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Five-membered heterocycles as novel molecular scaffolds for targeting triple hydrogen bonding interactions

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List of Abbreviations

'	minutes
AAA	acceptor acceptor-acceptor
ADA	acceptor-donor-acceptor
Alloc	allyloxycarbonyl
APCI	atmospheric pressure chemical ionization
aq.	aqueous
Boc	<i>tert</i> -butyloxycarbonyl
Cbz	benzyloxycarbonyl
CH ₂ Cl ₂	dichloromethane
CH ₃ CN	acetonitrile
CHCl ₃	chloroform
CV	cyclic voltammetry
d	doublet
DAD	donor-acceptor-donor
dd	doublet of doublets
DDD	donor-donor-donor
DFT	density functional theory
DIEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
dt	doublet of triplets
ESI	electrospray ionization
Et ₂ O	diethylether
Et ₃ N	triethylenamine
EtOAc	ethyl acetate
Fmoc	9-fluorenylmethyl carbamate
FRET	fluorescence resonance energy transfer
hrs	hours
H-bonds	hydrogen bonds
HRMS	High resolution mass spectrometry
(<i>i</i> Pr ₂)NH	isopropylamine
IR	infrared
<i>J</i>	coupling constant
K	kelvin
LC-MS	liquid chromatography mass spectrometry
m	multiplet
M	molar
m.p.	melting point
MeCN	acetonitrile
MHz	megahertz
ML	monolayer

Moz	<i>p</i> -methoxy-benzyloxycarbonyl
MS	mass spectrometry
MW	microwave
NEt ₃	triethylamine
nm	nanometer
NMR	nuclear magnetic resonance
PMBA	<i>p</i> -methoxy-benzyl alcohol
Pom	pivaloyl-oxy-methyl
PPh ₃	triphenylphosphine
ppm	parts per million
PS	polystyrene
Py	pyridine
q	quartet
r.t.	room temperature
s	singlet
SAMs	self-assembled monolayers
Sat.	saturated
SPM	scanning probe microscopies
STM	scanning tunneling microscopy
t	triplet
t-BuOH	<i>tert</i> -butyl alcohol
TBAF	tetrabutylammonium fluoride
Tf ₂ O	trifluoromethanesulfonic anhydride
TFA	trifluoroacetic acid
TFMSA	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSI	trimethylsilyl iodide
TOF	time of flight
UHV	ultra-high vacuum
UV	ultraviolet
UV-Vis	ultraviolet-visible
V	volts
δ	chemical shift
ε	extinction coefficient
π bonds	pi bonds

Abstract

Due to its prominent directionality and strength, H-bonds are ones of the most widely used non-covalent interactions in supramolecular chemistry. Despite its relative high strength (energy of an H-bond in the gas phase typically ranges between 0–5 Kcal mol⁻¹) in comparison with other non-covalent interactions, association of two molecules by means of a single H-bond leads to complexes displaying low thermodynamical stabilities, thus limiting their exploitation in the non-covalent synthesis of functional materials for real-world applications. Thereby, when stronger interactions are required, the general engineering approach focuses on the covalent synthesis of rigid planar molecular scaffolding in which several H-bonding donating (D) and accepting (A) moieties are arranged into a so-called ‘*H-bonding array*’. Due to the selective recognition processes and to the tunability of their association strength, multiple H-bonding arrays have become an indispensable molecular module in the tool-box of supramolecular chemists, allowing, through selective self-assembly and/or self-organization processes, the bottom-up preparation of functional materials such as liquid crystals, patterned surfaces and supramolecular polymers. In principle, the stability of H-bonded supramolecular complexes could be modulated in an indefinite number of ways. For example, when stronger interactions (*e.g.*, higher association constant values) are required, the increase of the number of the H-bonding sites represents one of the efficient strategy to reinforce the stability of the ultimate assembly. Nevertheless, a strong K_a value is not always requested. In fact, whilst highly stable complexes are required in the field of supramolecular polymers, whose properties at the molecular level (such as degree of polymerization, D_p , and viscosity) result linearly correlated to the K_a values, these may instead be detrimental for the construction of more sophisticated hierarchized nano-architectures, arising from a delicate interplay between internal (*e.g.* π - π stacking, solvophobic/solvophilic interactions) and external (*e.g.* time, temperature, concentration, etc.) factors.

The aim of this thesis is to design and synthesize novel triple H-bonding arrays (DAD, ADD and DDD) based on five-membered heteroaromatic rings. The proposed use of thiolyl, oxolyl, azolyl, and triazolyl scaffoldings for recognition systems, it is intended as a mean to better achieve the control on the binding properties and selectivity of triple H-bonded recognition arrays, allowing an easy tunability of the binding motifs. With the variation of the substituents and the heteroatom onto the hetero-aromatic rings, it has been intended to create a selection of versatile, structurally similar, host-guest pairs complexes that display different association constants (K_a) in order to better match the requirements of different supramolecular applications.

Focusing on the most relevant factors that influence the association constants of hydrogen bonded complexes, in the first part of *Chapter 1* the reader is introduced on how specific H-bonding arrays, featuring wide ranges of K_a values (spanning among eight orders of magnitude) can be designed. Subsequently, the second part is focused on the physical and chemical properties of a large variety of H-bonding assembled molecular modules that upon self-assembly and self-organization processes opened new ways towards novel fascinating applications.

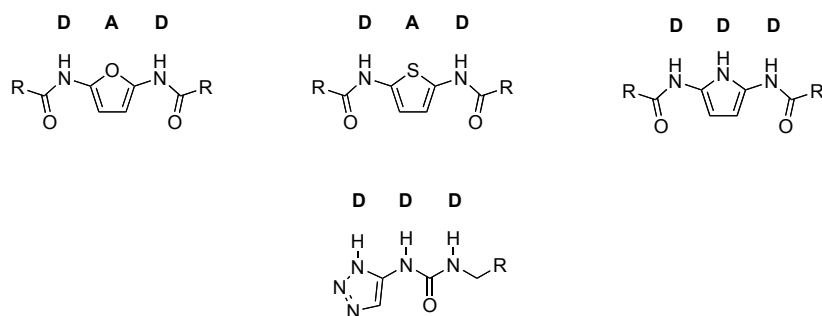


Figure 1 Designed *H*-bonding arrays based on 5-membered heterocycles.

Chapter 2 deals with the description of the synthetic efforts undertaken towards the preparation of the DAD and DDD H-bonding arrays. The first two subsections (2.1-2) describe the retrosynthetic approaches and the results of the unsuccessful methodological routes (through Buchwald-Hartwig amidation cross-coupling reactions, reduction of azido-derivatives and nucleophilic addition of organo-metallic reagents to isocyanate derivatives as produced through *Curtius* rearrangement) tackled to introduce amidic and/or ureidic functions at the 2-position of five-membered heteroaromatic rings.

Several DAD H-bonding arrays based on thiolyl scaffolding were successfully synthesized (*sections 2.3*).

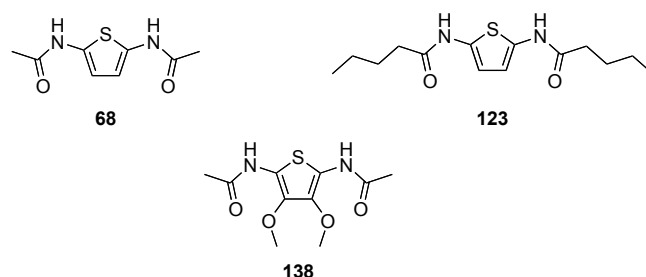


Figure 2 Synthesized thiolyl DAD H-bonding arrays.

In *section 2.4* are presented the synthetic step undertaken in the attempt to generate DAD arrays based on oxalyl derivatives. Unfortunately the introduction of electron-donating groups such as amidic or carbamic functions to the ring led to very unstable intermediates,

and thus the amido-oxolyl derivatives capable of recognition mediated by triple H bonding were never isolated.

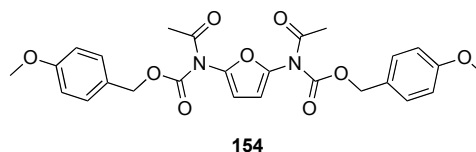


Figure 3 Synthesized oxolyl-protected DAD H-bond array.

The synthetic strategies towards the synthesis of DDD arrays based on of azolyl scaffolding are described in *section 2.5*. Protected azolyl module **182** (see *Figure 4*) was synthesized in thirteen steps starting from the pyrrole module. Unfortunately, due to the complications encountered in the cleavage of the N-azolyl protecting group, the synthesis of the azolyl DDD H-bonding arrays based could not be finally accomplished.

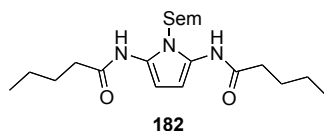


Figure 4 Synthesized azolyl-protected DDD H-bond array.

Section 2.6 presents the synthesis of newly designed self-adapting ADD/DDD H-bonding array based on ureido-triazolyl scaffoldings. Exploiting the prototropic equilibrium of the triazole nucleus the modules synthesized are expected to show an ADD or a DDD arrangement of the binding sites depending on the H-bonding functionalities of the complementary guest used for the complexation.

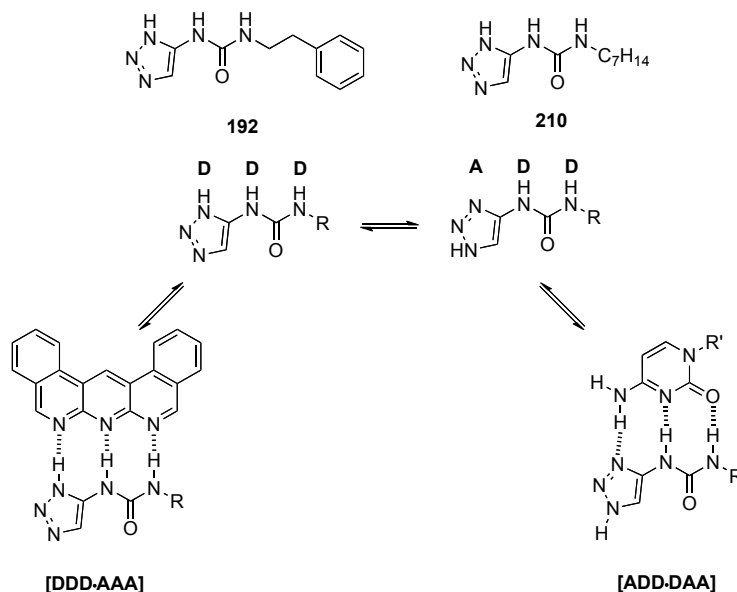


Figure 5 Synthesized triazolyl-based ureido H-bonding arrays. Prototropic self-adapting properties: from a DDD to a ADD H-bonding array.

Due to solubility limitations in common organic solvents (*e.g.*, CDCl_3 and CD_2Cl_2), the molecular recognition ability in solution could not be studied and further modifications of the molecular structural properties are required.

Résumé

Grâce à leur directionnalité prééminente ainsi qu'à leur force, les ponts hydrogène sont l'une des interactions non-covalentes les plus exploitées en chimie supramoléculaire. Malgré leur force relativement élevée en comparaison avec d'autres interactions non-covalentes (l'énergie d'un pont hydrogène en phase gazeuse se situe typiquement entre 0 et 5 Kcal mol⁻¹), l'association de deux molécules au moyen d'un pont hydrogène simple mène à des complexes présentant des stabilités thermodynamiques faibles, limitant ainsi leur exploitation dans la synthèse non-covalente de matériaux fonctionnels menant à de réelles applications. Dès lors, lorsque des interactions plus fortes sont nécessaires, l'approche d'ingénierie habituelle se concentre sur la synthèse covalente d'échafaudages moléculaires rigides et planaires dans lesquels plusieurs fonctionnalités donneurs (D) et accepteurs (A) de ponts hydrogènes sont arrangées dans ce que l'on appelle un '*réseau de ponts hydrogène*'. Grâce aux procédés de reconnaissances spécifiques et au contrôle de leur force d'association, les réseaux de ponts hydrogène multiples sont devenus des modules moléculaires indispensables dans la boîte à outils des chimistes supramoléculaires, permettant, *via* des procédés sélectifs d'auto-assemblage et/ou auto-organisation, la préparation *bottom-up* de matériaux fonctionnels tels que des cristaux liquides, des surfaces à motifs et des polymères supramoléculaires. En principe, la stabilité des complexes supramoléculaires à base de ponts hydrogène peut être modulée d'un nombre infini de manières. Par exemple, lorsque des interactions plus fortes (*e.g.*, des valeurs de constante d'association élevées) sont requises, augmenter le nombre de sites de ponts hydrogène représente une stratégie efficace pour renforcer la stabilité de l'assemblage final. Néanmoins, une valeur élevée de K_a n'est pas toujours nécessaire. En effet, alors que des complexes hautement stabilisés sont requis dans le domaine des polymères supramoléculaires, dont les propriétés à l'échelle moléculaire (tel que le degré de polymérisation D_p , et la viscosité) corréleront linéairement aux valeurs des K_a , ces dernières peuvent également être néfastes à la construction de nano-architectures hiérarchisées plus sophistiquées, résultant d'une interaction délicate entre des facteurs internes (comme par exemple du π - π stacking, des interactions solvophobiques/solvophiliques) et externes (tels que le temps, la température, la concentration etc.).

L'objectif de cette thèse est l'élaboration et la synthèse de nouveaux réseaux de ponts hydrogène (DAD, ADD, DDD) basés sur des cycles hétéroatomiques à cinq chaînons. Nous proposons l'utilisation d'échafaudages thioly, oxoly, azoly, et triazoly comme systèmes de reconnaissance, afin de réaliser un meilleur contrôle des propriétés de liaison et de la sélectivité des réseaux de reconnaissance à ponts hydrogène triples, permettant ainsi une transformation aisée des motifs de liaison. La variation des substituants et de l'hétéroatome

sur les cycles hétéroaromatiques permettrait de créer une sélection de complexes de paires *host-guest* versatiles et de structure similaire, présentant ainsi différentes constantes d'association (K_a) pour mieux répondre aux différentes demandes d'applications supramoléculaires.

Se concentrant sur les facteurs les plus pertinents qui influencent les constantes d'association des complexes à base de ponts hydrogène, le lecteur est introduit dans la première partie du *Chapitre 1* sur la façon dont peuvent être élaborés des réseaux spécifiques à base de ponts hydrogène présentant une large gamme de valeurs de K_a (s'étendant sur un ordre de huit de magnitude). Ensuite, la deuxième partie traite des propriétés physiques et chimiques d'une grande variété d'assemblages par ponts hydrogène de modules moléculaires qui après auto-assemblage et auto-organisation ont ouvert de nouvelles voies à l'élaboration de nouvelles applications fascinantes.

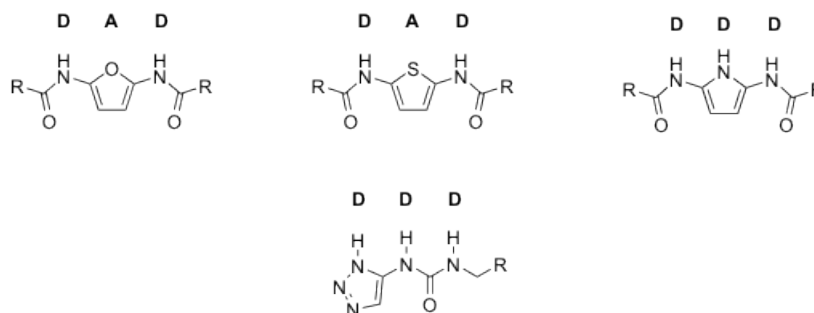


Figure 1 Réseaux de ponts hydrogène élaborés sur base d'hétérocycles à 5 membres.

Le *Chapitre 2* présente la description des efforts synthétiques réalisés pour la préparation des réseaux de ponts hydrogène DAD et DDD. Les deux premières sous-sections (2.1-2) décrivent les approches rétrosynthétiques et les résultats des voies méthodologiques non fructueuses (*via* des réactions de *cross-coupling* d'amidation de Buchwald-Hartwig, réduction de dérivés azido et addition nucléophile de réactifs organométalliques à des dérivés isocyanate comme produit par le réarrangement de *Curtius*) entreprises pour introduire les fonctions amidiques et/ou uréidiques en position 2 des cycles hétéroaromatiques à cinq chaînons.

Plusieurs réseaux de ponts hydrogène DAD à base de thiolyl ont été synthétisés avec succès (*section 2.3*).

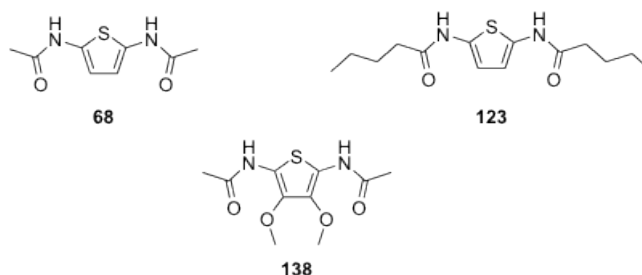


Figure 2 Réseaux de ponts hydrogène DAD synthétisés, protégés par du thiolyl.

Dans la *section 2.4* sont présentées les étapes synthétiques réalisées pour générer les réseaux DAD à base de dérivés oxalyl. Malheureusement, l'introduction sur le cycle de groupements électrodonneurs tels que des fonctions amidiques ou carbamiques a mené à des intermédiaires très instables. Dès lors, les dérivés amido-oxolyl capables de reconnaissance *via* des ponts hydrogène triples n'ont jamais été isolés.

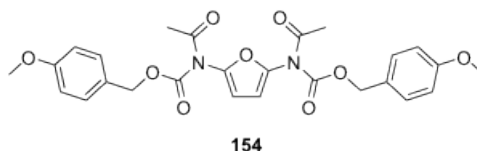


Figure 3 Réseau de ponts hydrogène DAD oxolyl-protégé synthétisé.

Les stratégies synthétiques menant à la synthèse des réseaux DDD à base d'azolyl sont décrites dans la *section 2.5*. Le module protégé par le groupement azolyl **182** (voir *Figure 4*) a été synthétisé en treize étapes à partir du module pyrrole. Malheureusement, à cause de complications rencontrées lors du clivage du groupement protecteur N-azolyl, la synthèse des réseaux de ponts hydrogènes DDD protégés par l'azolyl n'a finalement pu être réalisée.

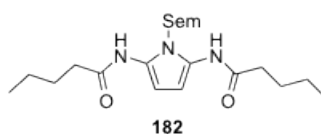


Figure 4 Réseau de ponts hydrogène DDD azolyl-protégé synthétisé.

La *Section 2.6* présente la synthèse de réseaux de ponts hydrogène auto-adaptant ADD/DDD, nouvellement élaborés à partir d'échafaudages ureido-triazolyl. Grâce à l'équilibre prototropique du noyau triazole, nous nous attendons à ce que les modules synthétisés présentent un arrangement des sites de liaisons ADD ou DDD, selon les fonctionnalités ponts hydrogène des *guest* complémentaires utilisés pour la complexation.

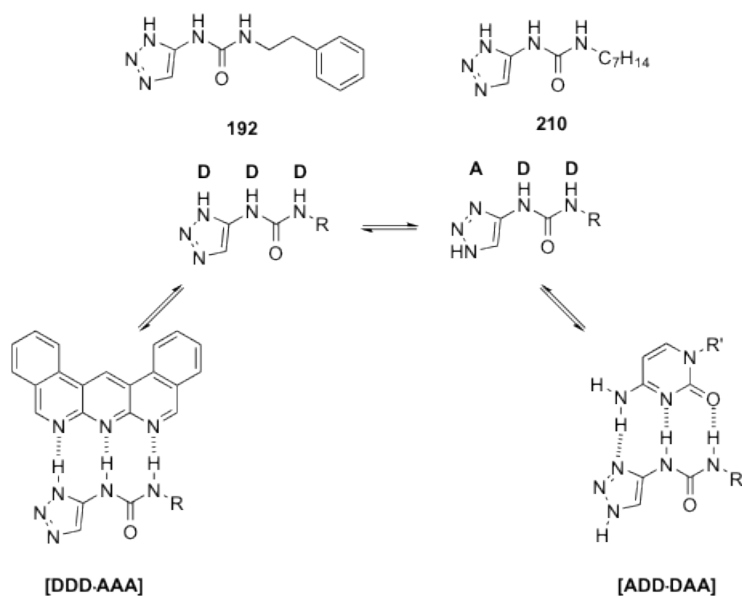


Figure 5 Réseaux de ponts hydrogène ureido synthétisés à base de triazole. Propriétés auto-adaptantes prototropiques: d'un réseau ponts hydrogène DDD à ADD.

Dû aux limitations de solubilité dans les solvants organiques communs (tels que CDCl_3 et CD_2Cl_2), la capacité de reconnaissance moléculaire en solution n'a pu être étudiée. De plus amples modifications des propriétés moléculaires structurales sont dès lors

Riassunto

Grazie alla marcata direzionalità e forza presentate, i legami idrogeno rappresentano uno delle interazioni non covalenti più usate in chimica supramolecolare. Nonostante la forza di legame sia maggiore in confronto ad altre interazioni non covalenti (l'energia di un legame idrogeno in fase gassosa varia in genere tra 0-5 Kcal mol⁻¹), l'associazione di due molecole per mezzo di un singolo legame idrogeno porta alla formazione di complessi con scarsa stabilità termodinamica, limitandone lo sfruttamento nella sintesi non covalente di materiali funzionali.

L'approccio per ottenere interazioni non covalenti più forti è basato sulla sintesi di moduli molecolari planari in cui siano presenti diverse funzioni donatrici (D) e accettrici (A) di legame idrogeno disposti a formare i così detti '*H-bonding arrays*'.

Gli *H-bonding arrays* sono diventati moduli indispensabili per la fabbricazione di materiali funzionali quali cristalli liquidi, superfici organizzate e polimeri supramolecolari, tramite l'approccio '*bottom-up*' a causa della loro selettività nei processi di riconoscimento e alla possibilità di modulare la loro forza di legame

La stabilità termodinamica dei complessi supramolecolari formati tramite legami idrogeno può essere variata in diversi modi. Ad esempio, quando sono richieste interazioni più forti (es. costanti di associazione più elevate) e' possibile aumentare il numero di funzioni accettrici e/o donatrici all'interno dell' *array*. Complessi particolarmente stabili sono richiesti nel campo della polimerizzazione supramolecolare, dove le proprietà macroscopiche (es. grado di polimerizzazione, D_p , e viscosità) sono linearmente correlate al valore della K_a . Alti valori della costante di associazione possono essere dannosi, invece, nella costruzione di nano-architetture gerarchizzate, dove ordine a livello nano e microscopico e' raggiunto, non solo tramite legami a idrogeno, ma tramite l'effetto concertato di fattori interni (es. π - π stacking, interazioni solvofobiche/solvofiliche) ed esterni (es. tempo, temperatura, concentrazione, *etc.*).

L'obiettivo di questa tesi è progettare e sintetizzare nuovi array di tripli legami idrogeno (DAD, ADD e DDD) basati sulle molecole di tiofene, furano, pirrolo e triazolo. Utilizzando anelli a 5 termini e' infatti possibile ottenere una famiglia di coppie *host-guest*, che presentano una simile struttura chimica ma differenti costanti di associazione. La modulazione della K_a in questi sistemi può avvenire tramite la variazione dell'etroatomo sull'anello o tramite l'introduzione di sostituenti nelle posizioni β , permettendo così la costruzione di una libreria di moduli molecolari versatili in grado di rispondere al meglio ai requisiti dalle diverse applicazioni supramolecolari.

Concentrandosi sui fattori che influenzano le costanti di associazione dei complessi formati tramite legami idrogeno, nella prima parte del *Capitolo 1* viene descritto come modificazioni strutturali degli array portano alla formazione di complessi i cui valori di K_a

variano in un intervallo di 8 ordini di grandezza. La seconda parte e' invece focalizzata sulle proprieta' chimico-fisiche di nuovi materiali funzionali formati tramite processi di auto-assemblaggio e auto-organizzazione degli array precedentemente descritti.

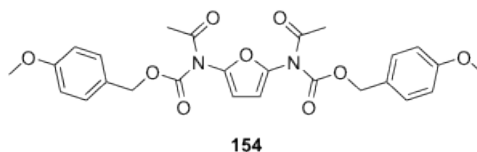


Figura 1 Progettazione di array di legami idrogeno basati su etero cicli a 5 termini.

Nel *Capitolo 2* vengono mostrati i tentativi di sintesi intrapresi per la preparazione degli array di legami idrogeno di tipo DAD e DDD .

I primi 2 paragrafi (2.1-2) descrivono l'analisi retro-sintetica e gli studi metodologici effettuati al fine di sviluppare una via sintetica per l'introduzione di funzioni ammidiche e/o ureidiche in posizione 2 degli anelli etero-aromatici. Le metodologie descritte sono: la reazione di ammidazione per accoppiamento ossidativo di *Buchwald-Hartwig*, la riduzione di azido-derivati e l'addizione nucleofila di reagenti organo-metallici a isocianati prodotti tramite il riarrangiamento di *Curtius*.

Diversi DAD array di legami idrogeno basati sulla molecola di tiofene sono stati sintetizzati con successo (*paragrafo 2.3*).

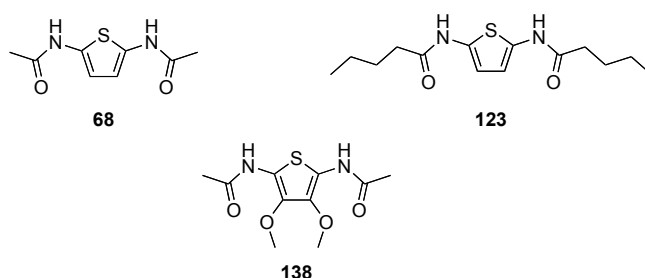


Figura 2 DAD array di legami idrogeno basati sulla molecola di tiofene sintetizzati.

Nel *paragrafo 2.4* sono presentati gli step sintetici affrontati nel tentativo di generare DAD array basati su derivati ossolici. Sfortunatamente l'introduzione di gruppi elettron-donatori (ammidi o carbammati) sull'anello conduce alla formazione d'intermedi particolarmente instabili. Per questo motivo sistemi DAD di legami a idrogeno basati su derivati ammidici della molecola di furano non sono mai stati isolati.

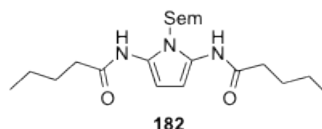


Figura 3 DAD array di legame idrogeno basato su scheletro furanico sintetizzato con la funzione ammidica protetta.

Nel *paragrafo 2.5* sono descritte le strategie sintetiche affrontate nel tentativo di sintetizzare DAD array basati sulla molecola di pirrolo. L'intermedio azolico protetto **182**

(vedi *Figura 4*) è stato sintetizzato in tredici passaggi sintetici partendo dalla molecola di pirrolo. Sfortunatamente, a causa delle complicazioni incontrate durante la rimozione del gruppo protettore dell'azoto pirrolico, la sintesi di moduli DDD basati su derivati azolici non è stata portata a termine.

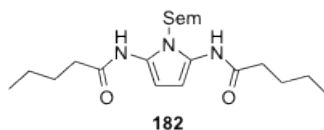


Figure 4 DDD array di legame idrogeno basato sulla molecola di pirrolo sintetizzato con l'azoto dell'eterociclo protetto.

Il *paragrafo 2.6* presenta la sintesi di moduli auto adattabili ADD/DDD basati su derivati ureido-triazolici. Sfruttando l'equilibrio prototropico del nucleo triazolico il modulo sintetizzato dovrebbe mostrare una disposizione ADD o DDD dei siti di legame che dipende dal modulo complementare usato nel processo di complessazione.

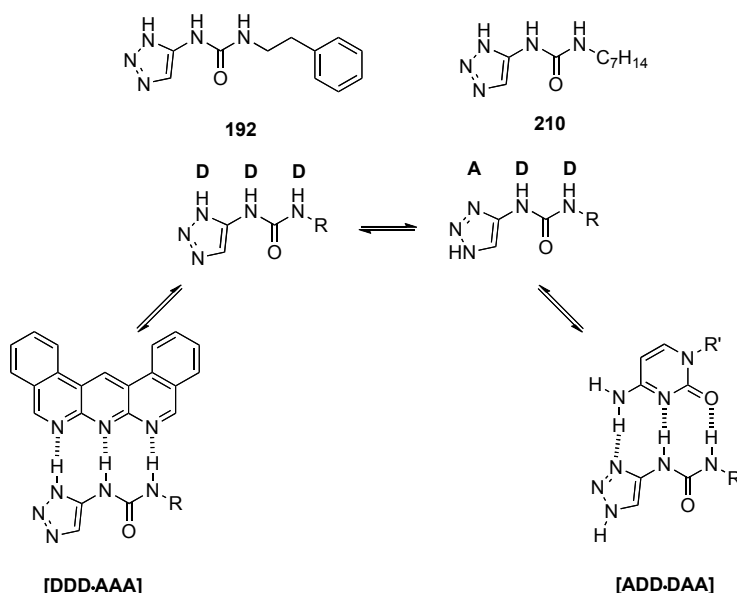


Figure 5 Array di legami idrogeno basati su derivati ureidotriazolici sintetizzati. Proprieta' di auto-adattamento: da DDD a ADD array.

Le capacita' di riconoscimento molecolare di questi sistemi in soluzione non sono state studiate a causa della loro limitata solubilita'. Ulteriori modifiche strutturali sono pertanto necessarie.

Introduction

The concept of hydrogen-bonding, namely the interaction between a positively polarized hydrogen atom linked to an electron-withdrawing heteroatom (donor of the H-bonding, D) and an electron-rich heteroatom (acceptor of the H-bonding, A), was firstly unravelled in 1919 by Huggins,^[1] attracting over the years previous attention. Even though allocated among the “weak” interactions, hydrogen bonding plays crucial role in controlling both the structure and function of many biological processes. Highly specific patterns of complementary *inter*- and *intra*-molecular hydrogen bonds are in fact involved in a manifold of pivotal biological activities, such as maintaining the integrity of biomolecular structures, information storage and transfer, replication and catalysis.^[2] Because of its specific features, namely strength, selectivity and directionality, H-bonding has ultimately become the most useful interaction within the supramolecular chemistry toolbox, allowing thus the creation of several host–guest complexes with novel advanced materials applications in the form of hydrogen bonded macromolecules,^[3, 4] liquid crystalline derivatives,^[5, 6] highly structured supramolecules^[7] and patterned surfaces.^[8]

The theoretical description of H-bonding established that this interaction arises from a complicated superposition of five distinguished terms (electrostatic, exchange repulsion, polarization energy, charge transfer energy and dispersion forces),^{[9] [10]} among which the electrostatic aspect mainly dominates.^[11] Indeed, this prevailing coulumbic component of the bond results pivotal in the control of the stability of the assembly^[12] and accounts for the relationship between the bond strength and the geometry of the D··H··A spatial arrangement.^[13] Specifically, an effective interaction between the lone pair of the heteroatom and the electron-deficient hydrogen is favored by a linearity of the D··H··A system. Ideally, the best situation possible would involve an angle of 180°, but usually, because of the influence of the other components to the bond, it amounts to $160 \pm 20^\circ$.

The energy of an H-bond in the gas phase typically ranges between 0–5 Kcal·mol⁻¹, a content of energy considerably weaker than that corresponding to covalent bonds, but significantly larger to that of dipolar or London dispersion forces (< 2 Kcal·mol⁻¹). Increasing the positive polarization of the donor (D) proton and/or increasing the negative polarization of the acceptor (A) atom are both expected to increase the strength of the interaction (10–45 Kcal·mol⁻¹).^[14, 15]

Fine understanding and control of the binding properties of H-bond arrays sets an important challenge for organic chemists towards the design of new molecular building blocks to be used in the H-bonding driven *non-covalent synthesis* of novel structured functional materials. The deeper the knowledge on the different factors influencing the fate of the H-bonding formation and persistence, the easier will be the tuning of the interaction,

paving the way to the obtainment of *ad hoc* systems for specific material sciences applications.

Before reasoning on the practical solutions adopted by researchers in order to gain understanding and control on the polyvalent H-bonding tool, in the first part of this introduction I will thoroughly discuss the different factors influencing the association constant of H-bonding-based supramolecular complexes. In the second part, I will then summarize the recent achievements in the preparation of novel H-bonding building blocks, and their use in the preparation of hierarchized supramolecular architectures, focusing on the strategies adopted to control the final assemblies, and ultimately their properties.

1.1 Tuning of the association constant

Association of two molecules by means of a single H-bond entity leads to complexes with low stabilities. When stronger interactions are required, an increase of the number of hydrogen bonding sites on the molecule involved in the interaction, represents an efficient strategy to reinforce the stability of the ultimate assembly, represented by an increase in the association constant value (K_a) of the final supramolecular complex.

Nevertheless, a strong K_a is not always requested. In fact, whilst highly stable complexes are required in the field of supramolecular polymers, whose properties at the molecular level (such as degree of polymerization, D_p , and viscosity) result linearly correlated to the K_a ,^[16] these may instead be detrimental for the construction of more sophisticated hierarchized nano-architectures, arising from a delicate interplay between internal (*e.g.* π - π stacking, solvophobic/solvophilic interactions) and external (*e.g.* time, temperature, concentration, etc.) factors.

Research towards complementary units showing higher and higher stability has led in the last two decades to the preparation of a large number of H-bonding recognition systems able to interact through the formation of up to eight simultaneous H-bonds.^[17] Specifically, many different linear arrays of equidistant H-bonding sites characterized by different sequences of A and D units, are now available for the construction of nano-structured materials, offering a very versatile range of K_a , varying along eight orders of magnitude.

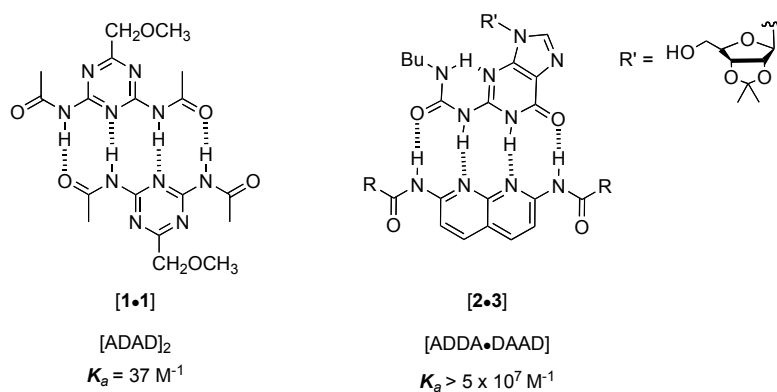


Figure 1. Chemical structure of complexes formed by dimerization of array **1** (self-complementary ADAD array, left), and by hetero-association of arrays **2** and **3** (complementary ADDA and DAAD arrays, right).

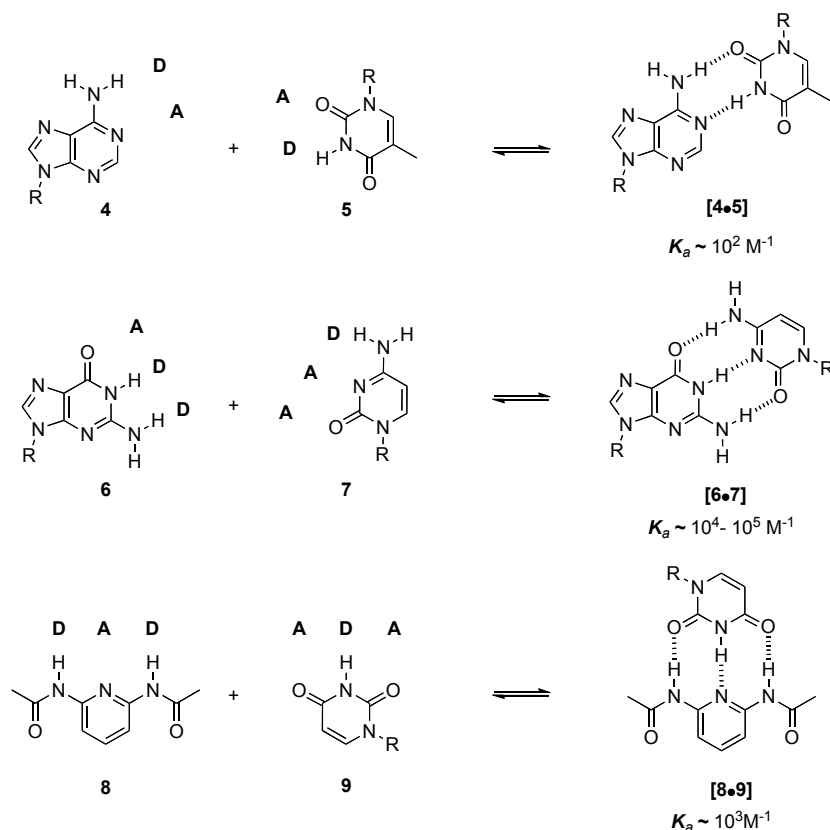
Although the strength of the supramolecular interaction increases with the increment of H-bonding sites on the molecule, it is also true that among systems containing the same number of binding sites, a significant difference in the stability of the final complex (K_a) can be caused by other factors, such as *i*) the mutual arrangement of the binding sites, *ii*) the pre-organization of the molecular module, and *iii*) the eventual presence of substituents.

An intriguing example of this phenomenon is represented by the two systems represented in *Figure 1*. Both the complexing duets assemble into the supramolecular complex *via* formation of four H-bonds: in the case on the left, a self-complementary ADAD system interacts with a K_a of 37 M^{-1} ; in the second an ADDA unit interacts with a complementary DAAD, with and K_a of $5 \times 10^7 \text{ M}^{-1}$. The significant difference in the observed K_a (*i.e.*, seven orders of magnitude), clearly results attributable to the difference of the disposition of the relative D and A binding sites. These observations indicate that other factors, not only the number of H-bond binding sites, might play an important role in the control of the features of the supramolecular interaction, allowing further tuning of the same interaction.

1.1.1 Tuning of the association constant value through variation of the number and the mutual arrangement of the binding sites

As briefly anticipated, the number of H-bonding interactions strongly influences the K_a value of a complementary complexing pair. A linear correlation between the number of binding sites present on a molecule, and the free energy of complexation event in which that same molecule is involved, was firstly observed by *Schneider* and co-workers in 1989.^[18] This phenomenon is well represented by the two sets of base pairs represented in *Scheme 1*. The [Adenine•Thymine] couple in fact, presents only two binding sites and assembles forming a

[DA•AD] complex characterized by a K_a of 10^2 M^{-1} . The [Cytosine•Guanine] couple, characterized by the presence of an extra binding site, forms instead a [DAA•ADD] complex characterized by a K_a of $10^4\text{--}10^5 \text{ M}^{-1}$, indicating that a further binding site in the [Cytosine•Guanine] couple increases the stability of the complex of two orders of magnitude (*Scheme 1*).



Scheme 1. Formation equilibria of complexes [4•5], [6•7] and [8•9]. The reported average K_a values are measured in CDCl_3 . R group is intended as a linear alkyl chain.

However, the work of *Schneider* fails to explain the great discrepancy in the K_a values of the [Cytosine•Guanine] couple respect to the [ADA•DAD] array formed between the hetero-complementary diacetylaminopyridine (**8**) and uracyl (**9**). **5**, firstly introduced by *Hamilton* in 1987,^[19] and destined to become a *leit-motif* in supramolecular recognition processes, self-assembles to **9** displaying a K_a value of *ca.* 10 M^{-1} , 100 times smaller compared to K_a value found for the [6•7] complex.

As later observed by *Jorgensen* and co-workers,^[20, 21] the stability of a complex in fact, does not exclusively depend on the number of binding sites but also on the spatial arrangement of the A and D functionalities present on the molecule. Differences in the K_a can in fact be deeply influenced not only by the interactions occurring between two binding sites situated one in front of the other, but also with the neighbours of the complementary binding site, the so-called *secondary electrostatic interactions* (*Figure 2*). These interactions were

represented in *Jorgensen's model*, which highlighted the stabilization and destabilization caused by the secondary electrostatic attraction and repulsion between polarized atoms in adjacent H-bond sites. The four negative interactions in the [DAD•ADA] ([5•6]) complex account for the decreased stability of this complex respect to the [DDA•AAD] ([3•4]) one.

Analyzing 58 different combinations of H-bonding systems *via* NMR titrations in CDCl_3 , *Schneider*^[22] demonstrated that the total free energy (ΔG) of formation of H-bond complexes can be precisely represented within $\pm 1.8 \text{ KJ}\cdot\text{mol}^{-1}$, by adding the contributions of attractive primary interactions, whose value has been calculated equal to $7.9 \text{ KJ}\cdot\text{mol}^{-1}$, to the contributions of the secondary interactions, each one equal to $2.9 \text{ KJ}\cdot\text{mol}^{-1}$, but considering whether their contribution is attractive or repulsive (*Figure 2*).

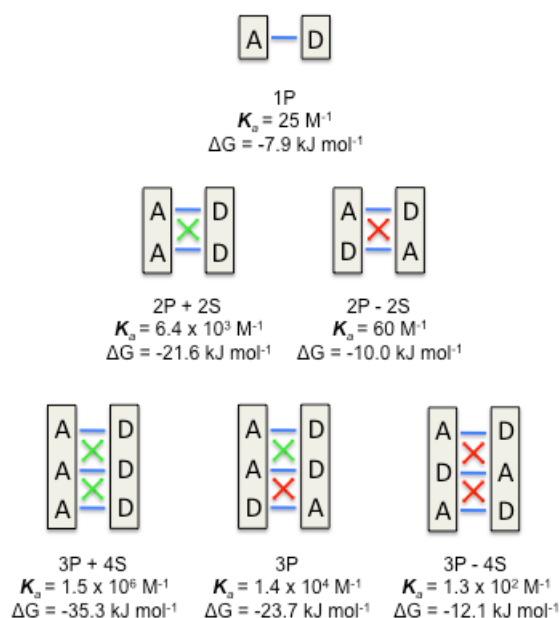
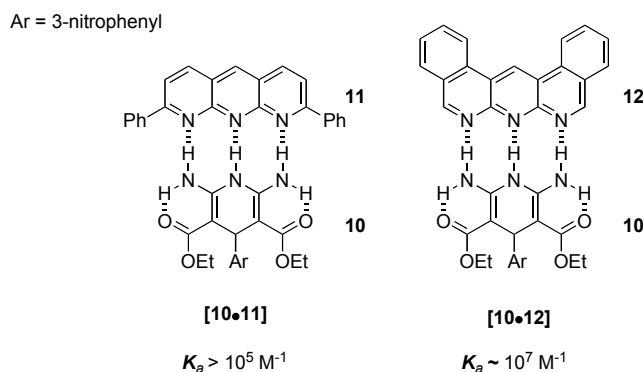


Figure 2. Possible arrangements of the binding sites in hydrogen bonded complexes with predicted values for ΔG^0 and K_a in CDCl_3 . Blue line: H-bond interaction; green arrow: attractive interaction; red arrow: repulsive interaction; P : primary interaction; S : secondary interaction, repulsive or attractive.

According to *Jorgensen's* theoretical model, the highest association constants should be expected from [AAA•DDD] arrays where all the secondary electrostatic interactions are attractive.



Scheme 2. [AAA•DDD] complexes and relative association constant values.

In this context, *Zimmermann* and *Murray* ^[23] were the first to design, synthesize and study a triple donor DDD array based on dihydropyridine **10** characterized by a K_a of 10^5 M^{-1} upon ^1H -NMR titration experiments in CDCl_3 with the complementary AAA molecule **11**. An ulterior increase in strength for a [DDD•AAA] was reported by *Djurdevic* and coworkers, who subsequently developed a chemically more stable system **[10•12]** which instead presented a higher K_a of 10^7 M^{-1} in CH_2Cl_2 , as resulted by UV measurements (*Scheme 2*).^[24]

Whilst, as shown in *Figure 2*, the possible combinations for the organization of three adjacent H-bonding binding sites into a linear scaffold result only three, in the case of four binding sites, up to six different dimers can be formed, two of which producing self-complementary arrays (*Figure 3*).

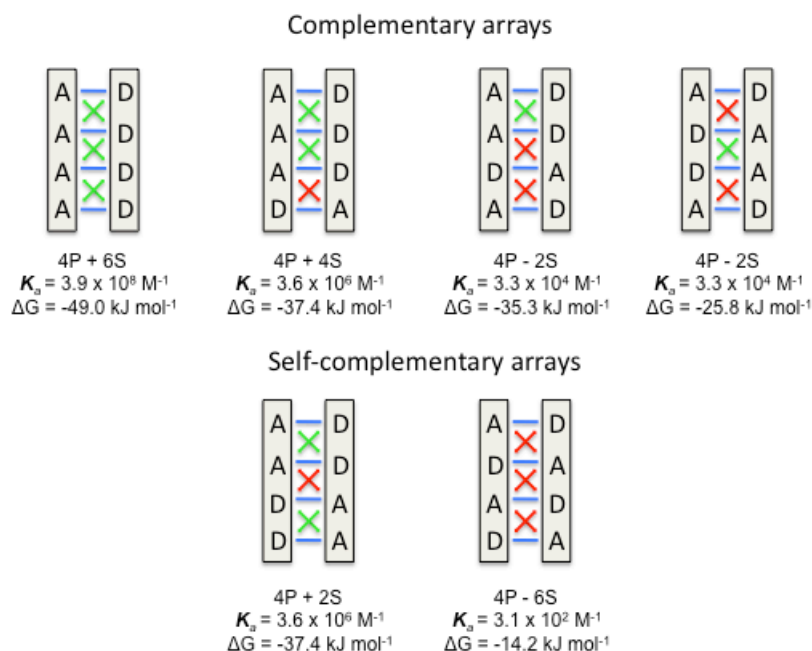
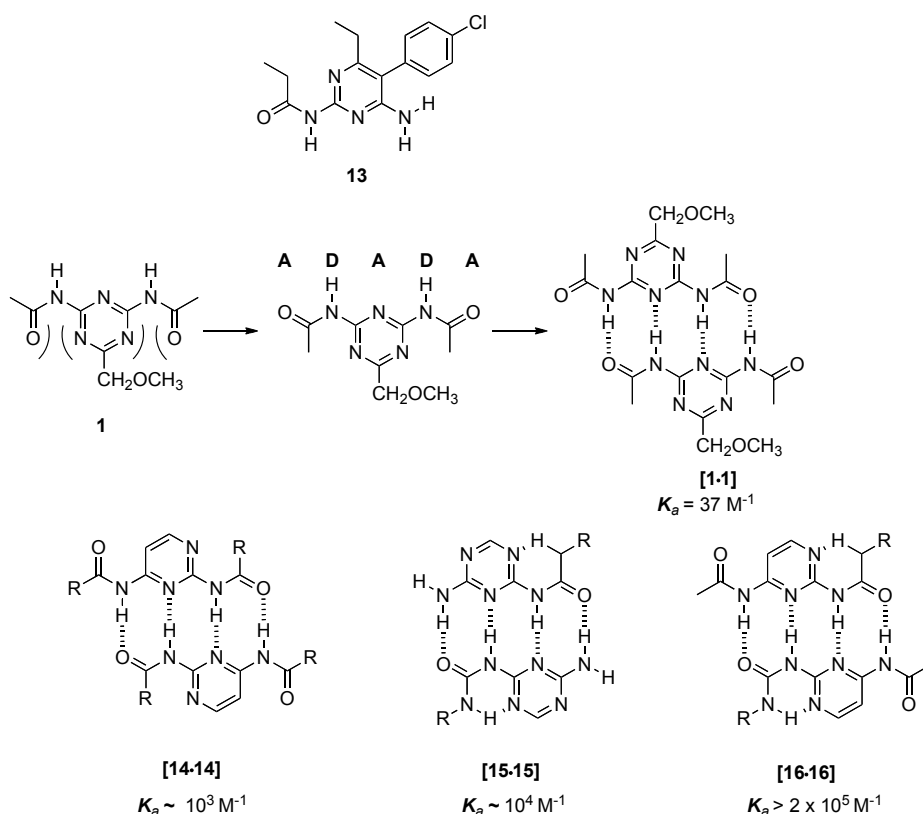


Figure 3. Possible arrangements of the binding sites in quadruple hydrogen bonded complexes with predicted values for ΔG^0 and K_a in CDCl_3 .

