-C10	1.477(3)	C1-C2	1.472(3)
C1-C4	1.431(3)	C4-C5	1.420(3)
C5-C6	1.362(2)	C6-C7	1.409(3)
C7-C13	1.507(2)	C8-C9	1.510(3)
C10-C11	1.522(3)		

Bond Angles (degrees)

C3-S-C12	101.86(9)	C13-O2-C14	115.7(1)
C2-N1-C3	118.4(2)	C3-N2-C4	113.8(2)
C1-N3-C7	118.5(2)	C2-N4-C8	127.2(2)
C2-N4-C10	117.9(1)	C8-N4-C10	114.6(2)
N3-C1-C2	121.9(2)	N3-C1-C4	123.3(2)
C2-C1-C4	114.8(2)	N1-C2-N4	115.9(2)
N1-C2-C1	119.2(2)	N4-C2-C1	124.9(2)
S-C3-N1	111.7(1)	S-C3-N2	119.0(1)
N1-C3-N2	129.3(2)	N2-C4-C1	124.5(2)
N2-C4-C5	120.2(2)	C1-C4-C5	115.4(2)
Cl-C5-C4	118.3(1)	Cl-C5-C6	120.2(2)
C4-C5-C6	121.4(2)	C5-C6-C7	118.0(2)
N3-C7-C6	123.4(2)	N3-C7-C13	115.4(2)

C6-C7-C13	121.2(2)	N4-C8-C9	111.8(2)
N4-C10-C11	113.1(2)	O1-C13-O2	124.0(2)
O1-C13-C7	125.4(2)	O2-C13-C7	110.7(2)

Dihedral Angles (degrees)

C12-S-C3-N1	178.9(1)	C12-S-C3-N2	-1.5(2)
C14-O2-C13-O1	1.9(3)	C14-O2-C13-C7	-177.9(2)
C3-N1-C2-N4	-178.3(2)	C3-N1-C2-C1	1.2(3)
C2-N1-C3-S	178.8(1)	C2-N1-C3-N2	-.8(3)
C4-N2-C3-S	-179.6(1)	C4-N2-C3-N1	-.0(3)
C3-N2-C4-C1	.4(3)	C3-N2-C4-C5	179.9(2)
C7-N3-C1-C2	-180.0(2)	C7-N3-C1-C4	.9(3)
C1-N3-C7-C6	-1.2(3)	C1-N3-C7-C13	-179.5(2)
C8-N4-C2-N1	177.5(2)	C8-N4-C2-C1	-1.9(3)
C10-N4-C2-N1	4.9(3)	C10-N4-C2-C1	-174.5(2)
C2-N4-C8-C9	-88.6(2)	C10-N4-C8-C9	84.2(2)
C2-N4-C10-C11	-84.8(2)	C8-N4-C10-C11	101.6(2)
N3-C1-C2-N1	180.0(2)	N3-C1-C2-N4	-.6(3)
C4-C1-C2-N1	-.8(3)	C4-C1-C2-N4	178.6(2)
N3-C1-C4-N2	179.2(2)	N3-C1-C4-C5	-.3(3)
C2-C1-C4-N2	-.0(3)	C2-C1-C4-C5	-179.5(2)
N2-C4-C5-Cl	.1(3)	N2-C4-C5-C6	-179.6(2)
C1-C4-C5-Cl	179.6(1)	C1-C4-C5-C6	-.1(3)
Cl-C5-C6-C7	-179.8(1)	C4-C5-C6-C7	-.1(3)
C5-C6-C7-N3	.8(3)	C5-C6-C7-C13	179.0(2)
N3-C7-C13-O1	-4.2(3)	N3-C7-C13-O2	175.5(2)
C6-C7-C13-O1	177.4(2)	C6-C7-C13-O2	-2.8(3)

