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

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Presented by

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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 (\textit{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 (\textit{e.g.} \(\pi-\pi\) stacking, solvophobic/solvophilic interactions) and external (\textit{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 thioly, oxolyl, azolyl, and triazolyl scaffolds for recognition systems, it is intended as a mean to better achieve the control on the binding properties and selectivity of triple H-bonding 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](image1.png)

**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 rethrosynthetic 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](image2.png)

**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-oxyl derivatives capable of recognition mediated by triple H bonding were never isolated.

![Figure 3](image1)

**Figure 3** Synthesized oxyl-protected DAD H-bond array.

The synthetic strategies towards the synthesis of DDD arrays based on 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](image2)

**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](image3)

**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$_2$Cl$_2$), 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 proéminente 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) corrèlent linéairement aux valeurs de \(K_a\), 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 \(\pi-\pi\) 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 thiolyl, oxolyl, azolyl, et triazolyl 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-assembly 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 thiolyt ont été synthétisés avec succès (section 2.3).
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 carbamique 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.

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.

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 CDCl₃ et CD₂Cl₂), la capacité de reconnaissance moléculaire en solution n’a pu être étudiée. De plus amples modifications des propriétés moléculaires structurelles 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 puo’ essere variata in diversi modi. Ad esempio, quando sono richieste interazioni piu’ 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. \(\pi-\pi\) 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 puo’ avvenire tramite la variazione dell’etrotomo sull’anello o tramite l’introduzione di sostituenti nelle posizioni \(\beta\), 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 è invece focalizzata sulle proprietà chimico-fisiche di nuovi materiali funzionali formati tramite processi di auto-assembleggi 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
Riassunto

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.

Le capacità di riconoscimento molecolare di questi sistemi in soluzione non sono state studiate a causa della loro limitata solubilità. Ulteriori modifiche strutturali sono pertanto necessarie.
Chapter 1

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 ± 20°.

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 persistance, 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.
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 $37 \text{ M}^{-1}$; 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

![Image of chemical structures](image-url)
[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-DAD] complex characterized by a $K_a$ of $10^4$–$10^5$ 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](image-url)

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 CDCl₃, *Schneider*[^22] demonstrated that the total free energy ($\Delta G$) of formation of H-bond complexes can be precisely represented within $\pm 1.8$ KJ·mol⁻¹, by adding the contributions of attractive primary interactions, whose value has been calculated equal to 7.9 KJ·mol⁻¹, to the contributions of the secondary interactions, each one equal to 2.9 KJ·mol⁻¹, but considering whether their contribution is attractive or repulsive (*Figure 2*).

![Figure 2](image)

*Figure 2.* Possible arrangements of the binding sites in hydrogen bonded complexes with predicted values for $\Delta G^0$ and $K_a$ in CDCl₃. 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.

In this context, Zimmermann and Murray 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 $^1$H-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$_2$Cl$_2$, as resulted by UV measurements (Scheme 2).

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).

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

**Figure 3.** Possible arrangements of the binding sites in quadruple hydrogen bonded complexes with predicted values for $\Delta G^0$ 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] Following *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 [ADAD]₂ self-complementary complexes whose *Kₘ* values ranged from 10² to 10⁵ M⁻¹. The strength of [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](image)

**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.](image)

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 $10^6$ 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 ($K_a > 10^7$ 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]: 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 amicid 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 complemetary (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 $[8\cdot9]$ ($K_a = 10^3$ 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 $[6\cdot7]$ complex between Guanine and Cytosine ($K_a \sim 10^4$–$10^5$ M$^{-1}$).
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.\textsuperscript{[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)](image)

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 $5 \times 10^7$ 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](image)

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$_6$D$_6$.

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$_6$D$_6$ however only the unfolded conformer is present and self associates with a $K_a$ value of $9 \times 10^6$ 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 $10^6$ 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.[30] They investigated the effects of two different substituents, X₁ and X₂ 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 diacylaminotriazines employed in the study of the electronic effects of substituents on the Kₐ.](image)

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. Kₐ in CDCl₃ measured via NMR titration experiments, ranged from 12 M⁻¹ (ΔG = 1.4 Kcal·mol⁻¹) for 29h (X₁ = X₂ = -OMe) to 97 M⁻¹ (ΔG = 2.7 Kcal·mol⁻¹) in the case of 29c (X₁ = -NO₂; X₂ = -H), highlighting that the presence of electron withdrawing...
groups decreases the electron density on the triazine nucleous 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 the these effects, further analysis were not carried out.

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

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).\textsuperscript{[23]} The dihydro pirydinic 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 consider 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 $^1$H-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 pyrimidone 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 pyridiminol form. Hence when R = CF$_3$ the 99% of the molecules are present in solution as the self-complementary DADA pyrimidinol tautomer, while when R = alkyl the pyrimidone 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 $47 \text{ M}^{-1}$.[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 complimentary (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](image.png)

**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 recognassance of complementary triple H-bond motifs of diacetylaminopyridines and uracil derivatives ($K_a < 10^3$ 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 $[33\cdot 34]_n$ that exhibit a thermotropic liquid crystalline behavior over a large temperature range.$^{43}$ The increased rigidity of the system in $[35\cdot 36]_n$ due to the presence of a dialcoxyanthracene core to connect the H-bond groups give raise instead to a birifrangent and highly viscous lyotropic crystalline phase in apolar solvents.$^5$

![Scheme 14](attachment:image.png)

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

It was only with the introduction of self-complementary AADD and complementary ADDA and DAAD units displaying high association constant ($K_a > 10^6$ 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$^{15}$ 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 oligophenilvynilene (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 (\(\mu\)M 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](image)

**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 ($\lambda_{\text{exc}} = 365$ nm).

![Figure 8](image)

**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.\textsuperscript{[48, 51]} UG and DAN were respectively appended onto polystirene (PS) and poly(butylmethacrylate) (PMBA), 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 hypotesis 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**).
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.\textsuperscript{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, \textit{41}, with its three-fold symmetry \textit{3x}(DAD), formed the vertices of the network while the straight edges corresponded to nome completo PTCDI, \textit{42} \textit{[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 \textasciitilde{} 5 \times 10^{-11} \text{ 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 \textit{42} were sublimed onto the surface, close packed islands and short chains similar to those reported in previous studies of PTCDI were observed.\textsuperscript{53, 54} Subsequently, \textit{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 C_{60} clusters as showed in Figure 10c.\textsuperscript{[55, 56]} These C_{60} 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.

![Chemical structures of PTDCI 41 and melamine 42](image)

**Figure 10** Self-assembly of PTDCI 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 PTDCI-melamine network. Inset: high resolution view of the Ag/Si(111) substrate surface; c) STM image (-2.0 V, 0.1 nA) of C_{60} heptamers on a PTDCI-melamine network. Inset, high resolution view showing an individual cluster. Scale bar = 5 nm.

Very similar hydrogen bonding arrays were used respectively by Ortega\textsuperscript{[57]} and Barth\textsuperscript{[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 naphtalene 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 (IIb), 44 (IIc) and of a 1:1 mixture of the two components (IId), 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 $5 \times 10^{-11}$ mbar) after deposition at submonolayer 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 °), (BDATB : Q = 47.3 °), (NTDCI/BDATB : Q = 47.3 °)

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 nm$^2$ 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 uracil moiety and an antracenyl 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, [(45·46)\(_n\)], 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, [(47·45)·(46·45)\(_n\)·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 × 41.5 nm² and 12 × 12 nm², 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 × 40 nm²). The lower right inset shows an aggregate of 10 (7.7 × 7.7 nm²); f-g) proposed models and zoomed STM image of trimeric and pentameric assemblies, respectively.
1.2.3 Nanoscopic and microscopic hierarchized architectures