The first example of a dimerization occurring through a quadruple hydrogen bonding

was observed in 1992 in the crystal structure of the pyrimidinic derivative **13** (Scheme 3), even though no stability investigation were carried out for this system in solution.^[25] Followingly Meijer^[26] and coworkers reported a complete study on the stability of self-complementary ADAD quadrupole H-bond systems based on diaminoacetyltriazine (**1**). Although originally synthesized in order to create a stronger DAD module compared to **8**, molecule **1** eventually presented an ADADA motif. In fact, due to electrostatic repulsion between the lone pairs of the carbonyl oxygen and of the nitrogen atoms in the triazinic ring, the amidic groups are compelled to adopt an unfavorable *cis*-like conformation including also the carbonyl oxygen's in the groups potentially available to perform H-bond interactions. Self-association of **1** occurs through a quadruple ADAD array with an association constant of 37 M^{-1} .

Structural modifications of the di-amidotriazine motif, allowed Meijer^[27] and coworkers to create a library of $[\text{ADAD}]_2$ self-complementary complexes whose K_a values ranged from 10^2 to 10^5 M^{-1} . The strength of $[\text{ADAD}]_2$ complexes cannot be ulteriorly improved, because of the consistent number of secondary repulsive interactions, which negatively influence the maximum limit (Figure 3).

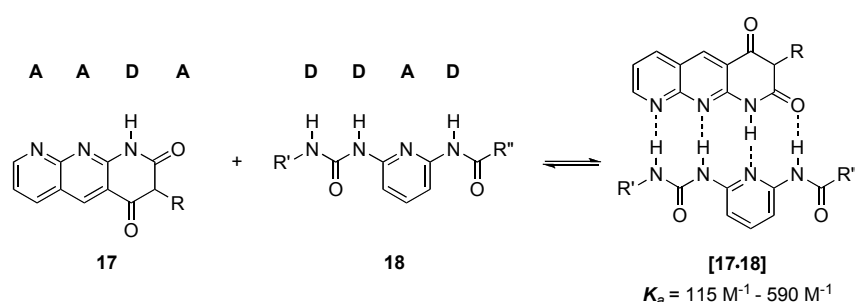


Scheme 3. Self-complementary (ADAD) arrays.

At present only four of the six possible arrangements of quadruple hydrogen bonding arrays have been synthetically achieved since there are no report of formation of [AADA·DDDD] and [AAAD·DDDA] complexes.

Kuhl and co-workers developed a family of (AADA) arrays based on a tetraazaanthracene derivative (**N12**) and a series of complementary (DDAD) urea analogues (**N13**, Scheme 4).^[28]

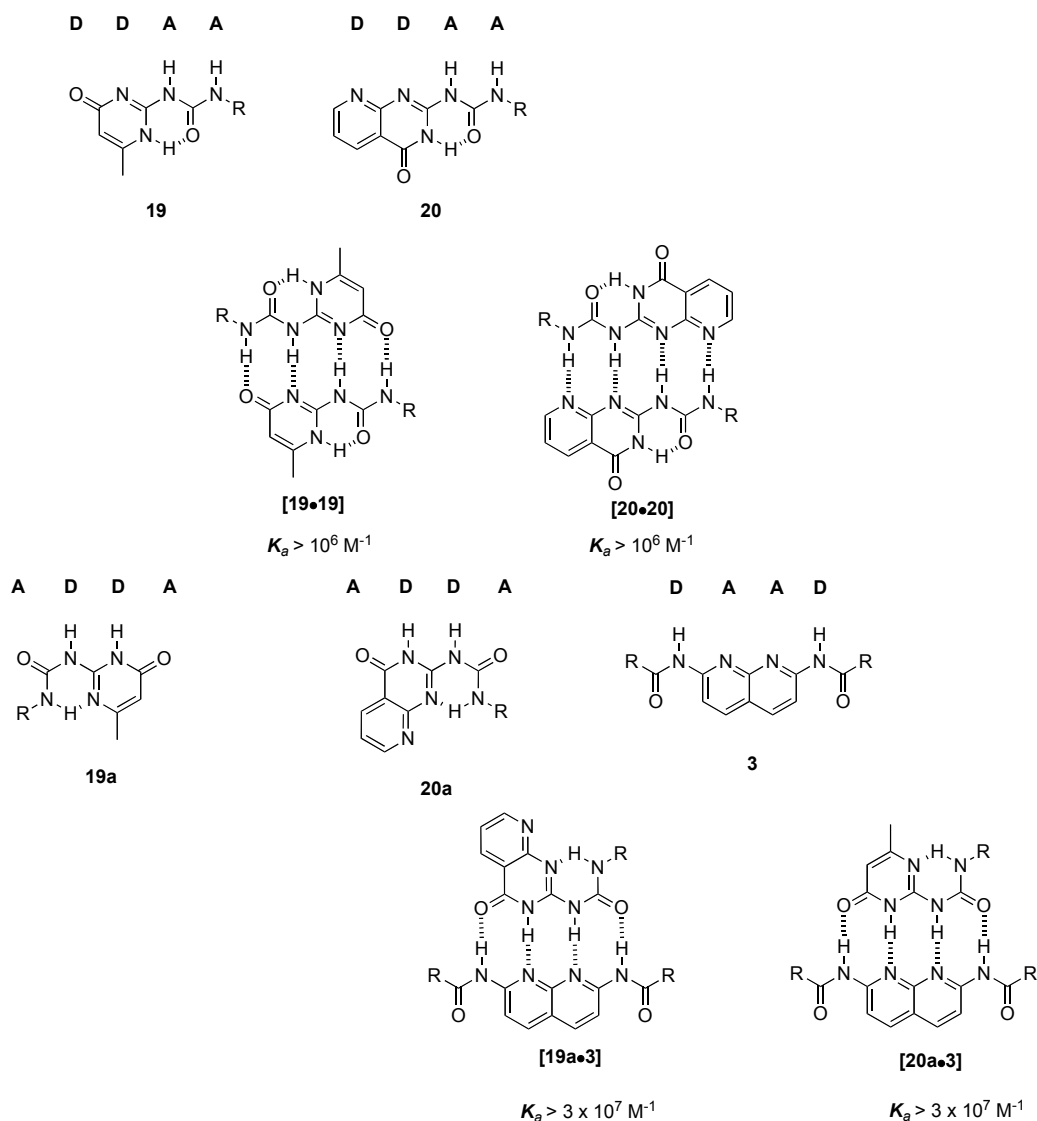
Compared to [ADAD]₂, [AADA·DDAD] complexes present a lower number of secondary repulsive interactions (4 vs. 6); nonetheless the measured association constant present dramatically low values, ranging from 115 to 590 M⁻¹.



Scheme 4. [AADA·DDAD] complexes; highest stability achieved when R' = Ph and R'' = *n*-Bu.

Highly stable complexes were instead obtained with self-complementary (AADD) arrays. Among these the most famous are Meijer's ureidopyrimidone UPy (**19**)^[29] and Zimmermann's deapterin DeAp (**20**,) Scheme 5)^[30]. UV experiments assessed the K_a for complexes [19·19] and [20·20] in the order of magnitude of 10⁶ M⁻¹. Notwithstanding **19** and **20** were designed to present a self-complementary (AADD) arrangement of the binding sites, tautomeric equilibrium can transform it to an (ADDA) array (Scheme 5, **19a-20a**) These structural modifications allow the occurrence of stronger H-bonding interaction ($K_a > 10^7 \text{ M}^{-1}$) in the presence of the complementary (DAAD) diamidonaphthyridine (**3**) to obtain [ADDA·DAAD] complexes^[31].

Whilst Schneider's rules generally resulted in discrete agreement with the experimental values measured for [AADD]₂ dimers, critical differences were instead observed for other arrangements, such as in the case of molecules **19** and **20**. In fact, as highlighted in Scheme 5, the heteroaromatic cores of these modules can undergo a series of complex conformational and tautomeric transformations, which ultimately influence the value of K_a , making an *a priori* prediction of this value really complicated. A discussion on the influence on the K_a due to the presence of different conformers and tautomers for a given molecule will be treated in the following section.



Scheme 5. (AADD) and (ADDA) arrays for molecules **19** and **20**.

1.1.2 Modulation of the association constant value through pre-organization

The energy required for a host molecule to adopt the necessary conformation to assemble with its complementary guest, negatively reflects on the stability of the emerging complex, since an entropic cost has to be paid to fix the binding sites in a determined conformation. Host molecules that do not undergo significant conformational reorganization upon binding to a guest are defined *pre-organized*.

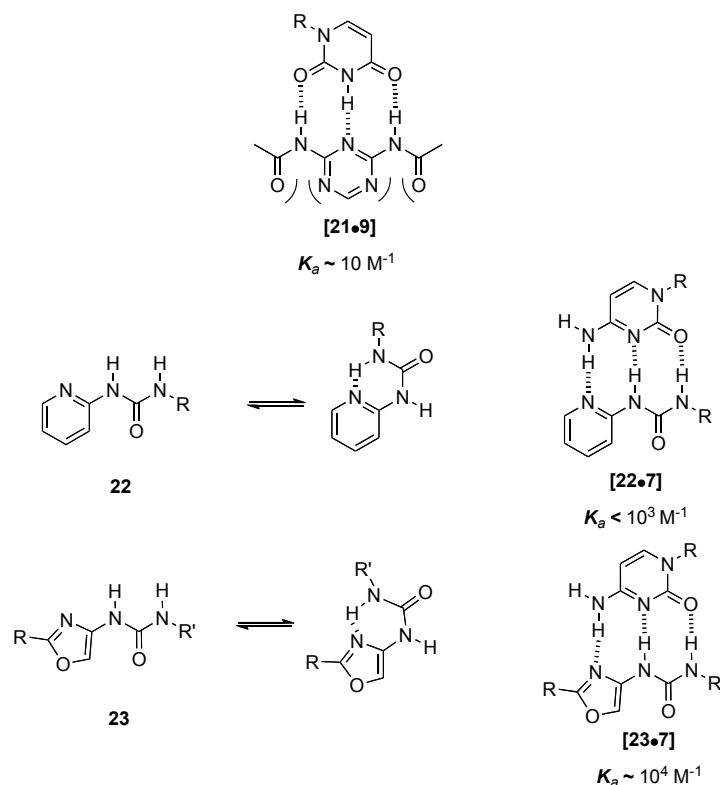
Pre-organization is generally achieved by means of rigid and planar scaffolds, in which the punctual H-bond binding sites are placed on heteroaromatic cores (*e.g.*, the pyrimidone unit in **19** and the pyrido-pyrimidone unit in **20**). The degree of pre-organization that can be reached using such kind of structures strongly reduces the energy losses. However

issues associated with the partial conformational freedom of the peripheral functional groups and with the tautomeric equilibria of the heteroaromatic cores still subsist.

1.1.2.1 Conformational equilibria

The amido and ureido groups are by far the most exploited functional groups used for H-bond formation, due both to their donor and acceptor abilities and to their synthetic accessibility. An interesting feature regarding amidic functional groups regards the partial freedom of rotation along the C-N bond that in some cases allows a switch between the *cis* and the *trans* conformation. As shown in *Scheme 6*, electrostatic repulsion between the carbonyl oxygen and the nitrogen's lone pair in the (DAD) diacetylaminotriazine (**23**) forces the amide in the *cis* conformation when the molecule is uncomplexed with the complementary (ADA) uracyl.^[26] The entropic cost for the conformational reorganization induced upon complexation with **9**, is paid with a sensible decrease of K_a (10 M^{-1}), whose value resulted two orders of magnitude lower if compared to the one of the analogous [**8·9**] ($K_a = 10^3\text{ M}^{-1}$).

At the contrary, ureidic groups have the tendencies to form six-membered ring intramolecular H-bonds (*Etter's Rule*).^[32] For example ureidopyridine **22** presents an (ADD) arrangement of the binding sites similar to the one of Guanine. When in solution, the molecule adopts a "folded" conformation (**22a**) due to the formation of a *intra*-molecular H-bond. The energy required for the reorganization of the structure back to the linear (ADD) array able to complex Cytosine, causes a decrease in the K_a (10^3 M^{-1}) of two orders of magnitude if compared to the values observed for the analogous [**6·7**] complex between Guanine and Cytosine ($K_a \sim 10^4\text{--}10^5\text{ M}^{-1}$).



Scheme 6. Representation of the effects on the K_a associated to the *cis-trans* equilibrium of amides and with the folding-unfolding process of ureido groups.

Recently, *Odashima* reported that the presence of a six- or a five-membered heteroaromatic rings was a predominant factor in determining the equilibrium between the unfolded and folded conformer of heterocyclic ureas with an ADD array.^[33] Computational studies highlighted that six-membered heterocyclic ureas, including the pyridin-2-yl structure of **N18**, are destabilized by steric repulsion between H-3 of the pyridine ring and the carbonyl oxygen on the urea when on the open linear form. Thus, the conformational equilibrium is biased toward the folded conformer **22a** stabilized by intramolecular hydrogen bonding.

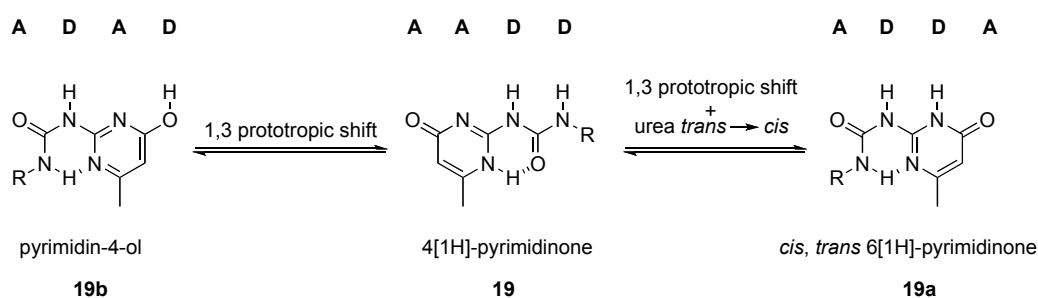
In contrast, five-membered heterocyclic ureas, such as oxazol-4-yl urea derivatives **23**, more easily maintain the open linear conformation, thanks to a less important steric repulsion. As a consequence of the higher stability of the open form of the oxazolyl ureas, **23** is able to bind Cytosine 100 times stronger than **22** (*Scheme 6*).

1.1.2.2 Tautomerism

Tautomeric equilibria often result in a change of the spatial rearrangement of the binding sites that can alter the expected association constant and lower the fidelity of the

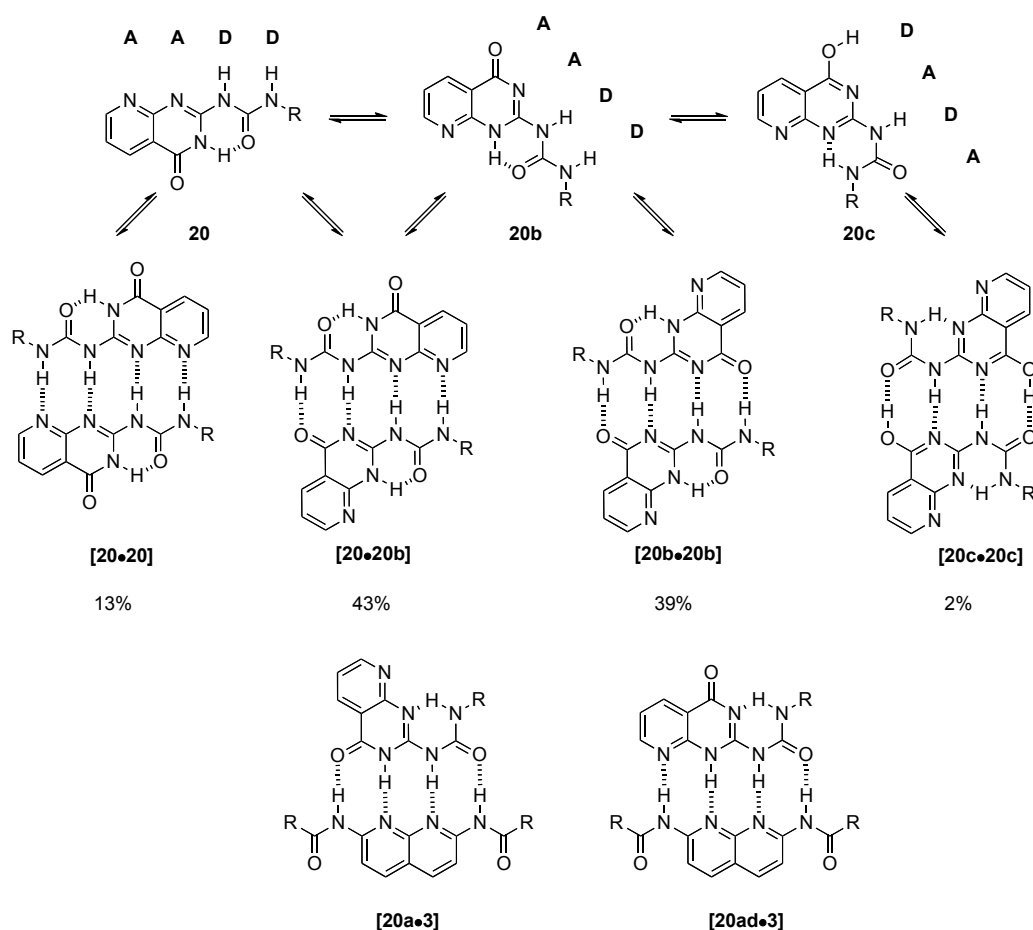
recognition process. UPy (**19**) and DeAp (**20**) provide notable examples to clarify this concept.

As depicted in *Scheme 8*, **19** presents in solution two different tautomers in equilibrium between them: the previously discussed (ADDA) **19a**, and **19b** presenting an (ADAD) array. The presence of these two tautomeric forms of **19** in solution negatively affects the efficiency of the self-complementary assembly, resulting in a lower value for the dimerization K_d compared to the expected. This decrease is mainly attributable to two distinguished phenomena: on one side, **19b** presents a high number of secondary repulsive interactions, hampering the extent of the H-bond, on the other, being **19a** not self-complementary, also negatively affects the dimerization process.



Scheme 7 Tautomeric equilibria in UPy (**19**)

Similarly, the DeAp system described by Zimmerman also adopts 5 different tautomers/conformers **20-20d** three of which are self-complementary. However in CDCl_3 solution, dimerization occurs for the 98% through a preferred AADD arrangement (*Scheme 9*). While the ADDA tautomers is formed only when in the presence of the complementary DAAD array.

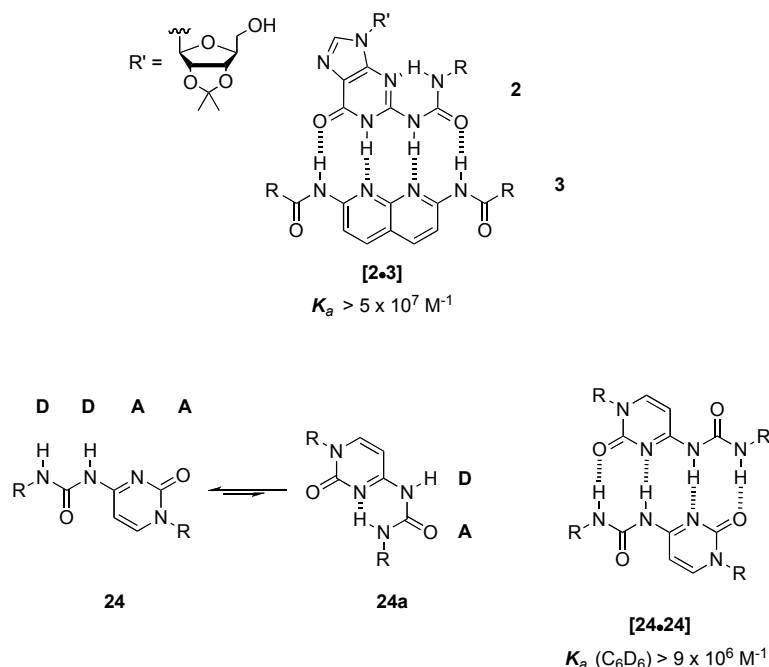


Scheme 8. Tautomeric equilibria of **20**. The values between brackets indicate the relative percentages of self-complementary dimers present in solution in CDCl_3 . **20a** and **20d** are two different tautomers presenting (ADDA) arrangement.

The formation of a non self-complementary (ADDA) tautomer in both of these examples represents anyway an advantage, since self-complementarity is not always suited for many applications. **19** as well as **20** associate with the (DAAD) module DAN (**3**) (K_a 10^7 M^{-1}). The high constant, could have been higher in absence of the self association processes involving the other tautomers. This phenomenon influences not only the K_a but also the *fidelity* (F)^[34] of the recognition event. F defines the ratio of concentration of the desired complexes to the concentration of all associated species. Thus, the fidelity of a system will range from 0 to 1: $F = 1$ indicates exclusive formation of desired species and $F = 0$ exclusive formation of undesired associated species.

Nucleobases are known to have fixed tautomeric forms and since this, in principle, would allow a recognition processes free from competition with undesired tautomers, in recent years the interest in Guanine and Cytosine based multiple H-bond arrays is grown. The ureidoguanine derivative **2**, developed by *Zimmermann* and coworkers, forms a very stable [ADDA•DAAD] complex with **3**.^[35] The association constant for this system, measured by fluorescence titration experiments, was assessed to a value of $5 \times 10^7 \text{ M}^{-1}$, value is of the

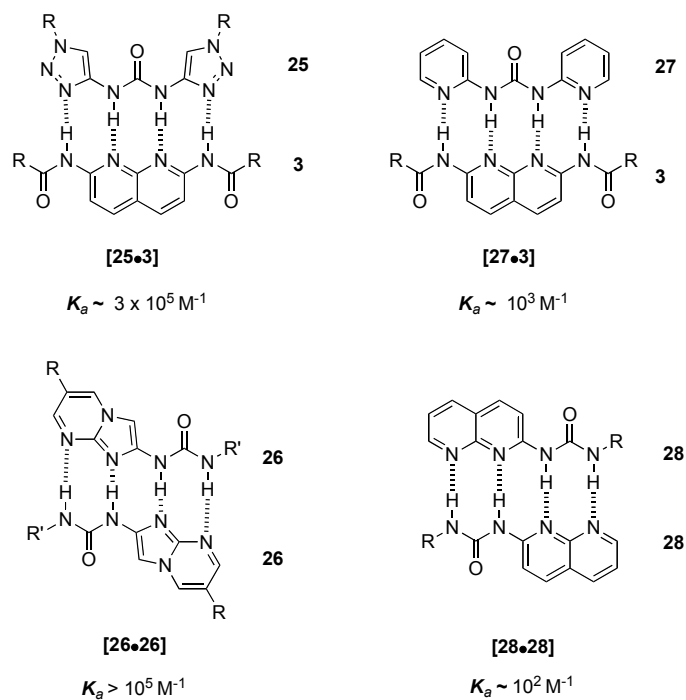
same order of magnitude of the K_a observed for complexes **[19a·3]** and **[19a·3]**. Moreover, while the F value of **[19a·3]** and **[19a·3]** is around 0.6 due to the competitive formation of self-complementary dimerization products of N(Upy) and NDeAP, the F value for the **[2·3]** is closed to 1 ($F > 0.999$) even at very low concentration values.



Scheme 9. (Top) Representation of the **[ADDA·DAAD]** complex formed between the **[2·3]** and relative association constant value. (Bottom) Representation of the conformational equilibrium of **24** and **(DDAA)₂** dimer **[24·24]** and relative association constant measured in C_6D_6 .

In *Scheme 10* is reported the Cytosine derivative **24** designed by *Hailes* and co-workers. **24** presents an (AADD) array capable of self-association that like module **2** does not undergo tautomeric equilibrium.^[36] This motif can, in principle, fold through an intramolecular H-bonds forming **24a**; however in C_6D_6 however only the unfolded conformer is present and self associates with a K_a value of $9 \times 10^6 \text{ M}^{-1}$.

Another way to overcome the drawbacks regarding tautomerism, was recently reported by *Odashima*, whom synthesized an (ADDA) array and a self-complementary (AADD) array based on five membered heterocyclic structures (*Scheme 11*).^[37, 38] Specifically, *N,N'*-di-4-triazolylurea **25** can form very stable complexes with the complementary (DAAD) unit **3**, whilst **26** self-associates with a dimerization constant of 10^4 M^{-1} . Since the energy required to unfold this kind of structures is minor if compared to the one needed to unfold similar scaffolds based on six membered heteroaromatic rings (*e.g.*, **27** and **28**), the measured association constants resulted considerably higher.

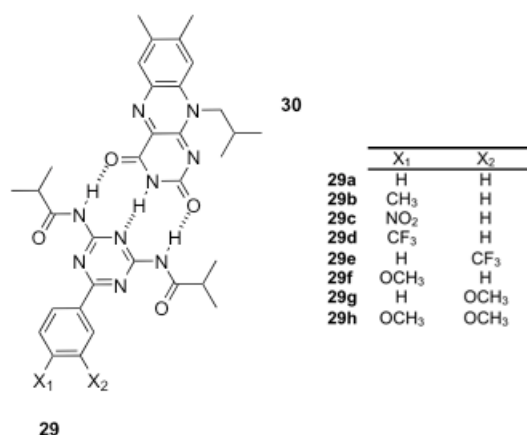


Scheme 10. Differences in K_a between (ADDA) and (AADD) arrays based respectively on five-membered (left) and six membered (right) heterocyclic structure.

1.1.3 Tuning of the association constant value through substituent-effects

The other important way to tune the stability of H-bond complexes regards the control of the electronic effects of the substituents. Often, in the H-bond scaffolds reported in literature the functionalities involved in the binding phenomena are placed on aromatic structures generally allowing a good through-bond communication of electron densities. Substituents therefore can affect the association constant of the H-bond complexes in two principal ways: they can shuffle the electronic distributions on the binding sites varying the positive charge on H-bond donors and/or the negative charge upon the acceptors, and they can stabilize or destabilize a specific tautomer respect to another.

The first study of the modulation of the association constant of H-bond complexes of complementary linear array containing multiple binding sites induced by the presence of specific substituents was carried out by *Deans* and *Rotello* in 1997.^[39] They investigated the effects of two different substituents, X_1 and X_2 in the [ADA·DAD] H-bond complex formed between the acyldiaminotriazine derivatives **29** and flavin **30** (*Scheme 12*).



Scheme 11. Host-Guest systems based on flavin and diacyldiaminotriazines employed in the study of the electronic effects of substituents on the K_a .

It is important to notice that the steric hindrance of the side chains of the acyl groups with the phenyl moiety favors the *trans*-like conformation of the amidic group inducing the stabilization of the (DAD) towards the (ADADA) array, thus enhancing the affinity of **N28** for the flavin host. The electronic properties of the triazine core are modulated by the aryl substituents. Since the steric effects are identical for all the molecules involved in the study, the change in the stability of the complexes can be directly attributed to the electronic effects of the substituents. K_a in CDCl₃ measured *via* NMR titration experiments, ranged from 12 M⁻¹ ($\Delta G = 1.4$ Kcal·mol⁻¹) for **29h** ($X_1 = X_2 = -OMe$) to 97 M⁻¹ ($\Delta G = 2.7$ Kcal·mol⁻¹) in the case of **29c** ($X_1 = -NO_2$; $X_2 = -H$), highlighting that the presence of electron withdrawing

groups decreases the electron density on the triazine nucleus influencing the H-bond capability of the three binding sites. Thus, if the central nitrogen atom becomes a worse acceptor due to the decrease of its basicity, the amidic protons become better donors since their positive electrostatic potential is intensified. The effects on the protons overcome the negative effect of the hydrogen atom resulting in an increase (in absolute value) of the free energy of association and of the K_a . The large difference in binding constants between the *p*-methoxy receptor **29f** and the *m*-methoxy receptor **29g** indicates a substantial resonance contribution to the modulation of flavin recognition in these triazine based hosts. Due to the complex additivity of these effects, further analysis was not carried out.

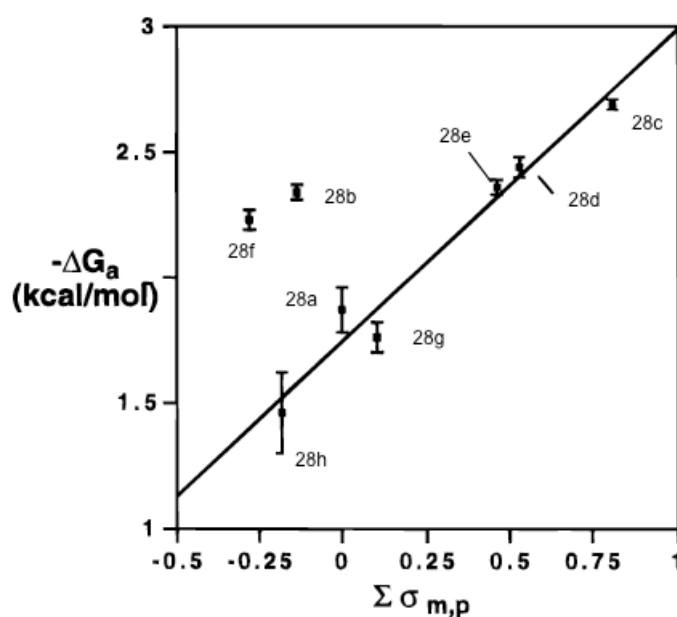
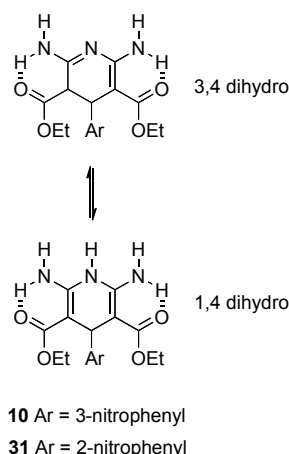


Figure 4. Plot of the binding energies vs. $\Sigma\sigma_{m,p}$ for the complexes [29-30].

In *Figure 4* a plot of the binding energy ($-\Delta G_a$) versus $\Sigma\sigma_{m,p}$ indicates a linear correlation between the free energy of association and the electronic character of the substituents.

Another example of how substituents can affect the tautomeric equilibrium of an H-bonding module, is represented by *Zimmermann's* (DDD) (*Scheme 13*).^[23] The dihydro pyridinic ring may exist in two different tautomers, the 1,4 dihydro form and the 3,4 dihydro form. Their relative equilibrium is so strongly dependent on the nature of the Ar substituent in position 4 that can be considered as a sort of convenient tautomeric 'shift'.



Scheme 12. Tautomeric equilibrium of the dihydropyridine ring in Zimmermann's DDD array.

Thus, in deuterated DMF, **10** exists exclusively in the 1,4-dihydro form, while **31** is entirely in the 3,4-dihydro form, presumably due to a combination of steric and resonance effects. In CDCl_3 , the ^1H -NMR spectrum of **31** showed in the presence of the 3,4-dihydro form, while that of **10** indicated a solvent-induced shift in the equilibrium to a *ca.* 67:33 mixture of 1,4-dihydro and 3,4-dihydro forms.

Switching between the pyrimidinone and the pyrimidinol tautomer in UPy allows a conversion from an AADD array to an ADAD arrangement. This can be achieved instead through modulation of the electronic characteristics of the functionality in the 6-position of these heterocycles. In CDCl_3 electron withdrawing groups destabilize the enone structure of the pyrimidinone tautomer, thereby promoting the pyrimidinol form. Hence when $\text{R} = \text{CF}_3$ the 99% of the molecules are present in solution as the self-complementary DADA pyrimidinol tautomer, while when $\text{R} = \text{alkyl}$ the pyrimidinone form is the predominant form in solution (Figure 5).

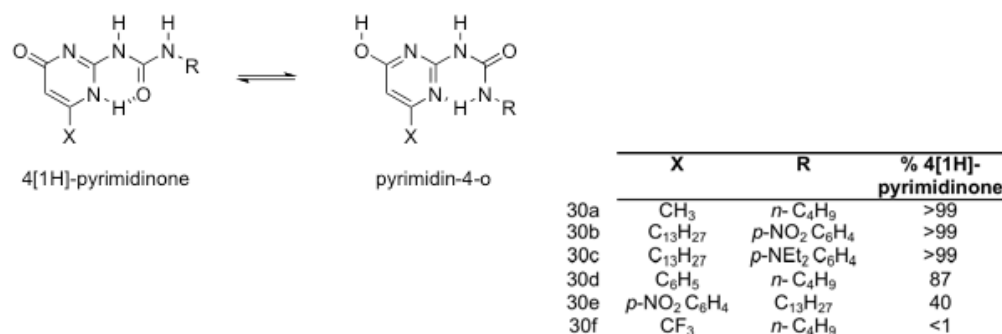
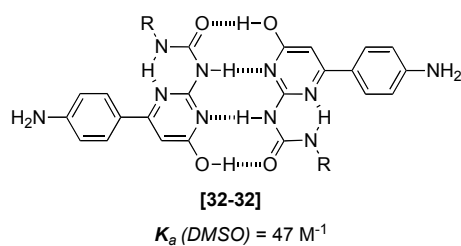


Figure 5. Influence of the X substituent in the equilibrium between the pyrimidinone and pyrimidinol tautomer of UPy. The values are measured in CDCl_3 .

Hailes and co-worker found a completely reversed situation in DMSO, where electron-withdrawing or poorly electron-donor substituents favor the enone tautomer that is

present in the monomeric form (Scheme 14). 4-aminophenyl instead favors the DADA array that despite the high competitiveness for this solvent dimerizes with an association constant of 47 M^{-1} .^[40]



Scheme 13. Association through an ADAD array of 4-aminophenyl substituted UPy module in DMSO and relative association constant.

1.2 Hydrogen-bonding arrays as recognition units in supramolecular architectures

Application of multiple H-bond arrays as associating end groups to create bifunctional complementary (A-B) or self-complementary (A-A) monomers allows the formation, in principle, of all known structures of polymers, including linear homo- and copolymers, cross-linked networks, and (hyper)branched structures.^[16]

In such kind of hydrogen bonding supramolecular polymers the degree of polymerization (DP) is determined by the association constant of the interacting groups. Low K_a values in fact results in low DP in isotropic solutions, however, in the liquid crystalline state, the interactions are stabilized by excluded volume interactions and the DP can result hence much higher.^[41]

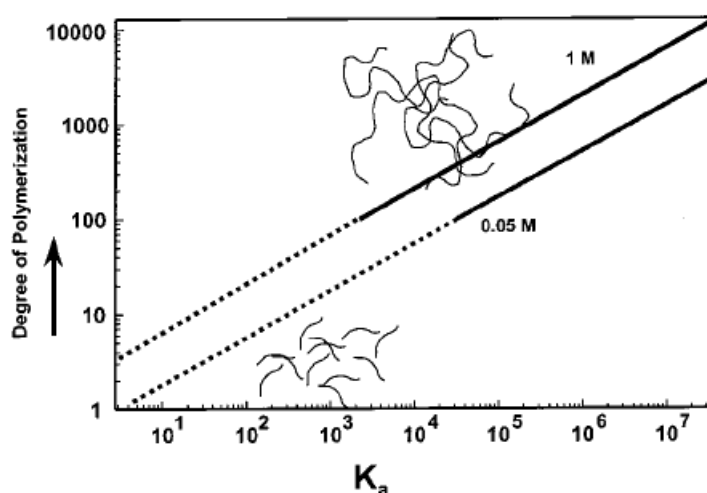


Figure 6 Theoretical relationship between the association constant K_a and DP, using a simple isodesmic association function, or “multistage open association” model.

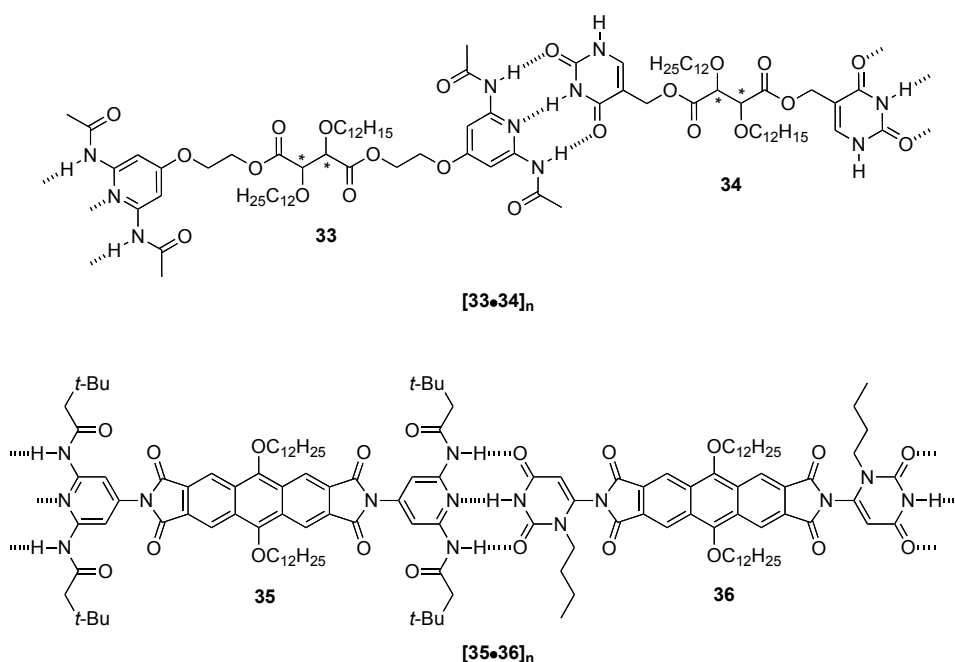
Elevated association constant might not be an asset instead where a certain degree of dynamicity is expected. This is for example the case when hydrogen bonding arrays are used to drive the formation of pre-defined highly regular and defect free hetero-molecular 2D structures on surfaces, through a self-assembly process.^[42] Slowing down the binding/unbinding rate between the components a high K_a may impede the natural ability of a self-assembled system to self-correct and to reach the thermodynamically most favourable structure.

Low association constant are then generally preferred in processes of hierarchical self-organization, where order at the molecular and at the macroscopic level is achieved not only by hydrogen bonding but through the concerted action of an ensemble of weak non-covalent interactions. Hydrogen bonding arrays carried by molecular building blocks specifically designed for the formation of well-defined complex superstructures, through

these kind of processes, in fact display association constant that generally do not exceed 10^5 M^{-1} .

1.2.1 Supramolecular polymer

The group of Lehn is recognized to be the first to develop a supramolecular main-chain polymer. In these firsts examples the association process was driven by the recognition of complementary triple H-bond motifs of diacetylaminopyridines and uracil derivatives ($K_a < 10^3 \text{ M}^{-1}$) and enforced by liquid crystallinity.^[6] Association in a 1:1 ratio of the bifunctional monomers **33** and **34** resulted in the formation of supramolecular polymer chains **[33•34]_n** that exhibit a thermotropic liquid crystalline behavior over a large temperature range.^[43] The increased rigidity of the system in **[35•36]_n** due to the presence of a dialcoxyanthracene core to connect the H-bond groups give rise instead to a birifrangent and highly viscous lyotropic crystalline phase in apolar solvents.^[5]



Scheme 14 Chemical structure of Lehn's Hydrogen bonded supramolecular polymers enforced by liquid crystallinity. **[33•34]_n**: thermotropic liquid crystalline phase, **[36•35]_n**: lyotropic liquid crystalline phase.

It was only with the introduction of self-complementary AADD and complementary ADDA and DAAD units displaying high association constant ($K_a > 10^6 \text{ M}^{-1}$) that the formation of H-bond supramolecular polymer became possible in dilute solution. Since the first example reported by Meijer,^[44] UPy^[4, 45-47], DeAp^[48, 49], UG^[35] have found an extensive use as motif to

assembly main chain polymers or to achieve cross-link.

In a recent example *Abbel*^[50] and co-workers generated a red-green-blue H-bond supramolecular copolymer using three different chromophores difunctionalized with UPy (19) : a blue emitting oligofluorene (**37**), a green emitting oligophenylvinylene (**38**) and a red emitting perylenebisimide (**39**). Thanks to the high stability of the UPy dimerization the degree of polymerization reached was sufficiently high to create white photoluminescent H-bond polymers both in solution at very low concentration values (μM regime) and in spin coated films. In CHCl_3 solution, excitation at the maximum absorption wavelength of **1** ($\lambda_{\text{exc}} = 364 \text{ nm}$) of a mixture of the chromophores at a ratio **37/38/39** = 59:33:8 resulted in simultaneous photoluminescence of comparable intensity over the whole visible spectrum leading to white light emission due to partial energy transfer.

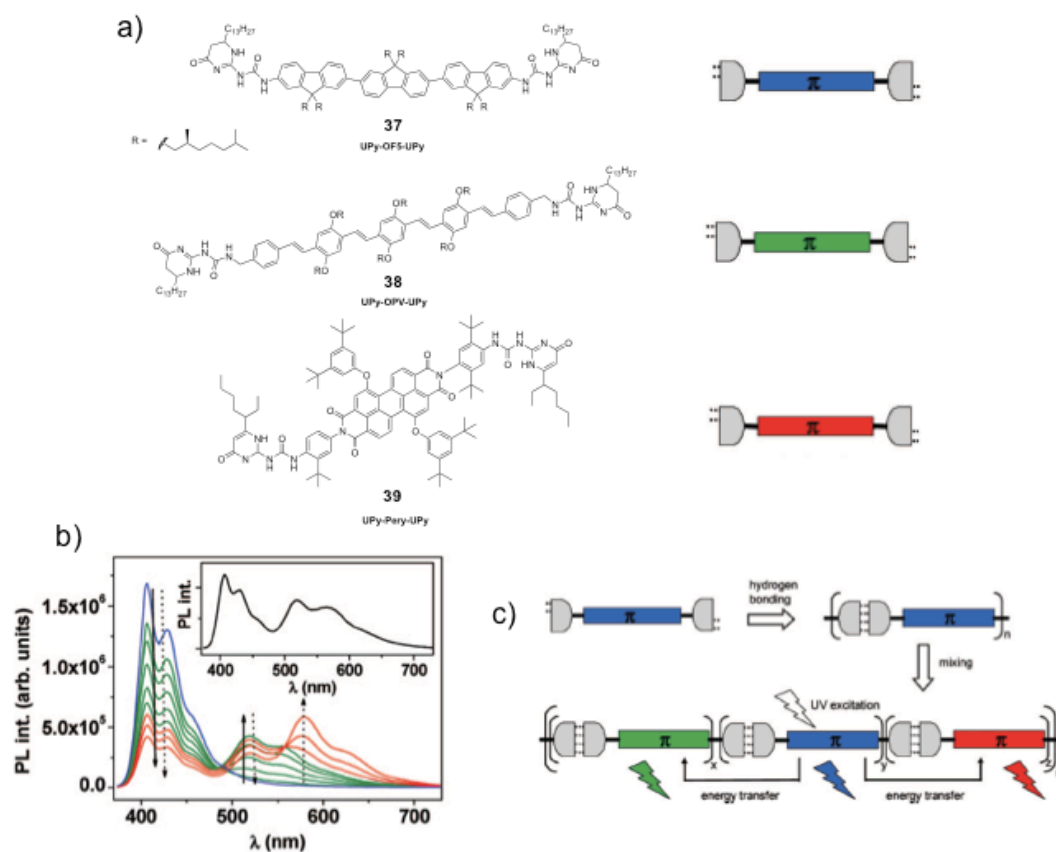


Figure 7 a) Chemical structure of **37**, **38** and **39**; b) Titration experiment in chloroform solution (blue: pure **37**, green: successive addition of **38**, red: further addition of **39**). The solid arrows indicate spectral changes upon addition of **38** to **37**, the dotted arrow upon addition of **39** to a mixture of **37** and **38**. The inset shows the spectrum corresponding to a ratio of 59:33:8.

The high viscosities presented by the ternary mixtures allowed spin coating onto quartz substrate from concentrated ODCB solution (4.5-9 mM) generating photoluminescent films. AFM images of the obtained films showed very smooth, featureless surfaces that closely resembled those of the pure components. No indications of phase separation could be found at

various compositions, suggesting that supramolecular statistical copolymers were present in these mixed films. A white photoluminescent film (CIE coordinates of 0.33 and 0.31; *Figure 8*) was achieved with a mixture of the chromophores in a ratio of **37/38/39** of 84:10:6 (λ_{exc} = 365 nm).

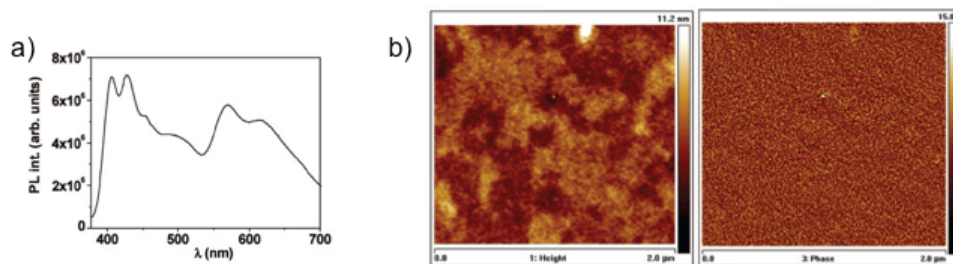


Figure 8 a) Simultaneous photoluminescence of all three di-UPy chromophores (ratio 84:10:6) in a thin spin coated film; c) AFM height (left) and phase (right) images of thin film spin coated from a 80:10:10 mixture of the three chromophores. The z-scale corresponds to a height of 10 nm.

Strong H-bond complexes are useful not only to grow main chain polymers but also in the formation of cross-linked networks within polymer chains. In this respect a noteworthy example is the one reported by *Zimmermann* in which UG and the complementary DAN motifs are used to gain more control over the physical properties of bicomponent polymeric mixtures and to prepare polymer blends.^[48, 51] UG and DAN were respectively appended onto polystyrene (PS) and poly(butylmethacrylate) (PBMA), two polymers that are immiscible under normal conditions. It was found that intermolecular recognition between two different polymer coils occurred, connecting PS and PBMA chains at the molecular level. The mixture of UG-PBMA(**40**) and DAN-PS (**41**) formed colorless and transparent films with no evidence of phase separation on either the nano- or macroscopic scale. Differential scanning calorimetry (DSC) of a 1:1 ratio of a **1/2** mixture afforded intermediate glass transition temperatures (T_g) values (73 and 80 °C respectively) between those of the individual components (T_{g1} = 43 °C , T_{g2} = 104 °C) consistent with the hypothesis of the formation of a polymer blend (*Figure 9c*). Meanwhile, Size-Exclusion Chromatography (SEC) analysis suggested concentration-dependent reductions in the retention time for a 1:1 mixtures, indicating the formation of larger superstructures characteristic of a self-assembled network (*Figure 9b*).