Compound **38b**

Formule brute:	$C_{20}H_{22}N_4O_2S$
Poids moléculaire:	382.5
Coefficient d'absorption linéaire	μ = 0.198 mm^{-1} (Mo (Kα))
Solvant de recristallisation	CDCl3
Densité Do = ?	Dx = 1.366 ($gr.cm^{-3}$)
Diffractomètre	STOE IPDS

Géométrie de la maille

Système cristallin: Triclinique	Groupe d'espace: $P\ \bar{1}$
a = 7.8181 (10) (Å)	α = 89.577 (15)°
b = 10.9830 (13)(Å)	β = 79.907 (15)°
c = 11.1607 (15)(Å)	γ = 80.382 (15)°
V = 930.0 (2)($Å^3$)	Z = 2
Nombre de réflexions pour l'affinement des paramètres:	5929 (5.3° < 2 θ < 51.0°)

Forme et dimensions du cristal

Forme: prisme; Couleur: jaune
Dimensions: 0.089 x 0.119 x 0.320 mm
Mode de fixation: RS3000

Conditions expérimentales pour la collection des intensités

Température:	150 K	Longueur d'onde (Å)	0.7107
Mode de balayage	φ-scan	$\Delta\varphi$ / image	2 (°)
T Irradiation / image (°)	5 (min)	φ min, max =	0 - 270
Distance cristal / IP	70 (mm)	Nombre d'images	135
EMS	0.009	Moyenne (I/σ(I))	10.4
Limites angulaires	5.3° < 2 θ < 51.0°		
Limites d'indices	-9 < h < 9 ; -13 < k < 13 ; -13 < ℓ < 13		

Nombre de réflexions mesurées: 9958

Réduction des données

Corrections :	LP	☒	
	Disp. anomale	☒	
	Absorption	☒	T min. , max. = 0.9704 , 0.9829

Nombre de réflexions observables	2033	|Fo| > 4σ(Fo)
Nombre de réflexions non-observables	1375	
Nombre de réflexions uniques	3408	R_{int} pour 6550 réfl. équivalentes =

0.048

Statistique des réflexions

Facteur de température global	1.61 ($Å^2$)
Distribution des $<E^2>$: centrique	$<E^2-1> = 1.031$

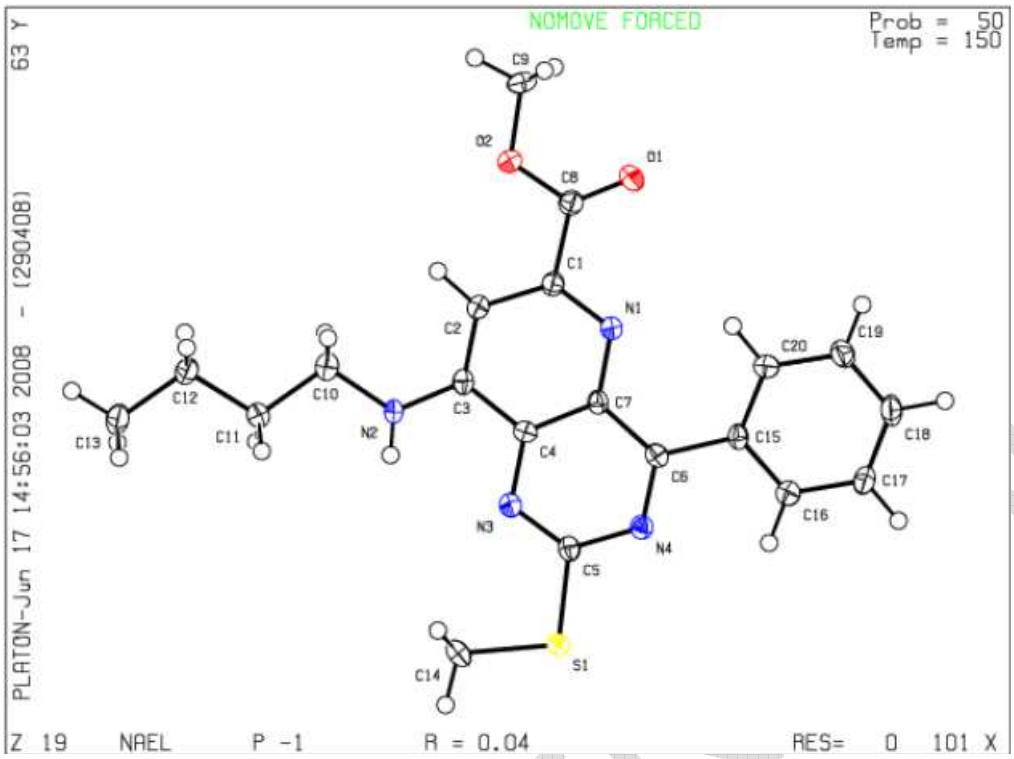
Résolution et affinement de la structure