One of the first examples in which supramolecular order is achieved in structures hierarchically organized from hydrogen bonding interactions was described by the group of Meijer.\textsuperscript{[60]} (Figure 14). Monomer 48 and 49 consist of functionalized ureidotriazine bearing solubilising chains. This design allowed the formation of hierarchically self-organized columnar aggregates. Self-association via the ADAD ureidotriazinic units leads to the formation of dimers with large and planar aromatic cores surrounded by flexible chains. The dimers are responsible to the formation of random coil polymers, resulting in viscous solutions, in CHCl\textsubscript{3}. Higher degree of order was instead reached in non-polar solvents as they are unable to solvate the aromatic cores. In dodecane, for instance, the ensemble of H-bond, solvophobic and $\pi-\pi$ interactions induced the formation of polymeric columnar structures (Figure 14), whose presence was determined by Small-Angle Neutron Scattering (SANS) experiments. SANS measurements showed that the radii of the columns are independent from the concentration, and values of 15 nm for molecule 48 (consistent with a column constituted of stacked dimers), and of 17 nm in the case of 49 were obtained. The length of the columns is instead concentration dependent and ranged from a minimum of 100 nm to a maximum value of 190 nm (about 60 molecules) for a 1.0 wt% solution. Control onto the helicity of the assembly was achieved by tuning the nature of the solubilizing chains. A large Cotton effect in the absorption band of the aromatic cores is in fact observed for 2b, due to the preferential handedness of the helical arrangement induced by the presence of the chiral peripheral chains.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure14.png}
\caption{a) chemical structures of monomer 1 and 2 c) Circular dichroism spectra of 2b in dodecane. a, Concentration dependence of $\Delta\varepsilon$ ($\Delta\varepsilon$ is the Cotton effect normalized to concentration). Inset, typical CD spectrum.}
\end{figure}
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 CHCl₃ and dodecane at room temperature (Figures 15b, 15c). The absorption band measured in a CHCl₃ 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 CHCl₃.[63] In dodecane (1.4–5 M), the absorption maximum of OPV is blue shifted (λₘₐₓ = 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 (λₘₐₓ = 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.\textsuperscript{[65]}

![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\textsubscript{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 oligophenyleneethinylene (OPE) functionalized with melamine (53), a double DAD array, was recently reported by Yagay.\textsuperscript{[66]} In this work the authors described the formation in CHCl\textsubscript{3} of discrete rosettes (53\textsubscript{1} \times 54\textsubscript{1}), via the co-assembly of 53 with the complementary cyanaurate derivative 54, presenting a double ADA array (Figure 16). The dimension of the assembly were investigated by Dinamic 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 \(D_{h} = 50\) 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\times10^{-5} 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 $3.2 \pm 0.3$ nm while the cross-sectional diameter was found to be $8 \pm 2$ nm.

![Chemical structure of 53 and 54](image)

**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 (5x10^-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. 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 $\pi-\pi$ stacked aggregates to a situation where free PBI 55 chromophores could be detected. This result implies that $\pi-\pi$ stacked aggregates of 55 are disrupted by the addition of 54 to form new hydrogen-bonded aggregates in diluted condition. $\pi-\pi$ 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 mm 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 uracil 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. Absorption 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 anthracenyl ends, which stimulate the self-organization of the system into the mentioned vesicular-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](image)

**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.

1.4 References


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](image)

*R*.

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 *Kₐ* 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](image)

**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. 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](image)

**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](image_url)

**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 Rethrosynthetic analysis

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

![Figure 1](image_url)

**Figure 1.** DAD triple hydrogen bonding arrays based on di-amidooxoyl and di-amido thiolyl 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, thiolyl, 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\textsuperscript{[7]} and 2-aminofuran,\textsuperscript{[8, 9]} but they have failed to isolate these compounds due to their lability. Moreover, there are still no reports of diaminosubstituted derivatives.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{Chemical structures of 2-aminofuran, 2-aminothiophene and 2-aminopyrrole.}
\end{figure}

As a consequence of this instability, every retrosynthetic strategy involving the formation of an amino derivative intermediate, has to be avoided \textit{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 \(\alpha\) positions. Screening the literature, we identified different methodologies suitable for these purposes: \textit{i}) the Buchwald-Hartwig amidation cross-coupling reaction, \textit{ii}) the formation of azido-derivatives and \textit{iii}) the formation of isocyanate via the \textit{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.

\subsection*{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\textsuperscript{[10, 11]} and Hartwig.\textsuperscript{[12, 13]} The first example of amidation of a five membered heterocyclic structure was reported by Buchwald \textit{et al.} in 2001.\textsuperscript{[14]} In this work, 2-iodo and 2-bromothiophene were coupled with pyrrolidinone, using Cul as catalyst and \textit{trans}-1,2-cyclohexanediamicine as ligand, in the presence of K\textsubscript{3}PO\textsubscript{4}, generating the adduct 76, in high yields (96%-97\%) (Scheme 1).

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme1.png}
\caption{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 K\textsubscript{3}PO\textsubscript{4}. Cul was used as catalyst in 1 mol\% for 2-iodothiophene and 10 mol\% for the bromo derivative. All the yields reported were obtained using \textit{trans}-1,2-cyclohexanediamine (10 mol\%) as Cu ligand.}
\end{scheme}
The group of Padwa demonstrated in 2003 that oxygenated substituents on the heteroaromatic ring can be tolerated by Cu(I)-based catalytic systems.\textsuperscript{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 \(N,N\)-dimethylethane-1,2-diamine or racemic \textit{trans}-1,2-cyclohexanediamine as ligand, in the presence of K\(_3\)PO\(_4\) or K\(_2\)CO\(_3\).

\[
\begin{align*}
R' \ \text{O} \ \text{Br} & \quad \rightarrow \quad R' \ \text{O} \ \text{N} \ R'' \\
77, R' = \text{CHO} & \quad 80, R' = \text{CHO}, R'' = \text{H}; R''' = \text{Ph} \\
78, R' = \text{CO}_2\text{Me} & \quad 81, R' = \text{CO}_2\text{Me}, R'' = \text{H}; R''' = \text{Ph} \\
79, R' = \text{H} & \quad 82, R' = \text{H}, R'' = \text{R''' = -(CH}_2)_2\text{)}_2 \text{Me} \\
& \quad 83, R' = \text{H}, R'' = \text{H}; R''' = \text{n-C}_8\text{H}_{15}
\end{align*}
\]

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

\textit{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.\textsuperscript{16, 17} As demonstrated by Williams and co-workers, amines are not formed during this reaction, which proceeds instead through the formation of a thiaatriazolinic intermediate (Scheme 3).\textsuperscript{18}

\[
\begin{align*}
\text{R} \ \text{O} \ \text{S} \ \text{H} & \quad \xrightarrow{\text{H}^+} \quad \text{R} \ \text{N}_3 \\
\text{R} \ \text{O} \ \text{S} & \quad \xrightarrow{\text{H}^+} \quad \text{R} \ \text{N}_3 \\
\text{R} \ \text{O} \ \text{S} & \quad \xrightarrow{\text{H}^+} \quad \text{R} \ \text{N}_3 \\
\end{align*}
\]

\textbf{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.\textsuperscript{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.\textsuperscript{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 TsN\(_3\) to generate the triazene salt 84. After its isolation, the instable triazene salt was reacted with Na\(_2\)P\(_2\)O\(_7\)+10 H\(_2\)O affording 85 in 55% yield.
Scheme 4 Zanirato’s synthesis of 2-azidothiophene (85). a) n-BuLi, THF, -78 °C, 2 h; b) Na2P2O7·10H2O, 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 carbbamic 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, carbbamic 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
Results and Discussion

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 amide 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 amide 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).

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>mol% of CuI</th>
<th>Eq. of amide</th>
<th>Base</th>
<th>T (°C)</th>
<th>Time (hrs)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>H</td>
<td>10</td>
<td>4</td>
<td>K$_3$PO$_4$</td>
<td>110</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>ii</td>
<td>Bz</td>
<td>10</td>
<td>4</td>
<td>Cs$_2$CO$_3$</td>
<td>110</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>iii</td>
<td>H</td>
<td>10</td>
<td>4</td>
<td>K$_3$PO$_4$</td>
<td>110</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>iv</td>
<td>Bz</td>
<td>10</td>
<td>4</td>
<td>Cs$_2$CO$_3$</td>
<td>110</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>v</td>
<td>H</td>
<td>10</td>
<td>4</td>
<td>K$_3$PO$_4$</td>
<td>130</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>vi</td>
<td>Bz</td>
<td>10</td>
<td>4</td>
<td>K$_3$PO$_4$</td>
<td>130</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>vii</td>
<td>Bz</td>
<td>30</td>
<td>4</td>
<td>K$_3$PO$_4$</td>
<td>130</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>viii</td>
<td>Bz</td>
<td>50</td>
<td>4</td>
<td>K$_3$PO$_4$</td>
<td>130</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>ix</td>
<td>Bz</td>
<td>50</td>
<td>10</td>
<td>K$_3$PO$_4$</td>
<td>130</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

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 Cs$_2$CO$_3$ or K$_3$PO$_4$ 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 $^1$H-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 thiolyl derivatives, due to the presence of the sulfur as poisoning atom, deactivating the catalyst. Three different Palladium-based catalysts were used: a) [Pd(PPh$_3$)$_3$], b) Pd(OAc)$_2$/(S)-Binap, c) Pd(OAc)$_2$/Xanthphos.
Results and Discussion

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

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 \(\alpha\) 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 \(\alpha\) positions with amide 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).