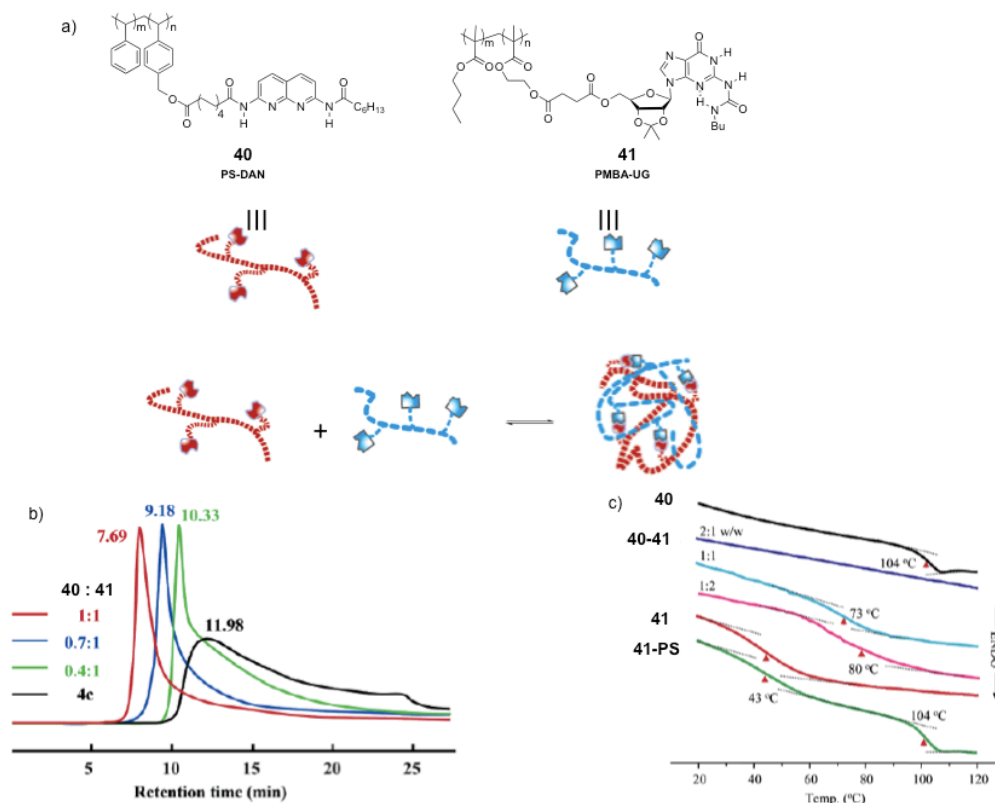


Figure 9 a) molecular structure of PS-DAN (**39**) and PMBA-UG (**40**) and schematization of the formation of the blend; b) SEC of **39** and various weight ratios of **40** and **39** in toluene on a single column (HR4E). Ten microliters of the solution (2.3 g/dL) were injected. A UV detector was used to detect DAN at 345 nm; c) DSC thermograms (2nd heating) of three mixtures of **1** and **2** (2:1, 1:1, and 1:2 w/w) and three controls (**39**, **40**, and a mixture of **40** and polystyrene).

1.2.2 Self-assembly on surfaces

One of the first examples of a bi-molecular network on surfaces, in which the high ordered system is held together by H-bonding interactions, was reported by *Beton, Champness* and co-workers.^[52] In their work the authors described the formation of a highly regular porous networks on surface driven by the formation of hydrogen bonding patterns. Among the main components of this system, melamine, **41**, with its three-fold symmetry 3x(DAD), formed the vertices of the network while the straight edges corresponded to nomen completo PTCDI, **42** [2x(DAD)]. The repetition of these units gave rise to a regular nanoporous honeycomb network on a Ag/Si(111) metallic surface.

This network was obtained under Ultra-High Vacuum (UHV, base pressure $\sim 5 \times 10^{-11}$ mbar) conditions and investigated through Scanning Tunnelling Microscopy (STM) technique. In *Figure 10*, the single components, the formation of the porous network and the relative STM images are displayed. When 0.1–0.3 monolayers (ML) of **42** were sublimed onto the surface, close packed islands and short chains similar to those reported in previous studies of PTCDI were observed.^[53, 54] Subsequently, **1** was deposited in concomitance with the annealing of the

system at 100 °C. Annealing provided the adequate energy to the PTCDI molecules to detach from the irregular assemblies and to diffuse onto the surface. Interactions of the molecular species through hydrogen bonding interactions generated the *nuclei* of the hexagonal network, which then expanded capturing other diffusing molecules. Differently from the hexagonal porous networks obtained by the deposition of single molecular species, this type of bimolecular assembly yields much larger porous, well-suited to allocate heptameric C₆₀ clusters as showed in *Figure 10c*.^[55, 56] These C₆₀ clusters formed in different pores are aligned, and all oriented parallel to the principal axes of the Si(111) surface. Smaller fullerene clusters, formed by two up to five molecules, were also observed.

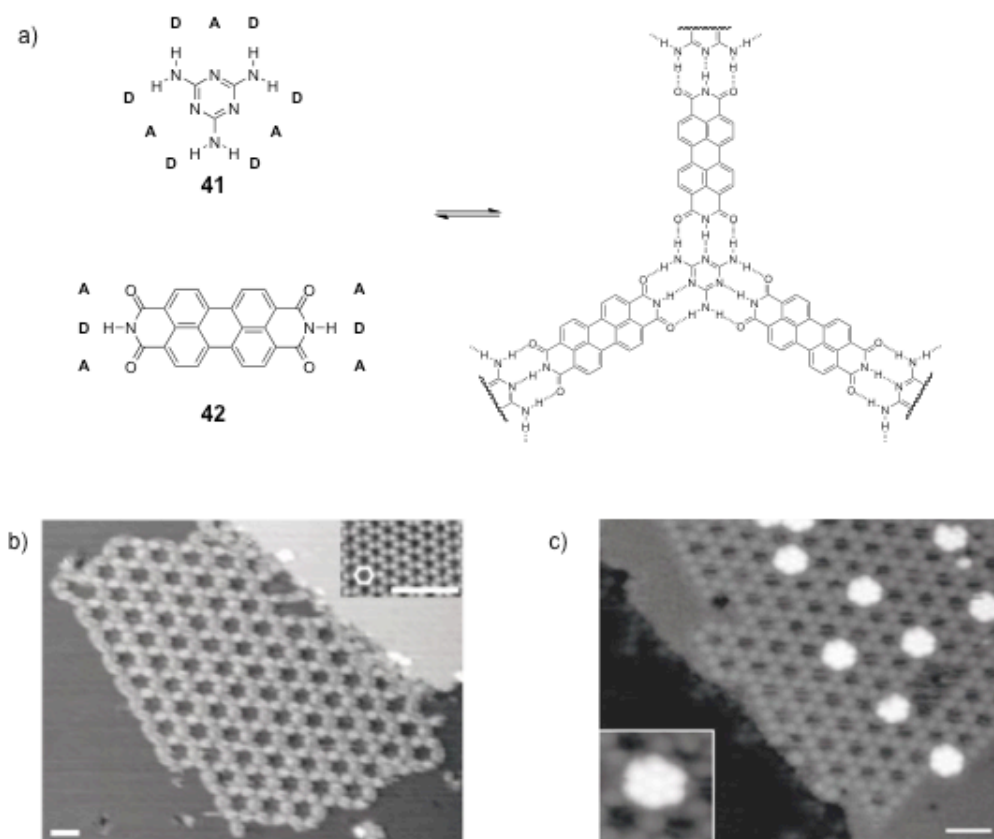


Figure 10 Self-assembly of PTCDI **41** and melamine **42** on Ag/Si(111) surface. a) Chemical structures of **41** and **42**; b) STM image (-2.0 V, 0.1 nA) of the PTCDI-melamine network. Inset: high resolution view of the Ag/Si(111) substrate surface; c) STM image (-2.0 V, 0.1 nA) of C₆₀ heptamers on a PTCDI-melamine network. Inset, high resolution view showing an individual cluster. Scale bar = 5 nm.

Very similar hydrogen bonding arrays were used respectively by *Ortega*^[57] and *Barth*^[58] to obtain highly ordered bi-component networks on Au surfaces.

In the first of these examples, Ortega's group achieved a two-dimensional (2D), binary supramolecular structure formed by packing of monodimensional heterogeneous rows onto Au(111) surfaces. The monodimensional rows are formed by self-assembly through complementary ADA-DAD arrays respectively of naphthalene tetracarboxylic diimide (**43**,

NTDCI) and 1,4-bis-(2,4-diamino-1,3,5,-triazine)-benzene (**44**, BDATB) which is a linear version of melanine. In *Figure 11* are presented STM images for the self assembled monolayer structures of pure **43** (*11b*), **44** (*11c*) and of a 1:1 mixture of the two components (*11d*), while in the respective bottom panels are presented the calculated gas-phase geometry of the tetrameric structures of these molecule. The STM experiments were performed under ultrahigh vacuum conditions (base pressure below 5×10^{-11} mbar) after deposition at sub-monolayer coverage and additional annealing at 177 °C. Homo-molecular deposition of NTCDI and BTADB resulted in highly regular patterned surfaces, in which the order into the supramolecular lattice is achieved by the formation of 4 (2+2) hydrogen bonds within the components of the assembly. Mutual recognition through the two triple hydrogen bonding arrays in the **43/44** system steered the arrangement towards a monodimensional wire-like assembly. The frontal NH-N and NH-O bond distances are 1.63 and 1.71 Å, respectively, whereas the lateral HNH-O bond is 3.07 Å long. Such a difference reflects a weaker hydrogen bond between the 1D chains, as compared to the stronger interactions along the chains in the **43** and **44** assemblies, where the observed distances of the lateral HNH-O bonds are respectively of 2.02 and 2.13 Å.

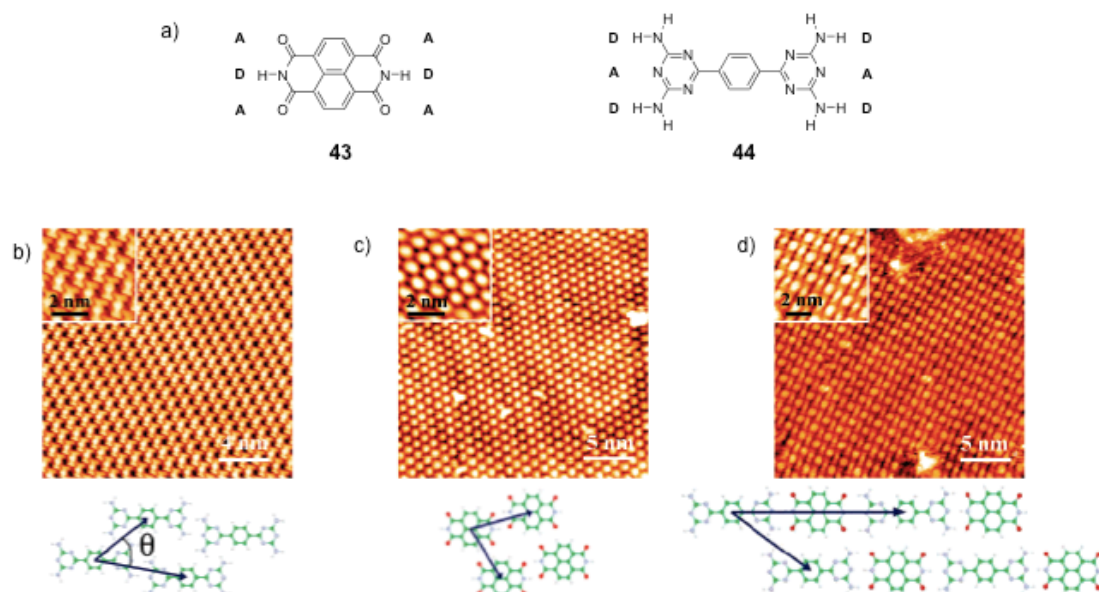


Figure 11 Self Assembly of a NTCDI and PTCDI a) chemical structure of NTCDI and BDATB a) STM image of the BDATB monocomponent supramolecular organization on Au(111) (-0 V, 0.3 nA). b) STM image of NTDCI (-0.0 V, 0.03 nA). c) STM image of the bicomponent supramolecular organization (). In the bottom panels are presented the calculated tetrameric structure with the corresponding 2D lattice vectors (NTDCI : $Q = 47.3^\circ$), (BDATB : $Q = 47.3^\circ$), (NTDCI/BDATB : $Q = 47.3^\circ$)

Depending on coverage, the bicomponent system reported by *Barth* and co-worker that sees the 2x(ADA) array PTDCI (**42**) and the 2x(DAD) array BDATB (**44**) as molecular features, gave rise to a regular superlattice of 1D heteromolecular wires consisting of one or

two molecular rows, as well as 2D supramolecular ribbons. STM images were taken under UHV conditions after deposition of a 1:1 mixture of the components at different coverage, and subsequent annealing. The annealing was performed at 117 °C, for which an average of only one stacking fault per 10 000 nm² was found. Deposition slightly below 1 ML onto Au(11,12,12) yielded to a highly ordered superlattice composed of 2D ribbonlike structures. As shown clearly from the STM image in *Figure 12b* the regular array of steps on the Au(11,12,12) template surface plays an important role in imprinting the unidirectionality of the bicomponent supramolecular structure. A decrease in the coverage of the surfaces to 0.3 ML (*Figure 12c*) resulted instead in the formation of 1D double-row bimolecular wires. The STM image clearly shows alternating brighter and darker protrusions along the steps, which correspond respectively to **42** and **44**. A further lowering of the surface coverage to 0.15 ML leads to single-row bicomponent wires decorating the step edges (*Figure 12d*).

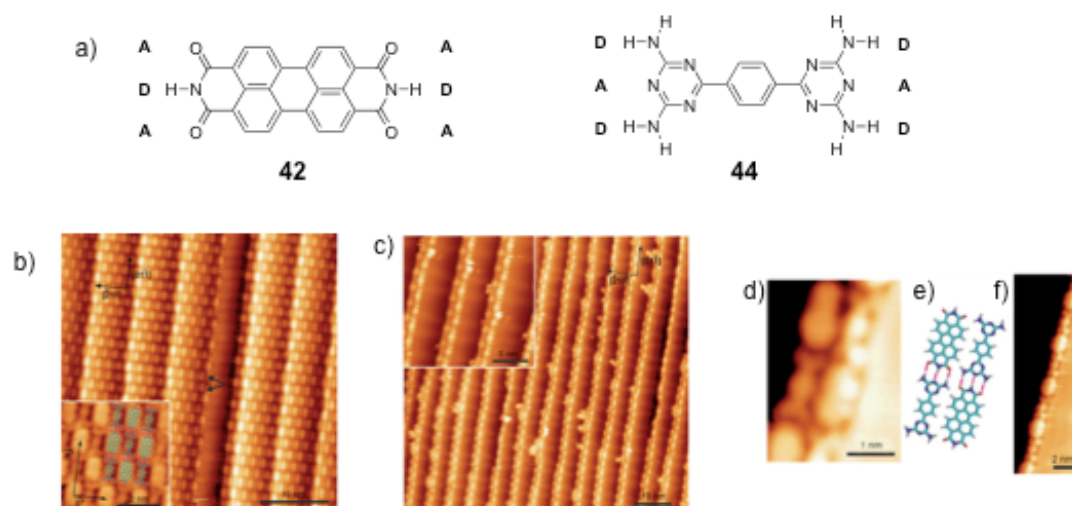


Figure 12 Self Assembly of a PTCDI and PTCDI a) chemical structure of **42** and **44** b) **42** and **44** bicomponent supramolecular organization on Au(11,12,12) at 390 °K, STM image (- 0.4 V, 0.034 nA) of seven terraces fully covered with the heteromolecular superlattice. The small arrows indicate a stacking fault propagating over several terraces. Inset: High-resolution STM image (- 0.4 V, 0.034 nA) and corresponding structural model of the binary supramolecular lattice. c) Overview: STM image (- 1.72 V, 0.2 nA). Inset: STM image of a defect free area, brighter spots correspond to **42** molecules, darker ones to **44** (- 1.1 V, 0.05 nA) d) Well-resolved individual molecules within the double-row wires (-2.1V, 0.13 nA). e) model of the threefold hydrogen-bonding pattern promoting the directionality of the structure. f) Close up STM image of a well-ordered single row wire exhibiting a perfect 1:1 stoichiometry obtained after deposition of 0.15 ML of **42** and **44** (-0.9 V, 0.13 nA).

The first example of a simultaneous three components assembly on surfaces mediated by H-bond interactions was described by Bonifazi and co-workers.^[59] The authors here described a complex system characterized by linear module **45** and **46**, having complementary triply H-bond motifs (DAP and U) and **47** bearing one uracyl moiety and an anthracenyl group acting as a termination unit. Mutual recognition of the ADA and DAD triple hydrogen-

bonding arrays leads, upon annealing, to the formation of *wire-like* supramolecular assemblies, whose length can be tuned by the co-deposition of the mono-functional stopper molecule **47**.

2D organization on Ag(111) surface was investigated by means of Low Temperature STM technique (LT-STM) under UHV conditions at 77 K. Subsequent deposition of linear modules **45** and **46**, resulted in the formation of extended linear bimolecular wires, $[(\mathbf{45}\cdot\mathbf{46})_n]$, whose length is mainly determined by the size of the terraces of the silver substrate (*Figure 13*). The two different molecules can be easily distinguished within the wires as **45** is visualized as three aligned lobes and four lateral spokes corresponding to the acetyl residues, whereas **46** features two lateral protrusions typical of the hexyl chains. As expected, an attempt to assemble **46** and **47** resulted in disordered phases due to the absence of complementary H-bonding sites, while sequential sublimation of molecules **45**, **46**, and **47** on Ag(111) yielded the supramolecular assemblies, $[(\mathbf{47}\cdot\mathbf{45})\cdot(\mathbf{46}\cdot\mathbf{45})_n\cdot\mathbf{47}]$ that are terminated with the anthracenyl moiety of derivative **3**. Although precise control of the length of the molecular wires was not achieved in this study, it is postulated that by controlling the ratio of the molecular modules regular monodisperse self-assembling architectures on surfaces could be produced.

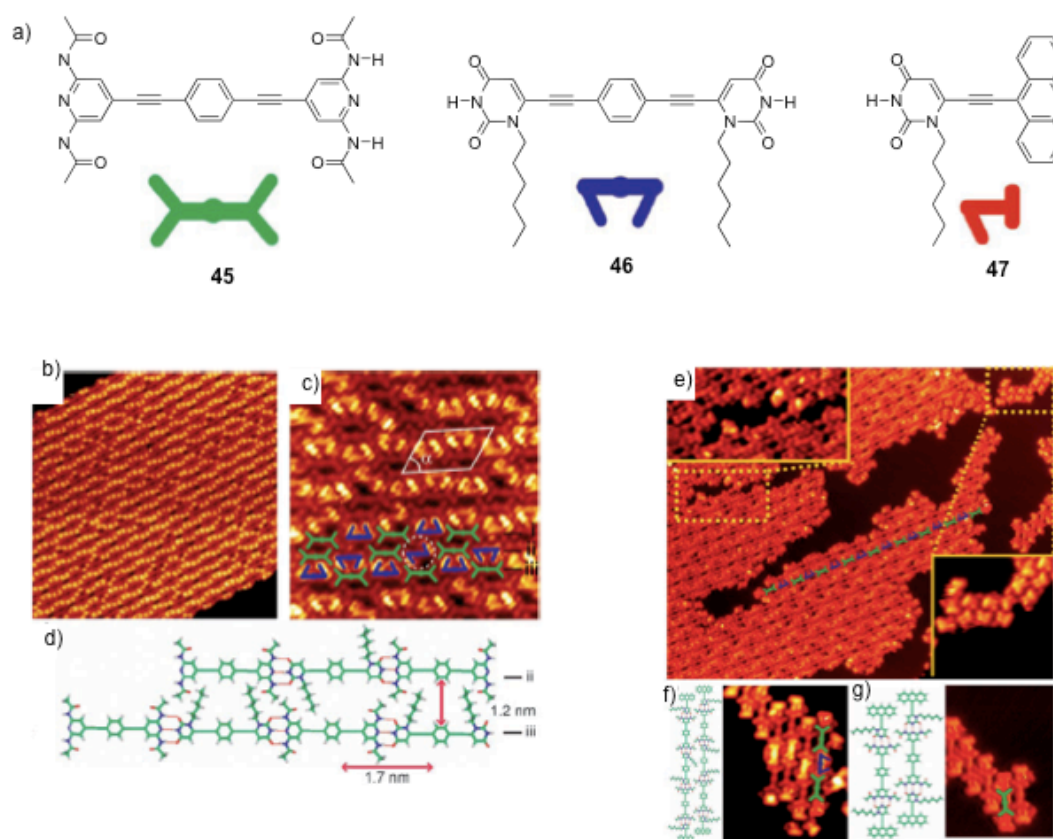
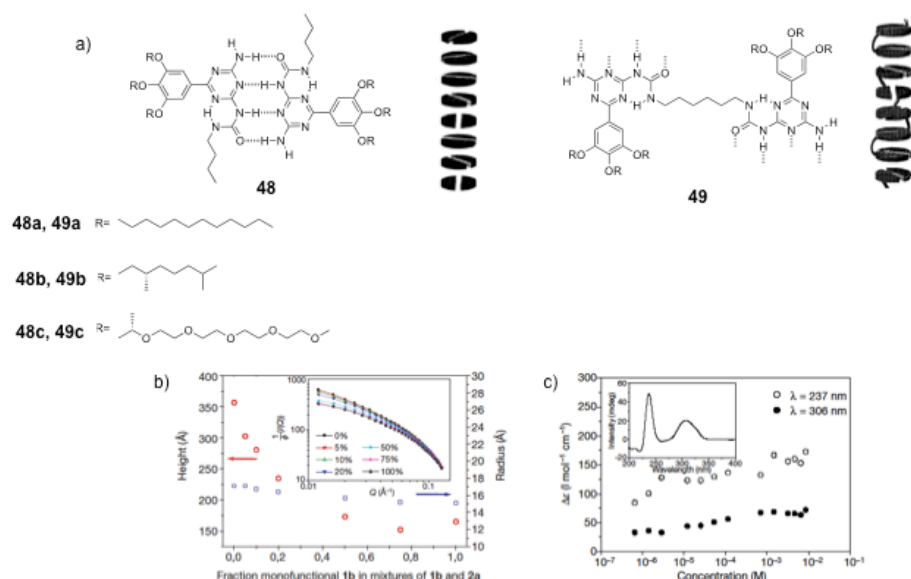


Figure 13 Self-assembly of **1**, **2**, and **3** on Ag(111) surface. a) Chemical structures of the molecular modules **1**, **2** and **3**; b-c) STM images of the self-organised molecular wires formed by **1** and **2** on Ag(111) under UHV conditions upon annealing at 383 K. ($41.5 \times 41.5 \text{ nm}^2$ and $12 \times 12 \text{ nm}^2$, respectively); d) the proposed model for the linear molecular wire assembly; e) STM image of the tricomponent submonolayer architecture formed upon sequential sublimation of **1**, **2** and **3** onto Ag(111) under UHV conditions ($50 \times 40 \text{ nm}^2$). The lower right inset shows an aggregate of **10** ($7.7 \times 7.7 \text{ nm}^2$); f-g) proposed models and zoomed STM image of trimeric and pentameric assemblies, respectively.

OR



The same ureido-triazinic H-bond motif has been used by *Schenning* and *Meijer*^[61, 62] to produce cylindrical stacks of oligo-phenylenevinylene (OPV) in dodecane. In this work OPV molecules functionalized with the ADAD ureidotriazinic array (Figure 15a, **50**, **51**, **52**) are considered the main features of the assembly. In particular, these modules are capable of hierarchically growing by subsequent hydrogen bond and π - π stacking interactions into chiral supramolecular columnar assemblies characterized by thermochromic reversibility in apolar media. In order to comprehend the formation of these assemblies and to study their physical properties, UV/Vis, fluorescence, and CD spectra of variously functionalized OPV derivatives **50**, **51** and **52** were recorded in CHCl_3 and dodecane at room temperature (Figures 15b, 15c). The absorption band measured in a CHCl_3 solution (1.4^{-5} M) and corresponding to the π - π^* transition of the OPV units was observed at 445 nm. The fluorescence maximum was, instead, located at 520 nm (Figure 15b). These values are characteristic for molecularly dissolved tetra(*p*-phenylene vinylene)s and the absence of a Cotton effect supports the fact that these oligomers are not aggregated in CHCl_3 .^[63] In dodecane (1.4^{-5} M), the absorption maximum of OPV is blue shifted ($\lambda_{\text{max}} = 438$ nm) with a strong vibronic shoulder at 480 nm. Moreover, the fluorescence was quenched by approximately one order of magnitude and the emission maximum was red-shifted ($\lambda_{\text{max}} = 550$ nm). This behavior is characteristic of aggregated OPV-oligomers. Additionally, CD measurements showed a strong bi-signed Cotton effect at the π - π^* band position with positive and negative signs at 420 nm and 465 nm, respectively. The zero-crossing of the bisignated CD spectrum occurs at 441 nm, close to the absorption maximum. The CD spectrum is thus, consistent with an exciton model in which the OPV dimers aggregate in a chiral supramolecular stack. SANS measurements also confirmed the presence of rigid cylindrical objects in deuterated dodecane solution, with a radius of 6 nm and the height of *ca.* 150 nm in the case of **50**. Temperature and concentration variable measurements clarified that the stability of the stack is function of the length of the phenylenevinylene backbone, as longer backbones are responsible for an increase of the π - π interactions.

These highly ordered columnar structures were also employed in a later work from the same groups to study the energy transfer processes between different self-organized chromophores in mixed stacks.^[64] Incorporation of a small percentage of **51** (OPV4, $n = 2$) (1.2 mol%) into a OPV3 stack, resulted in a very efficient quenching of the OPV3 fluorescence, indicating that energy transfer occurs within the supra-molecular stacks from the shorter oligomer to the longer one. In *Figure 15d* the temperature dependent photoluminescent spectra clearly shows how at high temperature (when the columnar stack is disrupted) the presence of **51** cannot be distinguished while at lower temperatures (when the

mixed stack exists) the spectrum resembles to a spectrum of molecularly dissolved **51**, consequence of the very efficient energy transfer.^[65]

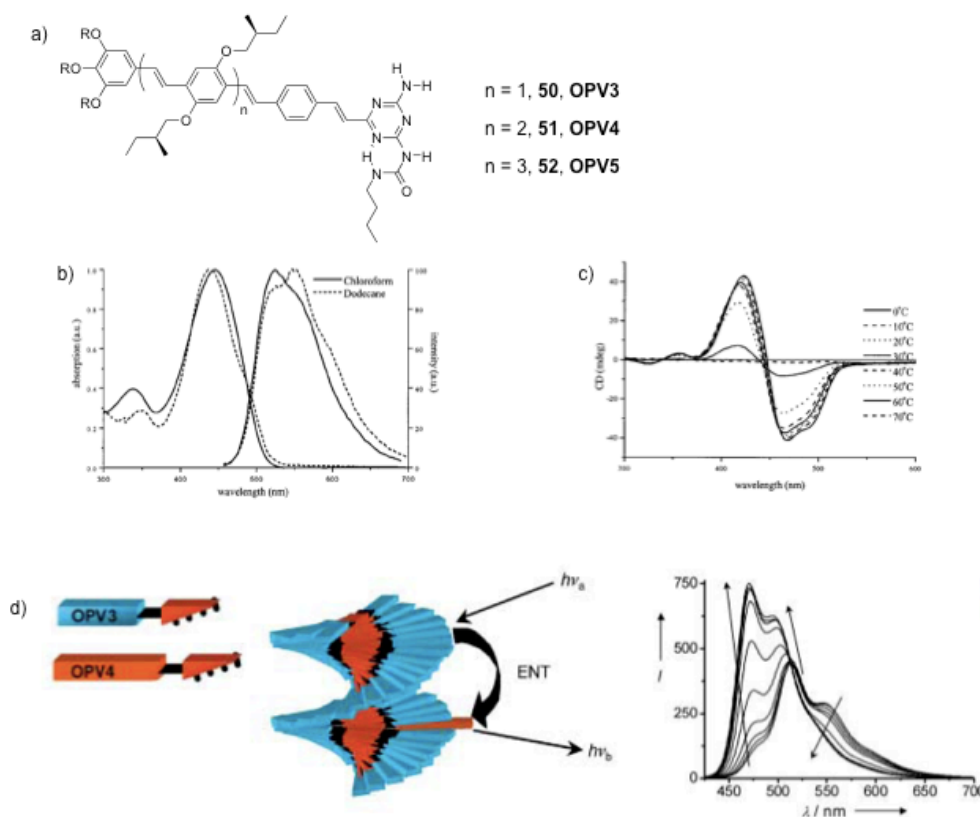


Figure 15 a) Chemical structures of the OPV molecules functionalized with the ureidtriazine array **50**, **51** and **5**; b) Normalized UV-Vis and fluorescence spectra of **2** in dodecane and CDCl_3 at room temperature; c) variable temperature CD spectra of **51** in dodecane; d) temperature-dependent photoluminescence spectra ($\lambda_{\text{max}} = 412 \text{ nm}$) of a solution of **50** (blue) in dodecane with 1.2 mol% trap molecules of **51** (red).

A further hierarchical assembly, this time consisting of oligophenyleneethynylene (OPE) functionalized with melamine (**53**), a double DAD array, was recently reported by Yagay.^[66] In this work the authors described the formation in CHCl_3 of discrete rosettes ($53_3 \times 54_3$), via the co-assembly of **53** with the complementary cyanurate derivative **54**, presenting a double ADA array (Figure 16). The dimension of the assembly were investigated by Dynamic Light Scattering (DLS) experiments that revealed the formation of aggregates with an average hydrodynamic diameter (D_h) of 8 nm, in agreement with the diameter of rosette assemblies with extended alkyl chains. In decane however, larger aggregated species (average $D_h = 50 \text{ nm}$) were obtained, indicating the formation of nano-objects hierarchically organized.

Morphological insights of the assemblies were gained through tapping mode AFM measurements. AFM images of a decane solution ($5 \times 10^{-5} \text{ M}$) spin-coated onto freshly cleaved Highly-Oriented Pyrolytic Graphite (HOPG), displayed a large number of toroidal nano-objects (Figure 16c), whose organization process is driven by extended face-to-face stacking

(H-type) interactions within the OPE fragments in non polar-solvents. The outer diameters of toroids are uniform at around 40 nm, in line with the value of D_h detected by DLS. The average height is 3.2 ± 0.3 nm while the cross-sectional diameter was found to be 8 ± 2 nm.

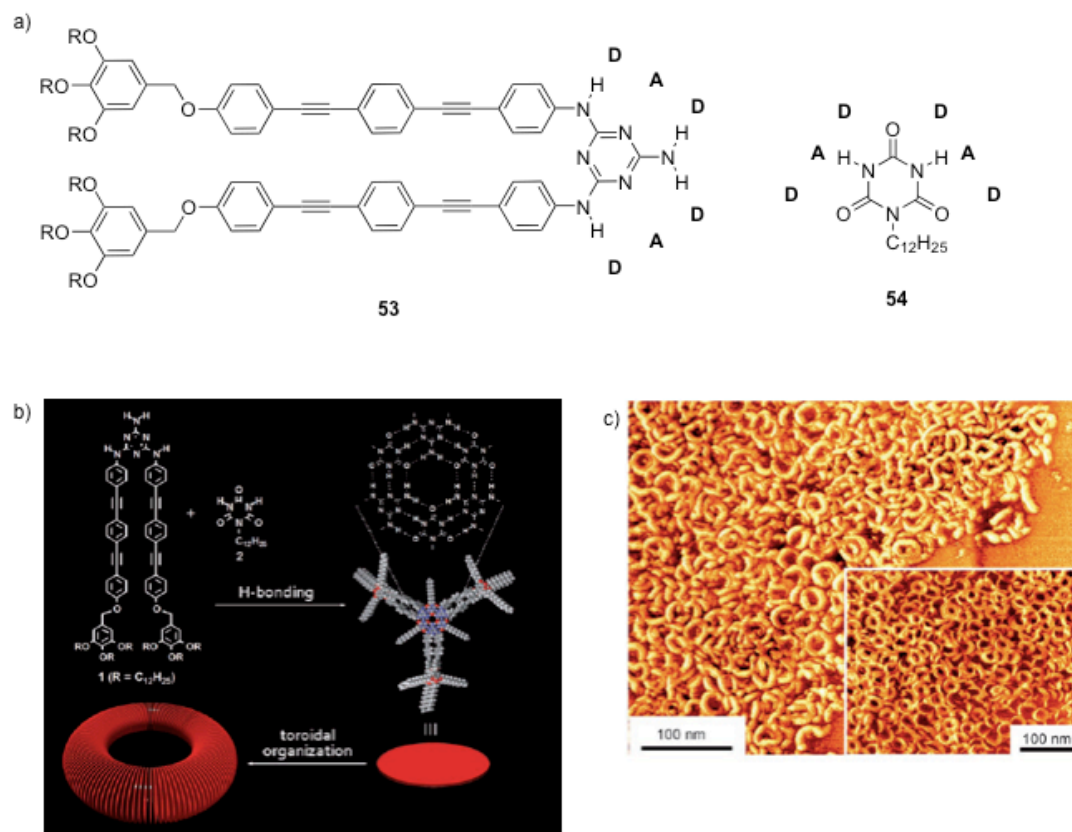


Figure 16 a) Chemical structure of **53** and **54**; b) representation of the self-organization process; c) AFM phase image of an equimolar mixture of **53** and **54** spin-coated from decane solution (5×10^{-5}) on HOPG. Inset: image obtained by low tapping force

The same triazine-cyanurate motif was again used by *Yagay* to hierarchically organize perylene bisimide chromophores (PBI) **55** into discrete 1D elongated nano-objects.^[67] As clearly reported in Figure 17, the system has been investigated by means of Uv/Vis titration experiments. Specifically, the addition of **54** to a 10mM solution of **55** in methycyclohexane (MCH) induced the spectral transitions from π - π stacked aggregates to a situation where free PBI **55** chromophores could be detected. This result implies that π - π stacked aggregates of **55** are disrupted by the addition of **54** to form new hydrogen-bonded aggregates in diluted condition. π - π interactions are restored upon condensation, and at a concentration of 250 mM precipitation of birifrangent crystalline filaments with lengths ranging from 10 nm to 100 nm occurred. The absorption spectrum of the filamentous precipitates presented an absorption maximum at 502 nm with a pronounced shoulder at 544

nm (Figure 17c, dotted line), analogous to that of the self-aggregated **55**. The spectrum is also characterized by the complete loss of the monomeric absorption at 525 nm (Figure 17), indicating that the PBI chromophores in the hydrogen-bonded supramolecular polymers are fully aggregated in the filaments. Field-emission Scanning Electron Microscopy (FE-SEM) revealed that these filaments are composed of intertwined thinner fibrils (approximately 100 nm long) that have a ribbonlike morphology.

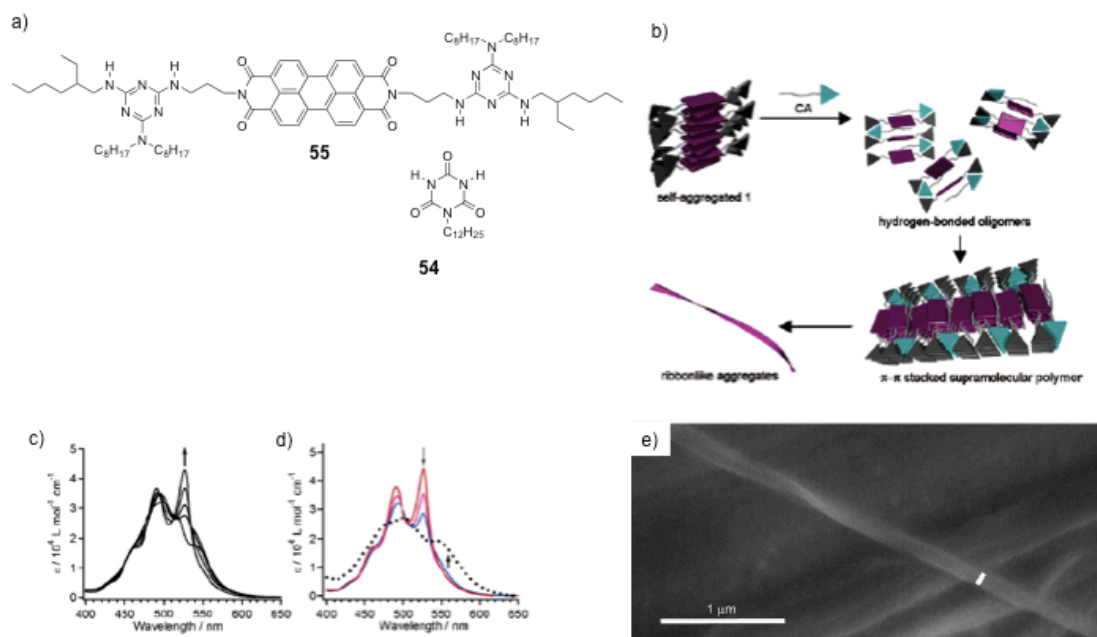


Figure 17 a) Chemical structures of **55** and **54**; b) schematic representation of the hierarchical self-organization process; c) UV/vis titrations of **55** (10 μM) with **54** (0, 2.5, 5.0, 7.5, and 10 μM) in MCH. The arrows indicate spectral changes upon addition of **54**; d) concentration-dependent UV/vis spectra of **55n**, **54n** in MCH (10, 50, and 250 μM , from red to blue). The arrows indicate spectral changes upon increasing concentration. Dotted line: the absorption spectrum of the filamentous precipitates obtained from a 300 μM solution.

The complementary ADA and DAD arrays of uracyl and diacetyldiamino-pyridine are the key features in the system designed by Bonifazi and co-workers^[68] illustrated in Figure 18, where molecule **47** and **56** self-organize in cyclohexane into spherical hollow architectures as effect of the delicate ensemble of H-bonding, π - π stacking and solvophobic interactions. Molecule **47** and **56** are strong luminophore in chyclohexane solution. Absopction spectra of a 1:1 mixture presented a red shift over the low energy band of **47** which was not observer for **47** alone, indicating the presence of π - π stacking, suggesting the formation of structures hierarchically organized after the preliminary self-assembly of module **47** and **56** through triple hydrogen bonding interactions.^[69]

The H-bond self assembled trimeric adduct [**47**•**56**•**47**] (Figure 18a) presents two solvophilic anthracenylic ends, which stimulate the self-organization of the system into the mentioned vescicular-like structures, since in this fashion the solvophobic interactions of the

polar DAP moieties result minimized.

Morphological insights of the adducts formed were gained through TEM and AFM microscopic techniques. Both TEM and AFM images of a dropcast solution of **47** and **56** (1:2 molar ratio) showed the presence of spherical vesicles with a diameter range of 80-180 nm. TEM and AFM analysis of a 1:2 molar ratio solution shows that also in this specific case spherical nanoparticles are formed but with a larger size distribution (150-500 nm) compared to those formed from a 1:1 stoichiometry, since under these conditions, there is a mixture of adducts of different stoichiometry exhibiting both solvophilic and solvophobic terminals.

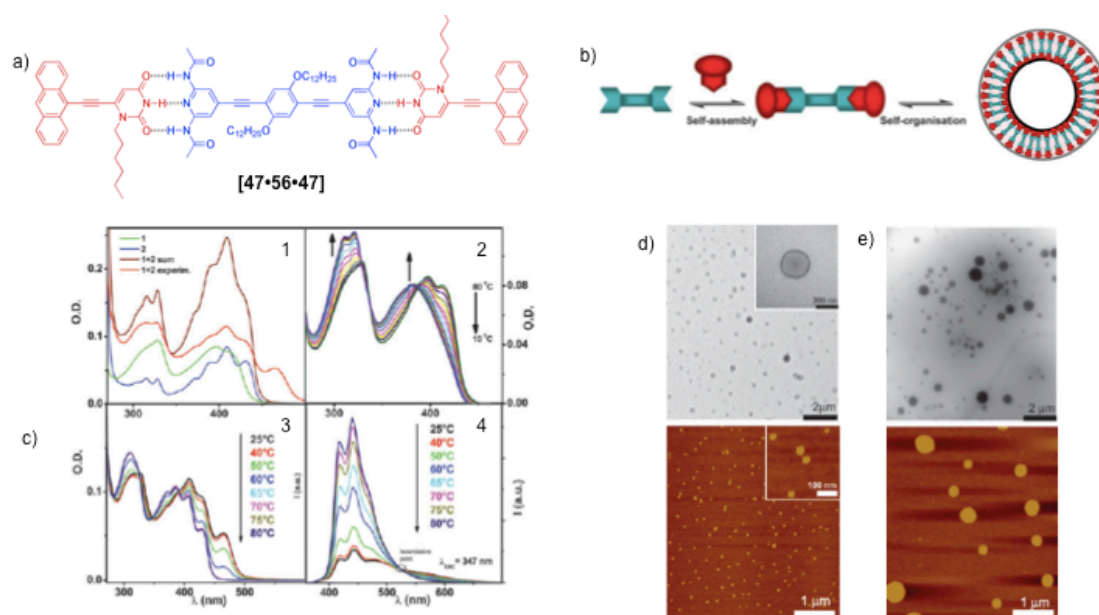


Figure 18 a) chemical structure of the trimeric [47-56-47] adduct; b) schematic representation of the hierarchical self organization process; c,1) Absorption spectrum of **47**, **56** and of their molecular adduct (1 : 2 ratio) experimental and calculated; c,2) variable-temperature absorption spectra of 1 in CHX; c,3) absorption and c,4) emission variable-temperature spectral changes of molecular adduct of 1 and 2 in the ratio 1 : 2.

1.3 Concluding remarks

Due to their selectivity in recognition processes and to the tunability of their strength, multiple hydrogen bonding arrays have become an indispensable building- block in the toolbox of supramolecular chemists, allowing the non-covalent generation of functional materials through self-assembly and/or self-organization processes.

Focusing on the most relevant factors that influence the association constants of hydrogen bonded complexes, in the first part of this chapter I have shown how specific H-bond based arrays, featuring wide ranges of K_a values (spanning among eight orders of

magnitude) can be designed. Subsequently, in the second part of this introduction I have focused on the physical and chemical properties of a large variety of building blocks and how their self-assembling and self-organizing abilities could open the way towards novel fascinating applications.

Conceptually the stability of supramolecular complexes formed through the association of complementary H-bond arrays could be modulated in an indefinite number of ways. Future investigations in this sense will allow the design of specific supramolecular building blocks to precisely match the requirements of a desired application.

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Results and discussion

Well-defined architectures obtained by hydrogen-bonding recognition *motifs* have become an important research topic in supramolecular chemistry such as supramolecular polymers, nanofibers, and stimuli-responsive assemblies.^[1-3]

To supply the demand for tunable and versatile molecular modules to be used in hydrogen bonding recognition processes, the intention of this project was to prepare linear array of H-bond based on five-membered heteroaromatic molecules. We postulated that the use of five-membered rings would allow a control onto the tunability of the binding properties of the arrays not otherwise reachable with other heteroaromatic scaffolds.

Introduction of amidic moieties onto the α position of the molecules of furan and thiophene would endow these species with a DAD character similar to *Hamilton's* diacetylaminopyridine (**8**)^[4] complementary to uracyl and thymine (*Figure 1*).

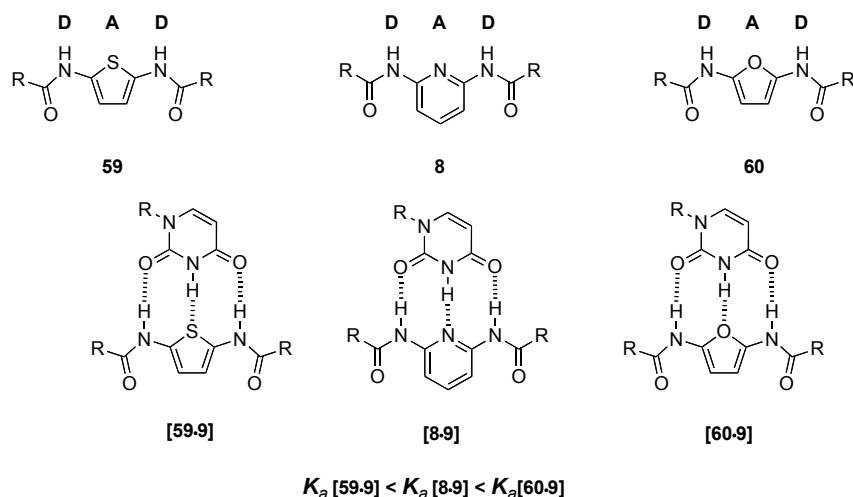


Figure 1 DAD modules based on the molecule of thiophene (**59**), pyridine (**8**) and furan (**60**), and schematic representation of their H-Bond complexes with complementary uracyl derivative **9**.

The modification of the electronegativity of the central H-Bond acceptor atom (A) can be seen as a first mean to tune the recognition properties of the DAD five-membered heterocyclic *motifs*. Oxygen is a better acceptor than nitrogen while sulphur is a worse one, therefore we expect that the resulting complexes of **59** and **60** with Uracyl (**9**) would present varying K_a values. With the synthesis of module **59** and **60** we intend thence to generate two molecular modules that display similar structural features but different binding properties to better match the requirement of different applications, both in material and bio sciences.

Further tuning can be achieved by mean of substituents onto the β positions of the ring. Steric repulsion between the R' groups and the carbonylic groups would result in a destabilization of the *trans*-like conformation ensuing in a decrease of the binding strength of

the array. Moreover Introduction of heteroatoms (number of the molecule) would then completely force the amidic groups towards the *cis*-like conformation. The resulting *cis*-conformers, should have the required geometrical features (*i.e.*: the presence of a tridentate coordination pocket) to make them suitable for metal complexation (*Figure 2*).

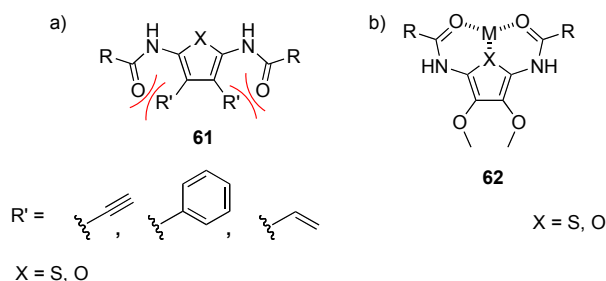


Figure 2 a) Schematic representation of the steric effects of the substituent onto the carbonylic groups in **61**. b) Representation of the complexation of metal ions operated by tetra substituted five-membered heteroaromatic rings.

Introduction of amidic moieties onto the α positions of pyrrole would result in a DDD spatial arrangement of the binding sites (*Figure 3*). Such kind of molecular modules are considered a true rarity among the family of H-Bond arrays, since at this day only one example (**10**) has been reported.^[5] Compared to **10** pyrrolic modules offer the possibility of functionalization onto the β positions of the ring, allowing real applicative perspectives in non-covalent synthesis.

Replacing the amidic moieties for ureidic functionalities, we expect then to create unprecedented DDDDD arrays (**65**).

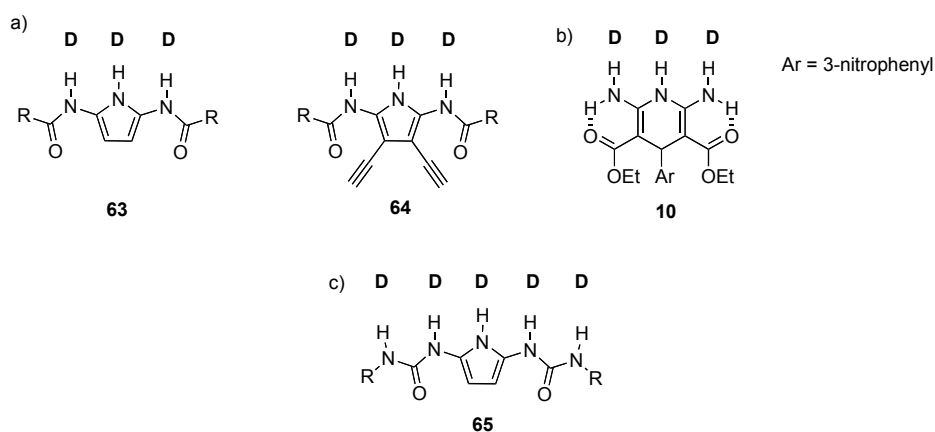


Figure 3 a) DDD H-Bonds arrays based on the molecule of pyrrole, the ethynilic moieties in **64** are intended as a mean to introduce further functionalization of the molecular module; b) *Zimmermann's* DDD array; c) diureidopyrrolic derivative scaffolding for DDDDD H-Bond interactions.

Exploiting the prototropic equilibrium of triazole rings, ureido triazolic derivatives were thought as self-adapting, stimuli-responsive H-Bond array. The nitrogen atom in position 1 on the ring can contemporarily act as a donor or an acceptor, accordingly to the 1,3

prototropic shift, therefore molecular module **66** can present either a DDD or an ADD arrangement.