Résolution:	Méthodes directes (SIR97)
Fonction minimisée :	$\Sigma\ (\omega\ (Fo-Fc)^2)$
Fonction de poids :	$\omega = 1/[\sigma^2(Fo) + 0.0002\ (Fo^2)]$
Nombre d'atomes affinés "iso" :	1 (H02)
Nombre d'atomes affinés "aniso":	27
Coordonnées des atomes d'hydrogène:	mixtes (voir remarques)
Programme	XTAL 3.2

Valeurs obtenues en fin d'affinement

Nombre de variables:	247
Nombre de réflexions :	2104
Nbe reflexions / Nbe de variables	8.5
Affinement par moindres carrés:	Full matrix
"shift/error":	moyen : 0.27 10^{-4} , Maximum : 0.56 10^{-3}
Résidus (delta F) ($eÅ^{-3}$):	-0.51 , 0.51
"Goodness of fit": S =	1.16(2)

Facteur résiduel final R = 0.036
Facteur résiduel pondéré ωR = 0.035



$C_{20}H_{22}N_4O_2S$ EX/94 $P\bar{1}$ 150K IPDS

Bond Distances (Angstroms)

S1-C5	1.758(2)	S1-C14	1.807(3)
O1-C8	1.204(3)	O2-C8	1.347(3)
O2-C9	1.444(3)	N1-C1	1.327(3)
N1-C7	1.364(3)	N2-C3	1.364(3)
N2-C10	1.455(3)	N3-C4	1.363(3)
N3-C5	1.319(3)	N4-C5	1.365(3)
N4-C6	1.330(3)	C1-C2	1.414(4)
C1-C8	1.510(3)	C2-C3	1.386(3)
C3-C4	1.437(3)	C4-C7	1.417(3)
C6-C7	1.442(3)	C6-C15	1.508(3)
C10-C11	1.524(4)	C11-C12	1.530(3)
C12-C13	1.528(4)	C15-C16	1.399(3)
C15-C20	1.401(3)	C16-C17	1.396(4)
C17-C18	1.386(4)	C18-C19	1.390(4)
C19-C20	1.397(4)		

Bond Angles (degrees)

C5-S1-C14	101.4(1)	C8-O2-C9	115.3(2)
C1-N1-C7	116.9(2)	C3-N2-C10	122.8(2)
C4-N3-C5	115.4(2)	C5-N4-C6	118.3(2)
N1-C1-C2	125.4(2)	N1-C1-C8	114.8(2)
C2-C1-C8	119.8(2)	C1-C2-C3	118.5(2)