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>mol% of CuI</th>
<th>Eq. of amide</th>
<th>Base</th>
<th>T (°C)</th>
<th>Time (hrs)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>H</td>
<td>10</td>
<td>1.2</td>
<td>K$_3$PO$_4$</td>
<td>110</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>ii</td>
<td>Bz</td>
<td>10</td>
<td>1.2</td>
<td>Cs$_2$CO$_3$</td>
<td>110</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>iii</td>
<td>H</td>
<td>30</td>
<td>4</td>
<td>K$_3$PO$_4$</td>
<td>130</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>iv</td>
<td>Bz</td>
<td>30</td>
<td>4</td>
<td>K$_3$PO$_4$</td>
<td>130</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>v</td>
<td>Bz</td>
<td>50</td>
<td>10</td>
<td>K$_3$PO$_4$</td>
<td>130</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>vi</td>
<td>Bz</td>
<td>100</td>
<td>10</td>
<td>K$_3$PO$_4$</td>
<td>130</td>
<td>16</td>
<td>0</td>
</tr>
</tbody>
</table>

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).

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>mol% of catalyst</th>
<th>Eq. of amide</th>
<th>Base</th>
<th>T (°C)</th>
<th>Time (hrs)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>H</td>
<td>5</td>
<td>1.2</td>
<td>K$_3$PO$_4$</td>
<td>110</td>
<td>16 hrs</td>
<td>0</td>
</tr>
<tr>
<td>ii</td>
<td>H</td>
<td>5</td>
<td>1.2</td>
<td>Cs$_2$CO$_3$</td>
<td>110</td>
<td>16 hrs</td>
<td>0</td>
</tr>
<tr>
<td>iii</td>
<td>Bz</td>
<td>5</td>
<td>4</td>
<td>K$_3$PO$_4$</td>
<td>110</td>
<td>16 hrs</td>
<td>0</td>
</tr>
<tr>
<td>iv</td>
<td>Bz</td>
<td>5</td>
<td>4</td>
<td>Cs$_2$CO$_3$</td>
<td>110</td>
<td>16 hrs</td>
<td>0</td>
</tr>
<tr>
<td>v</td>
<td>H</td>
<td>20</td>
<td>10</td>
<td>K$_3$PO$_4$</td>
<td>130</td>
<td>16 hrs</td>
<td>0</td>
</tr>
<tr>
<td>vi</td>
<td>Bz</td>
<td>20</td>
<td>10</td>
<td>K$_3$PO$_4$</td>
<td>130</td>
<td>16 hrs</td>
<td>0</td>
</tr>
</tbody>
</table>

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 thiolyl derivative thus obtained was added to a solution of TsN$_3$ (Scheme 6).

![Scheme 6](image)

Isolation of derivative 107 was not carried out due to its high instability. Therefore treatment with Na$_4$P$_2$O$_7$ was then performed directly on the crude of the reaction, but unfortunately this step resulted in decomposition.

![Scheme 7](image)

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 NaN$_3$ seemed to be a suitable technique.[24] Nevertheless, couplings of inactivated aryl halides with sodium azide, catalyzed by Cul, 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, Cul-catalyzed coupling reaction of aryl and vinyl halides with sodium azide, which provided a variety of aryl and vinyl azides.[27] (Scheme 8).
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.

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.

<table>
<thead>
<tr>
<th>entry</th>
<th>CuI (mol%)</th>
<th>Solvent</th>
<th>L-proline (mol%)</th>
<th>T (°C)</th>
<th>time (hrs)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>10</td>
<td>DMSO</td>
<td>30</td>
<td>70</td>
<td>24</td>
<td>0[b]</td>
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<td>DMSO</td>
<td>30</td>
<td>90</td>
<td>24</td>
<td>0[b]</td>
</tr>
<tr>
<td>iii</td>
<td>10</td>
<td>DMSO</td>
<td>30</td>
<td>110</td>
<td>6</td>
<td>0[c]</td>
</tr>
<tr>
<td>iv</td>
<td>30</td>
<td>DMSO</td>
<td>90</td>
<td>90</td>
<td>24</td>
<td>0[b]</td>
</tr>
<tr>
<td>v</td>
<td>30</td>
<td>DMSO</td>
<td>90</td>
<td>110</td>
<td>5</td>
<td>0[c]</td>
</tr>
<tr>
<td>vi</td>
<td>100</td>
<td>DMSO</td>
<td>150</td>
<td>90</td>
<td>24</td>
<td>0[b]</td>
</tr>
<tr>
<td>vii</td>
<td>30</td>
<td>H₂O/EtOH</td>
<td>90</td>
<td>90[a]</td>
<td>24</td>
<td>0[b]</td>
</tr>
<tr>
<td>viii</td>
<td>30</td>
<td>H₂O/EtOH</td>
<td>90</td>
<td>110[a]</td>
<td>6</td>
<td>0[c]</td>
</tr>
</tbody>
</table>

Table 5 Conditions tested for the proline promoted CuI catalized 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.
**Results and Discussion**

Scheme 10 Attempted synthesis of 110 via proline promoted CuI catalized 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 retросynthetic 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) (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 (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$_2$Cl$_2$ 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.
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.

<table>
<thead>
<tr>
<th>entry</th>
<th>R-MX</th>
<th>T (°C)</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>MeLi</td>
<td>-78 to r.t</td>
<td>0</td>
</tr>
<tr>
<td>ii</td>
<td>n-BuLi</td>
<td>-78 to r.t</td>
<td>0</td>
</tr>
<tr>
<td>iii</td>
<td>MeMgBr</td>
<td>-78 to r.t</td>
<td>0</td>
</tr>
<tr>
<td>iv</td>
<td>PhenylMgBr</td>
<td>-78 to r.t</td>
<td>0</td>
</tr>
<tr>
<td>v</td>
<td>Me₂CuLi</td>
<td>0 to r.t</td>
<td>0</td>
</tr>
<tr>
<td>vi</td>
<td>n-Bu₂CuLi</td>
<td>0 to r.t</td>
<td>0</td>
</tr>
</tbody>
</table>

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 di-amidic 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 stablespecies 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 amore 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.

\[
\begin{align*}
R' - H & \quad \longrightarrow \quad R' - N \quad \longrightarrow \quad R' - N \quad \longrightarrow \quad R' - N \quad \longrightarrow \quad R' - N \\
X = O, S, NH
\end{align*}
\]

**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).

\[
\begin{align*}
\text{N}_3 & \quad \text{S} & \quad \text{S} & \quad \text{N}_3 \\
\text{N} & \quad \text{O} & \quad \text{O} & \quad \text{N} \\
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O}
\end{align*}
\]

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

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

**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 $^1$H and $^{13}$C-NMR spectroscopy, high-resolution mass spectrometry, and IR spectroscopy ($^1$H-NMR spectrum is reported in Figure 1).
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 carbamimic nitrogen atoms.

![Figure 1](image)

**Scheme 1** a) Ac₂O, DMAP, Py, r.t. 4 hrs, 84%.

The reaction was initially conducted in CH₂Cl₂, with Ac₂O, 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 CH₂Cl₂ 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 CHCl₃ 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-orthogonal 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.