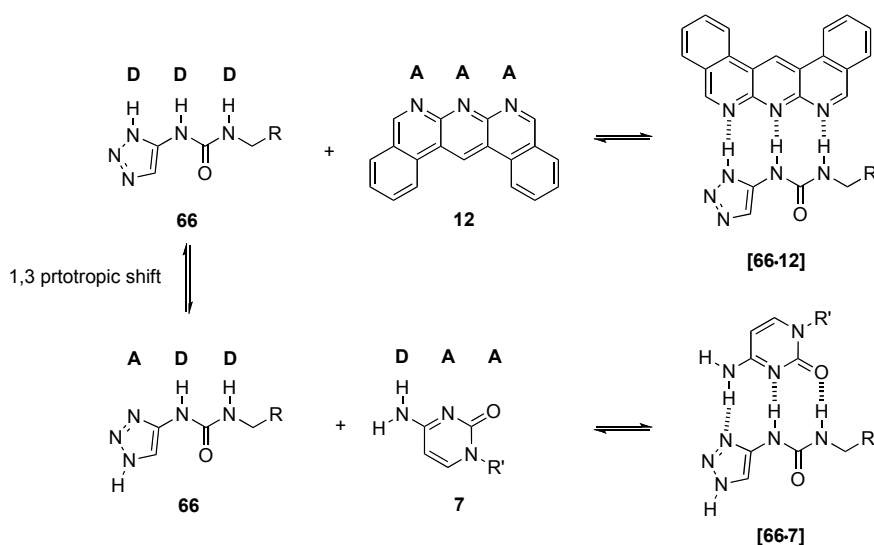


Figure 4 Schematic representation of the 1,3 prototropic shift in **66**, and equilibria of formation of complexes **[66-12]** (DDD•AAA) and **[66-7]** (ADD•DAA).

Ureido triazolic derivatives can, in principle, self-adapt to two different kind of complementary guests (*i.e.*, AAA and DAA) since the presence of the opportune counterpart will induce the switch between the DDD and the ADD form.

2.1 Retrosynthetic analysis

At the best of our knowledge there are no examples reported in the literature of five membered heteroaromatic structures disubstituted onto the α position with amidic functional groups, such as the ones reported in *Figure 1*.

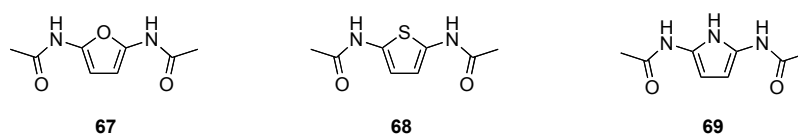


Figure 1. DAD triple hydrogen bonding arrays based on di-amidooxolyl and di-amido thieryl derivatives (**67**, **68**), and DDD triple hydrogen bonding array based on a di-amidoazolyl derivative (**69**).

A major challenge is indeed involved in the synthesis of these compounds, since oxolyl, thieryl, and azolyl derivatives, substituted with amino groups, are intrinsically not stable, despite their stabilized aromatic electronic configuration. In this regard, 2-aminothiophene, firstly synthesised by Stacy^[6] and co-workers in 1969, is stable only in an inert atmosphere below its melting point (12 °C). Heating above this temperature or exposure to air result in an immediate decomposition. Several groups have attempted the synthesis of 2-

aminopyrrole^[7] and 2-aminofuran,^[8, 9] but they have failed to isolate these compounds due to their lability. Moreover, there are still no reports of diaminosubstituted derivatives.

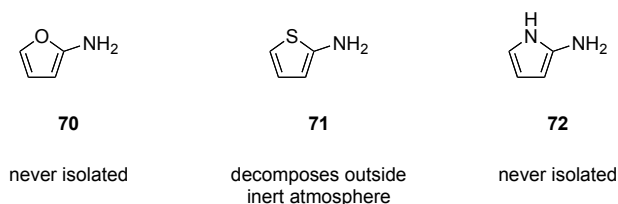


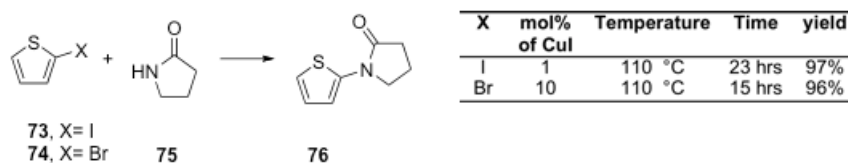
Figure 2. Chemical structures of 2-aminofuran, 2-aminothiophene and 2-aminopyrrole.

As a consequence of this instability, every retrosynthetic strategy involving the formation of an amino derivative intermediate, has to be avoided *a priori*. Therefore, the attention is necessarily focused on methodologies involving the formation of amides, or other stable intermediates containing a C-N bond at the α positions. Screening the literature, we identified different methodologies suitable for these purposes: *i*) the Buchwald-Hartwig amidation cross-coupling reaction, *ii*) the formation of azido-derivatives and *iii*) the formation of isocyanate via the *Curtius* rearrangement of acylazide derivatives.

Hereafter, we will give a brief overview of works where these three methodologies have been used for the functionalization of five membered heteroaromatic rings.

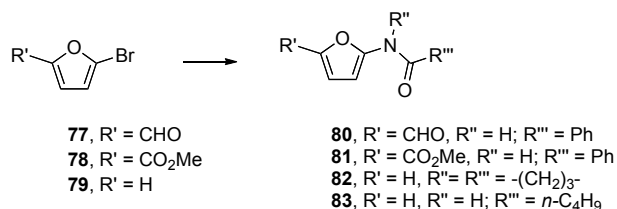
2.1.1 Cu(I) or Pd(0) based Buchwald-Hartwig amidation cross-coupling reactions

In recent years, C-N cross-coupling of aryl halides with amines and amides has been subject of intense studies, primarily by the groups of *Buchwald*^[10, 11] and *Hartwig*.^[12, 13] The first example of amidation of a five membered heterocyclic structure was reported by *Buchwald et al.* in 2001.^[14] In this work, 2-iodo and 2-bromothiophene were coupled with pyrrolidinone, using CuI as catalyst and *trans*-1,2-cyclohexanediamine as ligand, in the presence of K₃PO₄, generating the adduct **76**, in high yields (96%-97%) (*Scheme 1*).



Scheme1 Cu(I) catalyzed Buchwald-Hartwig cross-coupling reaction of 2-iodothiophene and 2-bromothiophene with pyrrolidinone. The reaction was conducted in 1,4-dioxane at 110°C with 1.2 eq. of amide and 2.0 eq of K₃PO₄. CuI was used as catalyst in 1 mol% for 2-iodothiophene and 10 mol% for the bromo derivative. All the yields reported were obtained using *trans*-1,2-cyclohexanediamine (10 mol%) as Cu ligand.

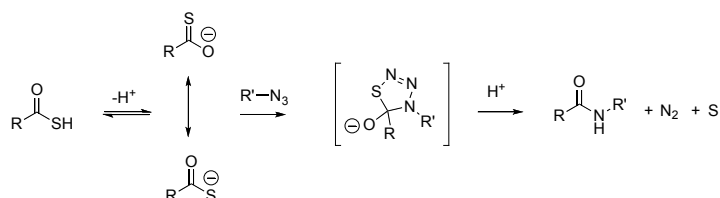
The group of *Padwa* demonstrated in 2003 that oxygenated substituents on the heteroaromatic ring can be tolerated by Cu(I)-based catalytic systems.^[15] Oxolyl derivatives **80** to **83** (*Scheme 2*) were thus prepared in high yields (62-98%), by coupling the corresponding 2-bromooxolyl derivatives with various primary and secondary amides, using CuI as catalyst and either *N*¹,*N*²-dimethylethane-1,2-diamine or racemic *trans*-1,2-cyclohexanediamine as ligand, in the presence of K₃PO₄ or K₂CO₃.



Scheme 2 Cu(I) catalyzed Buchwald-Hartwig cross-coupling reaction of 2-bromofuran derivatives with primary and secondary amides.

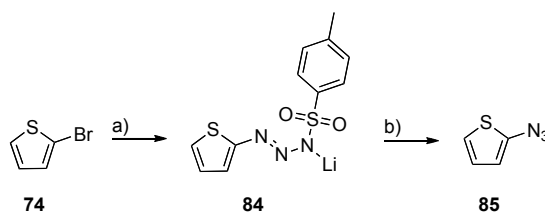
2.1.2 Synthesis of amides through reductive amination reaction of azido-derivatives

Formation of heteroaromatic rings substituted with azide functionalities is particularly appealing to the purposes of this thesis, since azides can be readily transformed into amidic functionalities by treatment with thioacids.^[16, 17] As demonstrated by *Williams* and co-workers, amines are not formed during this reaction, which proceeds instead through the formation of a thiatriazolinic intermediate (*Scheme 3*).^[18]



Scheme 3 Reaction mechanism for the formation of amidic functional groups by reaction of azides and thioacids.

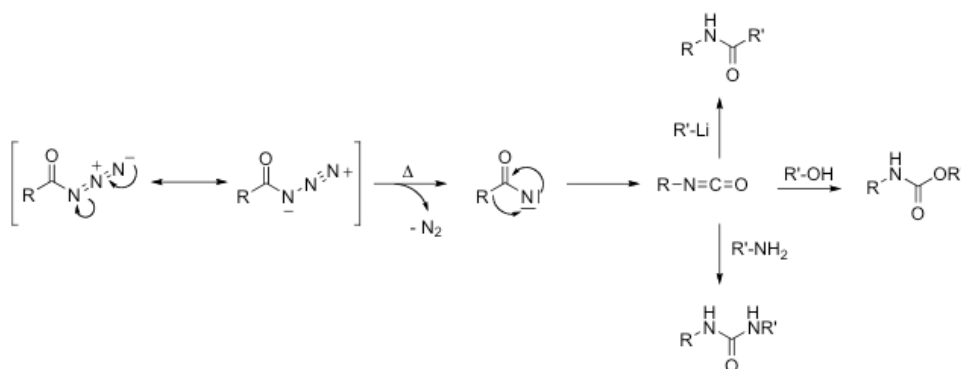
Formation of azidoderivatives of five-membered heterocyclic compounds such as thiophene, furan and selenophene has been described by several research groups.^[19, 20] As a general example of this application of methodology herewith we report the synthesis of 2-azidothiophene (**85**) as described by *Zanirato* and co-workers.^[21] According to this procedure the five-membered ring azido derivative was synthesized in two steps from 2-bromothiophene **74** (*Scheme 4*). Lithiation reaction of **74** with 1 eq. of *n*-BuLi, in THF, at -78 °C, was followed by treatment with TsN₃ to generate the triazene salt **84**. After its isolation, the instable triazene salt was reacted with Na₂P₂O₇·10 H₂O affording **85** in 55% yield.



Scheme 4 Zanirato's synthesis of 2-azidothiophene (**85**). a) *n*-BuLi, THF, -78 °C, 2 h; b) Na₂P₂O₇·10 H₂O, Et₂O, overnight.

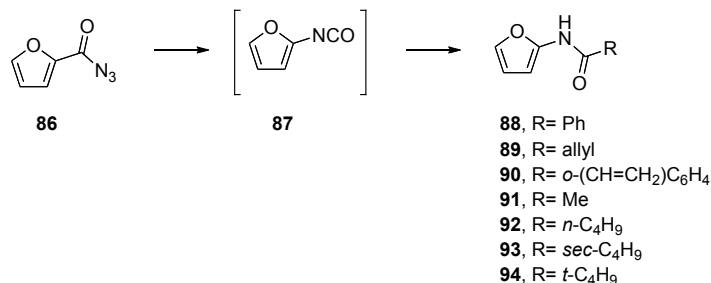
2.1.3 Synthesis of amides and cleavable carbamate derivatives through Curtius rearrangement reaction of nitrenes

The *Curtius* rearrangement is a nucleophilic rearrangement of nitrenes into isocyanate derivatives. Nitrenes are in turn generated by the thermal deazotation of acylazides.^[22, 23] Isocyanates formed by the *Curtius* rearrangement can then be reacted with organometallic species, to generate amidic functionalities. In alternative, they could react with alcohols or amines, forming carbamic or ureidic functional groups, respectively (*Scheme 5*).



Scheme 5 Mechanism of formation of isocyanate by *Curtius* rearrangement reaction of acylazides and subsequent formation of amidic, carbamic and ureidic derivatives.

The reaction of 2-oxolylacylazide (**86**) to give oxolyl amides through the formation of an isocyanate intermediate was firstly described by *Padwa* and co-workers.^[15]



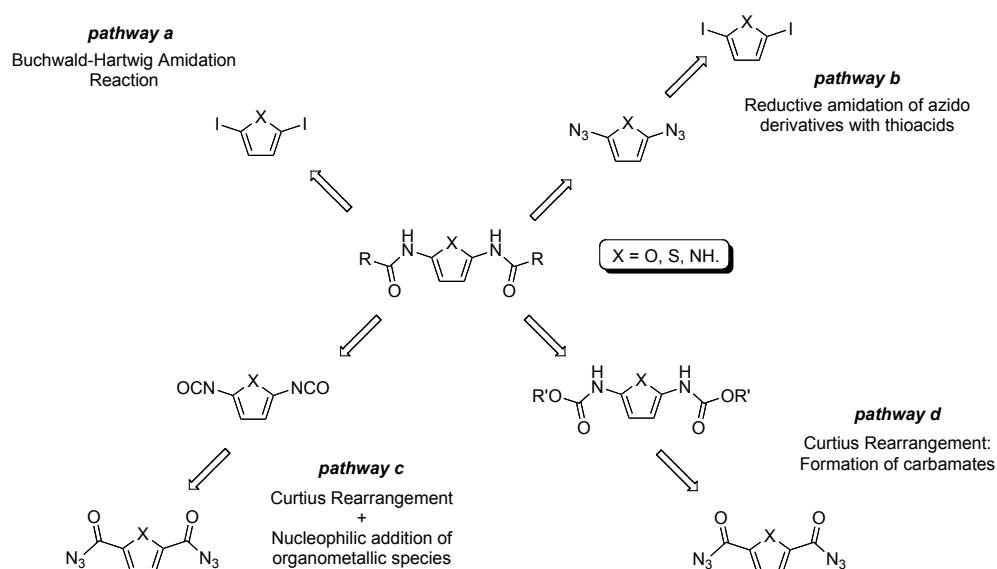
Scheme 6 Synthesis of various 2-amidofuran derivatives through formation of a isocyanate intermediates.

In this work, a family of α -amidofuran derivatives (from **88** to **89**, *Scheme 6*) was generated by reaction of **87** with the appropriate organo-cuprates. Isocyanate **87** was, in turn, formed *in situ*

by heating **86** at 90°C. Isolated yields were varying from moderate, when aryl and alkyl cuprates were used (~ 60%), to low, with allylic and vinylic cuprates (< 30%).

2.1.4 Proposed Retrosynthetic Pathways

Considering our literature screening, four different retrosynthetic pathways were envisaged (*Scheme 7*). According to *pathway a*, the desired DAD and DDD arrays evolve from five-membered heteroaromatic iodo (or bromo) derivatives, via direct C-N cross coupling reaction with amides. In *pathway b*, the key step consists in the reductive amidation with thioacids of five-membered heteroaromatic azido derivatives. Both *pathway c* and *pathway d* are based on the Curtius rearrangement reaction of nitrenes to give isocyanates. The former route involves a nucleophilic addition of organometallic reagents to the isocyanate, to generate amides in one step. Concerning instead *pathway d*, five-membered heteroaromatic amidic derivatives evolve from isocyanate via preliminary formation of a carbamic functional groups.



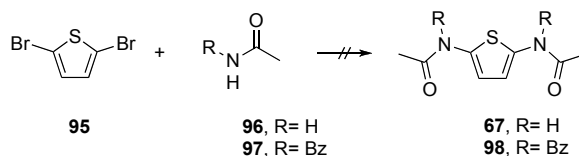
Scheme 7 Proposed retrosynthetic pathways towards DAD and DDD H-Bond arrays based on 5-membered heteroaromatic derivatives.

2.2 Firsts synthetic attempts

2.2.1 Pathway a. Copper(I) or Palladium(0) catalyzed Buchwald-Hartwig amidation of heterocyclic halides

In the preliminary study for the formation of five-membered heterocyclic derivatives substituted in α position with amidic functionalities, we investigated the reaction of 2,5-diiodothiophene, 2,5-dibromothiophene and *N*-tosyl-2,5-dibromopyrrole with acetamide and benzylacetamide.

The first methodological work was carried out on 2,5-dibromothiophene (on a 1 mmol scale) using a catalytic system constituted of CuI, as a source of Cu(I), and N^1,N^2 -dimethylethane-1,2-diamine as ligand. The results collected are summarized in *Table 1*.



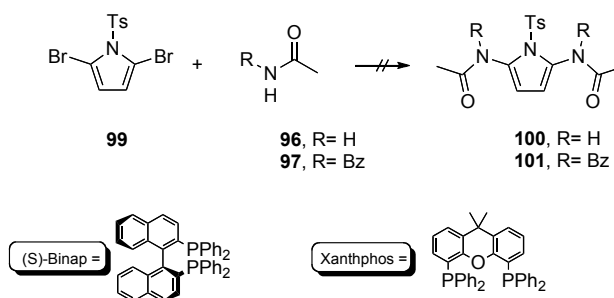
Scheme 1 Cu(I) catalyzed Buchwald-Hartwig cross coupling reaction of **95** with acetamide (**96**) and benzylacetamide (**97**).

entry	R	mol% of CuI	Eq. of amide	Base	T (°C)	Time (hrs)	Yield (%)
<i>i</i>	H	10	4	K ₃ PO ₄	110	16	0
<i>ii</i>	Bz	10	4	Cs ₂ CO ₃	110	16	0
<i>iii</i>	H	10	4	K ₃ PO ₄	110	16	0
<i>iv</i>	Bz	10	4	Cs ₂ CO ₃	110	16	0
<i>v</i>	H	10	4	K ₃ PO ₄	130	8	0
<i>vi</i>	Bz	10	4	K ₃ PO ₄	130	8	0
<i>vii</i>	Bz	30	4	K ₃ PO ₄	130	8	0
<i>viii</i>	Bz	50	4	K ₃ PO ₄	130	8	0
<i>ix</i>	Bz	50	10	K ₃ PO ₄	130	8	0

Table 1 Conditions tested for the Buchwald-Hartwig amidation of **95**. All the reaction resulted in decomposition.

Reaction was initially performed with acetamide, using either Cs₂CO₃ or K₃PO₄ as base and toluene or 1,4-dioxane as solvent (entries *i* and *ii*). However, it resulted almost exclusively in polymerization of the starting material (as seen from the crude ¹H-NMR and MS-analysis) and no traces of the desired product were found in the reaction crude. In the attempt to favorably shift the reaction equilibrium, 2,5-dibromothiophene was reacted with a more nucleophilic secondary amide, *i.e.* benzylacetamide (entries *iii* and *iv*), but the reaction output did not substantially change. The same results were then observed when the temperature (entries *v* and *vi*), the percentage of catalyst (entries *vii* and *viii*) and the equivalents of amide (entry *ix*) were increased.

Polymerization was again the major outcome (along with decomposition by-products) in the reactions of 2,5-diiodothiophene and *N*-tosyl-2,5-dibromopyrrole with acetamide and benzylacetamide. In the case of *N*-tosyl-2,5-dibromopyrrole also the Pd(0)-catalysis in the Buchwald-Hartwig amidation reaction was investigated, whereas this possibility was precluded with the thiophyl derivatives, due to the presence of the sulfur as poisoning atom, deactivating the catalyst. Three different Palladium-based catalysts were used: **a**) [Pd(PPh₃)₄], **b**) Pd(OAc)₂/(S)-Binap, **c**) Pd(OAc)₂/Xanthphos.



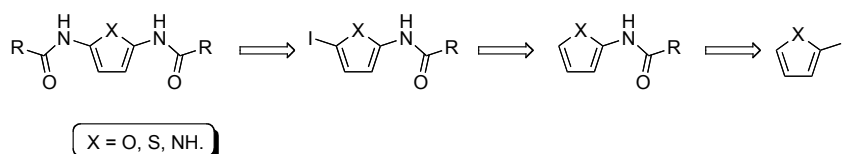
Scheme 2 Pd(0) catalyzed Buchwald-Hartwig cross coupling reaction of **99** with acetamide (**96**) and benzylacetamide (**97**).

entry	R	Catalytic system	Catalyst mol%	T (°C)	Time (hrs)	yield (%)
<i>i</i>	H	<i>a</i>	1	110	16	0
<i>ii</i>	Bz	<i>a</i>	1	110	16	0
<i>iii</i>	H	<i>b</i>	1	110	16	0
<i>iv</i>	Bz	<i>b</i>	1	110	16	0
<i>v</i>	H	<i>c</i>	1	110	16	0
<i>vi</i>	Bz	<i>c</i>	10	110	16	0
<i>vii</i>	Bz	<i>c</i>	10	130	16	0
<i>viii</i>	Bz	<i>c</i>	10	130	16	0
<i>ix</i>	Bz	<i>c</i>	20	130	16	0

Table 2 Conditions tested for the Buchwald-Hartwig amidation of **99**. All the reaction resulted in decomposition.

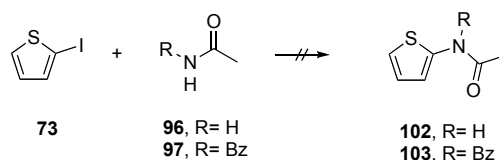
Classical conditions were used^[14] (Table 2), but they revealed to be too harsh to allow the survival of the heterocyclic nucleus, as confirmed by GC-MS analysis of the reaction crudes.

Considering all the above mentioned results, this approach was discontinued. We envisaged then a new three-steps synthetic route (Scheme 3). According to this pathway, we intended to perform a first Buchwald-Hartwig amidation on a monoiodo (or monobromo) derivative, followed by iodination of the free α position, in order to introduce the halide required for a second Buchwald-Hartwig reaction.



Scheme 3 Retrosynthetic pathway towards five-membered heteroaromatic rings di-substituted at the α positions with amidic functional groups.

At first, we decided to determine the best conditions for the coupling of 2-iodothiophene with acetamide and benzylacetamide (Scheme 4), due to the lack of related literature. The catalytic system was constituted, also in this case, of CuI, as a source of Cu(I), and of *N*¹,*N*²-dimethylethane-1,2-diamine as ligand (the results obtained are summarized in Table 3).



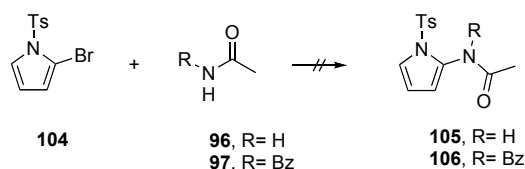
Scheme 4 Cu(I) catalyzed Buchwald-Hartwig cross coupling reaction of **73** with acetamide (**96**) and benzylacetamide (**97**).

entry	R	mol% of CuI	Eq. of amide	Base	T (°C)	Time (hrs)	Yield (%)
<i>i</i>	H	10	1.2	K ₃ PO ₄	110	16	0
<i>ii</i>	Bz	10	1.2	Cs ₂ CO ₃	110	16	0
<i>iii</i>	H	30	4	K ₃ PO ₄	130	16	0
<i>iv</i>	Bz	30	4	K ₃ PO ₄	130	16	0
<i>v</i>	Bz	50	10	K ₃ PO ₄	130	16	0
<i>vi</i>	Bz	100	10	K ₃ PO ₄	130	16	0

Table 3 Conditions tested for the Buchwald-Hartwig amidation of **73**. The starting material was fully recovered after every attempt.

When the reaction was conducted with 1.2 eq of acetamide at 110 °C, using 10 mol% of CuI (entries *i* and *ii*), no reaction took place and the starting material was fully recovered. The temperature, the equivalents of amide and the percentage of catalyst were then increased, and the amide was changed to benzylacetamide (entries *iii* to *vi*), but even under these conditions no reaction was observed.

[Pd(OAc)₂]/Xanthphos was used as catalytic system in the attempt to generate amidopyrrole derivatives **105** and **106**, starting from *N*-tosyl-2-bromopyrrole **104**. Unfortunately the reaction output followed the general trend observed for the reaction of 2-iodothiophene, and the starting material was fully recovered after every attempts.



Scheme 5 Pd(0) catalyzed Buchwald-Hartwig cross coupling reaction of **104** with acetamide (**96**) and benzylacetamide (**97**).

entry	R	mol% of catalyst	Eq. of amide	Base	T (°C)	Time (hrs)	yield (%)
<i>i</i>	H	5	1.2	K ₃ PO ₄	110	16 hrs	0
<i>ii</i>	H	5	1.2	Cs ₂ CO ₃	110	16 hrs	0
<i>iii</i>	Bz	5	4	K ₃ PO ₄	110	16 hrs	0
<i>iv</i>	Bz	5	4	Cs ₂ CO ₃	110	16 hrs	0
<i>v</i>	H	20	10	K ₃ PO ₄	130	16 hrs	0
<i>vi</i>	Bz	20	10	K ₃ PO ₄	130	16 hrs	0

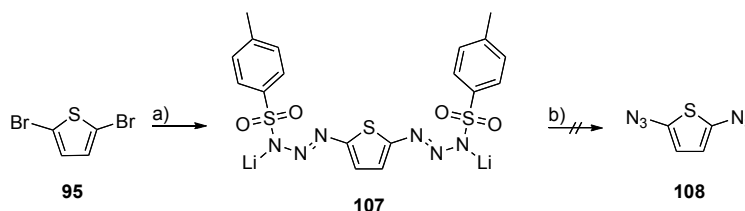
Table 4 Conditions tested for the Buchwald-Hartwig amidation of **104**. The starting material was fully recovered after every attempt.

On the light of the failure of the Buchwald-Hartwig amidation cross-coupling of five-membered heteroaromatic rings this approach was abandoned.

2.2.2 Pathway b. Formation of five-membered heteroaromatic azidic derivatives

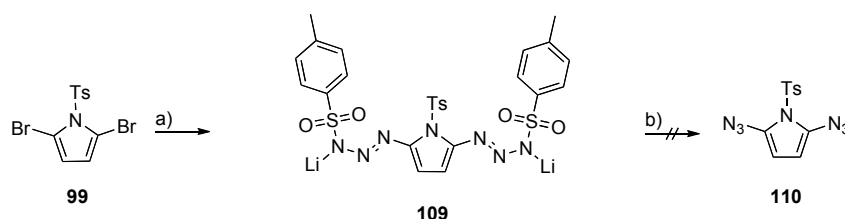
The formation of five-membered heteroaromatic structures bearing azido groups at the α positions was firstly studied on thiophene.

In order to synthesize derivative **108**, the procedure described by Zanirato^[21] for 2-bromothiophene was carefully followed, using 2,5-dibromothiophene **95** as starting material. Li/halogen exchange was performed with *n*-BuLi, and the dilithium thioly derivative thus obtained was added to a solution of TsN₃ (Scheme 6).



Scheme 6 a) *n*-BuLi, THF, -78 °C, 2 h, then Ts-N₃, not isolated; b) Na₄P₂O₇·10 H₂O aq., Et₂O, r.t., overnight, decomposition.

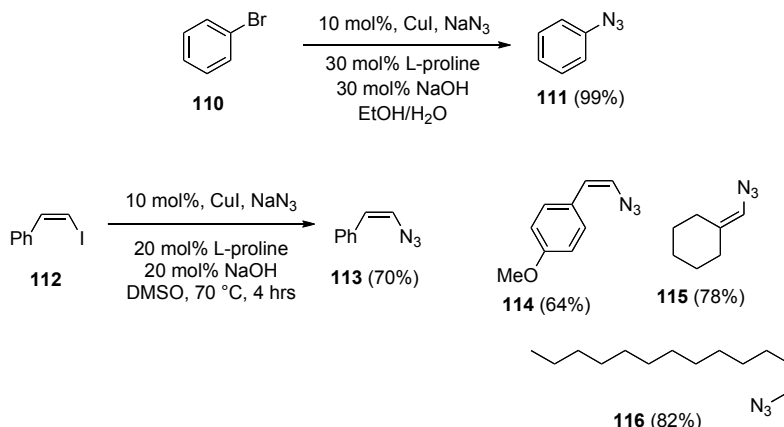
Isolation of derivative **107** was not carried out due to its high instability. Therefore treatment with Na₄P₂O₇ was then performed directly on the crude of the reaction, but unfortunately this step resulted in decomposition.



Scheme 7 a) *n*-BuLi, THF, -78 °C, 2 h, then Ts-N₃, not isolated; b) Na₄P₂O₇·10 H₂O aq., Et₂O, r.t., overnight, decomposition.

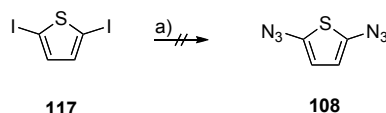
Since similar results were obtained with the use of *N*-tosyl-2,5-dibromopyrrole as substrate (Scheme 7), we did not proceed any further using the Zanirato's synthesis, in our attempt to form five membered heteroaromatic azidic derivatives, and we looked for a different methodology.

Cu(I) catalyzed Ullmann-type coupling with NaN₃ seemed to be a suitable technique.^[24] Nevertheless, couplings of inactivated aryl halides with sodium azide, catalyzed by CuI, result generally in low yields, mainly because the high temperatures required for completion of the reaction cause decomposition of the aryl azides.^[25] However, amino acids can be used as additives, to promote the coupling, thereby allowing the use of lower temperatures.^[26] In this context, Ma *et al.* described a proline-promoted, CuI-catalyzed coupling reaction of aryl and vinyl halides with sodium azide, which provided a variety of aryl and vinyl azides.^[27] (Scheme 8).



Scheme 8 Proline-promoted, CuI-catalyzed azidation reported by *Ma* and co-workers: examples of coupling with bromobenzene and various vinyl iodide derivatives.

Encouraged by the high yields achieved in relatively mild conditions and by the tolerance of the catalytic systems towards different functional groups, we screened different conditions for the α -azidation of 2,5-diiodothiophene (**117**). The results obtained are summarized in *Table 5*.



Scheme 9 Proline promoted CuI catalyzed azidation of 2,5-diiodothiophene. For conditions see *Table 5*.

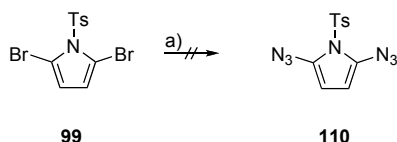
All the reactions were carried out on a 1 mmol scale using 4 ml of DMSO or a 3:1 H₂O/EtOH mixture as solvent. NaOH (crushed pellets) was used in stoichiometric ratio respect the equivalent of L-proline. The result obtained are summarized in *Table 5*.

entry	CuI (mol%)	Solvent	L-proline (mol%)	T (°C)	time (hrs)	Yield (%)
<i>i</i>	10	DMSO	30	70	24	0 ^[b]
<i>ii</i>	10	DMSO	30	90	24	0 ^[b]
<i>iii</i>	10	DMSO	30	110	6	0 ^[c]
<i>iv</i>	30	DMSO	90	90	24	0 ^[b]
<i>v</i>	30	DMSO	90	110	5	0 ^[c]
<i>vi</i>	100	DMSO	150	90	24	0 ^[b]
<i>vii</i>	30	H ₂ O/EtOH	90	90 ^[a]	24	0 ^[b]
<i>viii</i>	30	H ₂ O/EtOH	90	110 ^[a]	6	0 ^[c]

Table 5 Conditions tested for the proline promoted CuI catalyzed azidation of 2,5-diiodothiophene. [a] : microwave irradiation, [b] : complete recovery of the starting material, [c] : decomposition.

No reaction was observed and the starting material was fully recovered when the reaction temperature was kept under 90°C, even using CuI in stoichiometric quantities (entry *vi*), and when temperature was increased to 110°C decomposition was observed (entry *iii*, *v*, and *viii*).

When *N*-tosyl-2,5-dibromopyrrole was used as substrate for the reaction (*Scheme 10*), in the same conditions reported in *Table 5*, decomposition of the starting material occurred already at 90°C.

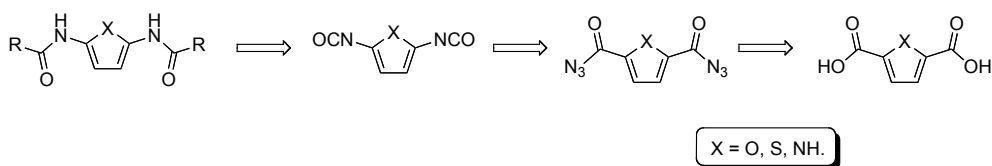


Scheme 10 Attempted synthesis of **110** via proline promoted CuI catalyzed azidation of **99**. The same conditions reported of *Table 5* were used for this reaction. Decomposition of the starting material occurred already at 90 °C.

Given these results, we did not proceed any further in the attempt towards the introduction of azido moieties at the α position of five-membered heteroaromatic molecules.

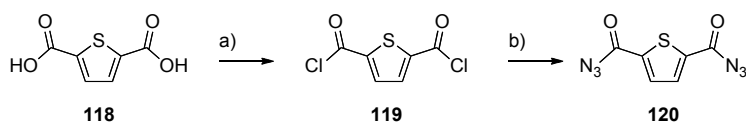
2.2.3 Pathway c. Nucleophilic addition of organo-metallic reagents onto isocyanate

Scheme 11 illustrates the retrosynthetic pathway c, based on the Curtius rearrangement of nitrenes. According to this pathway, the desired diamido derivatives are obtained by reaction of an organometallic reagent with the opportune diisocyanate, generated by thermal degradation of a diacylazide. The starting building block of this pathway should therefore bear two carboxylic functionalities at the α positions.



Scheme 11 Retrosynthetic pathway c towards diamido five-membered heteroaromatic derivatives.

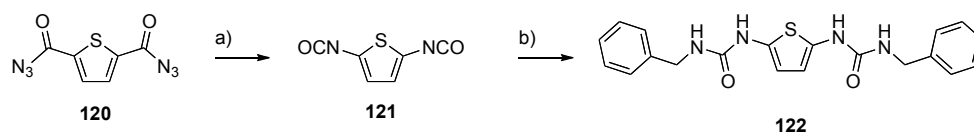
The first candidate investigated in this methodological study was thiophene, with the synthesis of the diacylazide derivative **120**, according to *Scheme 12*.



Scheme 12 a) $(\text{COCl})_2$ THF, DMF, 0 ° to r.t., not isolated; b) sat. NaN_3 aq. THF, 30', r.t., 72%.

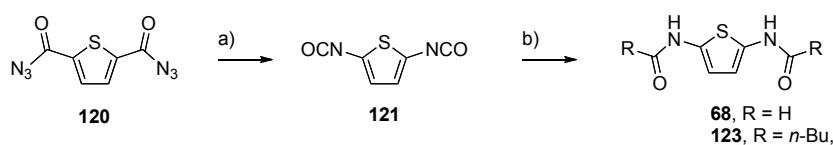
As a first step, **118** was chlorinated with $(\text{COCl})_2$, using a catalytic amount of DMF, and then reacted with NaN_3 . Molecule **120**, thus obtained in 72% yields, appeared as a white solid, turning rapidly brown upon air exposure. For this reason and due to its high explosive nature, **120** was generally stored in a CH_2Cl_2 solution (1M) at -20°C .

Diisocyanate **121** was then synthesised by refluxing **120** in toluene, even though all the purification attempts resulted in decomposition. However, addition of benzylamine resulted in the formation **122**, in 87% yield.



Scheme 14 a) toluene, reflux, 2 hrs., not isolated; b) benzylamine, THF, r.t. 2 hrs, 87%.

Once established the actual formation of the desired diisocyanate, its reaction with organometallic species was taken in consideration. To do so, the crude reaction mixture containing **121** was cooled down and treated with various organometallic species, as depicted in *Scheme 15* and *Table 6* (dialkyl-cuprates were prepared from the corresponding organolithium compounds, by reaction with CuCN). Since, however, all the attempts resulted in decomposition, this approach was discontinued.



Scheme 15 a) toluene, reflux, 2 h, not isolated; b) see *Table 5*.

entry	R-MX	T (°C)	yield
i	MeLi	-78 to r.t	0
ii	<i>n</i> -BuLi	-78 to r.t	0
iii	MeMgBr	-78 to r.t	0
iv	PhenylMgBr	-78 to r.t	0
v	Me ₂ CuLi	0 to r.t	0
vi	<i>n</i> -Bu ₂ CuLi	0 to r.t	0

Table 5 Condition tested for the formation of compounds **68** and **123**. All reactions resulted in decomposition.

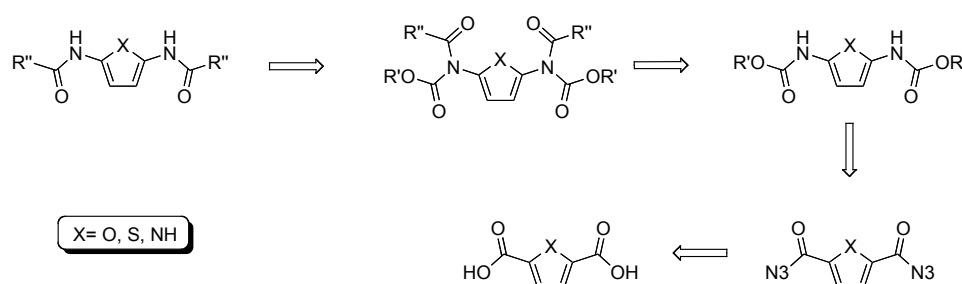
As reported in *Table 5* that summarizes the results collected, all the attempts made led to disappointing results. Each case, resulted in decomposition and no trace of the desired diamidic derivatives were found in the reaction crude.

On the light of the failure in utilizing the reaction between isocyanate and organometallic reagents to form derivatives **68** and **123**, this approach was discontinued.

2.2.4 Pathway d. Formation of cleavable carbamic derivatives by reaction of isocyanates and alcohols

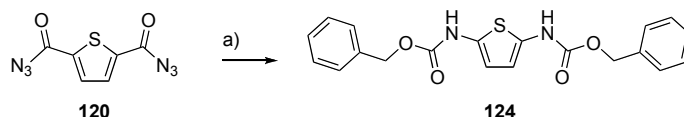
Synthesising the diureido derivative **122**, we demonstrated the possibility to produce highly stable species bearing two C-N bonds at the α position of the thiophene ring. However, the transformation of ureido groups into amides is a challenging task from the synthetic point of view. Therefore it was decided to trap the transient isocyanate with an alcohol, generating in this way a more versatile carbamic derivative. Then, as shown in *Scheme 16*, we envisaged a

two-step strategy, consisting in the acylation of the carbamic nitrogen, followed by cleavage of the carbamate.



Scheme 16 Retrosynthetic pathway d towards diamido five-membered heteroaromatic derivatives.

We began treating **120** with BzOH, to form the desired dicarbamic derivative **121**, isolated in 13% yield (Table 7, entry *i*).



Scheme 17 Synthesis of **121**. For conditions used see Table 6.

entry	solvent	eq. of benzyl alcohol	T (°C)	Time	Yield (%)
<i>i</i>	toluene	2.5	90	3 hrs	13
<i>ii</i>	toluene	3	reflux	2 hrs	8
<i>iii</i>	toluene	3	130 ^[a]	5'	54
<i>iv</i>	BzOH	excess	130 ^[a]	5'	62
<i>v</i>	BzOH	excess	130	5'	60
<i>vi</i>	mesitylene	3	130	5'	57

Table 7 Conditions tested for the synthesis of intermediate **124**. [a] : Microwave irradiation.

A sensible improvement in the yield was achieved performing the reaction under microwave irradiation, at 130°C (entries *iii* and *iv*). However, the evolution of two moles of gaseous nitrogen per mole of starting material caused overpressure problems, thus limiting the possibility of scaling up the reaction. It was therefore decided to perform the reaction in an open vessel, adding a millimolar solution of **120** via syringe pump into a flask containing BzOH, at 130°C (entries *v* and *vi*), affording **124** in 60% yield. Using this procedure, it was possible to scale-up the reaction to the multigram scale.

124 was isolated as a white, crystalline solid and it was fully characterized by ¹H and ¹³C-NMR spectroscopy, high-resolution mass spectrometry, and IR spectroscopy (¹H-NMR spectrum is reported in Figure 1).

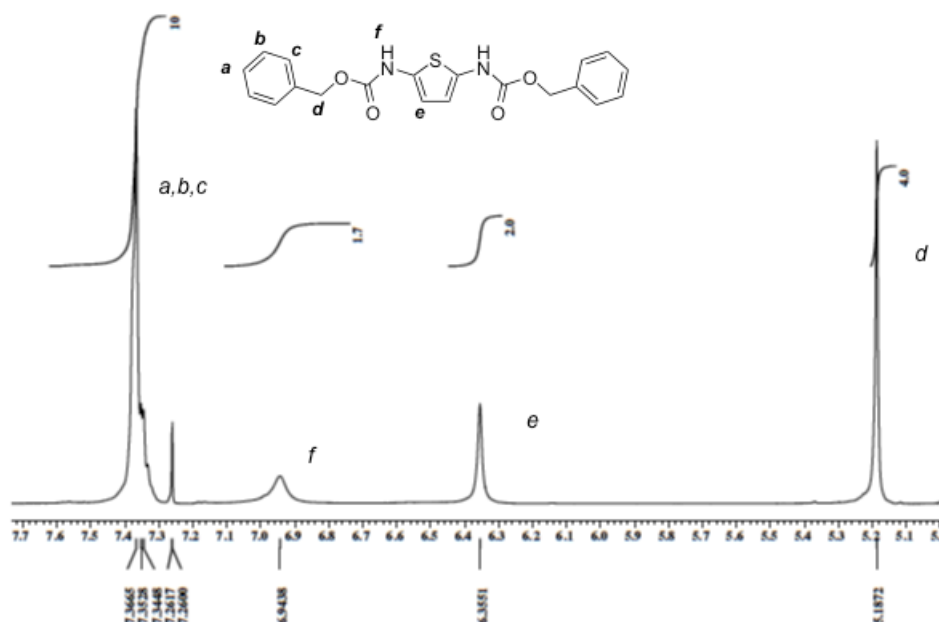
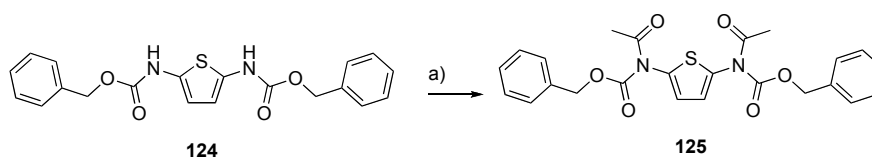


Figure 1 ^1H -NMR spectra of **124**. The spectra was recorded in CDCl_3 at r.t.

With the successful synthesis of this highly advanced intermediate, towards the achievement of diamido thioly derivatives, we eventually concluded our set of methodological studies.

2.3 Synthesis of Thioly-2,5-diamidic derivatives scaffolding for DAD hydrogen bonding interactions

The first step towards the preparation of compound **68** (presented in Section 2.1) starting from **124**, was the acetylation of the carbammic nitrogen atoms.



Scheme 1 a) Ac_2O , DMAP, Py, r.t. 4 hrs, 84%.

The reaction was initially conducted in CH_2Cl_2 , with Ac_2O , using DMAP as basic and nucleophilic catalyst. Complete conversion was reached in 12 hours, and the desired product was obtained in 80% yield. Nevertheless, the replacement of CH_2Cl_2 with pyridine led to a substantial increase of the reaction rate. In fact, with this solvent, complete conversion was obtained in 4 hours, together with a slight improvement in the isolated yield (84%).

A small transparent crystal of the bis-acetylated compound **125**, suitable for X-ray diffraction, was obtained by slow evaporation of a CHCl_3 solution.

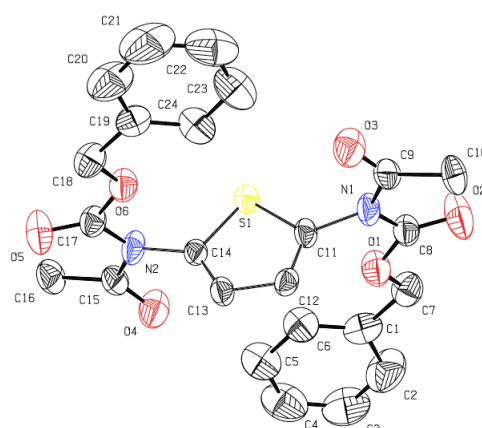
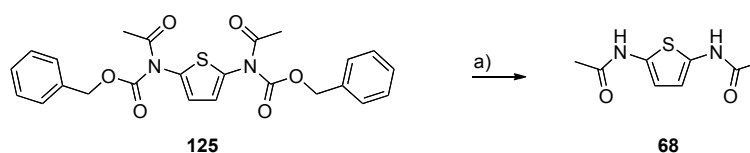


Figure 1 ORTEP representation of di-acylated compound **125** as determined by X-rays diffraction analysis. Atomic displacement parameters, obtained at 293 K, are drawn at the 30% probability level. Atoms color: yellow S, blue N, red O, white C.

The crystal structure was determined at 293 K and it was found to belong to the monoclinic space group *Pc*. The ORTEP representation, depicted in *Figure 1*, reveals the *quasi*-ortogonal arrangement of the carbamate groups with respect to the plane of the thiophene ring (both interplanar angles are *ca.* 89°).

The following step was the cleavage of the two *N*-protecting Cbz groups. In a first attempt, molecule **125** was treated either with TMS-Cl or with TMS-I. When TMS-Cl was used (*Table 1*, entries *i* and *ii*), additional 10 eq. of anisole were added to the reaction mixture.



Scheme 2 Deprotection of **125**. a) for conditions see *Table 1*.

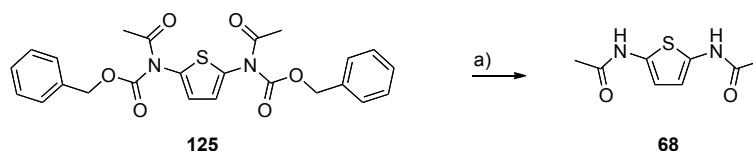
a)	TMS derivative	Solvent	Time	T (°C)	Yield (%)
<i>i</i>	TMS-Cl	CH ₂ Cl ₂	30'	r.t.	0
<i>ii</i>	TMS-Cl	CH ₂ Cl ₂	12 hrs	r.t.	0
<i>iii</i>	TMS-I	CH ₂ Cl ₂	30'	r.t.	0
<i>iv</i>	TMS-I	CH ₂ Cl ₂	12 hrs	r.t.	0
<i>v</i>	TMS-I	MeCN	12 hrs	r.t.	0
<i>vi</i>	TMS-I	MeCN	12 hrs	50	traces
<i>vii</i>	TMS-I	DMF	12 hrs	r.t.	0
<i>viii</i>	TMS-I	DMF	12 hrs	50	4
<i>ix</i>	TMS-I	DMF	1 hrs	80	0

Table 1 Conditions attempted for the deprotection of **125** using TMS-Cl and TMS-I.

No reaction was observed performing the reaction at r.t. (entries *i* to *v*, and *vii*), and the starting material was fully recovered. The solvent was therefore switched to MeCN or DMF, in order to increase reaction temperature (entries *vi*, *viii*, and *ix*). However, all the attempts done were unsuccessful: conditions *vi* (50°C in MeCN) led to the formation of traces (a faint spot on the TLC) of **68**, while conditions *viii* (50°C in DMF) afforded the desired product with

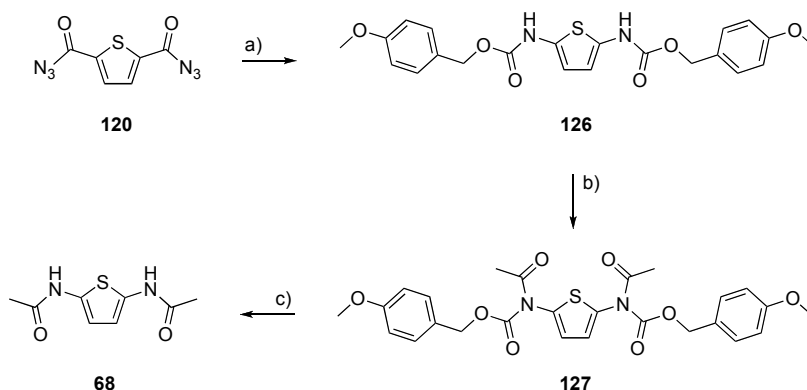
only 4% yield. Moreover, further increase of the temperature (80°C, entry *ix*) resulted in decomposition.