N2-C3-C2	124.3(2)	N2-C3-C4	118.1(2)
C2-C3-C4	117.7(2)	N3-C4-C3	117.8(2)
N3-C4-C7	123.3(2)	C3-C4-C7	118.9(2)
S1-C5-N3	120.0(2)	S1-C5-N4	112.9(2)
N3-C5-N4	127.1(2)	N4-C6-C7	120.4(2)
N4-C6-C15	115.0(2)	C7-C6-C15	124.6(2)
N1-C7-C4	122.6(2)	N1-C7-C6	121.9(2)
C4-C7-C6	115.5(2)	O1-C8-O2	124.0(2)
O1-C8-C1	124.6(2)	O2-C8-C1	111.4(2)
N2-C10-C11	110.5(2)	C10-C11-C12	112.6(2)
C11-C12-C13	112.3(2)	C6-C15-C16	117.5(2)
C6-C15-C20	124.0(2)	C16-C15-C20	118.5(2)
C15-C16-C17	121.3(2)	C16-C17-C18	119.6(2)
C17-C18-C19	119.8(3)	C18-C19-C20	120.8(2)
C15-C20-C19	120.0(2)		

Dihedral Angles (degrees)

C14-S1-C5-N3	-1.8(2)	C14-S1-C5-N4	178.6(2)
C9-O2-C8-O1	-.3(3)	C9-O2-C8-C1	179.0(2)
C7-N1-C1-C2	-1.6(4)	C7-N1-C1-C8	175.5(2)
C1-N1-C7-C4	1.1(3)	C1-N1-C7-C6	-178.9(2)
C10-N2-C3-C2	-6.8(4)	C10-N2-C3-C4	173.1(2)
C3-N2-C10-C11	-178.4(2)	C5-N3-C4-C3	-179.9(2)
C5-N3-C4-C7	-.8(3)	C4-N3-C5-S1	-178.6(2)
C4-N3-C5-N4	.9(4)	C6-N4-C5-S1	178.8(2)
C6-N4-C5-N3	-.7(4)	C5-N4-C6-C7	.3(3)
C5-N4-C6-C15	-177.8(2)	N1-C1-C2-C3	1.4(4)
C8-C1-C2-C3	-175.6(2)	N1-C1-C8-O1	-6.9(4)
N1-C1-C8-O2	173.8(2)	C2-C1-C8-O1	170.4(2)
C2-C1-C8-O2	-8.9(3)	C1-C2-C3-N2	179.4(2)
C1-C2-C3-C4	-.6(3)	N2-C3-C4-N3	-.6(3)
N2-C3-C4-C7	-179.8(2)	C2-C3-C4-N3	179.3(2)
C2-C3-C4-C7	.1(3)	N3-C4-C7-N1	-179.5(2)
N3-C4-C7-C6	.4(3)	C3-C4-C7-N1	-.4(4)
C3-C4-C7-C6	179.6(2)	N4-C6-C7-N1	179.7(2)
N4-C6-C7-C4	-.2(3)	C15-C6-C7-N1	-2.4(4)
C15-C6-C7-C4	177.7(2)	N4-C6-C15-C16	15.7(3)
N4-C6-C15-C20	-164.2(2)	C7-C6-C15-C16	-162.3(2)
C7-C6-C15-C20	17.8(4)	N2-C10-C11-C12	176.7(2)
C10-C11-C12-C13	175.5(2)	C6-C15-C16-C17	178.6(2)
C20-C15-C16-C17	-1.5(4)	C6-C15-C20-C19	-179.0(2)
C16-C15-C20-C19	1.1(4)	C15-C16-C17-C18	.7(4)
C16-C17-C18-C19	.6(4)	C17-C18-C19-C20	-1.1(4)
C18-C19-C20-C15	.2(4)		

Compound **43b**

Formule brute:	$(C_{22}H_{16}FN3O2S)\ (CHCl_3)$
Poids moléculaire:	524.8
Coefficient d'absorption linéaire	μ = 0.521 mm^{-1} (Mo (Kα))
Solvant de recristallisation	$CHCl_3$
Densité Do = ?	Dx = 1.505 ($gr.cm^{-3}$)
Diffractomètre	STOE IPDS