<table>
<thead>
<tr>
<th></th>
<th>TMS derivative</th>
<th>Solvent</th>
<th>Time</th>
<th>T (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>TMS-Cl</td>
<td>CH₂Cl₂</td>
<td>30’</td>
<td>r.t.</td>
<td>0</td>
</tr>
<tr>
<td>ii</td>
<td>TMS-Cl</td>
<td>CH₂Cl₂</td>
<td>12 hrs</td>
<td>r.t.</td>
<td>0</td>
</tr>
<tr>
<td>iii</td>
<td>TMS-I</td>
<td>CH₂Cl₂</td>
<td>30’</td>
<td>r.t.</td>
<td>0</td>
</tr>
<tr>
<td>iv</td>
<td>TMS-I</td>
<td>CH₂Cl₂</td>
<td>12 hrs</td>
<td>r.t.</td>
<td>0</td>
</tr>
<tr>
<td>v</td>
<td>TMS-I</td>
<td>MeCN</td>
<td>12 hrs</td>
<td>r.t.</td>
<td>0</td>
</tr>
<tr>
<td>vi</td>
<td>TMS-I</td>
<td>MeCN</td>
<td>12 hrs</td>
<td>50</td>
<td>traces</td>
</tr>
<tr>
<td>vii</td>
<td>TMS-Cl</td>
<td>DMF</td>
<td>12 hrs</td>
<td>r.t.</td>
<td>0</td>
</tr>
<tr>
<td>viii</td>
<td>TMS-Cl</td>
<td>DMF</td>
<td>12 hrs</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td>ix</td>
<td>TMS-I</td>
<td>DMF</td>
<td>1 hrs</td>
<td>80</td>
<td>0</td>
</tr>
</tbody>
</table>

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) dianinothiophene 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 amidodervative 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 byproducts 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) acetyc anhydride, DMAP, pyridine, r.t., 82%; c) TFA, CH₂Cl₂, 0 °C to r.t., see Table 3 for details.
Results and Discussion

<table>
<thead>
<tr>
<th></th>
<th>% of TFA</th>
<th>Solvent</th>
<th>Scavenger</th>
<th>Time</th>
<th>Temperature (°C)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>3%</td>
<td>CH₂Cl₂</td>
<td>none</td>
<td>4 hrs</td>
<td>0</td>
<td>44%</td>
</tr>
<tr>
<td>ii</td>
<td>5%</td>
<td>CH₂Cl₂</td>
<td>none</td>
<td>4 hrs</td>
<td>0</td>
<td>50%</td>
</tr>
<tr>
<td>iii</td>
<td>20%</td>
<td>CH₂Cl₂</td>
<td>none</td>
<td>1 hrs</td>
<td>0</td>
<td>47%</td>
</tr>
<tr>
<td>iv</td>
<td>5%</td>
<td>CH₂Cl₂</td>
<td>Anisole</td>
<td>30’</td>
<td>0</td>
<td>76%</td>
</tr>
<tr>
<td>v</td>
<td>20%</td>
<td>CH₂Cl₂</td>
<td>Anisole</td>
<td>5’</td>
<td>0</td>
<td>79%</td>
</tr>
</tbody>
</table>

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(2)= 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 amide 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 CH$_2$Cl$_2$/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 $^1$H and $^{13}$C-NMR spectroscopy, high-resolution mass spectrometry, and IR spectroscopy ($^1$H-NMR spectrum is reported in figure 3).

![Figure 3](image)

**Figure 3** $^1$H-NMR spectra of 123. The spectra was recorded in DMSO-$d_6$ at 80 °C. Due to the presence of conformers the structure ar 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 $^1$H-NMR techniques.

![Scheme 5](image)

**Scheme 5** $^1$H-NMR spectra of 123. The spectra was recorded in DMSO-$d_6$ at 80 °C. Due to the presence of conformers the structure ar 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 thiolyl 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.[20] Different bases and solvents were tested in order to optimize the yields of this latter reaction (Table 3).

<table>
<thead>
<tr>
<th>b)</th>
<th>Solvent</th>
<th>Base</th>
<th>Time (hrs)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>DMF</td>
<td>NaH</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>ii</td>
<td>DMF</td>
<td>NaOMe</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>iii</td>
<td>THF</td>
<td>NaH</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>iv</td>
<td>THF</td>
<td>NaOMe</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>v</td>
<td>Toluene</td>
<td>NaH</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>vi</td>
<td>Toluene</td>
<td>NaOMe</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>vii</td>
<td>Methanol</td>
<td>NaOMe</td>
<td>2</td>
<td>91</td>
</tr>
</tbody>
</table>

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$_2$SO$_4$, followed by an alkaline hydrolysis with LiOH (Scheme 8).

\[ \text{Scheme 8 a) } \text{Me}_2\text{SO}_4, \text{K}_2\text{CO}_3, \text{DMF, 60°C, 16 hrs, 83%; b) } 2\text{N LiOH, THF, r.t., 12 hrs, 94%}. \]

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

\[ \text{Scheme 9 a) } (\text{COCl})_2, \text{DMF, THF, 0°C to r.t. 3 hrs, then sat. NaN}_3 \text{aq.}, \text{not isolated; b) PMBA, 130°C, 5°, 79% over two steps; c) } \text{Ac}_2\text{O, DMAP, pyridine, r.t. 4 hrs. 81%; d) } \text{TFA (2%), CH}_2\text{Cl}_2, \text{0°C, 51%}. \]

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 (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 $^1$H and $^{13}$C-NMR spectroscopy, high-resolution mass spectrometry, and IR spectroscopy ($^1$H-NMR spectrum is reported in Figure4).
Subsequently, an acylation step was performed with Ac₂O, 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 CH₂Cl₂ 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 CHCl₃/MeOH solution. The crystal structure was determined at 293 K and found to belong to the monoclinic space group P2₁/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 Å. Both amides result in the cis-like conformation, which is stabilized by sulphur-oxygen non-bonded interactions, as already observed for molecule 68, with contact distances for both S(1)-O(3) and S(1)-O(4) of ca. 2.79 Å and by two intramolecular hydrogen bonding (N(1)-O(1) = 2.60 Å, N(2)-O(2) = 2.61 Å). The distance between the carbonylic oxygen atoms O(3) and O(4) is in both cases ca. 5 Å. 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.
**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.
Results and Discussion

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) Mel, K₂CO₃, DMF, 40 °C, 16 hrs, 74%; d) 2N LiOH, THF, r.t., 12 hrs, 94%; b) (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 Mel was ensued by a saponification step in a 9:1 1N 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 CHCl₃ 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.

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

Table 1 Condition used for the Curtius rearrangement of molecule 144. [a]: 3 eq. of triethylamine 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).
Results and Discussion

Figure 1 ORTEP representation of the two enantiomers of \textbf{146} (a) and magnification of the \textit{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 \textbf{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 \textbf{147}, leading to the pyrrolic intermediates \textbf{148}. The subsequent keto-enolic tautomerization of this system results in the de-aromatization of the furanic ring and subsequent formation of \textbf{149}.

\begin{center}
\textbf{Scheme 4} Proposed mechanism for the formation of molecule \textbf{149}.
\end{center}

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

\textbf{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 \textit{\alpha} positions with amicid groups, we decided to start our synthesis from furan-2,5-dicarboxylic acid \textbf{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 NaN₃) to give the product in 67% yield (Scheme 5).

\[
\begin{align*}
\text{HO-OC} & \xrightarrow{a)} (\text{COCl})_2, \text{THF, 0°C to r.t., 3 hrs, not isolated; b) sat. NaN}_3\text{aq. THF, r.t., 30', 67%}. \\
\text{150} & \rightarrow \text{151} \rightarrow \text{152}
\end{align*}
\]

Scheme 5 a) (COCl)₂, THF, 0°C to r.t., 3 hrs, not isolated; b) sat. NaN₃aq. 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 CH₂Cl₂ and CHCl₃, 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.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>eq. of PMBA</th>
<th>T (°C)</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>PMBA</td>
<td>excess</td>
<td>130</td>
<td>5'</td>
<td>0</td>
</tr>
<tr>
<td>ii</td>
<td>mesitylene</td>
<td>3</td>
<td>130</td>
<td>5'</td>
<td>0</td>
</tr>
<tr>
<td>iii</td>
<td>PMBA</td>
<td>excess</td>
<td>90</td>
<td>5'</td>
<td>73</td>
</tr>
<tr>
<td>iv</td>
<td>toluene</td>
<td>3</td>
<td>90</td>
<td>5'</td>
<td>71</td>
</tr>
<tr>
<td>v</td>
<td>THF</td>
<td>2</td>
<td>120[a]</td>
<td>5'</td>
<td>48</td>
</tr>
</tbody>
</table>