Consequently, we decided to abandon the TMS approach in favor of hydrogenolysis. Hydrogenation was conducted in MeOH, at atmospheric pressure of H₂. Very long reaction times (up to 4 days) and a high load of Pd(5%)/C (*i.e.*, stoichiometric quantities) were required for the reaction to go to completion and **68** was isolated in poor yield (11%).



Scheme 3 a) H₂, Pd(5%)/C, MeOH, r.t., 4 days, 11%

Considering these results, the Cbz group was replaced with the Moz protecting group, which is cleavable in milder conditions. In order to do so, a *Curtius* rearrangement was performed on **120** using PMBA to trap the transient isocyanate. Precipitation with pentane and chromatographic purification afforded the bis-(Moz protected) diaminothiophene **126** in 62% yield (Step a, *Scheme 4*). The rearrangement reaction was ensued by an acetylation step, conducted with a catalytic amount of DMAP, yielding the fully protected amidoderivative **127**. Simultaneous deprotection of both Moz groups was eventually achieved by means of acidic solvolysis in different CH₂Cl₂/TFA mixtures. Initially, 3 vol% of TFA in CH₂Cl₂ was used, leading to molecule **68** in 44% yield (*Table 1*, entry *i*). Then, in order to achieve better yields, the vol% of TFA was increased (entries *ii* and *iii*), but no substantial improvement was observed. Furthermore, traces of decomposition, together with a large number of by-products were present in the reaction crudes. We decided therefore to add an excess of anisole, scavenger for the *p*-methoxybenzyl carbocation, and, doing so, we increased to 79% the isolated yield for compound **68** (entry *v*).



Scheme 4 a) PMBA, 130 °C, 5', 62%; b) acetic anhydride, DMAP, pyridine, r.t., 82%; c) TFA, CH₂Cl₂, 0 °C to r.t., see *Table 3* for details.

a)	% of TFA	Solvent	Scavenger	Time	Temperature (°C)	Yield
<i>i</i>	3%	CH ₂ Cl ₂	none	4 hrs	0	44%
<i>ii</i>	5%	CH ₂ Cl ₂	none	4 hrs	0	50%
<i>iii</i>	20%	CH ₂ Cl ₂	none	1 hrs	0	47%
<i>iv</i>	5%	CH ₂ Cl ₂	Anisole	30'	0	76%
<i>v</i>	20%	CH ₂ Cl ₂	Anisole	5'	0	79%

Table 2 Conditions tested for the solvolysis of the Moz groups of **127**.

A monocrystal suitable for X-ray diffraction was obtained by slow evaporation of a 9:1 CHCl₃/MeOH solution. The crystal structure (depicted in *Figure 2*), belonging to the monoclinic Cc space group, clearly shows an unexpected *cis*-conformation of the amides probably stabilized by two sulphur-oxygen non-bonded interactions.^[28] The contact distances are respectively S(1)-O(2)= 2.82 Å and S(1)-O(1)= 2.86 Å

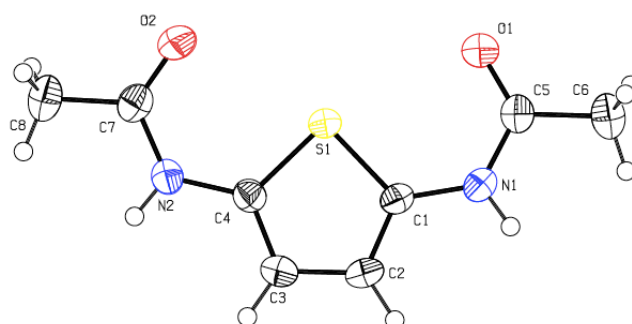
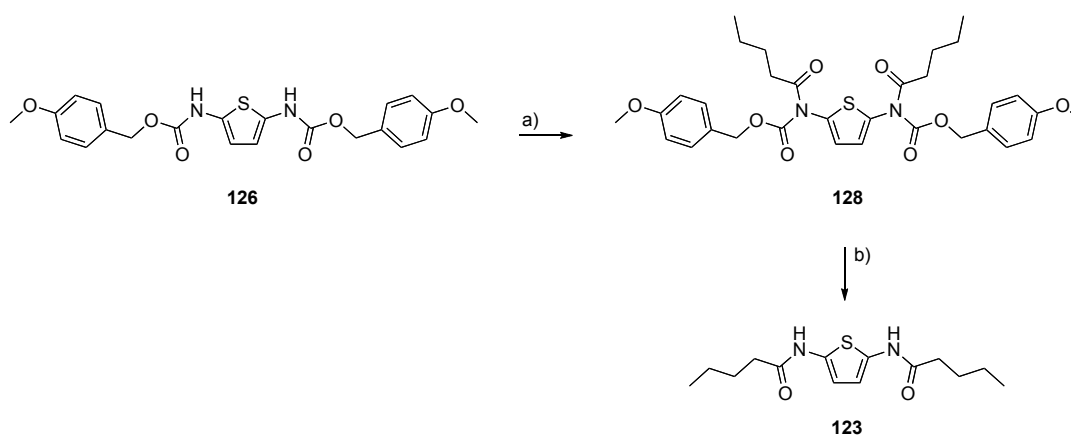


Figure 2 ORTEP representation of diacylated compound **68** as determined by X-rays diffraction analysis. Atomic displacement parameters, obtained at 293 K, are drawn at the 30% probability level. Atoms color: yellow S, blue N, red O, white C.

Compound **68** was, however, completely insoluble in chlorinated solvents. Therefore, in order to obtain a more suitable DAD thiolyl scaffold to study the binding properties in solution via ¹H-NMR techniques, we decided to synthesize molecule **123** that bears two *n*-butyl chains on the peripheral amidic moieties (*Scheme 5*).



Scheme 5 a) valeric anhydride, DMAP, pyridine, r.t., 77%; b) TFA, CH₂Cl₂, 0 °C to r.t., 16 hrs, 61%.

To this end, valeric anhydride was used to acylate the carbamic nitrogen of intermediate **126**, affording **128**. The final deprotection step was performed in a 95:5 CH₂Cl₂/TFA mixture, with 10 eq. of anisole, affording, after precipitation in hexane, **123** in 61% yield.

The structure of the new soluble DAD array was unambiguously determined by ^1H and ^{13}C -NMR spectroscopy, high-resolution mass spectrometry, and IR spectroscopy (^1H -NMR spectrum is reported in *figure 3*).

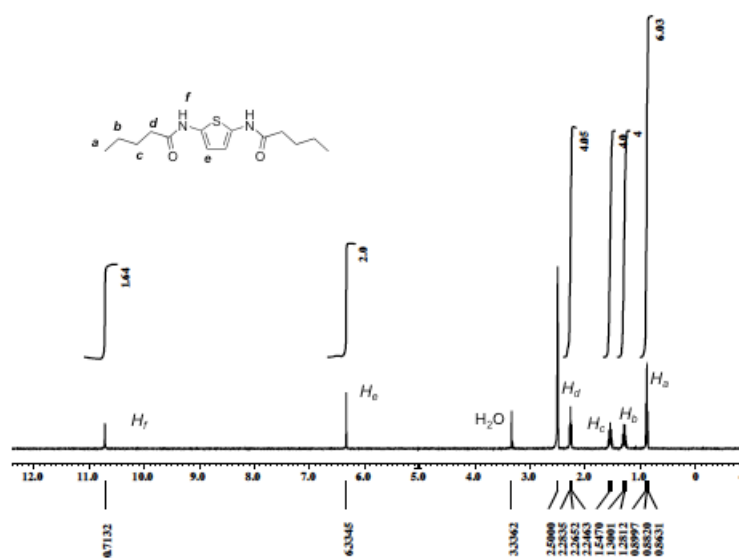
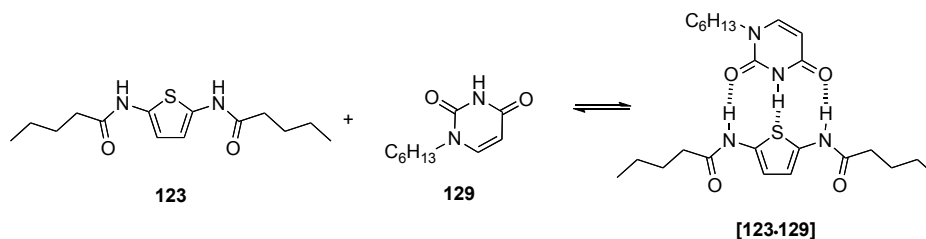


Figure 3 ^1H -NMR spectra of **123**. The spectra was recorded in $\text{DMSO}-d_6$ at 80°C . Due to the presence of conformers the structure at r.t. was unresolved.

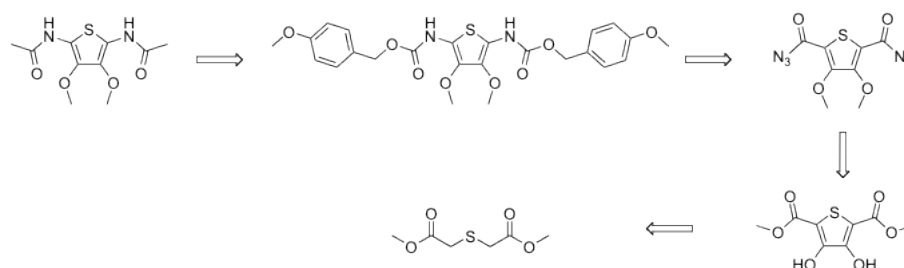
Having successfully synthesized diamido-oxolyl derivatives endowed with a DAD character, future work will focus on the determination of the binding properties of this new H-bond arrays. More in detail, the association with the complementary ADA uracyl derivative will be studied. Experiments to determine the stoichiometry of the assembly and to measure the association constant of the H-bond complex **[123·124]** (*Scheme 5*) will be performed by ¹H-NMR techniques.



Scheme 5 ^1H -NMR spectra of **123**. The spectra was recorded in $\text{DMSO}-d_6$ at $80\text{ }^\circ\text{C}$. Due to the presence of conformers the structure at r.t. was unresolved.

2.3.1 Displacing the *cis*-conformation endowing metal complexation

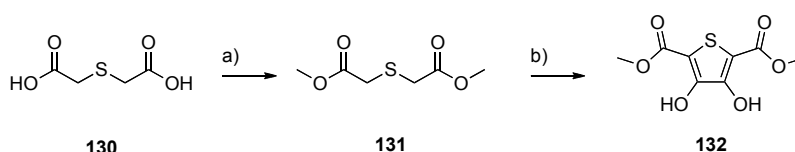
In order to force the amidic groups into a *cis*-like conformation to endow amidic thieryl derivatives with the capability of complexing metal ions, it was decided to introduce methoxy moieties onto the β position of the ring. The retrosynthetic pathway envisaged for the formation of such kind of derivative is illustrated in *Scheme 6*.



Scheme 6 Retrosynthetic pathway towards the 2,5-diamido-thiophene derivatives bearing methoxy groups onto the β positions.

According to this pathway, the amidic moieties in α position derive from the corresponding carbamic groups, which are in turn formed, starting from the acylazides, through a *Curtius* rearrangement. Introduction of the oxygenated moieties at the β position is instead obtained through cyclization of dimethylthiodiacetate with dimethyloxalate.

Intermediate **132** that bears carboxylate moieties at the α positions and two hydroxyl groups at the β positions of the ring was obtained in two steps from commercially available **130** (*Scheme 7*). An initial esterification was performed by means of TMS-Cl, to generate intermediate **131** in high yields (94%), followed by a *Hinsberg*-like condensation reaction with dimethyloxalate.^[29] Different bases and solvents were tested in order to optimize the yields of this latter reaction (*Table 3*).



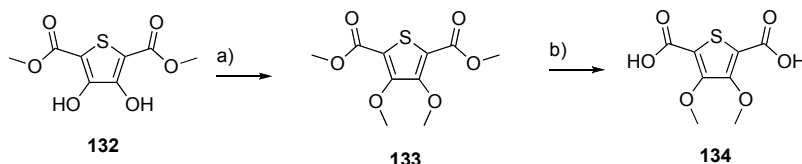
Scheme 7 a) TMS-Cl, MeOH, 0 °C to r.t. 12 hrs, 96%; b) dimethyloxalate, for details see *Table 3*.

b)	Solvent	Base	Time (hrs)	Yield (%)
i	DMF	NaH	6	0
ii	DMF	NaOMe	6	14
iii	THF	NaH	6	15
iv	THF	NaOMe	6	16
v	Toluene	NaH	6	20
vi	Toluene	NaOMe	6	18
vii	Methanol	NaOMe	2	91

Table 3 Conditions use for the *Hinsberg*-like cyclization of molecule **131** with dimethyloxalate (step b), *Scheme 7*).

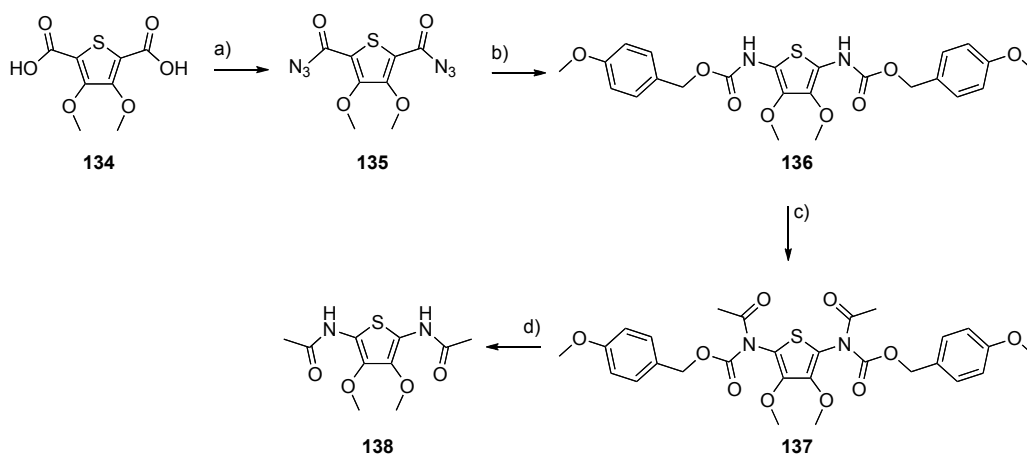
Using DMF as solvent and NaH as base, no reaction was observed (*Table 3*, entry *i*), while the use of NaOMe as base, or of THF and toluene as solvent, led to the formation of the desired product, even though in low yields (entries *ii* to *vi*). When MeOH was chosen as solvent, however, **132** was recovered in almost quantitative yield.

Afterwards, methylation of the free hydroxyl groups of **132** was performed with Me_2SO_4 , followed by an alkaline hydrolysis with LiOH (*Scheme 8*).



Scheme 8 a) Me_2SO_4 , K_2CO_3 , DMF, 60°C , 16 hrs, 83%; b) 2N LiOH, THF, r.t., 12 hrs, 94%.

We proceeded then with the transformation of the carboxylic groups into carbamates first and subsequently into amides, according to *Scheme 9*.



Scheme 9 a) $(\text{COCl})_2$, DMF, THF, 0°C to r.t. 3 hrs, then sat. NaN_3 aq., not isolated; b) PMBA, 130°C , 5', 79% over two steps; c) Ac_2O , DMAP, pyridine, r.t. 4 hrs. 81%; d) TFA (2%), CH_2Cl_2 , 0°C , 51%.

Diacylazido derivative **135** was prepared from **134** with a two-step, one-pot procedure. To do so, chlorination of the carboxylic moieties by means of $(\text{COCl})_2$ was ensued by treatment with NaN_3 . Intermediate **135** proved to be highly unstable, since decomposition occurred at r.t., few minutes after evaporation of the solvent. Therefore, the crude solution was directly treated with PMBA at 130°C . The whole procedure afforded, after chromatographic purification, **136** in an overall yield of 79% (3 steps). The chemical structure of **136** was unambiguously confirmed by ^1H and ^{13}C -NMR spectroscopy, high-resolution mass spectrometry, and IR spectroscopy (^1H -NMR spectrum is reported in *Figure 4*).

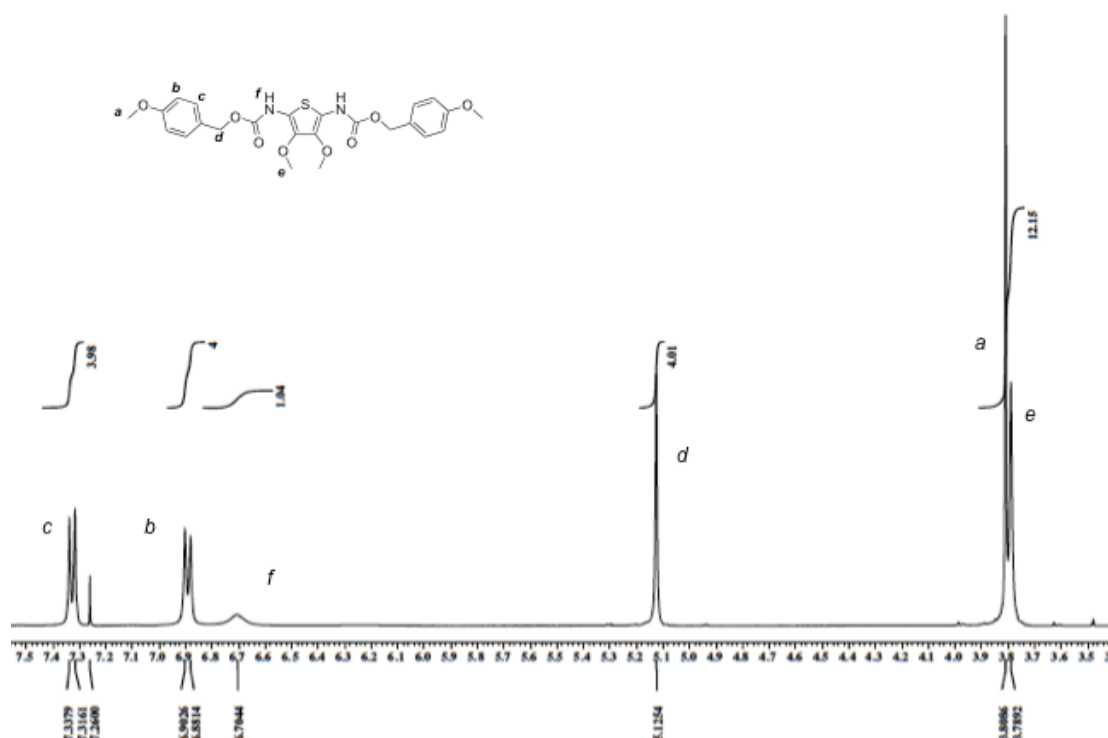


Figure 4 ^1H -NMR spectra of molecule **136** in CDCl_3 recorded at r.t.

Subsequently, an acylation step was performed with Ac_2O , affording the *N*-Moz bis-protected diamido-thiolyl derivative **137** in 81% yield. The final Moz-deprotection was achieved by acidic solvolysis with 2% TFA in CH_2Cl_2 mixture, affording **138** in 51% yield (*Scheme 9*, step d).

Suitable crystals of **138** for X-ray diffraction were obtained by slow evaporation of a 95:5 $\text{CHCl}_3/\text{MeOH}$ solution. The crystal structure was determined at 293 K and found to belong to the monoclinic space group $\text{P}2_1/\text{c}$. The ORTEP image (*Figure 5*) reveals the quasi-planar arrangement of the molecule, where O(3) and O(4) deviate from the plane of the molecule of less than $0.1\text{\AA}$. Both amides result in the *cis*-like conformation, which is stabilized by sulphur-oxygen non-bonded interactions,(ref) as already observed for molecule **68**, with contact distances for both S(1)-O(3) and S(1)-O(4) of ca. $2.79\text{\AA}$. and by two intramolecular hydrogen bonding ($\text{N}(1)\text{-O}(1) = 2.60\text{\AA}$, $\text{N}(2)\text{-O}(2) = 2.61\text{\AA}$). The distance between the carbonylic oxygen atoms O(3) and O(4) is in both cases ca. $5\text{\AA}$. The *cis*-like conformation of the amidic moieties, expected by our rational design of compound **138**, endows the molecule with a tridentate O-S-O coordination pocket, exploitable in metal coordination chemistry.

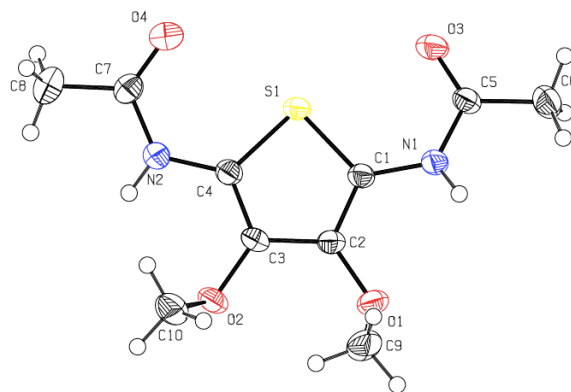
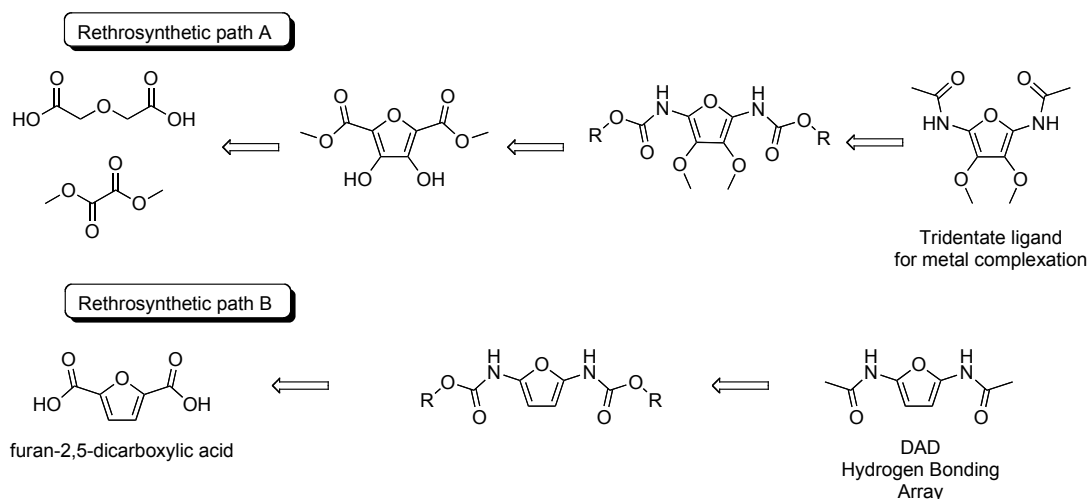


Figure 5 ORTEP representation of di-acylated compound **138** as determined by X-rays diffraction analysis. Atomic displacement parameters, obtained at 293 K, are drawn at the 30% probability level. Atoms color: yellow S, blue N, red O, white C.

2.4 Attempted synthesis towards Oxolyl-2,5-Diamido Derivatives

The retrosynthetic pathways for the formation of oxolyl derivatives, substituted at the α position with amidic functionalities, are presented in *Scheme 1*. Pathway A describes the approach towards molecular modules specifically designed for metal complexation, while pathway B describes the strategy adopted in the production of DAD arrays for nucleobases recognition. The key step in both the procedures is based on the Curtius rearrangement reaction that allows the transformation of the carboxylic moieties into carbamates.

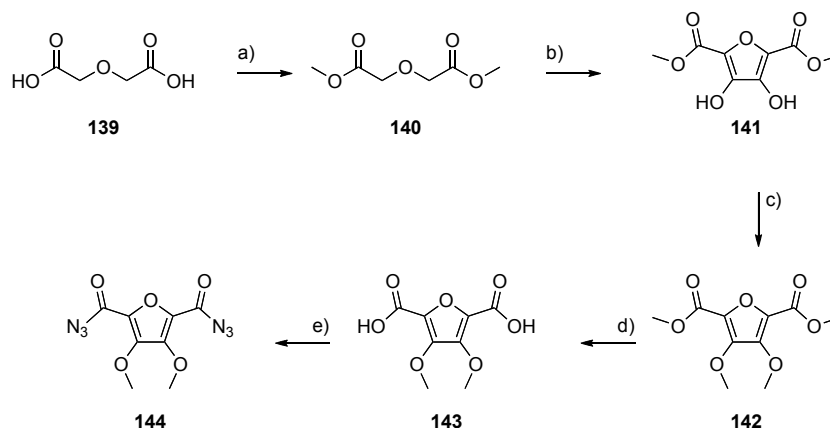


Scheme 1 Retrosynthetic pathways for the synthesis of oxolyl derivatives substituted with amides at the α positions.

In order to understand in a highly effective way the reactivity of oxolyl derivatives towards the *Curtius* rearrangement, and due to the high synthetical and economic cost of furan-2,5-dicarboxylic acid, it was decided to investigate the synthetical pathway A at first.

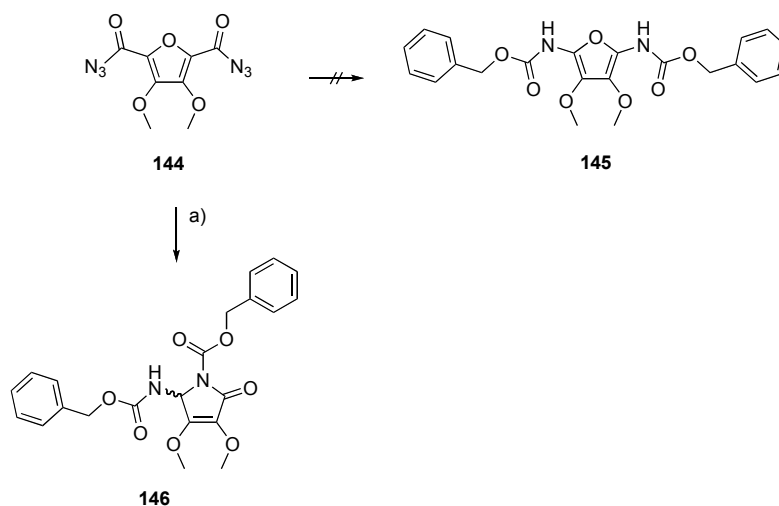
2.4.1 Attempted synthesis towards oxolyl-2,5-diamido derivatives for metal complexation

Accordingly with *Scheme 1*, the preparation of oxolyl cores functionalized in 2 and 5 position is centered around the synthesis of the key intermediate **144**. This furan derivative, presenting acylazide and methoxy moieties in α and β positions respectively, was obtained from diglycolic acid in 5 steps with an overall yield of 30% (*Scheme 2*).



Scheme 2 a) TMS-Cl, MeOH, 0 °C to r.t. 96%; b) dimethyl oxalate, NaOMe, DMF, 60 °C, 6 hrs, 55%; c) MeI, K₂CO₃, DMF, 40 °C, 16 hrs, 74%, d) 2*N* LiOH, THF, r.t., 12 hrs, 94%; e) (COCl)₂, THF, 0 °C to r.t., then sat. NaN₃ aq., 79%.

The synthesis of intermediate **144** started with the esterification of diglycolic acid by treatment with TMS-Cl in presence of MeOH giving the desired diester **140** in a 96% yield. Compound **140** was subsequently condensed with dimethyl oxalate (*Scheme 2*, step b), using NaOMe in DMF at 60 °C. After 4 hrs of reaction the resulting compound **141** was easily purified by re-crystallization from MeOH and recovered in 55% yield. Methylation of the hydroxylic groups in β positions with MeI was ensued by a saponification step in a 9:1 1*N* LiOH/THF solution. The so obtained compound **143** was then chlorinated with (COCl)₂ in freshly distilled THF at 0 °C and subsequently treated with NaN₃, to afford the desired product in 79% yield. Once **144** was obtained in reasonable amount we set up the investigation of the best reaction conditions for the accomplishment of the *Curtius* rearrangement.



Scheme 3 Synthetic pathway adopted for the preparation of the intermediate **146** a) benzyl alcohol, toluene, 90 °C, 4 hrs, 78%.

In this case we intended to use BzOH as nucleophile to trap the transient isocyanate resulting from the thermal degradation of **144**. During a first attempt (entry *i*, Table 1) a 1M solution of **144** in CHCl₂ was dripped slowly in hot BzOH. With our great surprise, the outcome of the reaction was not the expected dicarbamic derivatives **145** but compound **146** (as a racemic mixture). Suspecting that the high temperature employed, in combination with BzOH acidity, might catalyze the ring-opening of the furane nucleus, we decided to repeat the reaction at lower temperature (Table 1, entries *ii* to *vi*), with stoichiometric quantities of BzOH (entries *iv* to *vi*), and in presence of triethylamine as base (entry *iv*). Despite all the changes made, **146** was the only product formed in the reaction.

entry	solvent	eq. of benzyl alcohol	T (°C)	Time	Yield (%)
<i>i</i>	BzOH	excess	130	5'	77
<i>ii</i>	BzOH	excess	100	40'	74
<i>iii</i>	BzOH	excess	90	2 hrs	73
<i>iv</i>	toluene	2	80	5'	71
<i>v</i>	toluene	2	80	5'	75
<i>vi</i>	toluene ^[a]	2	80	5'	70

Table 1 Condition used for the *Curtius* rearrangement of molecule **144**. [a] : 3 eq. of triethylenamine were added to the reaction.

The structure of molecule **146** was confirmed by X-ray diffraction. Suitable crystals were obtained by vapour diffusion of hexane into a solution of **146** in CH₂Cl₂. The crystal structure was determined at 293 K and it was found to belong to the monoclinic space group *Pc* (Figure 1).

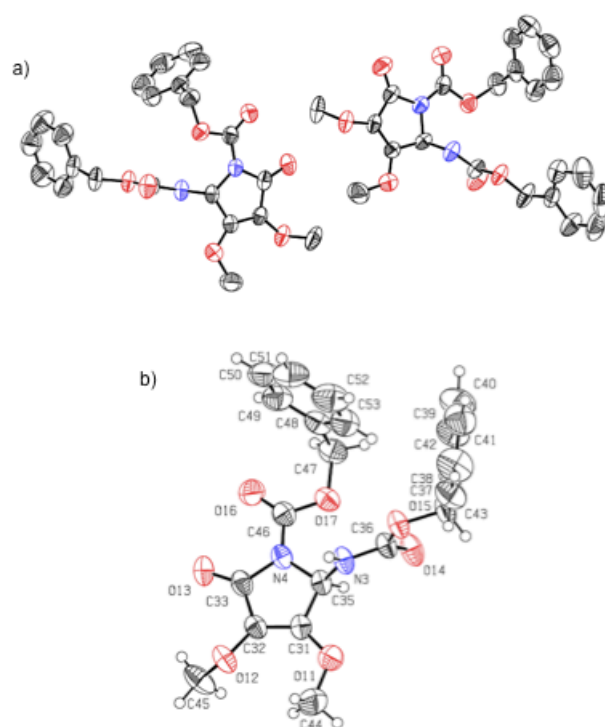
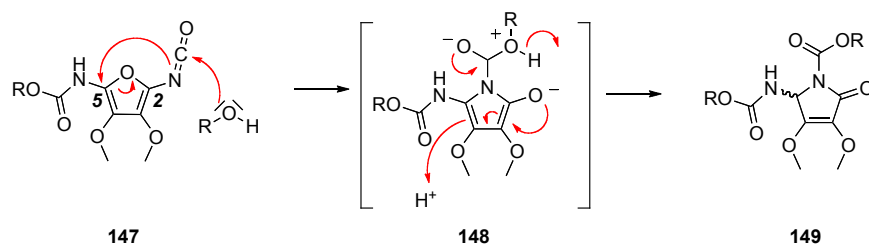


Figure 1 ORTEP representation of the two enantiomers of **146** (a) and magnification of the *R*-enantiomer (b) as determined by X-rays diffraction analysis. Atomic displacement parameters, obtained at 293 K, are drawn at the 30% probability level. Atom color: blue N, red O, white C.

The hypothetical mechanism that justifies the formation of **146** is presented in *Scheme 4*. After the formation of a first carbamate group at position 5, nucleophilic attack of the alcohol causes the opening of the electron rich furan ring of **147**, leading to the pyrrolic intermediates **148**. The subsequent keto-enolic tautomerization of this system results in the de-aromatization of the furanic ring and subsequent formation of **149**.



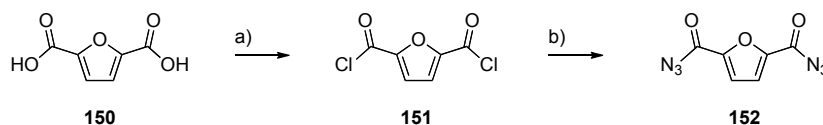
Scheme 4 Proposed mechanism for the formation of molecule **149**.

Considering the unexpected results achieved following the retrosynthetic pathway A this approach was discontinued.

2.4.2 Attempted synthesis towards oxolyl-2,5-diamido derivatives scaffolding for DAD triple hydrogen bonding interactions

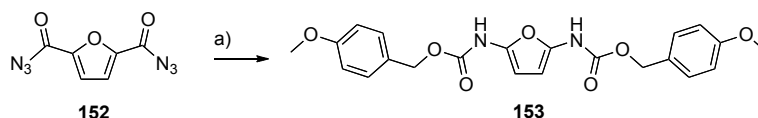
In order to produce oxolyl derivatives functionalized at α positions with amidic groups, we decided to start our synthesis from furan-2,5-dicarboxylic acid **150**. This diacid

was converted into the diacylazide **151** in two steps, with the general procedure already described for the formation of **152** (chlorination ensued by treatment with NaN_3) to give the product in 67% yield (Scheme 5).



Scheme 5 a) $(\text{COCl})_2$, THF, 0°C to r.t., 3 hrs, not isolated; b) sat. NaN_3aq , THF, r.t., 30', 67%.

Unfortunately, the preliminary attempts to prepare the intermediate **153**, via *Curtius* rearrangement of **152**, in presence of PMBA, at high temperature resulted in decomposition (Scheme 6, Table 2, entries *i* and *ii*). To overcome this problem, an optimization study was carried out in order to find the best operative conditions for this reaction. When the temperature was decrease to 90°C , decomposition occurred before the total conversion of the starting material (entries *iii* and *iv*). The best results were obtained under microwave irradiation, using THF as solvent, when the desired product was isolated in 48% yield (entry *v*). Moreover, we discovered that one of the most important factors influencing the reaction yield is the work-up procedure. **153** is in fact extremely sensible to acids and even the residual acidity of chlorinated solvents, like CH_2Cl_2 and CHCl_3 , is sufficient to cause its degradation within minutes. Therefore, after performing the *Curtius* rearrangement reaction, the solvents were immediately evaporated *in vacuo* and the crude residue was rapidly purified by chromatography.

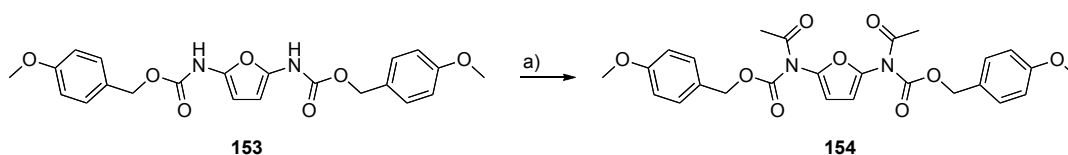


Scheme 6 Synthesis of **153**. For conditions used see Table 2.

entry	solvent	eq. of PMBA	T ($^\circ\text{C}$)	Time	Yield (%)
<i>i</i>	PMBA	excess	130	5'	0
<i>ii</i>	mesitylene	3	130	5'	0
<i>iii</i>	PMBA	excess	90	5'	73
<i>iv</i>	toluene	3	90	5'	71
<i>v</i>	THF	2	120 ^[a]	5'	48

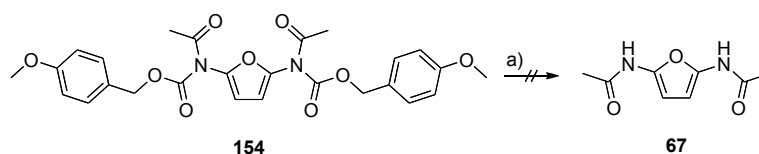
Table 2 Conditions used in the *Curtius* rearrangement of molecule **152** towards **153**. [a] : Reaction performed under microwave irradiation.

The acylation of intermediate **153** was performed using a large excess of acetic anhydride and stoichiometric quantities of DMAP, in order to decrease at minimum the reaction times. Under these conditions, total conversion was reached in ca. 30' and the desired bisacylated compound **154** was recovered in 58% yield (Scheme 7).



Scheme 7 a) acetic anhydride, DMAP, pyridine, r.t., 30', 58%.

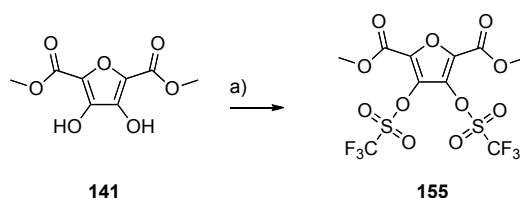
Deprotection of **154** was attempted by treatment with TFA, using an excess of anisole as cationic scavenger. In this context, depending from the solvent used, we could observe different results. Performing the reaction in a 1% TFA/CH₂Cl₂ mixture containing 50 eq. of anisole, decomposition occurred in 5 min. Using Et₂O as solvent, instead, the reaction proceeded at slower rate, giving us the possibility to observe the occurrence of the mono-deprotection reaction by ¹H-NMR and HR-LC-MS analysis. Unfortunately, even increasing the reaction time, it was not possible to isolate the fully deprotected compound **67** (Scheme 8). We concluded therefore that, once **67** is formed, being too labile to survive the acidic environment, it decomposes rapidly in the reaction media.



Scheme 8 a) TFA, anisole, CH₂Cl₂, 0 °C, 5', decomposition; or TFA, anisole, Et₂O, 0 °C, 5', decomposition.

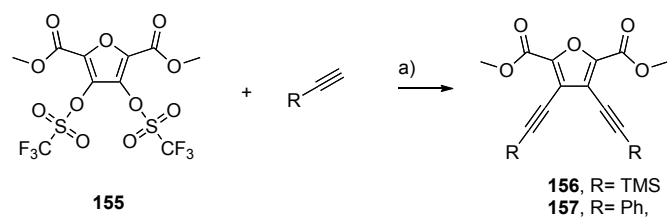
Given the intrinsic instability of furan nucleus bearing two electron-donor amidic moieties in α positions, the optimization work for the deprotection of the Moz group was discontinued.

To increase the stability of the furan nucleus it was decided to introduce electron-withdrawing ethynilic groups in the β positions. To this end, **155**, bearing two triflyl groups, was synthesized from **141**, by treatment with Tf₂O in 92% yield (Scheme 9).



Scheme 9 a) Tf₂O, DMAP, CH₂Cl₂, 0 °C, 30', 92%.

After the preparation of **155**, an optimization of the conditions for the Pd(0)-catalyzed *Sonogashira* cross-coupling reaction was carried out (Scheme 10). All the reactions in this study were performed under microwave irradiation, using [Pd(PPh₃)₂Cl₂] and CuI as catalysts. Reaction with TMSA (Table 3, entries *i* to *iv*) always resulted in a very complex mixture and the desired compound **157** was formed (as confirmed by GC-MS and ¹H-NMR spectroscopy) but it was never isolated. The same happened when phenylacetylene was coupled with **156** using (*i*-Pr)₂NH as solvent. When DIEA was used instead, the reaction output resulted cleaner and **158** was isolated in 22% yield (entry *vii*). Increase of the acetylene equivalents and of the catalyst percentage eventually allowed the recovery of the desired product in 41% yield (entries *viii* and *ix*).

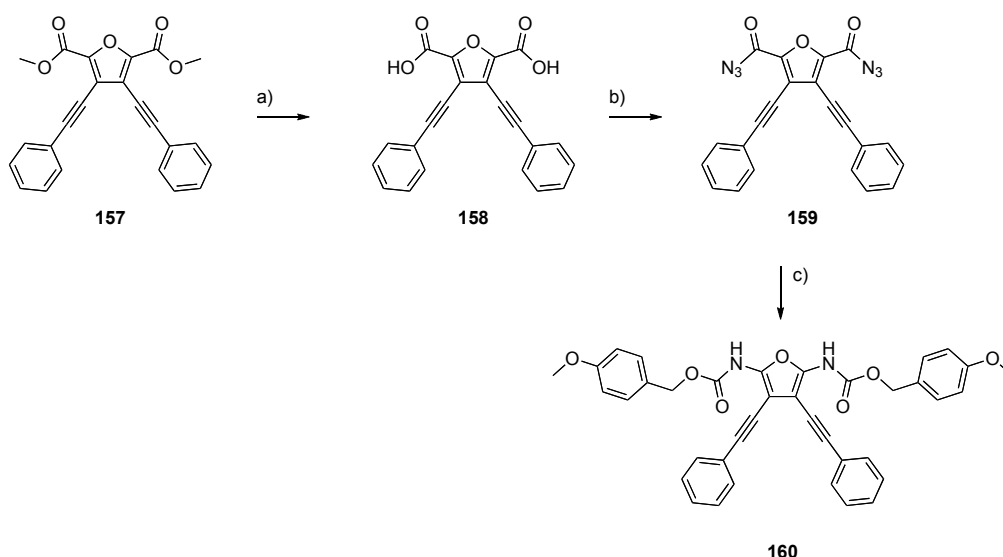


Scheme 10 Sonogashira coupling of **155** with TMS- and phenyl-acetylene. For conditions see Table 3.

entry	R	[Pd(PPh ₃) ₂ Cl ₂] mol%	R—C≡C— (eq.)	Solvent	T (°C)	Time (min)	Yield (%)
i	TMS	1	2	(<i>i</i> -Pr) ₂ NH	120	5	[a]
ii	TMS	1	4	(<i>i</i> -Pr) ₂ NH	120	5	[a]
iii	TMS	5	4	(<i>i</i> -Pr) ₂ NH	120	5	[a]
iv	TMS	10	4	DIEA	120	5	[a]
v	Ph	5	4	(<i>i</i> -Pr) ₂ NH	120	8	[a]
vi	Ph	5	4	(<i>i</i> -Pr) ₂ NH	130	8	[a]
vii	Ph	5	4	DIEA	110	8	22
viii	Ph	5	4	DIEA	130	8	26
ix	Ph	10	5	DIEA	130	8	41

Table 3 Conditions tested for the coupling of **156** with TMS- and phenyl-acetylene. [a]: product formed but not isolated.

After the optimization, **157** was converted in the dicarbamic derivative **160**. To do so, **158**, obtained by saponification in a LiOH/THF solution, was transformed into the diacylazido derivative **159**, according to the general procedures described in this thesis. Isolation of this intermediate was not possible due to its high instability and therefore it was immediately used in the following step.



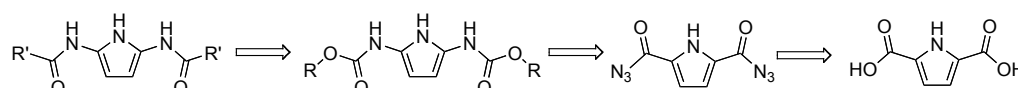
Scheme 11 a) 2N LiOH, THF, r.t., 12 hrs, 97%. b) (COCl)₂, THF, 0 °C to r.t., then sat. NaN₃ aq., not isolated; c) PMBA, THF, m.w. irr. 130 °C, 5', decomposition.

Surprisingly, the presence of the electron-withdrawing ethynilic moieties did not enhance the stability of the furan nucleus: **160**, in fact, undergoes degradation rapidly when solubilized in CHCl₃, DMSO or pyridine. Moreover, any attempt of acylation with Ac₂O resulted in complete decomposition of the starting material.

In conclusion, having established the intrinsic lability of furan derivatives with electron-donor-groups in α position, the synthesis of this kind of scaffolds was abandoned.

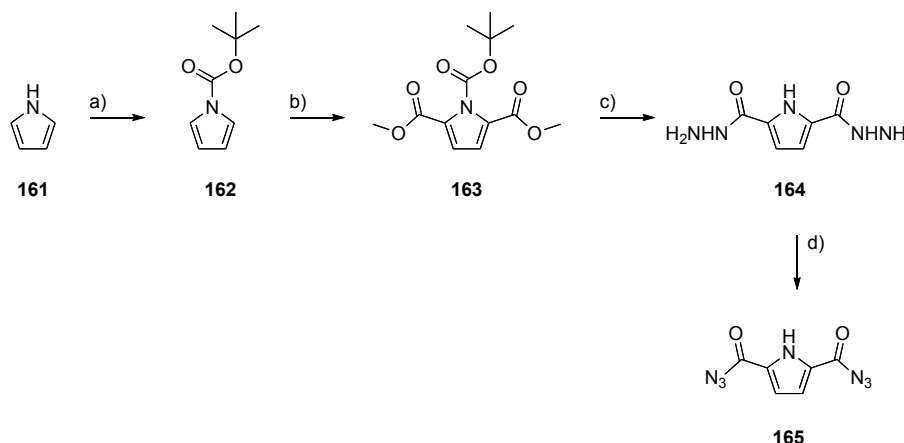
2.5 Towards the synthesis of azolyl-2,5-diamido derivatives scaffolding for triple Hydrogen Bonding interactions

The retrosynthetic strategy towards the formation of DDD triple H-Bond arrays based on pyrrole follows the same ideas envisaged for the synthesis of DAD arrays based on thiophene. As shown in *Scheme 1*, the diamido-pyrrolic DDD molecular module originates from the corresponding dicarboxylic derivative.



Scheme 1 Retrosynthetic pathway towards the obtention of DDD triple H-Bond arrays based on the molecule of pyrrole.

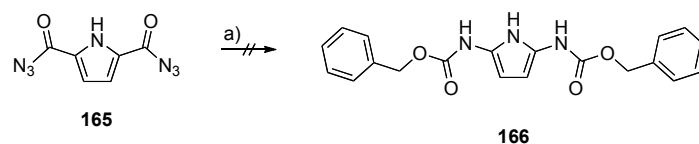
The synthetic approach began with the introduction of the required acylazide moieties into the α positions of the pyrrolic ring. The key building block **165** was obtained from pyrrole, in four synthetic steps (*Scheme 2*).



Scheme 2 a) $(\text{Boc})_2\text{O}$, DMAP, MeCN, 60°C , 88%; b) methyl-chloroformate, LDA, -78°C , 61%; c) N_2H_4 (64% aq.), MeOH, reflux, 16 hrs, 77%; d) NaNO_2 , dil. HCl, H_2O , 75%.

The pyrrolic nitrogen was initially Boc protected in 88% yield, using di-*tert*-butyl dicarbonate, in the presence of a catalytic amount of DMAP. Deprotonation of the α hydrogen atoms by means of freshly prepared LDA at -78°C , followed by treatment with methylchloroformate, afforded diester **163** in 61% yield. Decomposition was observed whenever reaction temperature exceeded -60°C , during the addition of methylchloroformate. Therefore, we could not exceed a 6 grams scale, due to practical difficulties in controlling the temperature during the scale-up. Boc deprotection and conversion of the carboxylate moieties into hydrazides was achieved by treatment of **163** with N_2H_4 under reflux. Finally, **165** was obtained from **164** by oxidation with NaNO_2 and HCl.

Different conditions were then tested for the thermal *Curtius* rearrangement of molecule **165** (Scheme 3 and Table 2). Nevertheless, none of them afforded the desired compound **166**, since they all resulted in decomposition.

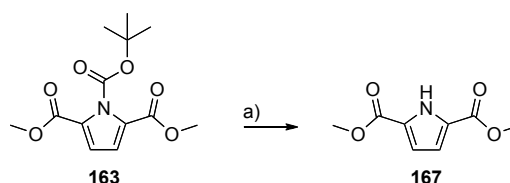


Scheme 3 Curtius rearrangement of molecule **166**. For conditions see Table 2.

a)	Solvent	Eq. of BzOH	Temperature	time	Yield
i	BzOH	excess	130° C	5'	0
ii	BzOH	excess	120° C	5'	0
iii	BzOH	excess	100° C	5'	0
iv	toluene	5	100° C	5'	0
v	toluene	5	60° C	30'	0
vi	THF	5	60° C	30'	0

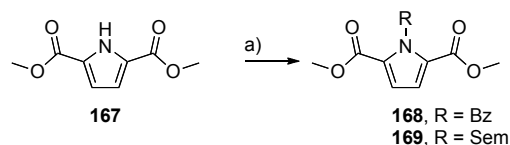
Table 2 Conditions tested for the *Curtius* rearrangement of **165**. All the attempts resulted in decomposition.