Géométrie de la maille

Système cristallin: Monoclinique	Groupe d'espace: $P2_1/c$
a = 6.2048 (3) (Å)	α = 90°
b = 15.3606 (7)(Å)	β = 96.664 (6)°
c = 24.4694 (12)(Å)	γ = 90°
V = 2316.4 (2)($Å^3$)	Z = 4
Nombre de réflexions pour l'affinement des paramètres:	8000 (6.6° < 2 θ < 51.8°)

Forme et dimensions du cristal

Forme: prisme; Couleur: jaune clair
Dimensions: 0.111 x 0.178 x 0.213 mm
Mode de fixation: RS3000

Conditions expérimentales pour la collection des intensités

Température:	150 K	Longueur d'onde (Å)	0.7107
Mode de balayage	φ-scan	$\Delta\varphi$ / image	1.0 (°)
T Irradiation / image (°)	3 (min)	φ min, max =	0 - 270
Distance cristal / IP	70 (mm)	Nombre d'images	270
EMS	0.008	Moyenne (I/σ(I))	9.94
Limites angulaires	4.4° < 2 θ < 51.8°		
Limites d'indices	-7 < h < 7 ; -18 < k < 18 ; -30 < ℓ < 30		

Nombre de réflexions mesurées: 20'424

Réduction des données

Corrections :	LP	☒	
	Disp. anomale	☒	
	Absorption	☒	T min. , max. = 0.8946 , 0.9494

Nombre de réflexions observables	2574	|Fo| > 4σ(Fo)
Nombre de réflexions non-observables	1927	
Nombre de réflexions uniques	4501	R_{int} pour 15'518 réfl. équivalentes = 0.058

Statistique des réflexions

Facteur de température global	2.47 ($Å^2$)
Distribution des $<E^2>$: centrique	$<E^2-1> = 0.994$

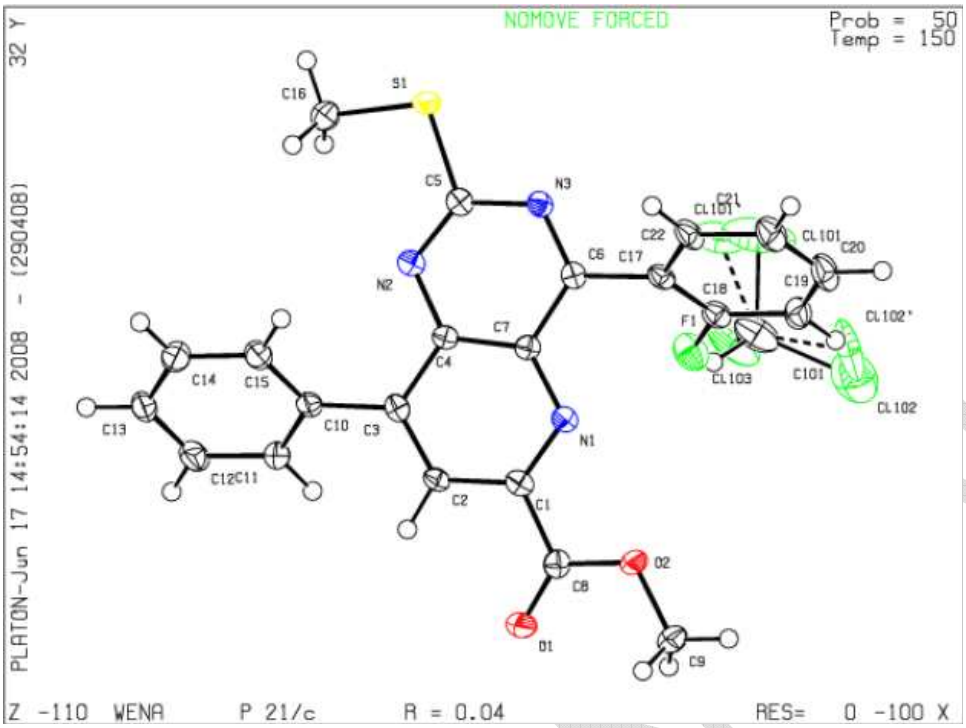
Résolution et affinement de la structure