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) acetyc 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.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>[Pd(PPh₃)₂Cl₂] mol%</th>
<th>R—≡—≡ (eq.)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>TMS</td>
<td>1</td>
<td>(i-Pr)₂NH</td>
<td>120</td>
<td>5</td>
<td></td>
<td>[a]</td>
</tr>
<tr>
<td>ii</td>
<td>TMS</td>
<td>1</td>
<td>(i-Pr)₂NH</td>
<td>120</td>
<td>5</td>
<td></td>
<td>[a]</td>
</tr>
<tr>
<td>iii</td>
<td>TMS</td>
<td>5</td>
<td>(i-Pr)₂NH</td>
<td>120</td>
<td>5</td>
<td></td>
<td>[a]</td>
</tr>
<tr>
<td>iv</td>
<td>TMS</td>
<td>10</td>
<td>DIEA</td>
<td>120</td>
<td>5</td>
<td></td>
<td>[a]</td>
</tr>
<tr>
<td>v</td>
<td>Ph</td>
<td>5</td>
<td>(i-Pr)₂NH</td>
<td>120</td>
<td>8</td>
<td></td>
<td>[a]</td>
</tr>
<tr>
<td>vi</td>
<td>Ph</td>
<td>5</td>
<td>(i-Pr)₂NH</td>
<td>130</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vii</td>
<td>Ph</td>
<td>5</td>
<td>DIEA</td>
<td>110</td>
<td>8</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>viii</td>
<td>Ph</td>
<td>5</td>
<td>DIEA</td>
<td>130</td>
<td>8</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>ix</td>
<td>Ph</td>
<td>10</td>
<td>DIEA</td>
<td>130</td>
<td>8</td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>

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](image)

Scheme 1 Rethrosynthetic 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](image)

Scheme 2 a) (Boc)₂O, DMAP, MeCN, 60°C, 88%; b) methyl-chloroformate, LDA, -78°C, 61%; c) N₂H₄ (64% aq.), MeOH, reflux, 16 hrs, 77%; d) NaNO₂, dil. HCl, H₂O, 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 N₂H₄ under reflux. Finally, 165 was obtained from 164 by oxidation with NaNO₂ 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.](image)

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

<table>
<thead>
<tr>
<th></th>
<th>Solvent</th>
<th>Eq. of BzOH</th>
<th>Temperature</th>
<th>time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>BzOH</td>
<td>excess</td>
<td>130° C</td>
<td>5'</td>
<td>0</td>
</tr>
<tr>
<td>ii</td>
<td>BzOH</td>
<td>excess</td>
<td>120° C</td>
<td>5'</td>
<td>0</td>
</tr>
<tr>
<td>iii</td>
<td>BzOH</td>
<td>excess</td>
<td>100° C</td>
<td>5'</td>
<td>0</td>
</tr>
<tr>
<td>iv</td>
<td>toluene</td>
<td>5</td>
<td>100° C</td>
<td>5'</td>
<td>0</td>
</tr>
<tr>
<td>v</td>
<td>toluene</td>
<td>5</td>
<td>60° C</td>
<td>30'</td>
<td>0</td>
</tr>
<tr>
<td>vi</td>
<td>THF</td>
<td>5</td>
<td>60° C</td>
<td>30'</td>
<td>0</td>
</tr>
</tbody>
</table>

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 N₂H₄ (Scheme 4), in order to subsequently introduce a more stable protecting group.

![Scheme 4](image)

Scheme 4 a) 64% N₂H₄aq., 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](image)

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

Scheme 9  a) 1N 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 staring 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 $^1$H-NMR spectrum of 174 is shown in Figure 1).

\[
\begin{array}{c}
\text{172} \quad \xrightarrow{a1} \quad \text{173, } R=H \\
\text{174, } R=C(=O)\text{C}_6\text{H}_5
\end{array}
\]

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

<table>
<thead>
<tr>
<th>a)</th>
<th>Solvent</th>
<th>Temperature (° C)</th>
<th>Time</th>
<th>Yield (%)</th>
<th>Ratio (%) 173/174</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>CH$_2$Cl$_2$</td>
<td>r.t.</td>
<td>24 hrs</td>
<td>60</td>
<td>20/80</td>
</tr>
<tr>
<td>ii</td>
<td>Pyridine</td>
<td>r.t.</td>
<td>24 hrs</td>
<td>63</td>
<td>24/76</td>
</tr>
<tr>
<td>iii</td>
<td>Pyridine</td>
<td>r.t.</td>
<td>72 hrs</td>
<td>decomposition</td>
<td></td>
</tr>
<tr>
<td>iv</td>
<td>Pyridine</td>
<td>60</td>
<td>2 hrs</td>
<td>decomposition</td>
<td>-</td>
</tr>
<tr>
<td>v</td>
<td>Pyridine</td>
<td>90</td>
<td>1 hr</td>
<td>decomposition</td>
<td>-</td>
</tr>
<tr>
<td>vi</td>
<td>Pyridine</td>
<td>60$^{[b]}$</td>
<td>30'</td>
<td>64</td>
<td>28/72</td>
</tr>
<tr>
<td>vii</td>
<td>Pyridine</td>
<td>60$^{[b]}$</td>
<td>30'</td>
<td>63</td>
<td>100/0</td>
</tr>
</tbody>
</table>

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 $^1$H-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 $^1$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$_2$Cl$_2$, r.t. 10' or DDQ, CH$_2$Cl$_2$, 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) (COCl)$_2$, THF, 0°C to r.t., then sat. NaN$_3$, $aq.$, not isolated; d) 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.

<table>
<thead>
<tr>
<th>a)</th>
<th>reagent</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time (hrs)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>KF (10 eq.)</td>
<td>DMF</td>
<td>r.t</td>
<td>24</td>
<td>[3]</td>
</tr>
<tr>
<td>ii</td>
<td>KF (10 eq.)</td>
<td>DMF</td>
<td>40</td>
<td>2</td>
<td>[b]</td>
</tr>
<tr>
<td>iii</td>
<td>HF-py (1 eq.)</td>
<td>THF</td>
<td>r.t</td>
<td>24</td>
<td>[a]</td>
</tr>
<tr>
<td>iv</td>
<td>HF-py (1 eq.)</td>
<td>THF</td>
<td>40</td>
<td>6</td>
<td>[b]</td>
</tr>
<tr>
<td>v</td>
<td>TBAF (1 eq.)</td>
<td>THF</td>
<td>r.t</td>
<td>6</td>
<td>[c]</td>
</tr>
<tr>
<td>vi</td>
<td>TBAF (1 eq.)</td>
<td>THF</td>
<td>40</td>
<td>6</td>
<td>[c]</td>
</tr>
<tr>
<td>vii</td>
<td>TBAF (1 eq.)</td>
<td>DMF</td>
<td>r.t</td>
<td>6</td>
<td>[a]</td>
</tr>
<tr>
<td>viii</td>
<td>TBAF (1 eq.)</td>
<td>DMF</td>
<td>40</td>
<td>6</td>
<td>[c]</td>
</tr>
</tbody>
</table>

**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%.
Results and Discussion

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

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

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-d₆ is reported in Figure 3).

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.

![Figure 3](image-url)
Scheme 14 Attempted cleavage of the Sem group from molecule 182.

<table>
<thead>
<tr>
<th></th>
<th>reagent</th>
<th>Solvent</th>
<th>T (° C)</th>
<th>Time (hrs)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>KF (10 eq.)</td>
<td>DMF</td>
<td>r.t.</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>ii</td>
<td>KF (10 eq.)</td>
<td>DMF</td>
<td>40</td>
<td>2</td>
<td>[a]</td>
</tr>
<tr>
<td>iii</td>
<td>HF-py (1 eq.)</td>
<td>THF</td>
<td>r.t.</td>
<td>24</td>
<td>[a]</td>
</tr>
<tr>
<td>iv</td>
<td>HF-py (1 eq.)</td>
<td>THF</td>
<td>40</td>
<td>6</td>
<td>[b]</td>
</tr>
<tr>
<td>v</td>
<td>TBAF (1 eq.)</td>
<td>THF</td>
<td>r.t.</td>
<td>6</td>
<td>[b]</td>
</tr>
<tr>
<td>vi</td>
<td>TBAF (1 eq.)</td>
<td>THF</td>
<td>40</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>vii</td>
<td>TBAF (1 eq.)</td>
<td>DMF</td>
<td>r.t.</td>
<td>6</td>
<td>[b]</td>
</tr>
<tr>
<td>viii</td>
<td>TBAF (1 eq.)</td>
<td>DMF</td>
<td>40</td>
<td>1</td>
<td>[b]</td>
</tr>
<tr>
<td>ix</td>
<td>6N HCl</td>
<td>MeOH</td>
<td>r.t.</td>
<td>1</td>
<td>[b]</td>
</tr>
<tr>
<td>x</td>
<td>BF₃-OEt₂</td>
<td>THF</td>
<td>r.t.</td>
<td>1</td>
<td>[b]</td>
</tr>
</tbody>
</table>

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 ethinylic substituents will be as well explored in order to create functionalizable molecular modules to be exploited in non-covalent synthesis.
Results and Discussion

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 pirroli 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 triazoyl-acylazide and its subsequent conversion into an ureido-triazole through a Curtius rearrangement reaction.