Considering these results, it was decided to introduce a protecting group for the pyrrolic nitrogen. Due to its low stability, the Boc group present in molecule **163** was removed by treatment with N_2H_4 (Scheme 4), in order to subsequently introduce a more stable protecting group.



Scheme 4 a) 64% N_2H_4 aq., MeOH, r.t., 5', 98%.

Unfortunately, very few protecting groups could be used for pyrroles when they are not stabilized by electron-withdrawing substituents, since most deprotection conditions, being too vigorous, would result in pyrrole decomposition. Having **167** in hand, we assessed the feasibility of introducing different protecting groups, cleavable by hydrogenation (Bz and Cbz), treatment with fluoride anion (Sem and TIPS), basic hydrolysis (Tosyl) or β -elimination of hydrogen, catalysed by Pd(0) (Aloc) (Scheme 5).



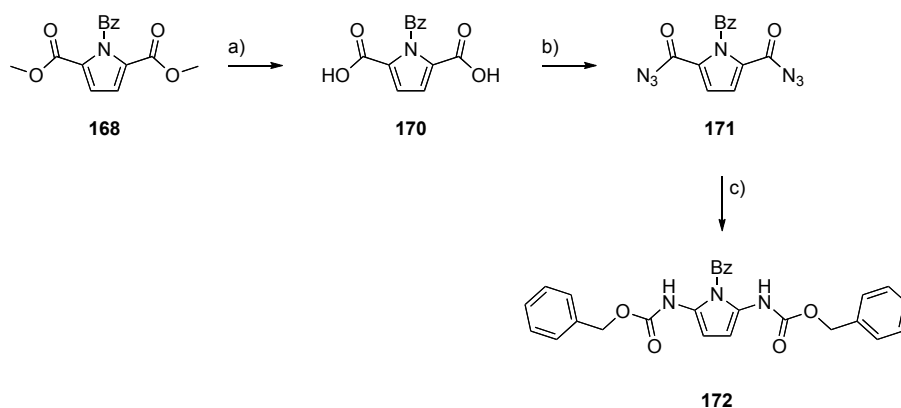
Scheme 5 a) NaH, R-X, DMF, r.t., 12 hrs, see Table 3.

entry	R	X	Time (hrs)	Yield (%)
<i>i</i>	Bz	Br	12	79
<i>ii</i>	Sem	Cl	12	85
<i>iii</i>	Cbz	Cl	12	0 ^[a]
<i>iv</i>	Aloc	Cl	12	0 ^[a]
<i>v</i>	Tosyl	Cl	12	0 ^[a]
<i>vi</i>	Tips	Cl	12	0 ^[a]

Table 3 Tentative conditions for the protection of the pyrrolic nitrogen of **167**. [a] : starting material was fully recovered.

Protection with benzyl and Sem proceeded in good yields (*Table 3*, entries *i* and *ii*), while introduction of bulkier groups was totally unsuccessful, probably due to the steric hindrance given by the carbonyl groups in β position to the pyrrolic nitrogen. In these latter cases the starting material was fully recovered (entries *iii* to *vi*).

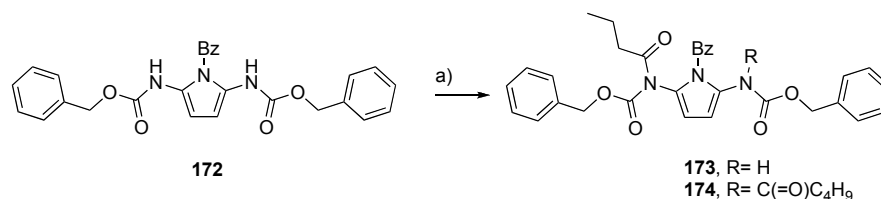
At this stage, we went on in the synthetic strategy towards DDD arrays using the *N*-benzyl protected pyrrolic derivative **168**, which was converted in the dicarbamic derivative **172** in three steps (*Scheme 6*). A first basic hydrolysis performed in LiOH/THF mixture gave the diacid **170** that, after acidification of the crude solution, was recovered by filtration, in 94% yield. **170** was then treated with (COCl)₂, in the presence of a catalytic amount of DMF, to generate a dichloride derivative, subsequently treated with NaN₃. The azido derivative **171** thus obtained was immediately reacted in a *Curtius* rearrangement with BzOH, to afford, after chromatographic purification, **172** in 55% yield (calculated with respect to **170**).



Scheme 9 a) 1*N* LiOH, THF, r.t., 12 hrs, 94%; b) (COCl)₂, THF, 0°C to r.t., then sat. NaN₃ aq., not isolated; d) BzOH, mesitylene, 130°C, 5', 55%.

To increase the solubility of the final compound, acylation was performed with valeric anhydride, endowing the molecule with solubilizing chains. Unfortunately, the reaction did not proceed as expected (*Scheme 7*). Using the standards conditions (*Table 4*, entries *i* and *ii*), a mixture of mono (**173**) and diacylated (**174**) compounds was obtained, and its separation proved to be very difficult. Increase of reaction time and temperature (entries *iii* to *v*) resulted in decomposition of the starting material. Instead, when the reaction was performed in the microwave at 60 °C, with a constant irradiation power of 60 watts (*Heating*

with cooling mode), **174** was exclusively formed in 63% yield (entry vii) (the ^1H -NMR spectrum of **174** is shown in Figure 1).



Scheme 10 a) valeric anhydride, DMAP, for details see Table 4.

a)	Solvent	Temperature (° C)	Time	Yield (%)	Ratio (%) 173/174
i	CH ₂ Cl ₂	r.t	24 hrs	60	20/80
ii	Pyridine	r.t	24 hrs	63	24/76
iii	Pyridine	r.t.	72 hrs	decomposition	-
iv	Pyridine	60	2 hrs	decomposition	-
v	Pyridine	90	1hr	decomposition	-
vi	Pyridine	60 ^[a]	30'	64	28/72
vii	Pyridine	60 ^[b]	30'	63	100/0

Table 4 Conditions tested for the acylation of **172**. [a]: Reaction performed under microwave irradiation with discontinued irradiation power. [b]: Reaction performed under microwave irradiation with a constant irradiation power of 60 Watts (*Heating with cooling mode*).

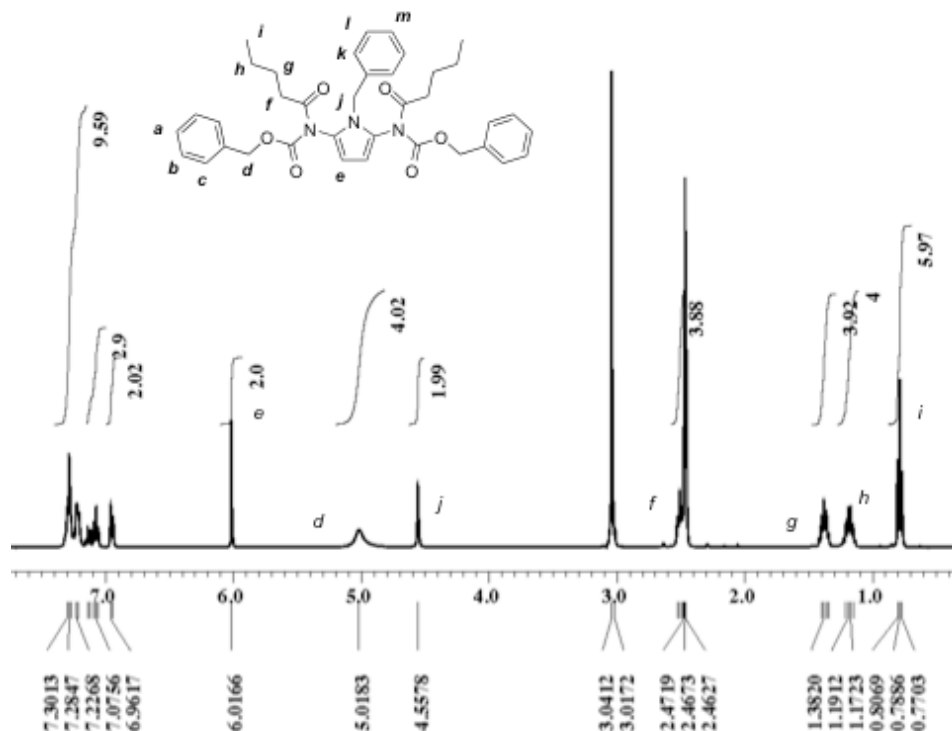
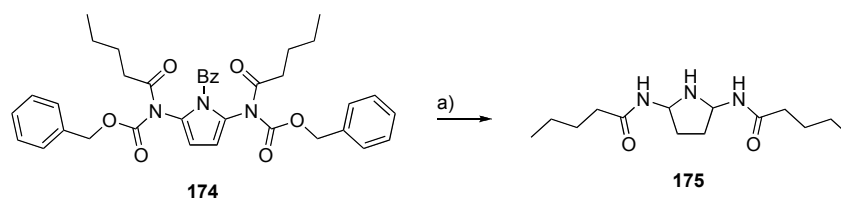


Figure 1 ^1H -NMR spectra of molecule **174** in DMSO- d_6 . Due to the presence of a rotamers the spectra was recorded at 80 °C. The structure at r.t. was unresolved.

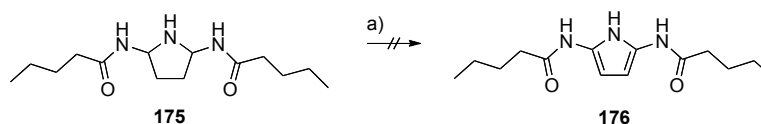
Once obtained the fully protected DDD pyrrolic scaffold, it was decided to sever the benzyl and the Cbz groups simultaneously, by hydrogenolitic cleavage. Unfortunately

hydrogenolysis at atmospheric pressure in MeOH, using Pd(5%)/C as catalyst, resulted not only in the desired deprotections, but also in the de-aromatization of the five membered ring (as indicated by $^1\text{H-NMR}$ spectra of the reaction crude).



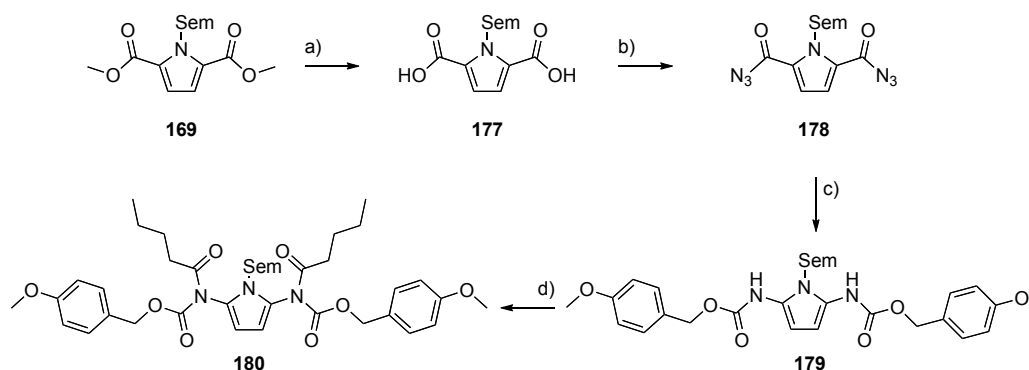
Scheme 8 a) H_2 , Pd(5%)/C, MeOH, r.t., 48 hrs, not isolated.

Since **175** resulted very unstable in solution, as well as in the solid form, a re-oxidation step was attempted directly on the crude, in order to obtain the desired aromatic derivative **176**. However, treatment of the reaction crude with oxidants as PCC or DDQ resulted in a rapid decomposition and no compound could be isolated (*Scheme 9*).



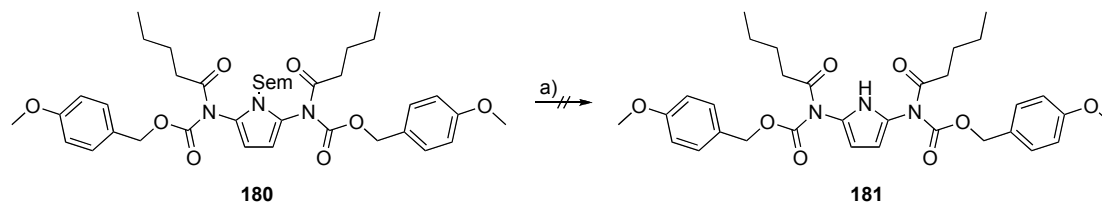
Scheme 9 a) PCC, CH_2Cl_2 , r.t. 10' or DDQ, CH_2Cl_2 , r.t., 10', decomposition.

Following these unsuccessful results the Cbz/Bz approach was discontinued and it was decided to synthesize the fully protected diaminopyrrole **180**, bearing a Sem group on the pyrrolic nitrogen, and two Moz groups on the amidic nitrogens. The synthesis of this compound (*Scheme 10*) goes through a pathway similar to the one already shown for molecule **174**: after saponification of the intermediate **169**, the unstable diacylazide **178** was reacted at high temperature with PMBA, to afford **179**, that was then acylated with valeric anhydride.



Scheme 10 a) 1N LiOH, THF, r.t., 12 hrs, 97%; b) $(\text{COCl})_2$, THF, 0°C to r.t., then sat. NaN_3 aq., not isolated; c) PMBA, mesitylene, 130°C , 5', 52% over two steps; d) valeric anhydride, DMAP, pyridine, r.t., 68%.

In a first approach to obtain the final fully deprotected DDD array, we decided to cleave the Sem group on the pyrrolic nitrogen before deprotection of the Moz group (*Scheme 11*). Three different reagents were investigated, namely KF, HF-pyridine, and TBAF. However, none of the reactions was successful, as summarized in *Table 5*. In a first attempt, **181** was added to a DMF suspension of KF and no reaction was observed after 24 hours (entry *i*); when temperature was increased to 40 °C, decomposition occurred rapidly (entry *ii*). The same results were achieved with HF.pyridine in THF (entries *iii* and *iv*).

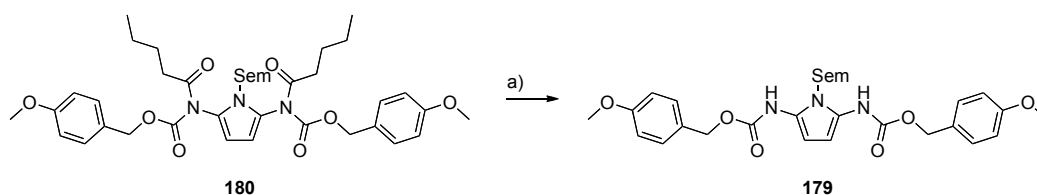


Scheme 11 Attempted cleavage of the Sem group from molecule **181**.

a)	reagent	Solvent	T (° C)	Time (hrs)	Yield (%)
<i>i</i>	KF (10 eq.)	DMF	r.t	24	— ^[a]
<i>ii</i>	KF (10 eq.)	DMF	40	2	— ^[b]
<i>iii</i>	HF.py (1 eq.)	THF	r.t	24	— ^[a]
<i>iv</i>	HF.py (1 eq.)	THF	40	6	— ^[b]
<i>v</i>	TBAF (1 eq.)	THF	r.t	6	— ^[a]
<i>vi</i>	TBAF (1 eq.)	THF	40	6	— ^[c]
<i>vii</i>	TBAF (1 eq.)	DMF	r.t	6	— ^[a]
<i>viii</i>	TBAF (1 eq.)	DMF	40	6	— ^[c]

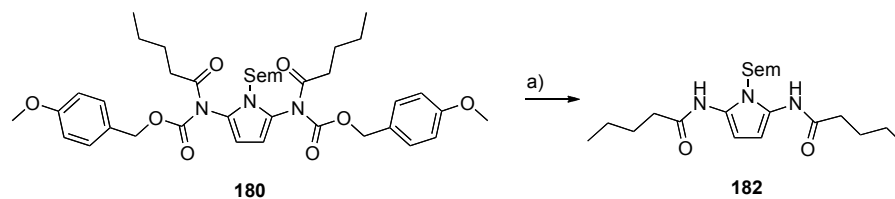
Table 5 Conditions attempted for the cleavage of the Sem group. [a]: No reaction. [b]: Decomposition, [c]: Formation of **182** (see *Scheme 14*).

Differently, reaction of **180** with TBAF gave quite an unexpected output. In fact, while no reaction was observed performing the reaction at r.t (entries *v* and *vii*), a temperature increase to 40 °C resulted in the cleavage of the acyl groups (entries *vi* and *viii*).



Scheme 12 a) TBAF, THF, 40°C, 1 hr, 67%.

Once the impossibility to sever the Sem group at this stage was assessed, we focused our attention on the deprotection of the peripheral amides. This step was performed by acidic solvolysis in a CH₂Cl₂/TFA mixture. Whilst at low volumetric percentage of TFA, no reaction occurred (*Table 6*, entries *i* and *ii*), when the percentage was increased to 30%, decomposition of the material was observed, and **182** was recovered only in 4% yield. Addition of an excess of anisole (50 eq.), acting as a scavenger for the *p*-methoxybenzyl carbocation, eventually increased the yield of the desired product up to 64%.



Scheme 13 a) TFA, anisole, CH₂Cl₂, 0°C to r.t., see Table 3.

a)	vol% of TFA	Eq. of anisole	Time	Yield (%)
<i>i</i>	3%	0	24 hrs	traces
<i>ii</i>	5%	0	24 hrs	traces
<i>iii</i>	30%	0	2 hrs	decomposition
<i>iv</i>	5%	10	4hrs	61
<i>v</i>	5%	50	2hrs	62
<i>vi</i>	30%	50	10'	64

Table 6 Conditions tested for the cleavage of the Moz groups.

Sem-protected pyrrole derivative **182** was easily purified by precipitation in pentane and its structure was unambiguously determined by ¹H and ¹³C-NMR spectroscopy, high-resolution mass spectrometry, and IR spectroscopy (¹H-NMR spectrum at r.t. in DMSO-*d*₆ is reported in Figure 3).

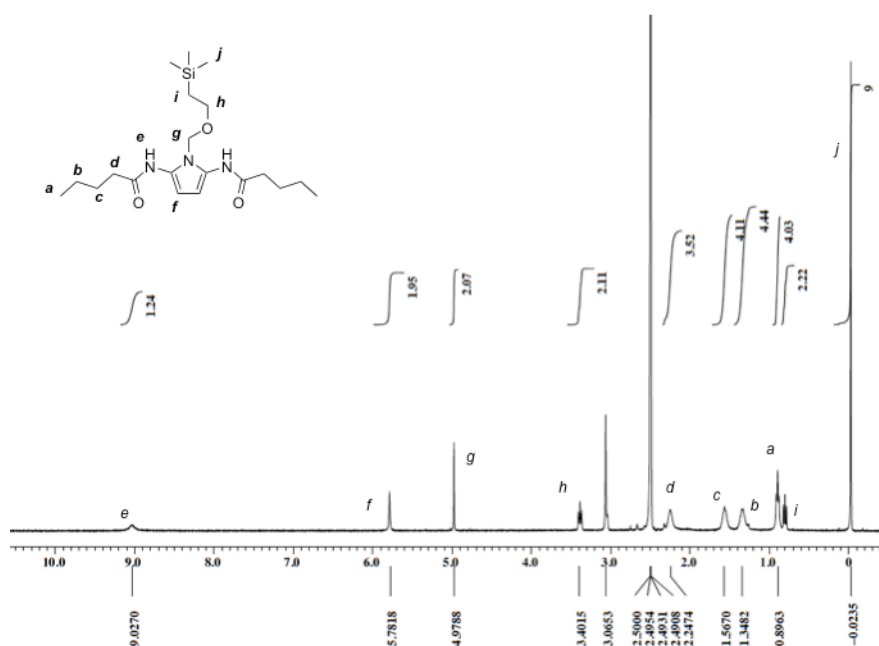
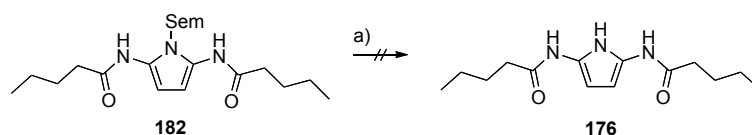


Figure 3 ¹H-NMR spectra of molecule **182** in DMSO-*d*₆ recorded at 80°C. Due to the presence of a rotamers the spectra was recorded at 80 °C. The structure at r.t. was unresolved.

Finally, two main approaches were used in the attempt to sever the Sem group from **182**, in order to obtain the target compound **176**, as shown in *Scheme 17* and *Table 7* : treatment with fluoride anion, and solvolysis in strong acidic media. Nevertheless, all the conditions tested revealed to be too harsh to allow the survival of the electron-rich pyrrolic scaffold and in each case a dark-brown, sticky oil was collected after the reactions.



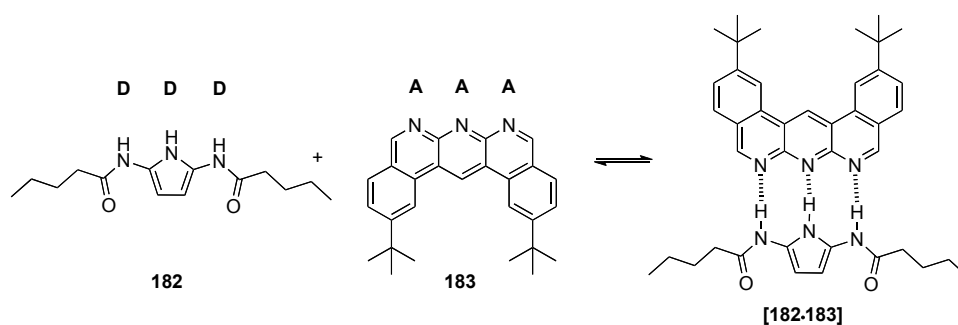
Scheme 14 Attempted cleavage of the Sem group from molecule **182**.

a)	reagent	Solvent	T (° C)	Time (hrs)	Yield (%)
i	KF (10 eq.)	DMF	r.t	24	— ^[a]
ii	KF (10 eq.)	DMF	40	2	— ^[b]
iii	HF-py (1 eq.)	THF	r.t	24	— ^[a]
iv	HF-py (1 eq.)	THF	40	6	— ^[b]
v	TBAF (1 eq.)	THF	r.t	6	— ^[b]
vi	TBAF (1 eq.)	THF	40	1	— ^[b]
vii	TBAF (1 eq.)	DMF	r.t	6	— ^[b]
viii	TBAF (1 eq.)	DMF	40	1	— ^[b]
ix	6N HCl	MeOH	r.t	1	— ^[b]
x	BF ₃ -OEt ₂	THF	r.t	1	— ^[b]

Table 7 Conditions attempted for the cleavage of the Sem group. [a]: Recovery of the starting material. [b]: Decomposition.

Due to the complications encountered in the last step of the synthesis (*i.e.*, cleavage of the pyrrolic protecting group) the synthesis of DDD arrays based on the molecule of pyrrole could not be accomplished during this doctoral work.

Future work will be focused on the research for a suitable protecting group that can be cleaved in relatively mild conditions in order to isolate the desired diamido pyrrolic derivatives. Following successful deprotection the work will move towards the study of the complexation of the DDD arrays with the complementary AAA guest **183** (*Scheme 15*), which will be synthesized according to the procedure reported by Leigh *et al.* The association constant values for complex [**182**•**183**] will be assessed using ¹H-NMR and UV techniques.



Scheme 15 Representation of the equilibria of formation of complex [**182**•**183**] (DDD-AAA).

Once that the binding properties of molecule **182** will be studied the synthetic work will proceed towards the formation of molecular modules based on diureido-pyrrole derivatives in order to build unprecedentedly reported DDDDD H-bond arrays. The possibility of introducing ethynyl substituents will be as well explored in order to create functionalizable molecular modules to be exploited in non-covalent synthesis.

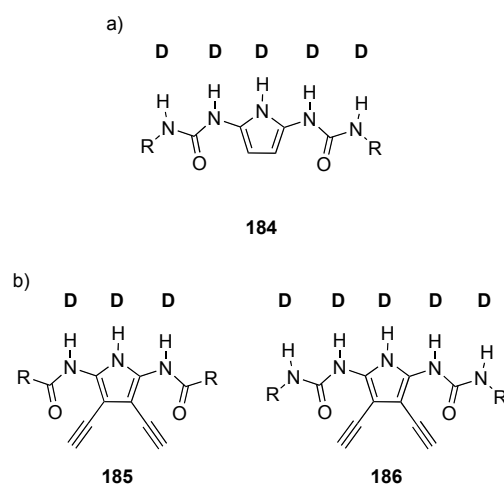
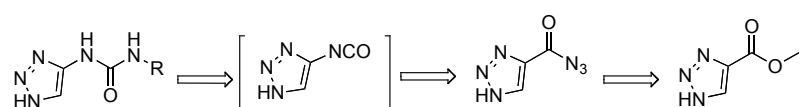


Figure 4 a) Diureido-pyrrole derivatives scaffolding for DDDDD quintuple H-bond interaction. b) Diamido-pyrrole derivative **185** (DDD), and diureido-pyrrole derivative **186** bearing ethynilic moieties onto the β positions of the pyrrole ring.

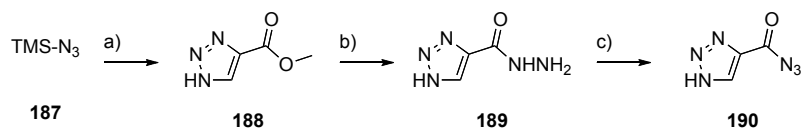
2.6 Synthesis of ureido-triazole derivatives as self-adapting ADD/DDD Hydrogen bonding modules

The strategy adopted for the preparation of self-adapting ADD/DDD modules based on the triazole core, substantially does not differ from the one applied for the others heterocyclic derivatives previously discussed. The key step of this approach (*Scheme 1*) revolves around the formation of a triazolyl-acylazide and its subsequent conversion into an ureido-triazole through a *Curtius* rearrangement reaction.



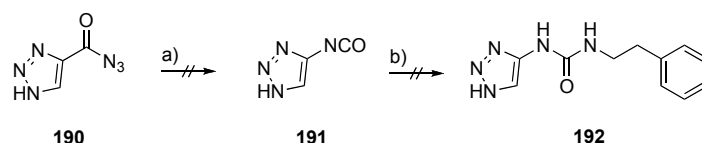
Scheme 1 Retrosynthetic analysis developed for the preparation of ureidotriazolyl derivatives.

Following this strategy, the triazolinic intermediate **190**, bearing the acylazide group in position 4, was synthesized in three steps from commercially available TMS-N₃. In the first step of this synthetic route the triazolinic ring was built via thermal 1,3-dipolar cycloaddition between TMS-N₃ and methyl propiolate in *neat* conditions. The resulting compound, obtained in 65% yield, was then treated with NH₂NH₂ to generate hydrazide **189** in 90 %yield. This intermediate underwent deazotation reaction by treatment with NaNO₂ in HCl, affording the triazol acylazide **190** in 65% yield.



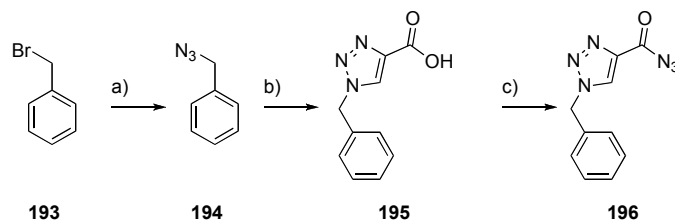
Scheme 2 a) methyl propiolate, 110 °C, 20 hrs, 65%; b) N_2H_4 64% *aq.*, EtOH, reflux, 30 hrs, 90%; c) NaNO_2 , dil. HCl, H_2O , 110°C, 6 hrs, 65%.

In the attempt to obtain the ureidotriazole **192**, the acylazide derivative **190** was heated in mesitylene at 130 °C for 40' and subsequently treated with phenethylamine (*Scheme 3*). Phenethylamine was chosen in order to generate insoluble ureidotriazolyl derivatives to simplify the purification and the characterization processes. Unfortunately this strategy did not afford the desired product but led to a very complex mixture of by-products, which was not possible to purify.



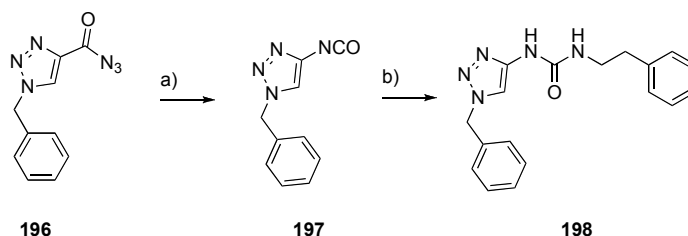
Scheme 3 Synthetic procedure used for the production of compound **192**. a) mesitylene, 140 °C, 40', not isolated; b) phenethylamine, r.t. 12 hrs, decomposition.

Considering these results, it was decided to introduce a protecting group on the triazolonic ring. For this purpose, the benzyl group seemed to be particularly appealing, due to the high yields usually associated with its hydrogenolytic cleavage.^[30] Therefore benzyl-protected triazolyl acylazide **196** was synthesized in three steps starting from commercially available benzyl bromide. The halide was in a first step transformed into benzyl-azide **194** in 80 % yield, by treatment with NaN_3 . Cu-catalysed 1,3-dipolar cycloaddition with propiolic acid afforded then **195** in 76% yields. The reaction was performed using CuSO_4 as precatalyst and Na-ascorbate as reducing agent. The acid derivative **195** was then reacted with $(\text{COCl})_2$ and subsequently treated with NaN_3 , to afford, after precipitation in pentane, the desired benzyl-protected triazolyl derivative **196** in 90% yields.



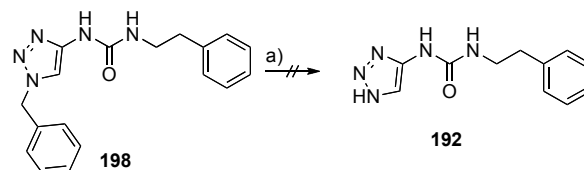
Scheme 4 a) NaN_3 , DMF, 65 °C, 12 h, 80%; b) propiolic acid, CuSO_4 , NaAscorbate, *t*-BuOH/ H_2O , r.t. 8 h, 76%, c) $(\text{COCl})_2$, THF, 0 °C to r.t., then sat. NaN_3 *aq.*, 90%.

196 was then converted into the benzyl-protected ureidotriazole **198** in a two steps-one pot procedure. Following this method, the starting material was initially heated at 140 °C to generate the intermediate **197**. This intermediate was not isolated but directly treated with phenethylamine to give the desired compound **198** in 53% yield, as white needles (*Scheme 5*)



Scheme 5 a) 1,4-dioxane, m.w. 140 °C, 40', not isolated; b) phenethyl amine, r.t., 30', 53%.

The hydrogenolytic cleavage of the benzyl protecting group was initially attempted in MeOH (*Table 1* at atmospheric pressure, entry *i* and at high pressure, entry *ii*) and subsequently in HCOOH (entry *iii*). Unfortunately, in all these three cases the reactions did not afford the expected ureido-triazole **198** but resulted in decomposition of the starting material.

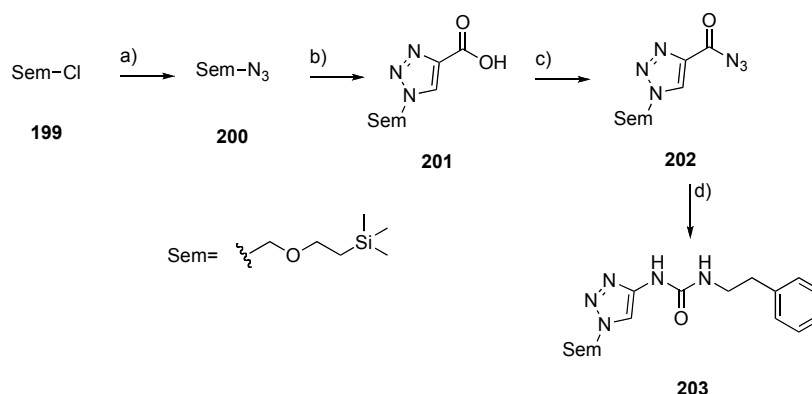


Scheme 6 Attempted hydrogenolytic cleavage of the benzyl protecting group. For more details see *Table 1*

a)	H ₂ pressure (bar)	Solvent	Time (hrs)	Yield (%)
<i>i</i>	1	MeOH	24	0
<i>ii</i>	8	MeOH	24	0
<i>iii</i>	-	HCOOH	24	0

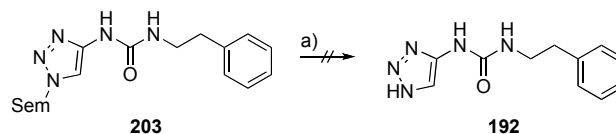
Table 1 Conditions used in the attempted hydrogenolytic cleavage of the benzyl protecting group. All the attempts resulted in decomposition.

Due to this unsuccessful result, it was decided to change the protecting group. Therefore, molecule **203**, bearing the Sem group, was synthesized (*Scheme 7*). To obtain this compound, the commercially available Sem chloride was treated with NaN₃ to afford **200** in 83% yield. The synthesis towards the protected ureido-triazole **203** proceeded then according to the same route developed for the synthesis of **198**. After the formation of **201** via Cu-catalysed 1,3-dipolar cycloaddition with propiolic acid (97% yield), and its subsequent transformation into the acyl-azide derivative **202**, *Curtius* rearrangement reaction was performed under microwave irradiation, affording the desired compound in 47% yield.



Scheme 7 a) NaN_3 , DMF, r.t., 12 hrs, 83%; b) propiolic acid, CuSO_4 , NaAscorbate, $t\text{-BuOH}/\text{H}_2\text{O}$, r.t. 8 hrs, 70%; c) $(\text{COCl})_2$, THF, 0 °C to r.t., then sat, NaN_3 aq., 98%; d) 1,4-dioxane, m.w. 140 °C, 40', then phenethylamine, r.t. 12 hrs 47%;

Unfortunately, the subsequent attempts to sever the Sem group from molecule **203** resulted to be unsuccessful. The conditions used revealed to be too harsh for the ureido-triazolic scaffold. Indeed, decomposition of the starting materials was observed when deprotection was attempted with HF·pyridine (*Table 2* entries *i* and *ii*), TBAF (entries *iii* to *vi*), HCl (entry *vii*) and $\text{BF}_3\cdot\text{Et}_2\text{O}$ (entry *viii*).



Scheme 8 Attempted cleavage of the Sem protecting group. For conditions see *Table 2*.

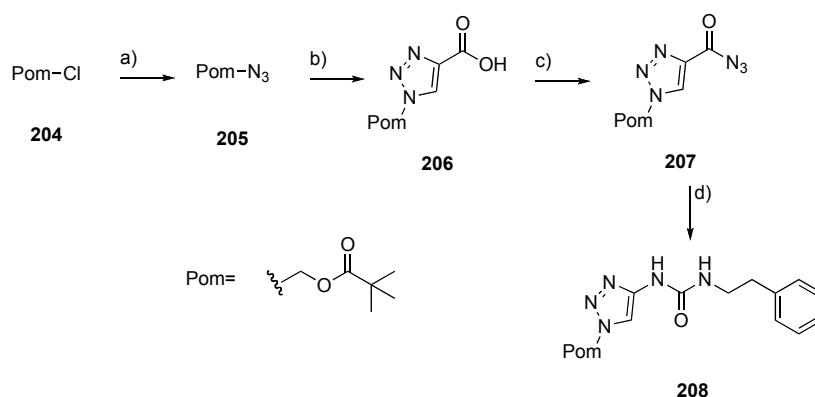
a)	reagent (equivalents)	Solvent	T (° C)	Time (hrs)	Yield (%)
<i>i</i>	HF·py (1 eq.)	THF	r.t	24	0
<i>ii</i>	HF·py (1 eq.)	THF	40	6	0
<i>iii</i>	TBAF (1 eq.)	THF	r.t	6	0
<i>iv</i>	TBAF (1 eq.)	THF	40	1	0
<i>v</i>	TBAF (1 eq.)	DMF	r.t	6	0
<i>vi</i>	TBAF (1 eq.)	DMF	40	1	0
<i>vii</i>	6 <i>N</i> HCl	MeOH	r.t.	1	0
<i>viii</i>	$\text{BF}_3\cdot\text{OEt}_2$	THF	r.t.	1	0

Table 2 Conditions used in the attempted hydrogenolytic cleavage of the Sem protecting group of molecule **203**. All the attempts resulted in decomposition.

Taking into account the results obtained, a further change in the protecting group was required. It was decided then to protect the pyrrolic ring with the pivaloyl oxymethyl (Pom) group, cleavable via trans-esterification in basic media.

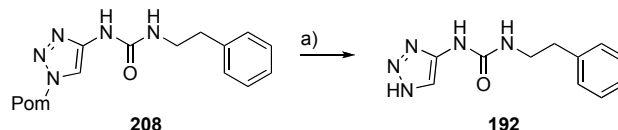
The approach leading to intermediate **208** is described in *Scheme 9*. In a first step, Pom-Cl was reacted with NaN_3 in order to generate the required azidic derivative **205** in 60% yield. The subsequent Cu-catalysed 1,3-dipolar cycloaddition with propiolic acid afforded then intermediate **206** in 82 % yield. Following this step, **206** was treated with $(\text{COCl})_2$, in presence of catalytic amounts of DMF. The chloride derivative obtained after evaporation of

the solvent was then added to a NaN₃ solution in order to form **207**, which was recovered after a basic work-up in 90% yield. A final *Curtius* rearrangement was then performed and the deriving isocyanate was reacted with phenethylamine, to afford **208** in 40 %yield.



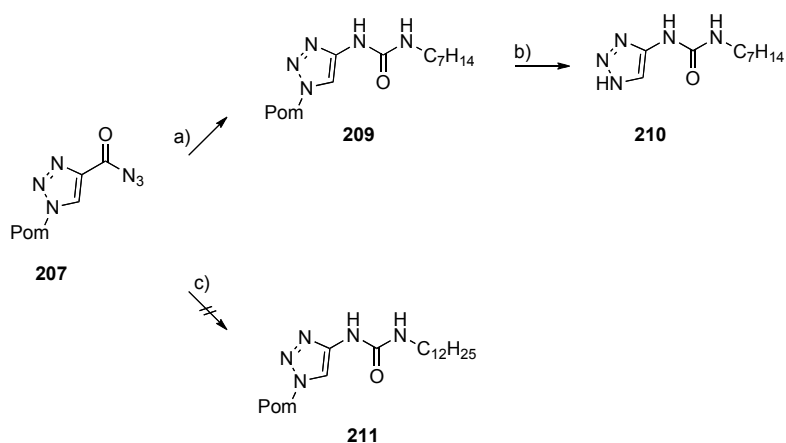
Scheme 9 a) NaN₃, H₂O, 90 °C, 12 hrs, 60%; b) propiolic acid, CuSO₄, NaAscorbate, *t*-BuOH/H₂O, r.t. 8 hrs, 82%; c) (COCl)₂, THF, 0 °C to r.t., then sat. NaN₃ aq., 90%; d) 1,4-dioxane, 140 °C, 40', then phenethylamine, r.t. 12 hrs 40%.

The Pom group was successfully cleaved from **208** in 45% yield via treatment with NaOMe in MeOH (*Scheme 10*). Then the trans-esterification process proceeded smoothly at r.t., and upon acidification, the desired compound **192** precipitated from the reaction mixture and easily purified by re-crystallization from MeOH.



Scheme 10 a) NaOMe, MeOH, r.t., 1 hr, 50%.

Due to the low solubility of **192** in CHCl₃, it was decided to introduce solubilizing chains onto the peripheral ureidic moiety. To achieve this target, **207** was reacted either with *n*-heptylamine or *n*-dodecylamine (*Scheme 11*). While the reaction with *n*-heptylamine proceeded with a reasonable yield of 40% to give **209**, reaction with *n*-dodecylamine surprisingly led to decomposition. This could be in principle attributed to the folding of the longer alkyl chains that can hamper the nucleophilic addition of the aminic group onto the isocyanate functionality.



Scheme 11 a) 1,4-dioxane, 140 °C, 40', then phenethylamine, r.t. 12 hrs 40%; b) NaOMe, MeOH, r.t., 1 hr, 70%; c) 1,4-dioxane, 140 °C, 40', then phenethylamine, r.t. 12 hrs. Decomposition.

Transesterification of the pivalate ester of **209** with NaOMe afforded in 70 %yield the free ureido-triazole **210**, that was fully characterized by ^1H and ^{13}C -NMR spectroscopy, high-resolution mass spectrometry, and IR spectroscopy (^1H -NMR spectrum at r.t. in $\text{DMSO}-d_6$ is reported in *Figure 1*).

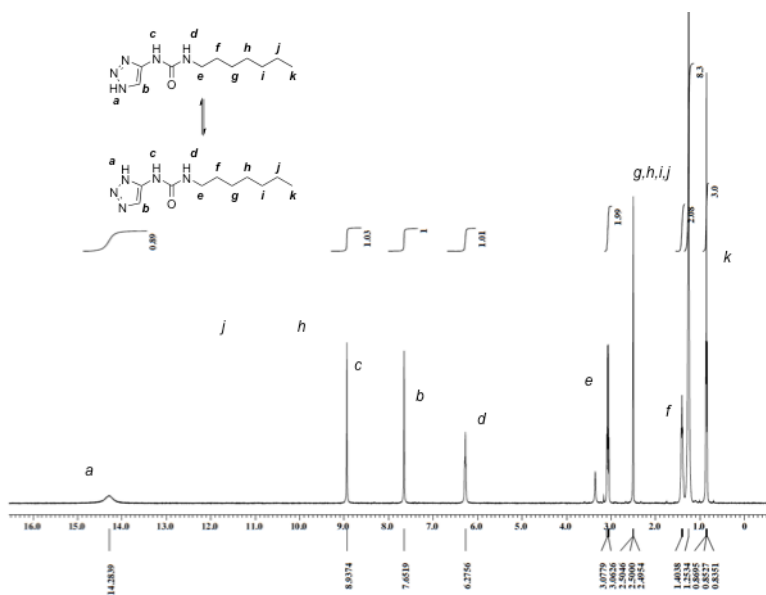


Figure 1 ^1H -NMR spectra of molecule **210** in $\text{DMSO}-d_6$ recorded at r.t.

Unfortunately molecule **210** solubility in CDCl_3 resulted approximately 0.1 mmol/ml and, at this concentration, the signals of the NH protons are indistinguishable from the background noise. Therefore the binding properties of the molecule could not be assessed in this solvent by ^1H -NMR titration techniques. The same problem was encountered when polar co-solvents (CD_3OD , $\text{THF}-d_4$) were used in combination with CDCl_3 in order to reach appreciable

concentration. *Figure 2* shows the ^1H -NMR of a 10 mM solution of **210** in a 95:5 $\text{CDCl}_3/\text{CD}_3\text{OD}$, and, as it can be observed, only one of the three NH protons (H_d) is barely detected in this solvents mixture.

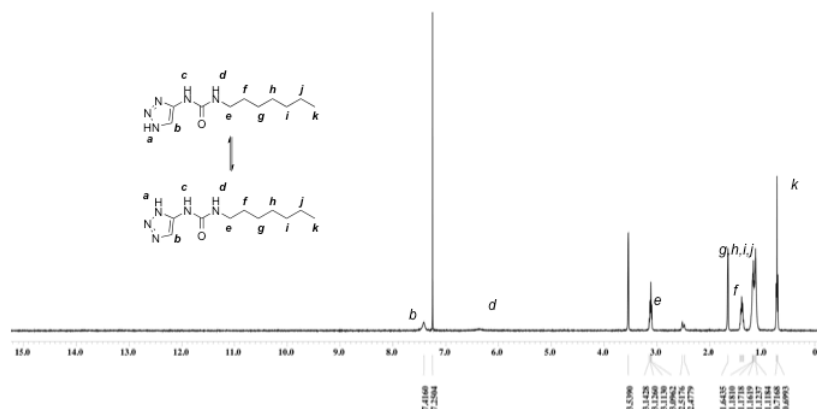
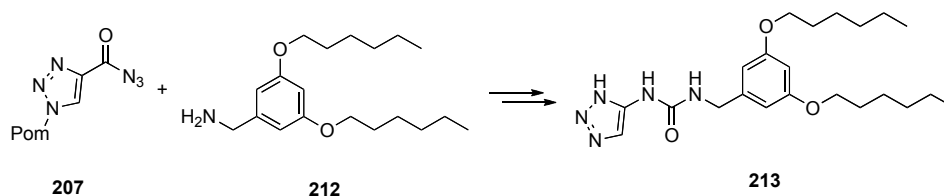


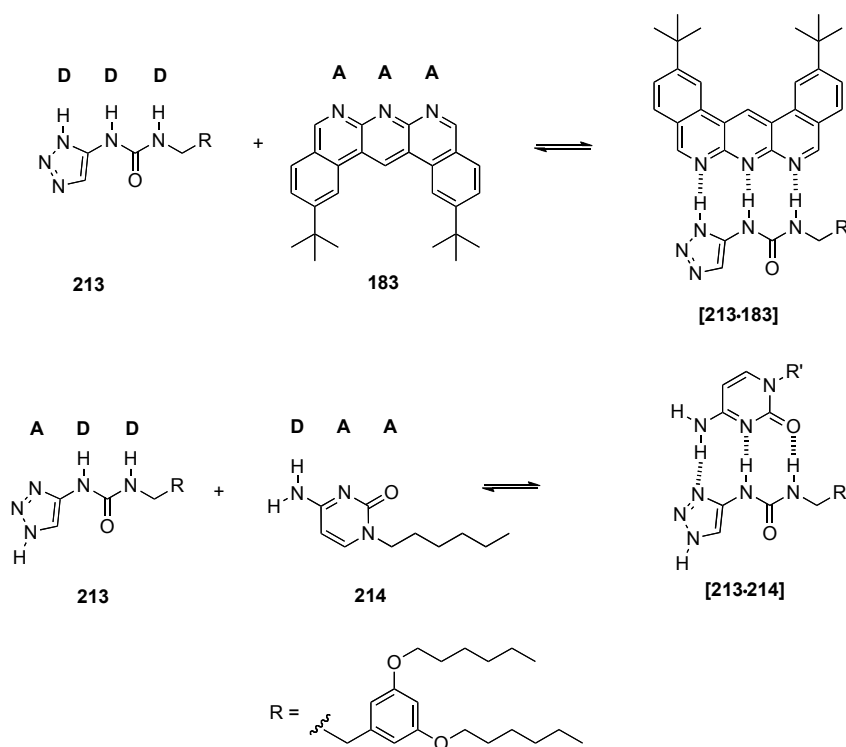
Figure 2 ^1H -NMR spectra of molecule **210** in 95:5 $\text{CDCl}_3/\text{CD}_3\text{OD}$ recorded at r.t. Protons H_a and H_b are not detected in this solvent mixture.

Since the binding properties of the ureido-triazole molecular modules synthesized (**192** and **210**) could not be assessed due to the lack of solubility, future work will be focused on the synthesis of more soluble ureido-triazole derivatives. A benzylic amine bearing solubilizing alkoxy chains will be prepared (**212**) and it will be used in the formation of the self/adapting ADD/DDD array **213** (*Scheme 12*).



Scheme 12 Schematic representation of the synthesis of the self-adapting ADD/DDD module **212**.

Modules **183** and **214** will be prepared in order to study the binding capabilities of **213** acting as an ADD and as DDD array.



Scheme 13 Representation of the equilibria of formation of complexes [213•183] (DDD-AAA) and [213•214] (ADD-DAA).

The association constant values for complexes [213•183] and [213•213] will be assessed using ¹H-NMR and UV techniques.

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Experimental Part

3.1 Instrumentation

Thin layer chromatography (TLC) were conducted on pre-coated aluminum sheets with 0.20 mm *Machevery-Nagel* Alugram SIL G/UV₂₅₄ with fluorescent indicator UV₂₅₄.