Résolution:	Méthodes directes (SIR97)
Fonction minimisée :	$\Sigma\ (\omega\ (Fo-Fc)^2)$
Fonction de poids :	$\omega = 1/[\sigma^2(Fo) + 0.0002\ (Fo^2)]$
Nombre d'atomes affinés "iso" :	-
Nombre d'atomes affinés "aniso":	35
Coordonnées des atomes d'hydrogène:	calculées
Programme	XTAL 3.2

Valeurs obtenues en fin d'affinement

Nombre de variables:	316
Nombre de réflexions :	2662
Nbe reflexions / Nbe de variables	8.4
Affinement par moindres carrés:	Full matrix
"shift/error":	moyen : 0.31 10^{-4} , Maximum : 0.36 10^{-3}
Résidus (delta F) ($eÅ^{-3}$):	-0.65 , 0.87
"Goodness of fit": S =	1.29(1)

Facteur résiduel final R = 0.041
Facteur résiduel pondéré ωR = 0.039



($C_{22}H_{16}FN3O2S$) ($CHCl_3$) EX/95 $P2_1/c$ 150K IPDS

Bond Distances (Angstroms)

S1-C5	1.754(3)	S1-C16	1.806(3)
F1-C18	1.338(3)	O1-C8	1.216(3)
O2-C8	1.335(3)	O2-C9	1.447(4)
N1-C1	1.327(3)	N1-C7	1.358(4)
N2-C4	1.369(4)	N2-C5	1.317(3)
N3-C5	1.374(3)	N3-C6	1.321(4)
C1-C2	1.416(4)	C1-C8	1.494(4)
C2-C3	1.370(4)	C3-C4	1.444(4)
C3-C10	1.493(4)	C4-C7	1.416(4)
C6-C7	1.442(4)	C6-C17	1.499(4)
C10-C11	1.406(4)	C10-C15	1.389(5)
C11-C12	1.400(4)	C12-C13	1.383(5)
C13-C14	1.389(4)	C14-C15	1.394(4)
C17-C18	1.380(4)	C17-C22	1.412(4)
C18-C19	1.386(4)	C19-C20	1.397(5)
C20-C21	1.379(5)	C21-C22	1.400(4)
C101-Cl101	1.750(5)	C101-Cl101'	1.80(1)
C101-Cl102	1.802(7)	C101-Cl102'	1.63(2)
C101-Cl103	1.763(4)	C101-Cl103	1.763(4)

Bond Angles (degrees)

C5-S1-C16	102.6(1)	C8-O2-C9	115.6(2)
C1-N1-C7	116.0(2)	C4-N2-C5	116.0(2)
C5-N3-C6	117.1(2)	N1-C1-C2	123.8(3)
N1-C1-C8	118.8(2)	C2-C1-C8	117.4(2)
C1-C2-C3	121.5(2)	C2-C3-C4	116.1(2)

C2-C3-C10	121.3(2)	C4-C3-C10	122.6(3)
N2-C4-C3	120.1(2)	N2-C4-C7	121.9(2)
C3-C4-C7	117.9(2)	S1-C5-N2	121.6(2)
S1-C5-N3	110.8(2)	N2-C5-N3	127.5(3)
N3-C6-C7	121.3(2)	N3-C6-C17	116.4(2)
C7-C6-C17	122.3(2)	N1-C7-C4	124.7(2)
N1-C7-C6	119.0(2)	C4-C7-C6	116.3(2)
O1-C8-O2	123.4(3)	O1-C8-C1	122.9(3)
O2-C8-C1	113.6(2)	C3-C10-C11	118.8(3)
C3-C10-C15	122.3(3)	C11-C10-C15	118.9(3)
C10-C11-C12	120.0(3)	C11-C12-C13	120.4(3)
C12-C13-C14	119.7(3)	C13-C14-C15	120.3(3)
C10-C15-C14	120.7(3)	C6-C17-C18	122.6(2)
C6-C17-C22	118.6(3)	C18-C17-C22	118.7(3)
F1-C18-C17	118.9(2)	F1-C18-C19	118.5(3)
C17-C18-C19	122.6(3)	C18-C19-C20	118.4(3)
C19-C20-C21	120.3(3)	C20-C21-C22	121.1(3)
C17-C22-C21	118.9(3)	Cl101'-C101-Cl102'	114.4(6)
Cl101-C101-Cl102	108.1(3)	Cl101'-C101-Cl103	103.7(3)
Cl101-C101-Cl103	112.7(2)	Cl102'-C101-Cl103	116.6(6)
Cl102-C101-Cl103	108.2(3)		