Scheme 1 Rethrosynthetic 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) N₂H₄ 64% aq., EtOH, reflux, 30 hrs, 90%; c) NaNO₂, dil. HCl, H₂O, 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 unsoluble 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 triazolinic ring. For this purpose, the benzyl group seemed to be particularly appealing, due to the high yields usually associated with its hydrogenolytic cleavage. 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 NaN₃. Cu-catalysed 1,3-dipolar cycloaddition with propiolic acid afforded then 195 in 76% yields. The reaction was performed using CuSO₄ as precatalyst and Na-ascorbate as reducing agent. The acid derivative 195 was then reacted with (COCl)₂ and subsequently treated with NaN₃, to afford, after precipitation in pentane, the desired benzyl-protected triazolyl derivative 196 in 90% yields.

Scheme 4  a) NaN₃, DMF, 65 °C, 12 h, 80%; b) propiolic acid, CuSO₄, NaAscorbate, t-BuOH/H₂O, r.t. 8 h, 76%, c) (COCl)₂, THF, 0 °C to r.t., then sat, NaN₃aq., 90%.
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 hydrogenolitic cleavage of the benzyl protecting group was initially attempted in MeOH (Table 1 at atmosferic 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

<table>
<thead>
<tr>
<th>a)</th>
<th>H(_2) pressure (bar)</th>
<th>Solvent</th>
<th>Time (hrs)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>1</td>
<td>MeOH</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>ii</td>
<td>8</td>
<td>MeOH</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>iii</td>
<td>1</td>
<td>HCOOH</td>
<td>24</td>
<td>0</td>
</tr>
</tbody>
</table>

**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 NaN\(_3\) 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) NaN₃, DMF, r.t., 12 hrs, 83%; b) propiolic acid, CuSO₄, NaAscobrate, t-BuOH/H₂O, r.t. 8 hrs, 70%; c) (COCl)₂, THF, 0 °C to r.t., then sat, NaN₃ aq., 98%; d) 1,4-dioxane, m.w. 140 °C, 40', then phenetylamine, 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 BF₃·Et₂O (entry viii).

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

<table>
<thead>
<tr>
<th>a) reagent (equivalents)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time (hrs)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>HF-py (1 eq.)</td>
<td>THF</td>
<td>r.t.</td>
<td>24</td>
</tr>
<tr>
<td>ii</td>
<td>HF-py (1 eq.)</td>
<td>THF</td>
<td>40</td>
<td>6</td>
</tr>
<tr>
<td>iii</td>
<td>TBAF (1 eq.)</td>
<td>THF</td>
<td>r.t.</td>
<td>6</td>
</tr>
<tr>
<td>iv</td>
<td>TBAF (1 eq.)</td>
<td>THF</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>v</td>
<td>TBAF (1 eq.)</td>
<td>DMF</td>
<td>r.t.</td>
<td>6</td>
</tr>
<tr>
<td>vi</td>
<td>TBAF (1 eq.)</td>
<td>DMF</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>vii</td>
<td>6N HCl</td>
<td>MeOH</td>
<td>r.t.</td>
<td>1</td>
</tr>
<tr>
<td>viii</td>
<td>BF₃·Et₂O</td>
<td>THF</td>
<td>r.t.</td>
<td>1</td>
</tr>
</tbody>
</table>

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 oxyimethyl (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 NaN₃ 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 (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 pivaloic ester of 209 with NaOMe afforded in 70 %yield the free ureido-triazole 210, that was fully characterized by $^1$H and $^{13}$C-NMR spectroscopy, high-resolution mass spectrometry, and IR spectroscopy ($^1$H-NMR spectrum at r.t. in DMSO-$d_6$ is reported in Figure 1).

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 $^1$H-NMR titration techniques. The same problem was encountered when polar co-solvents (CD$_3$OD, THF-$d_4$) were used in combination with CDCl$_3$ in order to reach appreciable
Results and Discussion

concentration. Figure 2 shows the $^1$H-NMR of a 10 mM solution of 210 in a 95:5 CDCl$_3$/CD$_3$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](image)

Figure 2 $^1$H-NMR spectra of molecule 210 in 95:5 CDCl$_3$/CD$_3$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](image)

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 $[213\cdot183]$ (DDD-AAA) and $[213\cdot214]$ (ADD-DAA).

The association constant values for complexes $[213\cdot183]$ and $[213\cdot213]$ will be assessed using $^1$H-NMR and UV techniques.

2.7 References


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/UV234 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 a 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) $^1$H 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$_3$: $\delta_H = 7.26$ ppm, $\delta_C = 77.16$ ppm, DMSO-d$_6$: $\delta_H = 2.50$ ppm, $\delta_C = 39.52$ ppm, D$_2$O: $\delta_H = 4.79$ ppm, Toluene-d$_8$: $\delta_H = 2.09$ ppm, $\delta_C = 20.40$, THF-d$_8$: $\delta_H = 3.58$ ppm, $\delta_C = 67.57$). Coupling constants ($J$) were given in Hz. Resonance multiplicity was described as $s$ (singulet), $d$ (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$_2$O (90%) to CH$_3$CN (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 ballons 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

\[ N,N'-(\text{thiophene-2,5-diyl})\text{diacetamide} \] (68)

![Chemical Structure](image)

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-d6): δ 10.77 (s, 2H, Hc), 6.32 (s, 2H, Hb), 2.0 (s, 1H, Ha); 13C-NMR (100 MHz, DMSO-d6): δ 167.80, 132.90, 108.46, 20.98; MS (ESI+) found for \([C_8H_10N_2O_2S + Na]^+\) 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,
Experimental Part

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

\(\text{N,N'-(thiophene-2,5-diyldipentanamide (123)}\)

To a solution of 128 (500 mg, 0.8 mmol) in CH\(_2\)Cl\(_2\) (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\(_3\)aq., H\(_2\)O (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

\(\text{1H-NMR (400 MHz, DMSO-d\(_6\))}: \delta 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;

\(\text{13C-NMR (100 MHz, DMSO-d\(_6\))}: \delta 168.69, 132.28, 107.05, 34.34, 27.26, 21.79, 13.69; \text{MS (ESI\(^+\)) found for [C\(_{14}\)H\(_{22}\)N\(_2\)O\(_2\)S + K\(^+\)]}\)

321.1039, calc. 321.1034; IR KBr (cm\(^{-1}\)) v: 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.