Column chromatography was carried out using *Merck Gerduran* silica gel 60 (particle size 40-63 μm). An automatic chromatography system, *Büchi sepacore* was used for the majority of purifications.

Microwave reactions were on an *Biotage AB Initiator microwave instrument* producing controlled irradiation at 2.450 GHz.

Melting points (m.p.) were measured on a *Büchi Melting Point B-545*. All of the melting points have been measured in open capillary tubes and have not been corrected.

Nuclear magnetic resonance (NMR) ^1H and ^{13}C spectra were obtained on a 400 MHz NMR (*Jeol JNM EX-400*) or 270 MHz (*Jeol JNM EX-270*). Chemical shifts were reported in ppm according to tetramethylsilane using the solvent residual signal as an internal reference (CDCl_3 : $\delta_{\text{H}} = 7.26$ ppm, $\delta_{\text{C}} = 77.16$ ppm, DMSO-d_6 : $\delta_{\text{H}} = 2.50$ ppm, $\delta_{\text{C}} = 39.52$ ppm, D_2O : $\delta_{\text{H}} = 4.79$ ppm, Toluene- d_8 : $\delta_{\text{H}} = 2.09$ ppm, $\delta_{\text{C}} = 20.40$, THF- d_8 : $\delta_{\text{H}} = 3.58$ ppm, $\delta_{\text{C}} = 67.57$). Coupling constants (J) were given in Hz. Resonance multiplicity was described as *s* (singlet), *d* (doublet), *t* (triplet), *q* (quartet), *quin* (quintet), *m* (multiplet) and *br* (broad signal). Carbon spectra were acquired with a complete decoupling for the proton.

Infrared spectra (IR) in KBr were recorded on a *Perkin-Elmer spectrum RX I FT-IR System*.

Liquid chromatography mass spectrometry (LC-MS) measurements were conducted on an *Agilent 6200 series TOF mass spectrometer* operating in positive mode. The analyte solutions were delivered to the ESI or APCI source by an *Agilent 1200 series LC system* at a flow rate of 0.25 mL/min. Typical elution gradient start from H_2O (90%) to CH_3CN (100%) for 20 minutes. ESI mode: Typical ESI conditions were, capillary voltage 2.0 kV; cone voltage 65 V; source temperature 150 °C; desolvation temperature 250°C; drying gas 5 L/min, nebuliser 60 psig. APCI: Typical APCI condition were, capillary voltage 2.0 kV; cone voltage 65 V; source temperature 250 °C; desolvation temperature 350°C; drying gas 5L/min; nebuliser 60 psig. Dry nitrogen was used as the ESI and APCI gas.

Mass spectrometry ESI-MS measurements were performed on a *Waters QToF2 mass spectrometer* operating in positive mode. The analyte solutions were delivered to the ESI source by a *Harvard Apparatus* syringe pump at a flow rate of 5 L/min. Typical ESI conditions were, capillary voltage 3.1 kV; cone voltage 20-50 V; source temperature 80 °C; desolvation temperature 120°C. Dry nitrogen was used as the ESI gas. For the recording of

the single-stage ESI-MS spectra, the quadrupole (rf-only mode) was set to pass ions from 50 to 1000 Th, and all ions were transmitted into the pusher region of the time-of-flight analyzer where they were mass analyzed with 1 s integration time.

3.2 Material and general methods

Chemicals were purchased from *Sigma Aldrich*, *Acros Organics*, *Fluorochem*, *ABCR*, *Polypeptide group* and *porphyrin systems* and were used as received. Resins for solid phase synthesis were purchased from *Novabiochem (Merck Chemicals)*. Solvents were purchased from *Sigma Aldrich*, and deuterated solvents from *Eurisotop*.

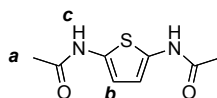
General solvents were distilled *in vacuo*. Anhydrous solvents as Et₂O, THF and toluene were distilled from Na/benzophenone; CH₂Cl₂ from phosphorus pentoxide; CHCl₃ and CH₃CN from CaH₂. Anhydrous DMF was purchased from *Acros Organics*.

Low temperature baths were prepared using different solvent mixtures depending on the desired temperature: -78°C with acetone/liquid N₂ or acetone/dry ice, -40°C with CH₃CN/liquid N₂, -10°C with ice/brine, and 0°C with ice/H₂O.

Anhydrous conditions were achieved by drying *Schlenk* line or 2-neck flasks by flaming with a heat gun under vacuum and then purging with argon. The inert atmosphere was maintained using argon-filled balloons equipped with a syringe and needle that was used to penetrate the silicon stoppers used to close the flasks' necks. The addition of liquid reagents was done by means of dried plastic or crystal syringes.

3.3 Experimental Procedures

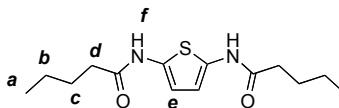
N,N'-(thiophene-2,5-diyl)diacetamide (**68**)



To a solution of **127** (340 mg, 0.6 mmol) in CH₂Cl₂ (5 ml), stirring at 0 °C were subsequently added anisole (651 µl, 6 mmol) and TFA (250 µl were subsequently added and the solution stirred for 2 hrs. The mixture was diluted with EtOAc (50 ml), washed with sat. NaHCO₃ (30 ml) *aq.*, H₂O (2 x 30 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. Precipitation of the residual oil from pentane afforded **68** as a white solid in 61% yield (72.4 mg, 0.37 mmol). m.p. 213-214 °C; ¹H-NMR (400 MHz, DMSO-*d*₆): δ 10.77 (*s*, 2H, *H_c*), 6.32 (*s*, 2H, *H_b*), 2.0 (*s*, 1H, *H_a*); ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 167.80, 132.90, 108.46, 20.98; MS (ESI⁺) found for [C₈H₁₀N₂O₂S + Na]⁺ 221.0377, calc. 221.0355; IR KBr (cm⁻¹) ν: 3247.67, 3097.80, 3000.77, 1747.82, 1666.51, 1645.07, 1587.57, 1556.98, 1480.04, 1494.54, 1426.57,

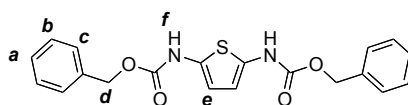
1370.33, 1323.44, 1323.44, 1306.00, 1288.25, 1031.69, 1014.81, 973.48, 875.91, 812.02, 777.49, 765.69, 712.77, 683.36, 618.95, 597.03, 520.53.

N,N'-(thiophene-2,5-diyl)dipentanamide (**123**)



To a solution of **128** (500 mg, 0.8 mmol) in CH_2Cl_2 (5 ml), stirring at 0 °C, anisole (870 μl , 8 mmol) and TFA (250 μl) were subsequently added and the solution stirred for 2 hrs. The mixture was diluted with EtOAc (50 ml), washed with sat. NaHCO_3 (30 ml) *aq.*, H_2O (2 x 30 ml), dried over MgSO_4 , filtered and concentrated *in vacuo*. Precipitation of the residual oil from pentane afforded **128** as a white solid in 61% yield (141 mg, 0.5 mmol). m.p. 161-162 °C ^1H -NMR (400 MHz, DMSO- d_6): δ 10.71 (s, 2H, H_f), 6.33 (s, 2H, H_e), 5.11 (s, 4H, H_d), 2.26 (t, $J = 7.5$ Hz, 4H, H_d), 1.54 (tt, $J_1 = 7.5$ Hz, $J_2 = 7.4$ Hz, 4H, H_c), 1.33-1.24 (m, 4H, H_b), 0.88 (t, $J = 7.3$ Hz, 6H, H_a), the spectra was recorded at 100 °C, due to the presence of rotamers, the structure at r.t. was unresolved; ^{13}C -NMR (100 MHz, DMSO- d_6): δ 168.69, 132.28, 107.05, 34.34, 27.26, 21.79, 13.69; MS (ESI $^+$) found for $[\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_2\text{S} + \text{K}]^+$ 321.1039, calc. 321.1034; IR KBr (cm^{-1}) ν : 3305.66, 3271.63, 2955.27, 2859.52, 1652.44, 1578.83, 1542.99, 1497.77, 1452.87, 1410.53, 1381.21, 1351.00, 1327.55, 1285.71, 1253.22, 1215.47, 1182.87, 1104.02, 1023.18, 962.91, 922.88, 808.88, 748.36, 729.97, 693.87, 540.87, 572.85, 512.85.

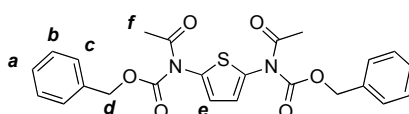
Benzyl thiophene-2,5-diyl dicarbamate (**124**)



To a solution of thiophene-2,5-dicarboxylic acid (2.1 g, 12.1 mmol) in anhydrous THF (30 ml) stirring at 0 °C, DMF (200 μl) and $(\text{COCl})_2$ (2.3 ml, 26.6 mmol) were subsequently added and the mixture stirred for 3 hrs. The solvents were then removed *in vacuo* and the residue redissolved in 20 ml of anhydrous THF. The resulting solution was added drop wise to a saturated NaN_3 *aq.* solution (4 ml), stirred for 30', diluted with Et_2O (50 ml), and then washed with sat. NaHCO_3 *aq.* (50 ml), H_2O (2 x 50ml), dried over MgSO_4 , and concentrated *in vacuo* at 25 °C to an approximate volume of about 5 ml. This solution was added drop wise to a flask containing a solution of benzyl alcohol (2.7 ml, 36.3 mmol) in mesitylene (5ml) at 130 °C stirred for 5', allowed to cool down to room temperature and then poured into pentane

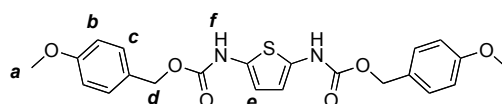
(100 ml). The precipitate was collected by suction filtration and purified by CC on SiO₂ (cyclohexane/EtOAc : 7/3). White solid, 58% yield (2.6g, 7.1mmol). m.p. 102-103 °C; ¹H-NMR (400 MHz, CDCl₃): δ 7.36 (*br*, 10H, *H_{a,b,c}*), 6.94 (*br*, 2H, *H_f*), 6.35 (*s*, 2H, *H_e*), 5.18 (*s*, 4H, *H_d*); ¹³C-NMR (100 MHz, CDCl₃): δ 160.84, 143.25, 139.03, 128.52, 127.02, 126.08, 116.14, 62.31; MS (APCI⁺) found for [C₂₀H₁₈N₂O₄S + H]⁺ 383.1040, calc. 383.1060; IR KBr (cm⁻¹) ν: 3284.80, 2948.59, 1712.62, 1697.86, 1586.33, 1552.22, 1503.73, 1454.41, 1378.68, 1289.80, 1245.01, 1062.42, 1049.48, 971.72, 910.12, 844.99, 798.93, 783.79, 735.59, 653.06, 589.98, 576.65, 514.58, 485.20, 410.02.

Benzyl thiophene-2,5-diylbis(acetylcarbamate) (**125**)



To a solution of **124** (357 mg, 0.93 mmol) in pyridine (5 ml), DMAP (114 mg, 0.93 mmol) and acetic anhydride (0.44 ml, 4.7 mmol) were subsequently added and the solution stirred for 2 hrs at r.t. The mixture was diluted with EtOAc (50 ml), washed with 1N HCl *aq.* (30 ml), sat. NaHCO₃ (30 ml) *aq.*, H₂O (30 ml), dried over MgSO₄, filtered and concentrated at the rotary evaporator. Purification by CC on SiO₂ (cyclohexane/EtOAc : 8/2) afforded **125** as a white solid in 84% yield (364 mg, 0.78mmol). m.p. 111-112 °C; ¹H-NMR (400 MHz, CDCl₃): δ 7.37-7.20 (*m*, 10H, *H_{a,b,c}*), 6.68 (*s*, 2H, *H_e*), 5.19 (*s*, 4H, *H_d*), 2.55 (*s*, 6H, *H_f*); ¹³C-NMR (100 MHz, CDCl₃): δ 172.09, 153.32, 137.84, 134.89, 128.76, 128.49, 127.52, 125.52, 68.87, 26.26; MS (ESI⁺) found for [C₂₄H₂₂N₂O₆S + K]⁺ 505.0841, calc. 505.0839; IR KBr (cm⁻¹) ν: 3027.76, 2947.29, 1743.96, 1711.76, 1583.62, 1561.51, 1467.54, 1382.21, 1286.06, 1251.27, 1100.08, 966.74, 903.91, 762.22, 734.61, 625.86, 579.93, 553.81, 512.68, 463.69, 420.22.

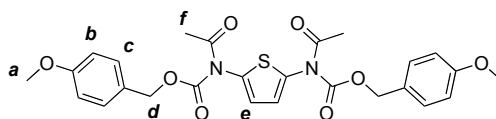
4-methoxybenzyl thiophene-2,5-diyl dicarbamate (**126**)



To a solution of thiophene-2,5-dicarboxylic acid (1.3 g, 7.5 mmol) in anhydrous THF (30 ml) stirring at 0 °C, DMF (200 ml) and (COCl)₂ (1.4 ml, 16.5 mmol) were subsequently added and the mixture stirred for 3 hrs. The solvents were then removed *in vacuo* and the residue re-dissolved in 20 ml of anhydrous THF. The resulting solution was added drop wise to a saturated NaN₃ *aq.* solution (4 ml), stirred for 30', diluted with Et₂O (50 ml), and then washed

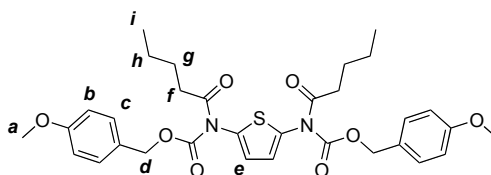
with sat. NaHCO_3 *aq.* (50 ml), H_2O (2 x 50ml), dried over MgSO_4 , and concentrated *in vacuo* at 25 °C to an approximate volume of about 5 ml. This solution was added drop wise to a flask containing a solution of PMBA (3.1 ml, 22.5 mmol) in mesitylene (5ml) stirring at 130 °C stirred for 5', allowed to cool down to room temperature and then poured into pentane (100 ml). The precipitate was collected by suction filtration and purified by CC on SiO_2 (cyclohexane/EtOAc : 7/3). White solid, 62% yield (2.0 g ,4.6 mmol). m.p. 92-93 °C; ^1H -NMR (400 MHz, CDCl_3): δ 7.28 (*d*, J = 8.6 Hz, 4H, H_c), 6.94 (*br*, 2H, H_f), 6.85 (*d*, J = 8.6 Hz, 4H, H_b), 6.30 (*s*, 2H, H_e), 5.09 (*s*, 4H, H_d), 3.78 (*s*, 6H, H_a); ^{13}C -NMR (100 MHz, CDCl_3): δ 159.82, 153.95, 132.73, 130.43, 127.94, 114.05, 112.42, 67.58, 55.40; MS (ESI^+) found for $[\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_6\text{S} + \text{Na}]^+$ 465.1102, calc. 465.1096; IR KBr (cm^{-1}) ν : 3287.15, 2958.44, 2837.93, 1698.38, 1690.99, 1615.47, 1585.69, 1553.70, 1515.92, 1466.48, 1376.69, 1337.93, 1284.15, 1239.25, 1174.45, 1109.37, 1074.98, 1032.41, 952.70, 816.81, 790.48, 771.83, 762.34, 645.47, 522.31, 512.30, 489.39.

4-methoxybenzyl thiophen-2,5-diylbis(acetylcarbamate) (127)



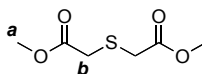
To a solution of **126** (1.8 g, 4.1 mmol) in pyridine (10 ml), DMAP (250 mg, 2.05 mmol) and acetic anhydride (1.9 ml, 20.5 mmol) were subsequently added and the solution stirred for 2 hrs at r.t. The mixture was diluted with EtOAc (50 ml), washed with 1N HCl *aq.* (30 ml), sat. NaHCO_3 (30 ml) *aq.*, H_2O (30 ml), dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification by CC on SiO_2 (cyclohexane/EtOAc : 8/2) afforded **127** as a white solid in 82% yield (1.7 g ,3.4 mmol). m.p. 98-100° C; ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.16 (*d*, J = 8.7 Hz, 4H, H_c), 6.84 (*d*, J = 8.7 Hz, 4H, H_b), 6.67 (*s*, 2H, H_e), 5.12 (*s*, 4H, H_d), 3.78 (*s*, 6H, H_a), 2.54 (*s*, 6H, H_f); ^{13}C -NMR (100 MHz, $\text{DMSO}-d_6$): δ 172.04, 159.73, 153.29, 137.78, 129.54, 126.94, 125.32, 114.00, 68.76, 55.29, 26.1881; MS (ESI^+) found for $[\text{C}_{26}\text{H}_{26}\text{N}_2\text{O}_8\text{S} + \text{Na}]^+$ 549.1302, calc. 549.1303; IR KBr (cm^{-1}) ν : 2997.15, 2941.50, 2842.66, 1894.46, 1750.42, 1717.35, 1644.89, 1586.42, 1614.54, 1511.24, 1465.24, 1416.71, 1375.45, 1303.52, 1245.46, 1174.00, 1100.49, 1038.35, 1016.53, 960.87, 896.14, 852.62, 821.85, 798.98, 764.46, 728.58, 636.77, 626.90, 556.36, 541.26, 518.05, 461.23, 429.28.

4-methoxybenzyl thiophene-2,5-diylbis(pentanoylcarbamate) (128)



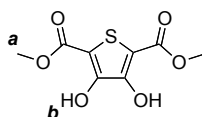
To a solution of **126** (1.4 g, 3.2 mmol) in pyridine (10 ml), DMAP (195 mg, 1.6 mmol) and valeric anhydride (1.9 ml, 9.6 mmol) were subsequently added and the solution stirred for 2 hrs at r.t.. The mixture was diluted with EtOAc (50 ml), washed with 1N HCl *aq.* (30 ml), sat. NaHCO₃ (30 ml) *aq.*, H₂O (30 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by CC on SiO₂ (cyclohexane/EtOAc : 8/2) afforded **128** as a white solid in 77% yield (1.5 g, 2.5 mmol). m.p. 63-64 °C; ¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.17 (*d*, *J* = 8.7 Hz, 4H, *H_c*), 6.86 (*d*, *J* = 8.7 Hz, 4H, *H_b*), 6.82 (*s*, 2H, *H_e*), 5.11 (*s*, 4H, *H_d*), 3.70 (*s*, 6H, *H_a*), 2.81 (*t*, *J* = 7.3 Hz, 4H, *H_f*), 1.53-1.46 (*m*, 4H, *H_g*), 1.30-1.21 (*m*, 4H, *H_h*), 0.84 (*t*, *J* = 7.5 Hz, 6H, *H_i*); ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 174.54, 159.10, 152.71, 137.57, 129.20, 127.10, 125.53, 113.75, 68.02, 55.03, 36.66, 26.49, 21.62, 13.77; MS (ESI⁺) found for [C₃₂H₃₈N₂O₈S + Na]⁺ 633.0287, calc. 633.0728; IR KBr (cm⁻¹) ν: 3084.85, 2957.61, 2870.71, 2837.89, 2358.40, 1901.86, 1747.58, 1724.35, 1614.07, 1587.46, 1564.41, 1512.08, 1480.54, 1466.25, 1454.43, 1375.24, 1375.24, 1302.82, 1282.89, 1268.81, 1240.24, 1205.71, 1181.19, 1076.18, 1029.71, 974.93, 849.47, 821.55, 802.70, 768.15, 753.41, 715.58, 683.18, 575.57, 558.39, 540.75, 517.31, 409.30.

Dimethyl 2,2'-thiodiacetate (**131**)



TMS-Cl (19.0 ml, 160 mmol) was added drop wise to a solution of 2,2'-thiodiacetic acid (11.0 g, 73.0 mmol) in anhydrous MeOH (50 ml) at 0 °C. The solution was then allowed to reach r.t., stirred overnight then diluted with Et₂O (40 ml) washed with sat. NaHCO₃ (2 x 30 ml) *aq.*, H₂O (30 ml), dried over MgSO₄, and filtered. Concentration *in vacuo* afforded **131** as a colorless liquid in 94% yield (12.2 g, 68.2 mmol). ¹H-NMR (400 MHz, CDCl₃): δ 3.83 (*s*, 6H, *H_a*), 3.34 (*s*, 4H, *H_b*); ¹³C-NMR (100 MHz, CDCl₃): δ 170.34, 52.58, 33.53. Spectral data in agreement with those previously reported.^[1]

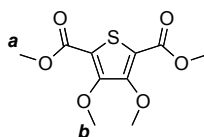
Dimethyl 3,4-dihydroxythiophene-2,5-dicarboxylate (**132**)



131 (24.0 g, 134 mmol) and dimethyl oxalate (23.0 g, 201 mmol) were added to a solution of NaOMe (18.1 g, 335 mmol) in MeOH (50 ml), and the mixture was refluxed for 6 hrs. The solution was then cooled down to 0 °C and the precipitate formed, filtered off and dissolved in H₂O (30 ml). The pH of the solution was adjusted to ca. 2 by addition of *conc.* HCl (37%)

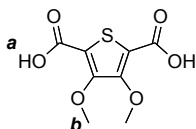
aq. The white precipitate formed was collected by suction filtration, thoroughly washed with H₂O and dried by azeotropic distillation with toluene. Yield 91% (28.2 g, 120 mmol). m.p. 180-181 °C; ¹H-NMR (400 MHz, CDCl₃): δ 9.30 (*s*, 2H, *H_b*), 3.92 (*s*, 6H, *H_a*), ¹³C-NMR (100 MHz, CDCl₃): δ 166.20, 152.00, 107.22, 52.70. Spectral data in agreement with those previously reported.^[1]

Dimethyl 3,4-dimethoxythiophene-2,5-dicarboxylate (**133**)

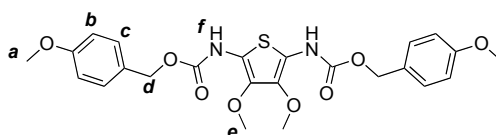


K₂CO₃ (8.0 g, 58.0 mmol) and Me₂SO₄ (1.7ml, 18 mmol) were added to a solution of **132** (1.7g, 7.2 mmol) in anhydrous DMF (20 ml) and the mixture was then heated to 60 °C and stirred overnight. The mixture was diluted with EtOAc (50 ml), washed with 1N HCl *aq.* (30 ml), sat. NaHCO₃ (30 ml) *aq.*, H₂O (30 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by CC on SiO₂ (cyclohexane/EtOAc : 8/2) afforded **133** as a white solid in 83% yield. (1.5g, 6.0 mmol). m.p. 86-87 °C; ¹H-NMR (400 MHz, CDCl₃): δ 3.97 (*s*, 6H, *H_a*), 3.85 (*s*, 6H, *H_b*); ¹³C-NMR (100 MHz, CDCl₃): δ 160.98, 154.05, 119.12, 61.98, 52.39. Spectral data in agreement with those previously reported.^[1]

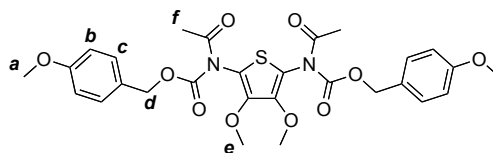
3,4-dimethoxythiophene-2,5-dicarboxylic acid (**134**)



A 2N LiOH *aq.* solution (20 ml) was added to a solution of **133** (2.3g, 8.8 mmol) in THF (2 ml), and stirred at r.t. overnight. The mixture was then cooled down to 0 °C and conc. HCl *aq.* added in until the formation of a white precipitate that was collected by suction filtration. Re-crystallization from MeOH afforded **134** as a white solid in 94% yield (1.9 g, 8.3 mmol). m.p. > 288 °C; ¹H-NMR (400 MHz, DMSO-*d*₆): δ 13.46 (*s*, 2H, *H_a*), 3.90 (*s*, 6H, *H_b*); ¹³C-NMR (DMSO-*d*₆): δ 161.41, 153.34, 119.82, 61.71. Spectral data in agreement with those previously reported.^[1]

4-methoxybenzyl 3,4-dimethoxythiophene-2,5-diylldicarbamate (136)

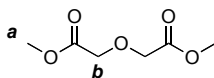
To a solution of **134** (320 mg, 1.1 mmol) in anhydrous THF (30 ml) stirring at 0 °C, DMF (50 μ l) and (COCl)₂ (204 μ l, 2.42 mmol) were subsequently added and the mixture stirred for 3 hrs. The solvents were then removed *in vacuo* and the residue re-dissolved in 20 ml of anhydrous THF. The resulting solution was added drop wise to a sat. NaN₃ *aq.* solution (4 ml), stirred for 30', diluted with Et₂O (50 ml), and then washed with sat. NaHCO₃ *aq.* (50 ml), H₂O (2 x 50ml), dried over MgSO₄, and concentrated *in vacuo* at 25 °C to an approximate volume of about 5 ml. This solution was added drop wise to a flask containing a solution of benzyl alcohol (2.7 ml, 36.3 mmol) in mesitylene (5ml) at 130 °C, stirred for 5', allowed to cool down to r.t. and then poured into pentane (100 ml). The precipitate was collected by suction filtration and purified by CC on SiO₂ (cyclohexane/EtOAc : 7/3). White solid, 79% yield (490 mg, 0.9 mmol). m.p. 90-91 °C; ¹H-NMR (400 MHz, CDCl₃): δ 7.33 (*d*, *J* = 8.5 Hz, 4H, *H_c*), 6.89 (*d*, *J* = 8.5 Hz, 4H, *H_b*), 6.66 (*br*, 2H, *H_f*), 5.12 (*s*, 4H, *H_d*), 3.81 (*s*, 6H, *H_a*), 3.79 (*s*, 6H, *H_e*); ¹³C-NMR (100 MHz, CDCl₃): δ 159.92, 153.44, 136.40, 130.48, 127.92, 115.47, 114.11, 67.70, 60.63, 55.42; MS (ESI⁺) found for [C₂₄H₂₆N₂O₈S + K]⁺ 541.1041, calc. 541.1022; IR (KBr, cm⁻¹) ν : 3351.63, 3271.65, 2959.63, 2990.81, 2545.23, 2062.88, 1726.68, 1693.95, 1614.95, 1586.48, 1571.44, 1514.74, 1483.18, 1444.73, 1401.39, 1365.34, 1303.33, 1243.11, 1218.49, 1173.00, 1117.84, 1109.99, 1081.72, 1053.17, 1035.73, 1004.73, 960.15, 945.82, 847.74, 828.26, 814.59, 807.51, 759.53, 737.92, 721.72, 669.97, 570.05, 547.01, 514.08, 427.42.

4-methoxybenzyl 3,4-dimethoxythiophene-2,5-diylbis(acetylcarbamate) (137)

To a solution of **136** (400 mg, 0.8 mmol) in pyridine (2 ml), DMAP (96 mg, 0.8 mmol) and acetic anhydride (370 μ l, 4.0 mmol) were subsequently added and the solution stirred for 2 hrs at r.t.. The mixture was diluted with EtOAc (40 ml), washed with 1N HCl *aq.* (10 ml), sat. NaHCO₃ (10 ml) *aq.*, H₂O (10 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by CC on SiO₂ (cyclohexane/EtOAc : 8/2) afforded **137** as a white solid in 81% yield (375 mg, 0.6 mmol). m.p. 88-90 °C; ¹H-NMR (400 MHz, CDCl₃): δ 7.18 (*d*, *J* = 8.7 Hz,

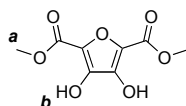
4H, H_c), 6.83 (*d*, $J = 8.7$ Hz, 4H, H_b), 5.13 (*s*, 4H, H_d), 3.76 (*s*, 6H, H_a), 3.68 (*s*, 6H, H_e); 2.53 (*s*, 6H, H_f); ^{13}C -NMR (100 MHz, CDCl_3): δ 171.92, 159.78, 153.32, 143.99, 129.55, 127.03, 118.73, 114.04, 68.81, 59.84, 55.35, 25.96; MS (ESI^+) found for $[\text{C}_{28}\text{H}_{30}\text{N}_2\text{O}_{10}\text{S} + \text{Na}]^+$ 609.1513, calc. 609.1517; IR KBr (cm^{-1}) ν : 3421.03, 3091.02, 2942.06, 2837.38, 2408.27, 2057.64, 1893.29, 1746.90, 1730.56, 1615.08, 1531.39, 1515.05, 1456.02, 1418.30, 1394.31, 1375.89, 1304.02, 1263.86, 1241.75, 1191.16, 1179.00, 1127.99, 1091.58, 1060.36, 1035.43, 1024.02, 954.55, 912.03, 864.58, 828.06, 814.88, 767.56, 744.37, 713.18, 643.47, 579.19, 543.10, 514.78, 480.52, 457.79, 437.18, 413.19.

Dimethyl 2,2'-oxydiacetate (**140**)

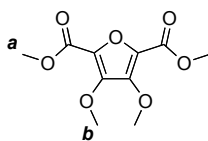


TMS-Cl (13.9 ml, 116.0 mmol) was added drop wise to a solution of 2,2'-oxydiacetic acid (4.1 g, 29.0 mmol) in anhydrous MeOH (50 ml) at 0 °C. The solution was then allowed to reach r.t., stirred overnight then diluted with Et_2O (40 ml) washed with sat. NaHCO_3 (2 x 30 ml) *aq.*, H_2O (30 ml), dried over MgSO_4 , and filtered. Concentration *in vacuo* afforded **140** as a white solid in 96% yield (4.4 g, 27.2 mmol). m.p. 60-61 °C; ^1H -NMR (400 MHz, CDCl_3): δ 4.16 (*s*, 4H, H_b), 3.67 (*s*, 6H, H_a); ^{13}C -NMR (100 MHz, CDCl_3): δ 170.09, 68.03, 51.93. Spectral data in agreement with those previously reported.^[5]

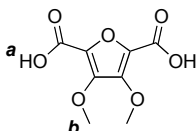
Dimethyl 3,4-dihydroxyfuran-2,5-dicarboxylate (**141**)



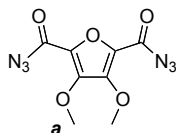
140 (13.5 g, 83.3 mmol), dimethyl oxalate (9.84 g, 83.3 mmol), DMF (500 ml) and NaH (5.3 g, 183.3 mmol) were subsequently charged into a 2 l flask equipped with a mechanical stirrer. MeOH (8.0 ml, 200 mmol) was added and the mixture heated up to 60 °C and stirred for 6 hrs. After concentration *in vacuo* the slurry formed was dissolved into H_2O (200 ml). The pH of the solution was adjusted to ca. 2 by addition of *conc.* HCl (37%) *aq.* The white precipitate formed was collected by suction filtration, thoroughly washed with H_2O and dried by azeotropic distillation with toluene. Yield 55% (9.9 g, 45.8 mmol). m.p. 217-218 °C; ^1H -NMR (400 MHz, $\text{dmsO}-d_6$): δ 10.29 (*br*, 2H, H_b), 3.78 (*s*, 6H, H_a), ^{13}C -NMR (100 MHz, $\text{dmsO}-d_6$): δ 161.41, 153.34, 119.82, 61.71. Spectral data in agreement with those previously reported.^[6]

Dimethyl 3,4-dimethoxyfuran-2,5-dicarboxylate (142)

K₂CO₃ (6.6 g, 48.3 mmol) and MeI (2.9 ml, 48.3 mmol) were added to a solution of **141** (3.0 g, 13.8 mmol) in anhydrous DMF (20 ml), and the mixture was stirred overnight at r.t.. The mixture was diluted with EtOAc (50 ml), washed with 1N HCl *aq.* (30 ml), sat. NaHCO₃ (30 ml) *aq.*, H₂O (30 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by CC on SiO₂ (cyclohexane/EtOAc : 8/2) afforded **142** as a white solid in 84% yield (2.6 g, 11.6 mmol). m.p. 89.2 °C; ¹H-NMR (400 MHz, CDCl₃): δ 4.03 (*s*, 6H, *H_a*), 3.88 (*s*, 6H, *H_b*), ¹³C-NMR (100 MHz, CDCl₃): δ 158.15, 147.22, 131.72, 61.98, 52.20. Spectral data in agreement with those previously reported.^[7]

3,4-dimethoxyfuran-2,5-dicarboxylic acid (143)

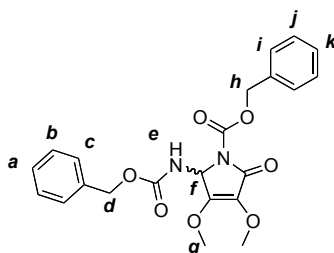
A 2N LiOH *aq.* solution (20 ml) was added to a solution of **142** (2.3g, 8.8 mmol) in THF (2 ml), and stirred at r.t. overnight. The mixture was then cooled down to 0 °C and conc. HCl *aq.* added in until the formation of a white precipitate that was collected by suction filtration. Re-crystallization from MeOH afforded **143** as a white solid in 94% yield (1.9 g, 8.3 mmol). m.p. >249 °C; ¹H-NMR (400 MHz, dms-*d*₆): δ 13.46 (*s*, 2H, *H_a*), 3.90 (*s*, 6H, *H_b*); ¹³C-NMR (dms-*d*₆): δ 161.41, 153.34, 119.82, 61.71. Spectral data in agreement with those previously reported.^[7]

3,4-dimethoxyfuran-2,5-dicarbonyl azide (144)

To a solution of **143** (468 mg, 2.1 mmol) in anhydrous THF (30 ml) stirring at 0 °C, DMF (50 μl) and (COCl)₂ (403 μl, 4.7 mmol) were subsequently added and the mixture stirred for 3 hrs. The solvents were then removed *in vacuo* and the residue re-dissolved in 20 ml of anhydrous THF. The resulting solution was added drop wise to a saturated NaN₃ *aq.* solution

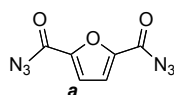
(4 ml), stirred for 30', diluted with Et₂O (50 ml), and then washed with sat. NaHCO₃ aq. (50 ml), H₂O (2 x 50ml), dried over MgSO₄. Evaporation of the solvents *in vacuo* at 10 °C afforded **144** as white solid in 67% yield. (345 mg, 1.4 mmol). ¹H-NMR (400 MHz, CDCl₃): δ 4.11 (s, 6H, H_a); ¹³C-NMR (100 MHz, CDCl₃): δ 162.05, 148.45, 133.121, 62.39.

Benzyl 2-(benzyloxycarbonylamino)-3,4-dimethoxy-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (146)



A solution of **144** (200 mg, 0.75 mmol), benzyl alcohol (155 µl, 1.5 mmol) in toluene (5 ml) was heated up at 90 °C and stirred for 4 hrs. The solution was cooled down to r.t. and poured into cold hexane (10 ml). The white precipitate was filtered off, re-crystallization from MeOH afforded **146** as a white solid in 77% yield (246 mg, 0.58 mmol). m.p 194.4 °C; ¹H-NMR (400 MHz, dms_o-d₆): δ 8.10 (d, *J* = 9.2 Hz, 2H, H_e), 7.34-7.28 (m, 10H, H_{a,b,c,l,j,k}), 5.93 (d, *J* = 9.2 Hz, 1H, H_f), 5.15 (diastereotopic protons, *dd*, *J*₁ = *J*₂ = 12.8 Hz, 2H, H_h), 4.99 (diastereotopic protons, *dd*, *J*₁ = *J*₂ = 12.1 Hz, 2H, H_d), 3.96 (s, 1H, H_l), 3.68 (s, 1H, H_g); ¹³C-NMR (100 MHz, CDCl₃): δ 164.42, 155.07, 152.38, 149.97, 130.10, 135.30, 128.73, 128.59, 128.54, 128.49, 128.32, 126.20, 68.23, 67.54, 62.37, 60.74, 59.65; MS (ESI⁺) found for [C₂₂H₂₂N₂O₇ + Na]⁺ 449.1314, calc. 449.1327; IR KBr (cm⁻¹) ν: 3281.95, 3060.75, 2954.93, 1793.69, 1702.32, 1680.64, 1544.98, 1456.24, 1377.45, 1358.56, 1331.16, 1281.62, 1255.45, 1221.02, 1190.80, 1149.91, 1092.99, 1055.67, 1007.53, 976.21, 957.46, 915.99, 871.46, 822.86, 777.76, 748.00, 734.92, 705.42, 694.97, 641.11, 599.46, 579.03, 557.18, 510.00, 493.79.

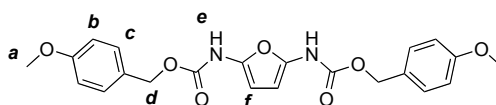
Furan-2,5-dicarboxylic azide (152)



To a solution of furan-2,5-dicarboxylic acid (900 mg, 5.8 mmol) in anhydrous THF (30 ml) stirring at 0 °C, DMF (30 µl) and oxalyl chloride (1.2 ml, 14.5 mmol) were subsequently added. After the addition the solution was allowed to warm up to r.t. and stirred for 3 hrs. The

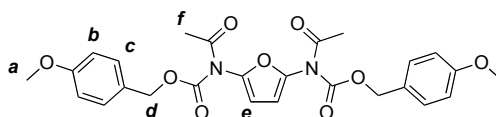
solvent and the excess oxalyl chloride were evaporated at the rotary evaporator and the residue re-dissolved into 20 ml of anhydrous THF. The resulting solution was added drop wise to a saturated aqueous solution of NaN₃ (4 ml) and stirred for 30'. The mixture was then diluted with Et₂O (50 ml), the organic phase was washed with saturated NaHCO₃ aq. and twice with H₂O, dried over MgSO₄ and filtered. Evaporation of the solvents at 20 °C afforded **152** as a white solid in 67% yield (800 mg, 3.8 mmol). ¹H-NMR (400 MHz, CDCl₃): δ 7.30 (s, 2H, H_a); ¹³C-NMR (100 MHz, CDCl₃): δ 162.38, 148.47, 120.18.

4-methoxybenzyl furan-2,5-diyl dicarbamate (**153**)



152 (400 mg, 0.9 mmol), *p*-methoxybenzyl alcohol (358 µl, 2.7 mmol), and THF (2 ml) were subsequently charged into a microwave vessel, the vessel was hermetically capped and heated under microwave condition at 120 °C for 5'. The crude mixture was concentrated in *vacuo* and rapidly filtered through a short SiO₂ plug (cyclohexane : EtOAc = 7:3). Precipitation from EtOAc/ pentane afforded **153** in 48% yield (222 mg, 0.52 mmol). Decomposition before melting 92-93 °C; ¹H-NMR (400 MHz, DMSO-*d*₆): δ 10.00 (br, 2H, H_e), 7.56 (d, *J* = 8.6 Hz, 4H, H_c), 7.28 (d, *J* = 8.6 Hz, 4H, H_b), 5.98 (s, 2H, H_f), 5.09 (s, 4H, H_d), 3.80 (s, 6H, H_a); ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 160.32, 150.95, 140.73, 130.73, 126.34, 111.15, 109.42, 67.58, 55.40; MS (ESI⁺) found for [C₂₂H₂₂N₂O₇ + Na]⁺ 449.1333, calc. 449.1325; IR KBr (cm⁻¹) ν: 3287.15, 2958.44, 2837.93, 1698.38, 1566.53, 1515.85, 1464.01, 1423.77 1371.34, 1306.00, 1288.25, 1031.69, 1014.81, 973.48, 875.91, 812.02, 777.49, 765.69, 712.77, 683.36, 618.95, 597.03, 520.53.

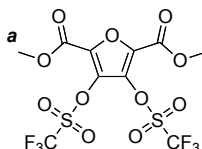
4-methoxybenzyl furan-2,5-diylbis(acetylcarbamate) (**154**)



To a solution of **153** (400 mg, 0.9 mmol) in pyridine (2 ml), DMAP (49 mg, 0.4 mmol) and acetyl anhydride (613 µl, 3.1 mmol) were subsequently added. The solution was stirred for 2 hrs at r.t. then was diluted with EtOAc, washed with 1N HCl aq., saturated NaHCO₃ aq., distilled H₂O, dried over MgSO₄, filtered and concentrated at the rotary evaporator. Purification by CC on SiO₂ (cyclohexane/EtOAc : 8/2) afforded **154** as a transparent oil in 68% yield (379 mg, 0.6 mmol). ¹H-NMR (400 MHz, CDCl₃): δ 7.28 (d, *J* = 8.5 Hz, 4H, H_c),

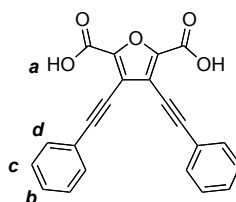
7.18 (*d*, $J = 8.5$ Hz, 4H, H_b), 6.22 (*s*, 2H, H_e), 5.07 (*s*, 4H, H_d), 3.76 (*s*, 6H, H_a) 2.39 (*s*, 6H, H_f); ^{13}C -NMR (100 MHz, CDCl_3): δ 171.49, 159.83, 152.48, 141.00, 129.80, 126.87, 114.07, 108.59, 68.83, 55.31, 25.46; MS (ESI^+) found for $[\text{C}_{26}\text{H}_{26}\text{N}_2\text{O}_9 + \text{Na}]^+$ 533.1544, calc. 533.1531; IR KBr (cm^{-1}) ν : 3010.46, 2960.22, 2388.18, 2348.71, 2058.78, 1788.03, 1753.39, 1614.14, 1587.83, 1566.53, 1515.85, 1464.01, 1423.77 1371.34, 1303.53, 1248.04, 1198.02, 1091.18, 1035.17, 1016.30, 974.39, 908.30, 822.93, 725.53, 691.78, 606.55, 573.62.

Dimethyl 3,4-bis(trifluoromethylsulfonyloxy)furan-2,5-dicarboxylate (**156**)



To a solution of **141** (6.3 g, 29.1 mmol) and DMAP (244 mg, 2.0 mmol) in anhydrous CH_2Cl_2 (20 ml) stirring at 0 °C a solution of triflic anhydride (10.1 ml, 61.1 mmol) in CH_2Cl_2 (10 ml) was added drop wise. The solution was stirred for 30' then was diluted with Et_2O (40 ml) washed with 1N HCl aq., saturated NaHCO_3 aq., distilled H_2O , dried over MgSO_4 , filtered and concentrated at the rotary evaporator. Purification by CC on SiO_2 (pentane/ Et_2O : 6/4) afforded **156** as a white solid in 92% yield (12.8 mg, 26.8 mmol). Decomposition before melting 80-81 °C. ^1H -NMR (400 MHz, CDCl_3): δ 4.01 (*s*, 6H, H_a); ^{13}C -NMR (100 MHz, CDCl_3): δ 155.38, 136.21, 132.33, 118.20 (*q*, $J_{\text{C-F}} = 320$ Hz), 53.08; MS (ESI^+) found for $[\text{C}_{10}\text{H}_6\text{F}_6\text{O}_{11}\text{S}_2]^+$ 479.9247, calc. 479.9255; IR KBr (cm^{-1}) ν : 2383.52, 1758.65, 1732.95, 1618.71, 1561.07, 1443.55, 1332.25, 1311.62, 1251.12, 1213.13, 1135.29, 1062.71, 965.94, 938.58, 874.25, 851.35, 803.79, 770.98, 725.97, 656.49, 606.02, 572.31, 537.74.

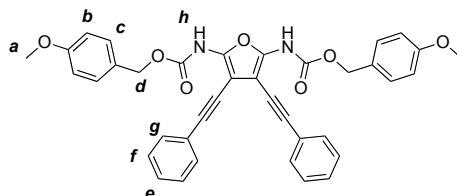
3,4-bis(phenylethynyl)furan-2,5-dicarboxylic acid (**158**)



To a solution of **157** (1.4 g, 4.5 mmol) in THF (2 ml) a 2N LiOH aq. solution (20 ml) was added, after stirring overnight at r.t. the mixture was cooled down to 0 °C and the pH was adjusted to 2 by addition of conc. HCl aq. The white precipitate was dried by azeotropic distillation with toluene. Yield 97% (1.2 g, 4.2 mmol). ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ 13.83 (*br*, 2H, H_a), 7.57-760 (*m*, 4H, H_d), 7.48-7.47 (*m*, 6H, $H_{b,c}$); ^{13}C -NMR (100 MHz, $\text{DMSO}-d_6$): δ 185.13, 148.87, 133.33, 127.48, 120.40, 118.60, 118.01, 100.00, 92.03; MS

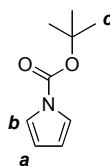
(ESI⁺) found for [C₂₂H₁₂O₅]⁺ 356.0687, calc. 356.0684; IR KBr (cm⁻¹) ν 3055.64, 2221.56, 1697.19, 1630.35, 1600.89, 1560.85, 1489.16, 1442.28, 1427.79, 1329.01, 1294.32, 1259.36, 1209.37, 1068.53, 1037.20, 998.97, 912.10, 863.54, 826.93, 753.01, 686.37, 544.23, 530.88.

4-methoxybenzyl 3,4-bis(phenylethynyl)furan-2,5-diyl dicarbamate (161)

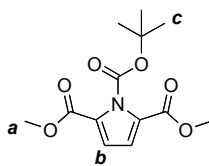


158 (290 mg, 0.81 mmol), PMBA (322 μ l, 2.4 mmol), and THF (2 ml) were subsequently charged into a microwave vessel, the vessel was hermetically capped and heated up in the microwave up at 120 °C for 5'. The crude mixture was then concentrated *in vacuo* and rapidly filtered through a short SiO₂ plug (cyclohexane : EtOAc = 7:3). Precipitation from EtOAc/pentane afforded **161** in 33% yield (212 mg, 0.34 mmol). Decomposition before melting (93 °C); ¹H-NMR (400 MHz, dms_o-d₆): δ 10.1 (*br*, 2H, *H_h*), 7.43 (*br*, 10H, *H_{e,f,g}*), 7.34 (*d*, *J* = 7.7 Hz, 4H, *H_c*), 6.88 (*d*, *J* = 7.7 Hz, 4H, *H_b*), 5.10 (*s*, 4H, *H_d*), 3.72 (*s*, *J* = 7.7 Hz, 4H, *H_a*), the spectra was recorded at 80 °C, due to the presence of rotamers, the structure at r.t. was unresolved; (ESI⁺) found for [C₃₈H₃₀N₂O₇ + Na]⁺ 649.1956, calc. 649.1945; IR KBr (cm⁻¹) ν 3219.47, 3005.65, 2837.20, 1708.09, 1612.14, 1587.21, 1465.86, 1442.58, 1374.42, 1302.58, 1282.24, 1245.38, 1214.62, 1176.73, 1115.78, 1069.23, 1028.62, 917.17, 823.51, 799.71, 780.30, 755.13, 687.78, 651.67, 635.85, 595.13, 556.69, 526.43, 438.36.