Dihedral Angles (degrees)

C16-S1-C5-N2	-5.0(3)	C16-S1-C5-N3	173.1(2)
C9-O2-C8-O1	-3.6(4)	C9-O2-C8-C1	178.1(2)
C7-N1-C1-C2	-2.7(4)	C7-N1-C1-C8	177.9(2)
C1-N1-C7-C4	3.0(4)	C1-N1-C7-C6	-178.1(2)
C5-N2-C4-C3	-179.5(2)	C5-N2-C4-C7	-.7(4)
C4-N2-C5-S1	177.4(2)	C4-N2-C5-N3	-.4(4)
C6-N3-C5-S1	-177.0(2)	C6-N3-C5-N2	1.0(4)
C5-N3-C6-C7	-.6(4)	C5-N3-C6-C17	179.4(2)
N1-C1-C2-C3	.6(4)	C8-C1-C2-C3	-179.9(3)
N1-C1-C8-O1	-174.8(3)	N1-C1-C8-O2	3.5(4)
C2-C1-C8-O1	5.7(4)	C2-C1-C8-O2	-175.9(2)
C1-C2-C3-C4	1.2(4)	C1-C2-C3-C10	-178.2(3)
C2-C3-C4-N2	178.0(3)	C2-C3-C4-C7	-.9(4)
C10-C3-C4-N2	-2.6(4)	C10-C3-C4-C7	178.5(3)
C2-C3-C10-C11	-42.7(4)	C2-C3-C10-C15	134.5(3)
C4-C3-C10-C11	137.9(3)	C4-C3-C10-C15	-44.8(4)
N2-C4-C7-N1	179.9(3)	N2-C4-C7-C6	1.0(4)
C3-C4-C7-N1	-1.3(4)	C3-C4-C7-C6	179.9(2)
N3-C6-C7-N1	-179.3(2)	N3-C6-C7-C4	-.4(4)
C17-C6-C7-N1	.8(4)	C17-C6-C7-C4	179.7(2)
N3-C6-C17-C18	-123.2(3)	N3-C6-C17-C22	53.4(3)
C7-C6-C17-C18	56.7(4)	C7-C6-C17-C22	-126.7(3)
C3-C10-C11-C12	177.3(2)	C15-C10-C11-C12	-.1(4)
C3-C10-C15-C14	-176.3(3)	C11-C10-C15-C14	.9(4)
C10-C11-C12-C13	-.3(4)	C11-C12-C13-C14	-.2(4)
C12-C13-C14-C15	1.1(4)	C13-C14-C15-C10	-1.5(4)
C6-C17-C18-F1	-.4(4)	C6-C17-C18-C19	177.1(3)
C22-C17-C18-F1	-177.0(2)	C22-C17-C18-C19	.5(4)
C6-C17-C22-C21	-178.5(2)	C18-C17-C22-C21	-1.8(4)
F1-C18-C19-C20	178.2(3)	C17-C18-C19-C20	.7(4)
C18-C19-C20-C21	-.6(5)	C19-C20-C21-C22	-.7(5)
C20-C21-C22-C17	1.9(4)		