\(\text{Benzyl thiophene-2,5-diyldicarbamate (124)}\)

To a solution of thiophene-2,5-dicarboxylic acid (2.1g, 12.1 mmol) in anhydrous THF (30 ml) stirring at 0 °C, DMF (200 µl) 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 NaN\(_3\)aq. solution (4 ml), stirred for 30’, diluted with Et\(_2\)O (50 ml), and then washed with sat. NaHCO\(_3\)aq. (50 ml), H\(_2\)O (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 SiO<sub>2</sub> (cyclohexane/EtOAc : 7/3). White solid, 58% yield (2.6g, 7.1mmol). m.p. 102-103 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.36 (br, 10H, H<sub>a,b,c</sub>), 6.94 (br, 2H, H<sub>f</sub>), 6.35 (s, 2H, H<sub>e</sub>), 5.18 (s, 4H, H<sub>d</sub>); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ 160.84, 143.25, 139.03, 128.52, 127.02, 126.08, 116.14, 62.31; MS (APCI<sup>+</sup>) found for [C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>S + H]<sup>+</sup> 383.1040, calc. 383.1060; IR<sub>KBr (cm</sub>-1<sub>-1</sub>) 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-diylibis(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. NaHCO<sub>3</sub> (30 ml) aq., H<sub>2</sub>O (30 ml), dried over MgSO<sub>4</sub>, filtered and concentrated at the rotary evaporator. Purification by CC on SiO<sub>2</sub> (cyclohexane/EtOAc : 8/2) afforded 125 as a white solid in 84% yield (364 mg, 0.78mmol). m.p. 111-112 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 7.37-7.20 (m, 10H, H<sub>a,b,c</sub>), 6.68 (s, 2H, H<sub>e</sub>), 5.19 (s, 4H, H<sub>d</sub>), 2.55 (s, 6H, H<sub>f</sub>); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ 172.09, 153.32, 137.84, 134.89, 128.76, 128.49, 127.52, 125.52, 68.87, 26.26; MS (ESI<sup>+</sup>) found for [C<sub>24</sub>H<sub>22</sub>N<sub>2</sub>O<sub>6</sub>S + K]<sup>+</sup> 505.0841, calc. 505.0839; IR KBr (cm<sup>-1</sup>) ν: 3027.76, 29.47.29, 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-diyldicarbamate (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)<sub>2</sub> (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 redissolved in 20 ml of anhydrous THF. The resulting solution was added drop wise to a saturated NaN<sub>3</sub> aq. solution (4 ml), stirred for 30’, diluted with Et<sub>2</sub>O (50 ml), and then washed
with sat. NaHCO₃ aq. (50 ml), H₂O (2 x 50 ml), 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 (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 SiO₂ (cyclohexane/EtOAc : 7/3). White solid, 62% yield (2.0 g ,4.6 mmol). m.p. 92–93 °C; ¹H-NMR (400 MHz, CDCl₃): δ 7.28 (d, J = 8.6 Hz, 4H, Hc), 6.94 (br, 2H, Hf), 6.85 (d, J = 8.6 Hz, 4H, Hb), 6.30 (s, 2H, He), 5.09 (s, 4H, Hd), 3.78 (s, 6H, Ha); ¹³C-NMR (100 MHz, CDCl₃): δ 159.82, 153.95, 132.73, 130.43, 127.94, 114.05, 112.42, 67.58, 55.40; MS (ESI⁺) found for [C₂₂H₂₂N₂O₆S + Na]⁺ 465.1102, calc. 465.1096; IR KBr (cm⁻¹) ν: 3287.15, 2958.44, 2837.93, 1698.38, 1690.99, 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, 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. 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 127 as a white solid in 82% yield (1.7 g, 3.4 mmol). m.p. 98-100 °C; ¹H-NMR (400 MHz, DMSO-d₆): δ 7.16 (d, J = 8.7 Hz, 4H, Hc), 6.84 (d, J = 8.7 Hz, 4H, Hb), 6.67 (s, 2H, He), 5.12 (s, 2H, Hd), 3.78 (s, 6H, Ha), 2.54 (s, 6H, Hf); ¹³C-NMR (100 MHz, DMSO-d₆): 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 [C₂₀H₂₀N₂O₈S + 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-d₆): δ 7.17 (d, J = 8.7 Hz, 4H, Hc), 6.86 (d, J = 8.7 Hz, 4H, Hb), 6.82 (s, 2H, He), 5.11 (s, 4H, Hd), 3.70 (s, 6H, Ha), 2.81 (t, J = 7.3 Hz, 4H, Hf), 1.53-1.46 (m, 4H, Hg), 1.30-1.21 (m, 4H, Hh), 0.84 (t, J = 7.5 Hz, 6H, Hi); ¹³C-NMR (100 MHz, DMSO-d₆): 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)**

\[
\text{O} \quad \text{S} \quad \text{O}
\]

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, Ha), 3.34 (s, 4H, Hb); ¹³C-NMR (100 MHz, CDCl₃): δ 170.34, 52.58, 33.35. Spectral data in agreement with those previously reported.[¹]

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

\[
\text{O} \quad \text{S} \quad \text{O}
\]

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%)
The white precipitate formed was collected by suction filtration, thoroughly washed with H$_2$O and dried by azeotropic distillation with toluene. Yield 91% (28.2 g, 120 mmol). m.p. 180-181 °C; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 9.30 (s, 2H, $H_b$), 3.92 (s, 6H, $H_a$), $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 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)**

\[
\begin{align*}
\text{K}_2\text{CO}_3 \ (8.0 \text{ g}, \ 58.0 \text{ mmol}) \ \text{and} \ \text{Me}_2\text{SO}_4 \ (1.7\text{ml}, \ 18 \text{ mmol}) \ \text{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. NaHCO$_3$ (30 ml) aq., H$_2$O (30 ml), dried over MgSO$_4$, filtered and concentrated in vacuo. Purification by CC on SiO$_2$ (cyclohexane/EtOAc : 8/2) afforded 133 as a white solid in 83% yield. (1.5g, 6.0 mmol). m.p. 86-87 °C; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 3.97 (s, 6H, $H_a$), 3.85 (s, 6H, $H_b$); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 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. Recrystallization from MeOH afforded 134 as a white solid in 94% yield (1.9 g, 8.3 mmol). m.p. > 288 °C; $^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 13.46 (s, 2H, $H_a$), 3.90 (s, 6H, $H_b$); $^{13}$C-NMR (DMSO-$d_6$): $\delta$ 161.41, 153.34, 119.82, 61.71. Spectral data in agreement with those previously reported.$^{[1]}$
4-methoxybenzyl 3,4-dimethoxythiophene-2,5-diyldicarbamate (136)

To a solution of 134 (320 mg, 1.1 mmol) in anhydrous THF (30 ml) stirring at 0 °C, DMF (50 µl) and (COCl)₂ (204 µl, 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, Hc), 6.89 (d, J = 8.5 Hz, 4H, Hb), 6.66 (br, 2H, Hf), 5.12 (s, 4H, Hd), 3.81 (s, 6H, Ha), 3.79 (s, 6H, He); 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) v: 3351.63, 3271.65, 2959.63, 2990.81, 2545.23, 2062.88, 1726.68, 1693.95, 1614.95, 1586.48, 1571.44, 1483.18, 1444.73, 1401.39, 1365.34, 1304.73, 1203.33, 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 µl, 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,
Experimental Part

4H, δ = 8.7 Hz, 4H, H_b), 5.13 (s, 4H, H_a), 3.76 (s, 6H, H_c), 3.68 (s, 6H, H_d); 2.53 (s, 6H, H_f); 13C-NMR (100 MHz, CDCl_3): δ 171.92, 159.78, 153.32, 143.99, 129.55, 127.03, 118.73, 114.04, 59.84, 55.35, 25.96; MS (ESI^+) found for [C_{28}H_{30}N_2O_10S + 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)

![Dimethyl 2,2'-oxydiacetate](image)

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); 13C-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)

![Dimethyl 3,4-dihydroxyfuran-2,5-dicarboxylate](image)

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, dmso-d_6): δ 10.29 (br, 2H, H_b), 3.78 (s, 6H, H_a), 13C-NMR (100 MHz, 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 (2.3 g, 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. Recrystallization 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, dmsod₆): δ 13.46 (s, 2H, H_a), 3.90 (s, 6H, H_b); ¹³C-NMR (dmsod₆): 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 Et$_2$O (50 ml), and then washed with sat. NaHCO$_3$ aq. (50 ml), H$_2$O (2 x 50ml), dried over MgSO$_4$. Evaporation of the solvents in vacuo at 10 °C afforded 144 as white solid in 67% yield. (345 mg, 1.4 mmol). $^1$H-NMR (400 MHz, CDCl$_3$): δ 4.11 (s, 6H, $H_a$); $^{13}$C-NMR (100 MHz, CDCl$_3$): 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)**

![Chemical structure of 146](image)

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; $^1$H-NMR (400 MHz, dmso-d$_6$): δ 8.10 (d, $J = 9.2$ Hz, 2H, $H_e$), 7.34-7.28 (m, 10H, $H_{a,b,c,d,j,k}$), 5.93 (d, $J = 9.2$ Hz, 1H, $H_j$), 5.15 (diastereotopic porotons, $dd$, , $J_1 = J_2 = 12.8$ Hz, 2H, $H_d$), 4.99 (diastereotopic porotons, $dd$, , $J_1 = J_2 = 12.1$ Hz, 2H, $H_d$), 3.96 (s, 1H, $H_l$), 3.68 (s, 1H, $H_g$); $^{13}$C-NMR (100 MHz, CDC13): 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 [C$_{22}$H$_{22}$N$_2$O$_7$ + 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-dicarbonyl azide (152)**

![Chemical structure of 152](image)

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, Hₐ), 13C-NMR (100 MHz, CDCl₃): δ 162.38, 148.47, 120.18.