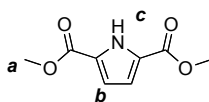
Tert-butyl 1*H*-pyrrole-1-carboxylate (162)



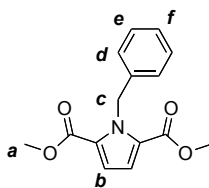
To a solution of pyrrole (11.0 g, 163.9 mmol) and di-*tert*-butyl dicarbonate (39.3 g, 180.3 mmol), in MeCN (100 ml), DMAP was added and the mixture was heated up to 60 °C and stirred for 8 hrs. The mixture was diluted with EtOAc (100 ml), washed with 1*N* HCl *aq.* (30 ml), sat. NaHCO₃ (30 ml) *aq.*, H₂O (30 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by CC on on Al₂O₃ (pentane/ Et₂O 5:5) afforded **162** as a colourless oil in 88% yield (24.0 g, 144 mmol). ¹H-NMR (400 MHz, CDCl₃): δ 7.24 (*t*, *J* = 2.0 Hz, 2H, *H_b*), 6.22 (*t*, *J* = 2.0 Hz, 2H, *H_a*), 1.60 (*s*, 9H, *H_c*); ¹³C-NMR (100 MHz, CDCl₃): δ 153.92, 122.43, 112.31, 53.16, 26.44. Spectral data in agreement with those previously reported.^[2]

1-*tert*-butyl 2,5-dimethyl 1*H*-pyrrole-1,2,5-tricarboxylate (163)

To a solution of (*i*-pr)₂NH (14.0 g, 138.3 mmol) in THF (200 ml) at $-78\text{ }^{\circ}\text{C}$ was added *n*-BuLi (86 mL of a 1.6 M solution in hexanes) dropwise via cannula. To the mixture was then added a solution of **162** (10.7 mL, 0.064 mol) in THF (45 mL) dropwise via cannula. The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 3 h before being transferred dropwise via a cooled cannula into a stirred solution of methyl chloroformate (14.8 mL, 0.19 mol) in THF (20 mL) $-78\text{ }^{\circ}\text{C}$. After 30' the reaction was quenched by addition of sat. NH₄Cl *aq.* (20 mL) diluted with EtOAc (100 ml), washed with 1*N* HCl *aq.* (100 ml), sat. NaHCO₃ (100 ml) *aq.*, H₂O (100 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by CC SiO₂ (cyclohexane/AcOEt 9:1) afforded **163** as a white solid in 61% yield (11.4 g, 40.1 mmol). m.p $77\text{--}78\text{ }^{\circ}\text{C}$; ¹H-NMR (400 MHz, CDCl₃): δ 6.83 (*s*, 2H, *H_b*), 3.86 (*s*, 6H, *H_a*), 1.66 (*s*, 9H, *H_c*); ¹³C-NMR (100 MHz, CDCl₃): δ 160.04, 148.85, 126.80, 115.94, 86.44, 52.15, 27.44. Spectral data in agreement with those previously reported.^[2]

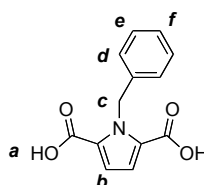
Dimethyl 1*H*-pyrrole-2,5-dicarboxylate (167)

To a solution of **163** (8.0 g, 28.3 mmol) in MeOH (20 ml), hydrazine monohydrate (5.0 g, 100 mmol) was added and the solution was stirred at r.t. for 15'. Concentration of the solvents *in vacuo* and precipitation of the residue with pentane afforded **167** as a white solid in 98% yield (5.1 g, 27.7 mmol). m.p $146\text{--}147\text{ }^{\circ}\text{C}$; ¹H-NMR (400 MHz, CDCl₃): δ 9.86 (*br*, 1H, *H_c*), 6.86 (*s*, 2H, *H_b*), 3.89 (*s*, 6H, *H_a*); ¹³C-NMR (100 MHz, CDCl₃): δ 160.88, 126.21, 115.68, 52.10. Spectral data in agreement with those previously reported.^[2]

Dimethyl 1-benzyl-1*H*-pyrrole-2,5-dicarboxylate (168)

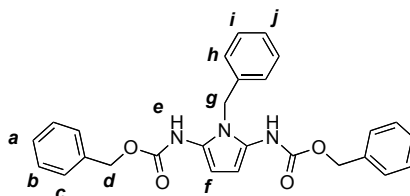
167 (3.4 g, 18.6 mmol) was added in portions to a suspension of NaH (489 mg, 20.4 mmol) in DMF (10 ml) at 0 °C. The mixture was then allowed to stir at r.t. for 30' then benzyl bromide (1.5 g 18.7 mmol) was added. After stirring overnight the reaction mixture was diluted with EtOAc (50 ml), washed with 1N HCl *aq.* (30 ml), sat. NaHCO₃ (30 ml) *aq.*, H₂O (30 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by CC on silica (cyclohexane/EtOAc : 8/2) afforded **168** as a white solid in 71% yield (3.6 g, 13.2 mmol). m.p. 111-112 °C; ¹H-NMR (400 MHz, CDCl₃): δ 7.27-7.19 (*m*, 3H, *H_{ef}*), 7.21 (*s*, 2H, *H_b*), 7.01-6.96 (*m*, 2H, *H_d*), 6.18 (*s*, 2H, *H_c*), 3.78 (*s*, 6H, *H_a*); ¹³C-NMR (100 MHz, CDCl₃): δ 161.05, 138.84, 128.49, 127.73, 127.02, 126.67, 117.16, 51.69, 49.30. Spectral data in agreement with those previously reported.^[3]

1-benzyl-1*H*-pyrrole-2,5-dicarboxylic acid (**170**)



A 2N LiOH *aq.* solution (20 ml) was added to a solution of **168** (2.3 g, 8.4 mmol) in THF (2 ml) and stirred at r.t. overnight. The mixture was then cooled down to 0 °C and conc. HCl *aq.* added until the formation of a white precipitate that was collected by suction filtration. Re-crystallization from MeOH afforded **170** as a white solid in 94% yield (1.9 g, 7.9 mmol). m.p. 172-174 °C; ¹H-NMR (400 MHz, DMSO-*d*₆): δ 13.39 (*s*, 2H, *H_a*), δ 7.37-7.30 (*m*, 3H, *H_{ef}*), 7.21 (*s*, 2H, *H_b*), 6.90-6.84 (*m*, 2H, *H_d*), 5.92 (*s*, 2H, *H_c*); ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 161.13, 137.43, 130.38, 128.64, 128.32, 124.12, 58.28, 51.67. Spectral data in agreement with those previously reported.^[3]

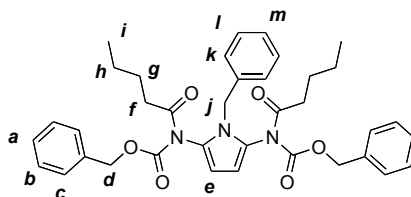
Benzyl 1-benzyl-1*H*-pyrrole-2,5-diylldicarbamate (**172**)



To a solution of **170** (890 mg, 3.6 mmol) in anhydrous THF (30 ml) stirring at 0 °C, DMF (200 μl) and (COCl)₂ (762 μl, 9.0 mmol) were subsequently added and the mixture stirred for 3 hrs. The solvents were then removed *in vacuo* and the residue re-dissolved in 20 ml of anhydrous THF. The resulting solution was added drop wise to a saturated NaN₃ *aq.* solution (4 ml), stirred for 30', diluted with Et₂O (50 ml), and then washed with sat. NaHCO₃ *aq.* (50 ml), H₂O (2 x 50ml), dried over MgSO₄, and concentrated *in vacuo* at 25 °C to an

approximate volume of about 5 ml. This solution was added drop wise to a flask containing a solution of benzyl alcohol (2.7 ml, 36.3 mmol) in mesitylene (5ml) at 130 °C stirred for 5', allowed to cool down to room temperature and then poured into pentane (100 ml). The precipitate was collected by suction filtration and purified by CC on SiO₂ (cyclohexane/EtOAc : 7/3). White solid, 56% yield (917 mg, 2.0 mmol). m.p. 178-180 °C; ¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.98 (*br*, 2H, *H_e*), 7.33 (*br*, 9H, *H_{a,b,i,j}*), 7.20-7.19 (*m*, 4H, *H_c*) 7.00-6.98 (*m*, 2H, *H_h*), 5.81 (*s*, 2H, *H_f*), 5.02 (*br*, 4H, *H_d*), 4.89 (*s*, 2H, *H_g*), the spectra was recorded at 80 °C, due to the presence of rotamers, the structure at r.t. was unresolved; ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 154.96, 138.28, 136.57, 128.13, 127.87, 127.61, 127.44, 126.56, 126.53, 123.78, 101.85, 65.60, 44.63; MS (APCI⁺) found for [C₂₇H₂₅N₃O₄ + H]⁺ 456.1918, calc. 456.1914; IR KBr (cm⁻¹) ν: 3286.61, 3033.45, 2359.70, 1715.34, 1703.53, 1585.27, 1543.89, 1519.63, 1455.69, 1420.50, 1313.25, 1248.30, 1214.71, 1150.32, 1093.48, 1074.57, 985.21, 920.56, 864.32, 818.45, 742.81, 695.53, 677.84, 584.26, 507.43, 480.72.

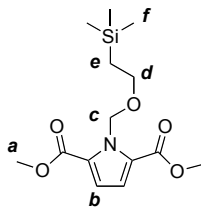
Benzyl 1-benzyl-1*H*-pyrrole-2,5-diylbis(pentanoylcarbamate) (**174**)



172 (400 mg, 0.9 mmol), DMAP (36 mg, 0.3 mmol), pyridine (10 ml) and valeric anhydride (890 μl, 4.5 mmol) were subsequently charged into a microwave vessel, the vessel was hermetically capped and heated up in the microwave up at 60 °C with a constant irradiation power of 60 watts for 30'. The mixture was diluted with EtOAc (50 ml), washed with 1*N* HCl *aq.* (30 ml), sat. NaHCO₃ (30 ml) *aq.*, H₂O (30 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by CC on SiO₂ (cyclohexane/EtOAc : 8/2) afforded **174** as a colorless oil in 73% yield (400 mg, 0.64 mmol); ¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.33-7.24 (*m*, 9H, *H_{a,b,l,m}*), 7.17-7.09 (*m*, 4H, *H_c*), 6.99-6.97 (*m*, 2H, *H_k*), 6.04 (*s*, 2H, *H_e*), 5.05 (*s*, 4H, *H_d*), 4.59 (*s*, 2H, *H_j*), 2.54 (*t*, *J* = 7.1 Hz, 4H, *H_f*), 1.41 (*tt*, *J₁* = 7.1 Hz, *J₂* = 7.2 Hz, 4H, *H_g*), 1.24-1.18 (*m*, 4H, *H_h*), 0.81 (*t*, *J* = 7.3 Hz, 6H, *H_i*), the spectra was recorded at 100 °C, due to the presence of rotamers, the structure at r.t. was unresolved; ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 174.57, 152.68, 135.88, 135.32, 135.18, 128.39, 128.01, 127.57, 127.40, 127.21, 124.00, 105.69, 68.30, 40.45, 38.61, 26.82, 22.10, 14.29; MS (ESI⁺) found for [C₃₇H₄₁N₃O₆ + Na]⁺ 646.2888, calc. 646.2877; IR KBr (cm⁻¹) ν: 3035.11, 2960.23, 2874.06, 1781.43, 1742.14, 1575.55, 1514.65, 1498.24, 1457.07, 1444.35, 1429.62, 1457.07, 1429.62, 1379.28, 1345.98, 1277.63, 1212.45, 1159.11, 1119.08, 1084.12, 1027.61, 995.93, 907.66, 880.84,

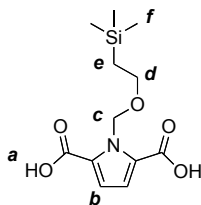
812.69, 765.12, 734.23, 696.34, 615.23, 598.95, 560.34, 503.65, 476.58, 453.04, 431.66, 419.28.

Dimethyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrole-2,5-dicarboxylate (169)



169 (3.4 g, 18.6 mmol) was added in portions to a suspension of NaH (489 mg, 20.4 mmol) in DMF (10 ml) at 0 °C. The mixture was then allowed to stir at r.t. for 30' then Sem-Cl (3.3 ml, 18.6 mmol) was added. After stirring overnight the reaction mixture was diluted with EtOAc (50 ml), washed with 1N HCl *aq.* (30 ml), sat. NaHCO₃ (30 ml) *aq.*, H₂O (30 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by CC on silica (cyclohexane/EtOAc : 8/2) **169** as a colorless oil in 71% yield. (3.6 g, 13.2 mmol). ¹H-NMR (400 MHz, CDCl₃): δ 6.92 (*s*, 2H, H_b), 6.24 (*s*, 2H, H_c), 3.85 (*s*, 6H, H_a), 3.52 (*t*, *J* = 8.2 Hz, 2H, H_d), 0.86 (*t*, *J* = 8.2 Hz, 2H, H_e), -0.07 (*s*, 9H, H_f); ¹³C-NMR (100 MHz, CDCl₃): δ 161.27, 128.19, 117.72, 76.95, 65.99, 51.96, 18.03, -1.29; MS (ESI⁺) found for [C₁₄H₂₃NO₅Si + Na]⁺ 336.1244, calc. 336.1238; IR KBr (cm⁻¹) ν: 2953.12, 2865.13, 1733.81, 1712.21, 1528.57, 1436.18, 1375.41, 1295.18, 1233.48, 1195.42, 1169.59, 1096.74, 1075.51, 990.49, 949.70, 859.35, 836.30, 809.49, 757.13, 650.12, 492.05, 467.10, 418.15;

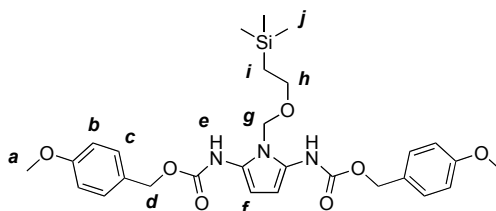
1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrole-2,5-dicarboxylic acid (177)



A 2N LiOH *aq.* solution (20 ml) was added to a solution of **169** (1.4 g, 4.5 mmol) in THF (2 ml) and stirred at r.t. overnight. The mixture was then cooled down to 0 °C and conc. HCl *aq.* added in until the formation of a white precipitate that was collected by suction filtration. White solid, 97% yield (1.2 g, 4.2 mmol). m.p 76-78 °C; ¹H-NMR (400 MHz, DMSO-*d*₆): δ 12.95 (*s*, 2H, H_a), 6.86 (*s*, 2H, H_b), 6.15 (*s*, 2H, H_c), 3.42 (*t*, *J* = 7.8 Hz, 2H, H_d), 0.75 (*t*, *J* = 7.8 Hz, 2H, H_e), -0.12 (*s*, 9H, H_f); ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 161.62, 128.57, 116.97, 72.59, 64.56, 17.19, -1.14; MS (ESI⁻) found for [C₁₂H₁₉NO₅Si + Cl]⁻ 284.1243, calc. 284.1250; IR KBr (cm⁻¹) ν: 2992.45 2953.69, 2895.38, 2614.84, 2559.16, 1859.87, 1707.87, 1668.28, 1519.17, 1455.08, 1418.07, 1374.69, 1289.48, 1245.49, 1194.70, 1139.86, 1104.65,

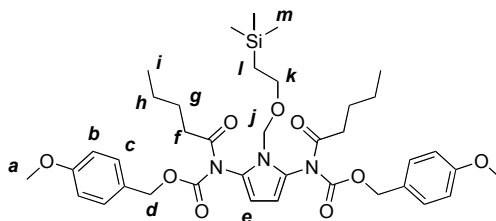
1088.89, 1034.52, 939.59, 914.84, 861.98, 837.91, 819.04, 780.92, 758.32, 703.44, 694.51, 610.18, 536.54, 504.56, 413.20.

4-methoxybenzyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrole-2,5-diylidicarbamate (179)



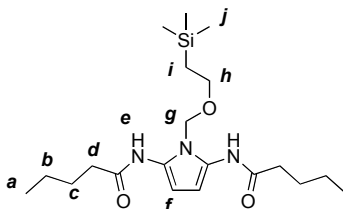
To a solution of **177** (1.0 g, 3.5 mmol) in anhydrous THF (30 ml) stirring at 0 °C, DMF (200 μ l) and (COCl)₂ (2.3 ml, 26.6 mmol) were subsequently added and the mixture stirred for 3 hrs. The solvents were then removed *in vacuo* and the residue re-dissolved in 20 ml of anhydrous THF. The resulting solution was added drop wise to a saturated NaN₃ aq. solution (4 ml), stirred for 30', diluted with Et₂O (50 ml), and then washed with sat. NaHCO₃ aq. (50 ml), H₂O (2 x 50ml), dried over MgSO₄, and concentrated *in vacuo* at 25 °C to an approximate volume of about 5 ml. This solution was added drop wise to a flask containing a solution of PMBA (1.2 ml, 10.5 mmol) in mesitylene (5ml) at 130 °C stirred for 5', allowed to cool down to room temperature and then poured into pentane (100 ml). The precipitate was collected by suction filtration and purified by CC on SiO₂ (cyclohexane/EtOAc : 7/3). 52% yield (1.0 g, 1.9 mmol). m.p. 121-122 °C; ¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.94 (*br*, 2H, *H_e*), 7.32 (*d*, *J* = 8.2 Hz, 4H, *H_c*), 6.92 (*d*, *J* = 8.2 Hz, 4H, *H_b*), 5.77 (*s*, 2H, *H_f*), 5.00 (*s*, 4H, *H_d*), 4.96 (*s*, 2H, *H_g*), 3.75 (*s*, 6H, *H_a*), 3.28 (*t*, *J* = 7.1 Hz, 2H, *H_h*), 0.73 (*t*, *J* = 7.1 Hz, 2H, *H_i*), -0.06 (*s*, 9H, *H_j*); ¹³H-NMR (100 MHz, DMSO-*d*₆): δ 159.62, 155.74, 130.43, 129.05, 123.83, 114.29, 102.63, 70.48, 66.29, 65.28, 55.61, 17.81, -0.89; MS (ESI⁺) found for [C₂₈H₃₇N₃O₇Si]⁺ 55.2398, calc. 55.2400; IR KBr (cm⁻¹) ν : 3605.84, 3443.17, 3261.93, 2999.61, 2953.19, 2897.95, 2835.60, 1884.98, 1697.00, 1613.66, 1588.23, 1517.60, 1466.00, 1441.11, 1418.61, 1367.75, 1303.74, 1292.57, 1248.40, 1219.09, 1135.05, 1081.59, 1064.68, 1037.38, 961.46, 851.92, 833.70, 771.59, 758.53, 738.14, 709.99, 680.37, 610.36, 557.15, 521.92, 443.99.

4-methoxybenzyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrole-2,5-diylbis(pentanoylcarbamate) (180)



179 (700 mg, 1.26 mmol), DMAP (36 mg, 0.3 mmol), pyridine (10 ml) and valeric anhydride (880 μ l, 4.4 mmol) were subsequently charged into a microwave vessel. The vessel was hermetically capped and heated in the microwave at 60 °C with a constant irradiation power of 60 watts for 30'. The mixture was diluted with EtOAc (50 ml), washed with 1N HCl *aq.* (30 ml), sat. NaHCO₃ (30 ml) *aq.*, H₂O (30 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by CC on SiO₂ (cyclohexane/EtOAc : 8/2) afforded **180** as a colorless oil in 68% yield (619 mg, 0.85 mmol). ¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.15 (*d*, *J* = 8.7 Hz, 4H, *H_c*), 6.84 (*d*, *J* = 8.7 Hz, 4H, *H_b*), 5.96 (*s*, 2H, *H_e*), 0.86 (*s*, 4H, *H_d*), 4.67 (*s*, 2H, *H_j*), 3.70 (*s*, 6H, *H_a*), 3.25 (*t*, *J* = 8.2 Hz, 2H, *H_k*), 2.66 (*t*, *J* = 7.1 Hz, 4H, *H_f*), 1.48 (*tt*, *J*₁ = 7.1 Hz, *J*₂ = 7.3 Hz, 4H, *H_g*), 1.29-1.21 (*m*, 4H, *H_h*), 0.81 (*t*, *J* = 7.3 Hz, 6H, *H_i*), 0.62 (*t*, *J* = 8.2 Hz, 2H, *H_l*), -0.11 (*s*, 9H, *H_m*), the spectra was recorded at 100 °C, due to the presence of rotamers, the structure at r.t. was unresolved; ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 175.80, 160.07, 153.78, 130.05, 127.60, 124.69, 114.31, 107.01, 72.45, 68.73, 66.91, 55.63, 31.38, 27.22, 22.69, 18.09, 14.33, -0.88; MS (ESI⁺) found for [C₃₈H₅₃N₃O₉Si + Na]⁺ 746.3447, calc. 746.3443; IR KBr (cm⁻¹) ν : 2957.50, 2973.58, 2837.63, 1784.29, 1734.38, 1613.82, 1585.61, 1515.39, 1464.90, 1405.31, 1377.18, 1247.60, 1176.29, 1081.70, 1035.03, 980.37, 940.24, 923.89, 860.22, 835.35, 769.35, 694.43, 667.87, 637.00, 613.04, 576.30, 522.15, 494.17, 483.01.

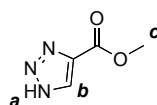
***N,N'*-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrole-2,5-diyl)dipentanamide (182)**



To a solution of **180** (508 mg, 0.7 mmol) in CH₂Cl₂ (5 ml), stirring at 0 °C anisole (2.2 ml, 21 mmol) and TFA (1.5 ml) were subsequently added and the solution stirred for 2 hrs. The mixture was diluted with EtOAc (50 ml), washed with sat. NaHCO₃ (30 ml) *aq.*, H₂O (2 x 30 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by CC on SiO₂ (cyclohexane/EtOAc : 7/3) afforded **182** as a white solid in 49% yield (135 mg, 0.34 mmol). m.p. 136-138 °C; ¹H-NMR (400 MHz, DMSO-*d*₆): δ 9.00 (*br*, 2H, *H_e*), 5.76 (*s*, 2H, *H_f*), 4.95

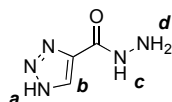
(*s*, 2H, H_g), 3.35 (*t*, $J = 8.0$ Hz, 2H, H_h), 2.21-2.18 (*m*, 4H, H_d), 1.53 (*br*, 4H, H_c), 1.30 (*m*, 4H, H_b), 0.86 (*m*, 6H, H_a), 0.77 (*t*, $J = 8.0$ Hz, 2H, H_i), -0.05 (*s*, 9H, H_j); ^{13}C -NMR (100 MHz, DMSO- d_6): δ 172.84, 123.95, 102.09, 70.64, 54.49, 35.51, 27.65, 22.49, 18.06, 14.38. -1.09; MS (ESI $^+$) found for $[\text{C}_{20}\text{H}_{37}\text{N}_3\text{O}_3\text{Si} + \text{Na}]^+$ 418.2496, calc. 418.2500; IR KBr (cm^{-1}) ν : 3250.78, 2956.52, 2930.60, 2873.74, 1656.50, 1584.24, 1559.14, 1526.22, 1466.80, 1415.99, 1370.49, 1290.67, 1263.87, 1250.31, 1188.93, 1061.27, 861.92, 836.47, 757.25, 700.12, 663.84, 612.45, 598.65, 570.31, 564.28, 511.19, 489.99.

Methyl 1*H*-1,2,3-triazole-4-carboxylate (**188**)



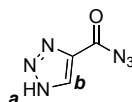
TMS- N_3 (5.0 g, 43.4 mmol) and methyl propiolate (1.74 g, 20.7 mmol) were subsequently charged into a resealable Schlenk vessel. The vessel was sealed and the mixture heated at 110° C for 24 hrs allowed to reach r.t. and poured into cold MeOH (15 ml). The precipitate formed was collected by suction filtration. Re-crystallization from MeOH afforded **188** as a white solid in 65% yield (1.7 g, 28.2 mmol) m.p. 117-118 °C; ^1H -NMR (400 MHz, CDCl_3): δ 15.72 (*br*, 1H, H_a), 8.60 (*s*, 1H, H_b), 6.35 (*s*, 2H, H_e), 3.80 (*s*, 3H, H_c); ^{13}C -NMR (100 MHz, CDCl_3): δ 161.53, 138.25, 139.03. Spectral data in agreement with those previously reported.^[8]

1*H*-1,2,3-triazole-4-carbohydrazide (**189**)



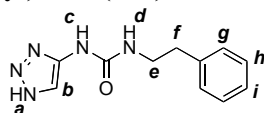
NH_2NH_2 (64% in H_2O) (1.7 g, 28.2 mmol) was added to a suspension of **188** (2.0 g, 40 mmol) in EtOH (20 ml), and the mixture was refluxed for 48 hrs. The solution was then cooled down at -20 °C and the white precipitate was collected by suction filtration and thoroughly washed with H_2O , MeOH, Et $_2\text{O}$. White solid, 92% yield (920 mg, 36.8 mmol). m.p. 250-251 °C; ^1H -NMR (400 MHz, DMSO- d_6): δ 15.42 (*br*, 1H, H_a), 9.68 (*br*, 1H, H_c), 8.27 (*s*, 1H, H_b), 4.44 (*br*, 2H, H_d); 3.80; ^{13}C -NMR (100 MHz, DMSO- d_6): δ 162.17, 139.89, 130.75. Spectral data in agreement with those previously reported.^[6]

1*H*-1,2,3-triazole-4-carbonyl azide (**190**)



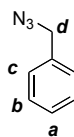
1.2 ml of HCl *aq.* (37%) were added to a suspension of **189** (200 mg, 1.57 mmol), in H₂O (10 ml) at 0 °C. NaNO₂ was added in portions (110 mg, 1.57 mmol) and the mixture stirred for 2 hrs. The pH was adjusted to ca.7 with the addition of 1N Na₂CO₃ *aq.* The obtained precipitate was filtered off, dissolved in CHCl₃ dried over MgSO₄ and concentrated *in vacuo*. White solid, 70% yield (152 mg, 1 mmol). ¹H-NMR (400 MHz, CDCl₃): δ 15.59 (*br*, 1H, *H_a*), 8.68 (*s*, 1H, *H_c*); ¹³C-NMR (100 MHz, CDCl₃): δ 166.23, 139.64, 131.84. Spectral data in agreement with those previously reported.^[6]

1-phenethyl-3-(1*H*-1,2,3-triazol-4-yl)urea (**192**)

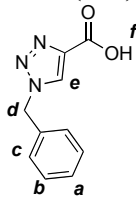


1N NaOH *aq.* (0.32 μl, 0.32 mmol) was added to a solution of **208** (50 mg, 0.15 mmol), in MeOH (3 ml) and the solution was stirred at r.t. for 10', the reaction was then quenched with the addition of sat. NH₄Cl *aq.* (5 ml). The mixture was diluted with AcOEt washed with H₂O (3 x 10 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. Precipitation from CHCl₃/pentane afforded **192** as a white solid in 45% yield (15 mg, 0.15 mmol). m.p. 173-174°C; ¹H-NMR (400 MHz, DMSO-*d*₆): δ 14.13 (*s*, 1H, *H_a*), 9.01 (*s*, 1H, *H_c*), 7.71 (*s*, 1H, *H_b*), 7.27-7.25 (*m*, 3H, *H_{h,i}*), 7.20-7.17 (*m*, 2H, *H_g*), 6.25 (*br*, 1H, *H_d*), 3.37-3.31 (*m*, 2H, *H_e*), 2.73 (*t*, *J* = 7.1 Hz, 2H, *H_f*); ¹³C-NMR (100 MHz, DMSO-*d*₃): δ 207.05, 154.85, 139.97, 129.22, 128.90, 126.63, 41.28, 36.37, 31.23; MS (APCI⁺) found for [C₁₁H₁₃N₅O + H]⁺ 232.1190, 232.1190; IR KBr (cm⁻¹) ν: 3313.9, 3012.14, 2746.6, 1692.1, 1645.6, 1567.2, 1536.7, 1252.3, 1107.3, 1091.4, 1014.4, 927.03.

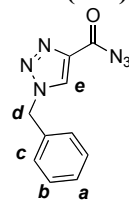
(Azidomethyl)benzene (**194**)



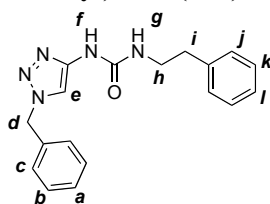
NaN₃ (3.5 g, 52 mmol) was added to a solution of benzylbromide (4.4 ml, 26 mmol) in DMF (5 ml) and the mixture was stirred at 65 °C for 12 hrs. The mixture was diluted with EtOAc (50 ml), washed with 1N HCl *aq.* (30 ml), sat. NaHCO₃ (30 ml) *aq.*, H₂O (30 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. Yellowish liquid, 80% yield (2.75 g, 20.8 mmol). ¹H-NMR (400 MHz, CDCl₃): δ 7.38-7.25 (*m*, 5H, *H_{a,b,c}*), 4.33 (*s*, 2H, *H_d*); ¹³C-NMR (100 MHz, CDCl₃): δ 138.95, 128.61, 127.93, 125.77, 55.23. Spectral data in agreement with those previously reported.^[9]

1-benzyl-1H-1,2,3-triazole-4-carboxylic acid (195)

$\text{CuSO}_4 \times 5 \text{ H}_2\text{O}$ (127 mg, 0.5 mmol) and Na ascorbate (401 mg, 2 mmol) were subsequently added to a solution of **194** (1.75 g, 10.1 mmol) and propiolic acid (780 mg, 11.1 mmol) in a 3 to 1 *t*-BuOH/ H_2O mixture (10 ml). The mixture was stirred at r.t. for 12 hrs then was diluted with CHCl_3 (50 ml) washed with sat. NH_4Cl *aq.* (2 x 40 ml), H_2O , dried over MgSO_4 , filtered and concentrated *in vacuo*. Precipitation from CH_2Cl_2 /pentane afforded **195** as a white solid in 70% yield (1.7 g, 7.0 mmol). m.p. 102-103°C; ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ 13.07 (*br*, 1H, H_f), 8.74 (*s*, 1H, H_e), 7.33-7.31 (*m*, 5H, $H_{a,b,c}$), 5.60 (*s*, 2H, H_d); ^{13}C -NMR (100 MHz, $\text{DMSO}-d_6$): δ 162.14, 140.42, 136.12, 129.56, 129.37, 128.83, 128.55, 53.56. Spectral data in agreement with those previously reported.^[10]

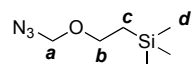
1-benzyl-1H-1,2,3-triazole-4-carbonyl azide (196)

To a solution of **195** (500 mg, 2.5 mmol) in anhydrous THF (30 ml) stirring at 0 °C, DMF (200 μl) and $(\text{COCl})_2$ (313 μl , 3.7 mmol) were subsequently added and the mixture stirred for 3 hrs. The solvents were then removed *in vacuo* and the residue re-dissolved in 20 ml of anhydrous THF. The resulting solution was added drop wise to a saturated NaN_3 *aq.* solution (4 ml), stirred for 30', diluted with Et_2O (50 ml), and then washed with sat. NaHCO_3 *aq.* (50 ml), H_2O (2 x 50ml), dried over MgSO_4 , and concentrated *in vacuo*. White solid, 90% yield (510 mg, 2.7 mmol). m.p. 102-103°C; ^1H -NMR (400 MHz, CDCl_3): 8.67 (*s*, 1H, H_e), 7.34-7.30 (*m*, 5H, $H_{a,b,c}$), 5.80 (*s*, 2H, H_d); ^{13}C -NMR (100 MHz, CDCl_3): δ 165.83, 141.23, 133.40, 129.52, 129.44, 128.46, 127.91, 54.76. Spectral data in agreement with those previously reported.^[10]

1-benzyl-3-(1-benzyl-1H-1,2,3-triazol-4-yl)urea (198)

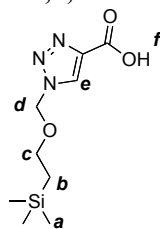
196 (150 mg, 0.66 mmol) and 1,4-dioxane (8 ml) were subsequently charged into a microwave vessel, the vessel was hermetically capped and heated in the microwave at 140 °C for 2 hrs. After cooling to r.t. phenethylamine (800 µl, 6.6 mmol) was added. The mixture was stirred at r.t. for 12 hrs and then poured into cold pentane (20 ml). Re-crystallization from MeCN of the precipitate collected afforded **198** as a white solid in 25% yield (53 mg, 0.16 mmol). m.p. 172-173°C ; ¹H-NMR (400 MHz, DMSO-*d*₆): δ 9.01 (*s*, 1H, *H_c*), 7.71 (*s*, 1H, *H_e*), 7.33-7.28 (*m*, 10H, *H_{a,b,c,j,k,l}*), 6.25 (*br*, 1H, *H_d*), 5.58 (*s*, 2H, *H_d*), 3.37-3.31 (*m*, 2H, *H_h*), 2.73 (*t*, *J* = 7.1 Hz, 2H, *H_i*); (100 MHz, DMSO-*d*₆): δ 154.33, 139.4, 134.01, 133.75, 130.66, 128.66, 127.81, 127.59, 126.43, 125.89, 125.22, 56.99, 41.52, 34.66. MS (APCI⁺) found for [C₁₈H₁₉N₅O₃ + H]⁺ 322.1740, calc. 322.1738; IR KBr (cm⁻¹) ν: 3713.3, 3329.6, 3090.9, 2563.5, 1674.4, 1589.3, 1496.0, 1451.86, 850.7, 822.6, 719.3, 698.3.

(2-(azidomethoxy)ethyl)trimethylsilane (200)



Sem-Cl (940 mg, 5.6 mmol) was added dropwise to a suspension of NaN₃ (1.5 g, 23 mmol), in anhydrous DMSO (3 ml) at r.t. and stirred for 12 hrs. The mixture was diluted with EtOAc (50 ml), washed with 1N HCl *aq.* (30 ml), sat. NaHCO₃ (30 ml) *aq.*, H₂O (30 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. Colourless liquid, 83% yield (825 mg, 4.6 mmol). ¹H-NMR (400 MHz, CDCl₃): δ 4.23 (*s*, 4H, *H_a*), 3.40 (*t*, *J* = 8.3 Hz, 2H, *H_b*), 0.79(*t*, *J* = 8.3 Hz, 2H, *H_c*), 0.01 (*s*, 9H, *H_d*); ¹³C-NMR (100 MHz, CDCl₃): δ 78.45, 67.40, 19.69, -1.11. Spectral data in agreement with those previously reported.^[11]

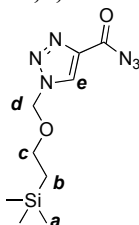
1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,3-triazole-4-carboxylic acid (201)



CuSO₄ × 5 H₂O (127 mg, 0.5 mmol) and Na ascorbate (401 mg, 2 mmol) were subsequently added to a solution of **200** (1.75 g, 10.1 mmol) and propiolic acid (780 mg, 11.1 mmol) in a 3:1 *t*-BuOH/H₂O mixture (10 ml). The mixture was stirred at r.t. for 12 hrs then was diluted with CHCl₃ (50 ml) washed with sat. NH₄Cl *aq.* (2 × 40 ml), H₂O, dried over MgSO₄, filtered and concentrated *in vacuo*. Precipitation from CH₂Cl₂/pentane afforded **201** as a white solid in 70% yield (1.7 g, 7.0 mmol). m.p. 156-157° C. ¹H-NMR (400 MHz, CDCl₃): δ 9.79 (*br*, 1H, *H_f*), 8.35 (*s*, 1H, *H_e*), 5.75 (*s*, 2H, *H_d*), 3.62 (*t*, *J* = 8.5 Hz, 2H, *H_c*), 0.93 (*t*, *J* = 8.5 Hz, 2H,

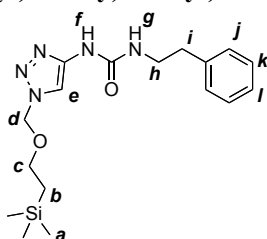
H_b), 0.01 (s, 9H, H_a); ^{13}C -NMR (100 MHz, CDCl_3): δ 164.20, 140.09, 128.28, 79.05, 68.27, 17.83, -1.40; MS (APCI) found for $[\text{C}_9\text{H}_{17}\text{N}_3\text{O}_3\text{Si} + \text{Cl}]^-$ 278.0743, calc. 278.0733; IR KBr (cm^{-1}) ν : 3726.01, 3113.4, 2953.8, 2902.4, 2742.2, 2636.6, 2554.7, 1688.5, 1555.9, 1435.4, 1251.6, 1126.7, 1099.9, 1054.9, 836.9.

1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,3-triazole-4-carbonyl azide (202)



To a solution of **201** (1.5 g, 6.17 mmol) in anhydrous THF (30 ml) stirring at 0 °C, DMF (200 μl) and $(\text{COCl})_2$ (600 μl , 7.4 mmol) were subsequently added and the mixture stirred for 3 hrs. The solvents were then removed *in vacuo* and the residue re-dissolved in 20 ml of anhydrous THF. The resulting solution was added drop wise to a saturated NaN_3 aq. solution (4 ml), stirred for 30', diluted with Et_2O (50 ml), and then washed with sat. NaHCO_3 aq. (50 ml), H_2O (2 x 50ml), dried over MgSO_4 , and concentrated *in vacuo*. White solid, 88% yield (1.4 g, 5.4 mmol). m.p. 102-103°C ; ^1H -NMR (400 MHz, CDCl_3): 8.30 (s, 1H, H_e), 5.71 (s, 2H, H_d), 3.57 (t, $J = 8.5$ Hz, 2H, H_c), 0.88 (t, $J = 8.5$ Hz, 2H, H_b), -0.01 (s, 9H, H_a); ^{13}C -NMR (100 MHz, CDCl_3): δ 165.74, 141.68, 127.90, 79.02, 68.23, 17.80, -1.43; MS (APCI $^+$) found for $[\text{C}_9\text{H}_{16}\text{N}_6\text{O}_2\text{Si} + \text{H}]^+$ 270.1257, calc. 270.1250; IR KBr (cm^{-1}) ν : 3089.5, 2952.6, 2146.4, 1703.2, 1527.0, 1360.4, 1237.8, 1213.1, 1110.9, 1063.7, 862.7, 836.1, 755.7

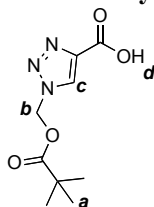
1-phenethyl-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,3-triazol-4-yl)urea (203)



202 (600 mg, 2.2 mmol) and 1,4-dioxane (8 ml) were subsequently charged into a microwave vessel, the vessel was hermetically capped and heated in the microwave at 140 °C for 2 hrs. After cooling to r.t. phenethylamine (320 μl , 2.6 mmol) was added. The mixture was stirred at r.t. for 12 hrs and then poured into cold pentane (20 ml). Re-crystallization from MeCN of the precipitate collected afforded **203** as a white solid in 47% yield (358 mg, 1.0 mmol). m.p. 102-103°C ; ^1H -NMR (400 MHz, CDCl_3): δ 9.55 (s, 1H, H_f), 7.77 (s, 1H, H_e), 7.29-7.20 (m, 3H, $H_{k,l}$), 7.19-7.17 (m, 2H, H_j), 6.07 (br, 1H, H_g), 5.55 (s, 2H, H_d), 3.62 (t, $J = 8.5$ Hz, 2H, H_c), 3.32-3.27 (m, 2H, H_i), 2.27 (t, $J = 7.2$ Hz, 2H, H_h), 0.93 (t, $J = 8.5$ Hz, 2H, H_b), 0.01 (s,

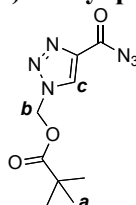
9H, H_a); ^{13}C -NMR (100 MHz, CDCl_3): δ 154.32, 139.46, 133.21, 131.32, 129.10, 127.77, 125.98, 79.90, 66.99, 41.53, 34.76, 23.75, -1.36; MS (APCI $^+$) found for $[\text{C}_{17}\text{H}_{27}\text{N}_5\text{O}_2\text{Si} + \text{Na}]^+$ 384.1836, calc. 384.1826; IR KBr (cm^{-1}) ν : 3725.1, 3098.7, 2945.5, 2172.1, 1700.9, 1677.3, 1525.0, 1349.8, 1250.6, 1210.8, 1120.0, 1063.7, 868.2, 811.1.

1-(pivaloyloxymethyl)-1H-1,2,3-triazole-4-carboxylic acid (206)

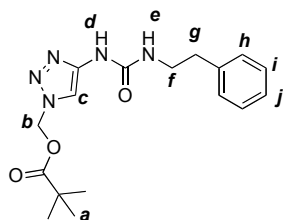


$\text{CuSO}_4 \times 5 \text{ H}_2\text{O}$ (180 mg, 0.72 mmol) and Na ascorbate (571 mg, 2.9 mmol) were subsequently added to a solution of **205** (2.25 g, 14.3 mmol), and propiolic acid (1.11 g, 15.9 mmol) in a 3:1 *t*-BuOH/ H_2O mixture (10 ml). The mixture was stirred at r.t. for 12 hrs then was diluted with CHCl_3 (50 ml) washed with sat. NH_4Cl *aq.* (2 x 40 ml), H_2O , dried over MgSO_4 , filtered and concentrated *in vacuo*. Precipitation from CH_2Cl_2 /pentane afforded **206** as a white solid in 82% yield (2.6 g, 11.7 mmol). m.p. 149-150° C, ^1H -NMR (400 MHz, CDCl_3): δ 9.85 (*br*, 1H, H_d), 8.45 (*s*, 1H, H_c), 6.29 (*s*, 2H, H_b), 1.19 (*s*, 9H, H_a), ^{13}C -NMR (100 MHz, CDCl_3): δ 177.87, 163.92, 139.71, 130.12, 69.87, 38.92, 26.86; Spectral data in agreement with those previously reported.^[12]

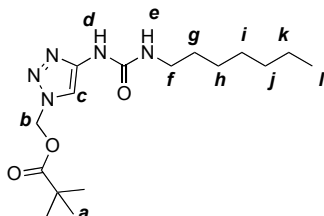
(4-(azidocarbonyl)-1H-1,2,3-triazol-1-yl)methyl pivalate (207)



To a solution of **206** (2.15 g, 9.47 mmol) in anhydrous THF (30 ml) stirring at 0 °C, DMF (200 μl) and $(\text{COCl})_2$ (1.0 ml, 11.4 mmol) were subsequently added and the mixture stirred for 3 hrs. The solvents were then removed *in vacuo* and the residue re-dissolved in 20 ml of anhydrous THF. The resulting solution was added drop wise to a sat. NaN_3 *aq.* solution (4 ml), stirred for 30', diluted with Et_2O (50 ml), and then washed with sat. NaHCO_3 *aq.* (50 ml), H_2O (2 x 50ml), dried over MgSO_4 , and concentrated *in vacuo*. White solid, 90% yield (2.1 g, 8.5 mmol). decomposition before melting; ^1H -NMR (400 MHz, CDCl_3): δ 8.40 (*s*, 1H, H_c), 6.26 (*s*, 2H, H_b), 1.18 (*s*, 9H, H_a), ^{13}C -NMR (100 MHz, CDCl_3): δ 177.94, 165.62, 141.42, 129.82, 69.82, 38.91, 26.84; MS (APCI $^+$) found for $[\text{C}_9\text{H}_{12}\text{N}_6\text{O}_3 + \text{H}]^+$ 253.0982, calc. 253.1044; IR KBr (cm^{-1}) ν : 3126.42, 2982.03, 2165.12, 1743.45, 1701.25, 1544.87, 1344.93, 1229.71, 1137.83, 1001.54, 954.65.

(4-(3-phenethylureido)-1H-1,2,3-triazol-1-yl)methyl pivalate (208)

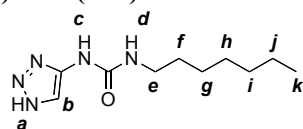
207 (300 mg, 1.19 mmol) and 1,4-dioxane (6 ml) were subsequently charged into a microwave vessel, the vessel was hermetically capped and heated in the microwave at 140 °C for 2 hrs. After cooling to r.t. phenethylamine (216 mg, 1.79 mmol) was added. The mixture was stirred at r.t. for 12 hrs and then concentrated *in vacuo*. Purification by CC on SiO₂ (cyclohexane/EtOAc : 6/4) afforded **208** as a white solid in 40% yield (172 mg, 0.5 mmol) m.p. 115-116 °C; ¹H-NMR (400 MHz, DMSO-*d*₆): δ 9.14 (s, 1H, *H_d*), 7.90 (s, 1H, *H_c*), 7.27-7.21 (m, 3H, *H_{i,j}*), 7.20-7.17 (m, 2H, *H_h*), 6.24 (br, 1H, *H_e*), 6.20 (s, 2H, *H_b*), 3.32-3.27 (m, 2H, *H_f*), 2.27 (t, *J* = 6.9 Hz, 2H, *H_g*), 1.09 (s, 9H, *H_a*), ¹³C-NMR (100 MHz, DMSO-*d*₆): 177.88, 154.43, 138.56, 133.34, 131.7, 126.98, 122.56, 119.87, 84.90, 43.56, 38.40, 32.22, 26.80; MS (APCI⁺) found for [C₁₇H₂₃N₅O₃ + H]⁺ 346.1877, calc. 346.1875; IR KBr (cm⁻¹) ν: 3043.2, 3319.7, 3224.3, 3103.0, 3034.2, 2968.4, 2873.6, 1755.2, 1688.3, 1640.2, 1577.3, 1251.8, 1162.9, 1118.2, 1029.2.

(4-(3-heptylureido)-1H-1,2,3-triazol-1-yl)methyl pivalate (209)

207 (800 mg, 3.2 mmol) and 1,4-dioxane (6 ml) were subsequently charged into a microwave vessel, the vessel was hermetically capped and heated in the microwave at 140 °C for 2 hrs. After cooling to r.t. *n*-heptylamine (548 mg, 4.76 mmol) was added. The mixture was stirred at r.t. for 12 hrs and then concentrated *in vacuo*. Purification by CC on SiO₂ (cyclohexane/EtOAc : 6/4) afforded **209** as a white solid in 40% yield (440 mg, 1.28 mmol) m.p. 89-90°C; ¹H-NMR (400 MHz, CDCl₃): δ 8.30 (s, 1H, *H_d*), 7.48 (s, 1H, *H_c*), 6.21 (s, 2H, *H_b*), 5.90 (br, 1H, *H_e*), 3.32-3.29 (m, 2H, *H_f*), 1.38-1.35 (m, 2H, *H_g*), 1.29-1.20 (m, 8H, *H_{h,i,j,k}*), 1.09 (s, 9H, *H_a*), 0.80 (t, *J* = 7.1 Hz, 3H, *H_l*); ¹³C-NMR (100 MHz, CDCl₃): 177.03, 154.60, 145.84, 112.21, 70.84, 40.23, 38.73, 31.79, 30.24, 28.94, 27.00, 26.80, 22.58, 14.46; MS (APCI⁺) found for [C₁₆H₂₉N₅O₃ + H]⁺ 340.2399, calc. 340.2404; IR KBr (cm⁻¹) ν: 3406.23,

3331.44, 2961.66, 2930.22, 2858.47, 1755.48, 1731.63, 1693.79, 1595.40, 1559.03, 1479.95, 1459.55, 1445.31, 1278.16, 1230.33, 1155.36, 1117.43, 1032.48, 987.77.

1-heptyl-3-(1*H*-1,2,3-triazol-4-yl)urea (**210**)



1*N* NaOH *aq.* (2.60 ml, 2.6 mmol) was added to a solution of **209** (400 mg, 1.18 mmol), in MeOH (3 ml) and the solution was stirred at r.t. for 10', the reaction was then quenched with the addition of sat. NH₄Cl *aq.* (5 ml). The mixture was diluted with AcOEt washed with H₂O (3 x 10 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by CC on SiO₂ (EtOAc) afforded **210** as a white solid in 70% yield (185 mg, 0.8 mmol). m.p. 166-167 °C; ¹H-NMR (400 MHz, DMSO-*d*₆): 14.23 (*br*, 1H, *H_a*), 8.90 (*s*, 1H, *H_c*), 7.62 (*s*, 1H, *H_b*), 6.25 (*br*, 1H, *H_d*), 3.44-3.30 (*m*, 2H, *H_e*), 1.40-1.37 (*m*, 2H, *H_f*), 1.26-1.16 (*m*, 8H, *H_{g,h,i,j}*), 0.82 (*t*, *J* = 7.0 Hz, 3H, *H_k*); ¹³C-NMR (100 MHz, DMSO-*d*₆): 154.90, 130.42, 127.01, 31.80, 31.23, 30.26, 28.95, 26.83, 22.58, 14.48; MS (APCI⁺) found for [C₁₀H₁₉N₅O + H]⁺ 226.1626, calc. 226.1616; IR KBr (cm⁻¹) ν : 3402.83, 2929.64, 2858.67, 2361.99, 1654.32, 1577.90, 1178.12, 1083.54, 1018.03, 700.73, 612.22, 498.95, 427.87.

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Curriculum Vitae

Simone Armani was born in Fidenza, Italy, in 1981. He received his BSc degree in Industrial Chemistry from the University of Parma in 2004 working under the supervision of Prof. Enrico Dalcanale. He move then to the group of Prof Marta Catellani for carrying out his MSc degree, working in the field of homogeneous catalysis (2005-2006). Then, he joined the groups of Davide Bonifazi and Maurizio Prato to accomplish a Ph.D. fellowship in cotutelle between the “Facultés Universitaires Notre-Dame de la Paix” (Namur, Belgium) and the “Università degli Studi di Trieste” (Trieste, Italy).