4-methoxybenzyl furan-2,5-diyldecarbamate (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-d₆): δ 10.00 (br, 2H, Hₑ), 7.56 (d, J = 8.6 Hz, 4H, Hₐ), 7.28 (d, J = 8.6 Hz, 4H, Hₗ), 5.98 (s, 2H, Hₒ), 5.09 (s, 4H, Hₑ), 3.80 (s, 6H, Hₐ); 13C-NMR (100 MHz, DMSO-d₆): 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(acetylecarbamate) (154)

To a solution of 153 (400 mg, 0.9 mmol) in pyridine (2 ml), DMAP (49 mg, 0.4 mmol) and acetyc 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, Hₗ).
Experimental Part

7.18 (d, J = 8.5 Hz, 4H, H₈), 6.22 (s, 2H, H₇), 5.07 (s, 4H, H₉), 3.76 (s, 6H, H₆); ¹³C-NMR (100 MHz, CDCl₃): 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 [C₆H₁₀N₂O₉ + 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 CH₂Cl₂ (20 ml) stirring at 0 °C a solution of triflic anhydride (10.1 ml, 61.1 mmol) in CH₂Cl₂ (10 ml) was added drop wise. The solution was stirred for 30' then was diluted with Et₂O (40 ml) 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 (pentane/ Et₂O : 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, CDCl₃): δ 4.01 (s, 6H, H₆); ¹³C-NMR (100 MHz, CDCl₃): δ 155.38, 136.21, 132.33, 118.20 (q, J_C-F = 320 Hz), 53.08; MS (ESI⁺) found for [C₁₀H₆F₆O₁₃S₂]⁺ 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 azotropic distillation with toluene. Yield 97% (1.2 g, 4.2 mmol). ¹H-NMR (400 MHz, DMSO-d₆): δ 13.83 (br, 2H, H₇), 7.57-760 (m, 4H, H₉), 7.48-7.47 (m, 6H, H₆); ¹³C-NMR (100 MHz, DMSO-d₆): δ 185.13, 148.87, 133.33, 127.48, 120.40, 118.60, 118.01, 100.00, 92.03; MS
(ESI\(^+\)) found for \([\text{C}_{22}\text{H}_{12}\text{O}_3]\) 356.0687, calc. 356.0684; IR KBr (cm\(^{-1}\)) \(\nu\) 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 \(\mu\)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 \(^\circ\)C for 5'. The crude mixture was then concentrated in vacuo and rapidly filtered through a short SiO\(_2\) plug (cyclohexane : EtOAc = 7:3). Precipitation from EtOAc/pentane afforded 161 in 33% yield (212 mg, 0.34 mmol). Decomposition before melting (93 \(^\circ\)C); \(^1\)H-NMR (400 MHz, dmso-\(d_6\)): \(\delta\) 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 \(^\circ\)C, due to the presence of rotamers, the structure at r.t. was unresolved; (ESI\(^+\)) found for \([\text{C}_{38}\text{H}_{30}\text{N}_2\text{O}_7]^+\) 649.1956, calc. 649.1945; IR KBr (cm\(^{-1}\)) \(\nu\) 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 \(^\circ\)C and stirred for 8 hrs. The mixture was diluted with EtOAc (100 ml), washed with \(1\)N HCl \(aq\). (30 ml), sat. NaHCO\(_3\) (30 ml) \(aq\.), H\(_2\)O (30 ml), dried over MgSO\(_4\), filtered and concentrated in vacuo. Purification by CC on on Al\(_2\)O\(_3\) (pentane/ Et\(_2\)O 5:5) afforded 162 as a colourless oil in 88% yield (24.0 g, 144 mmol). \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.24 (t, \(J = 2.0\) Hz, 2H, \(H_b\)), 6.22 (t, \(J = 2.0\) Hz, 2H, \(H_a\)), 1.60 (s, 9H, \(H_c\)); \(^1\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 153.92, 122.43, 112.31, 53.16, 26.44. Spectral data in agreement with those previously reported.\(^{[2]}\)
**Experimental Part**

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 °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 °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 °C. After 30’ the reaction was quenched by addition of sat. NH₄Cl aq. (20 mL) diluted with EtOAc (100 ml), washed with 1N 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 77-78 °C; ¹H-NMR (400 MHz, CDCl₃): δ 6.83 (s, 2H, H₆), 3.86 (s, 6H, H₄); 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 146-147 °C; ¹H-NMR (400 MHz, CDCl₃): δ 9.86 (br, 1H, H₅), 6.86 (s, 2H, H₆), 3.89 (s, 6H, H₄); ¹³C-NMR (100 MHz, CDCl₃): δ 160.04, 148.85, 126.80, 115.94, 86.44, 52.10. Spectral data in agreement with those previously reported.[²]

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

101
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, Hₑ,f), 7.21 (s, 2H, Hᵇ), 7.01-6.96 (m, 2H, Hᵈ), 6.18 (s, 2H, Hᶜ), 3.78 (s, 6H, Hᵃ); 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-1H-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-d₆): δ 13.39 (s, 2H, Hᵃ), δ 7.37-7.30 (m, 3H, Hₑ,f) 7.21 (s, 2H, Hᵇ), 6.90-6.84 (m, 2H, Hᵈ), 5.92 (s, 2H, Hᶜ); ¹³C-NMR (100 MHz, DMSO-d₆): 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-1H-pyrrole-2,5-diyldicarbamate (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
Experimental Part

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; 

\[ ^1H\text{-NMR (400 MHz, DMSO-d}_6\text{)}: \delta 8.98 (br, 2H, H_e), 7.33 (br, 9H, H_{a,b,l,m}), 7.20-7.19 (m, 4H, H_c) 7.00-6.98 (m, 2H, H_h), 5.81 (s, 2H, H_f), 5.02 (br, 4H, H_d), 4.89 (s, 2H, H_g), \]

the spectra was recorded at 80 °C, due to the presence of rotamers, the structure at r.t. was unresolved; \[ ^{13}C\text{-NMR (100 MHz, DMSO-d}_6\text{)}: \delta 154.96, 138.28, 136.57, 128.13, 127.87, 127.61, 126.56, 126.53, 123.78, 101.85, 65.60, 44.63; \]

MS (APCI+) found for [C\text{27}H\text{25}N\text{3}O\text{4} + H]\text{+} 456.1918, calc. 456.1914; IR KBr (cm⁻¹): 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-1H-pyrrole-2,5-diylbis(pentanoylcarbamate) (174)

\[ ^1H\text{-NMR (400 MHz, DMSO-d}_6\text{):} \delta 7.33-7.24 (m, 9H, H_{a,b,l,m}), 7.17-7.09 (m, 4H, H_f), 6.99-6.97 (m, 2H, H_d), 6.04 (s, 2H, H_e), 5.05 (s, 4H, H_g), 4.59 (s, 2H, H_j), 2.54 (t, J = 7.1 Hz, 4H, H_h), 1.41 (tt, J_1 = 7.1 Hz, J_2 = 7.2 Hz, 4H, H_k), 1.24-1.18 (m, 4H, H_h), 0.81 (t, J = 7.3 Hz, 6H, H_i), \]

the spectra was recorded at 100 °C, due to the presence of rotamers, the structure at r.t. was unresolved; \[ ^{13}C\text{-NMR (100 MHz, DMSO-d}_6\text{):} \delta 174.57, 152.68, 135.88, 135.32, 135.18, 128.39, 128.01, 127.57, 127.40, 127.21, 124.00, 105.69, 68.30, 40.45, 38.61, 26.82, 22.10, 14.29; \]

MS (ESI⁺) found for [C\text{27}H\text{25}N\text{3}O\text{6} + Na]\text{+} 646.2888, calc. 646.2877; IR KBr (cm⁻¹): 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.

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 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 174 as a colorless oil in 73% yield (400 mg, 0.64 mmol); \[ ^1H\text{-NMR (400 MHz, DMSO-d}_6\text{):} \delta 7.33-7.24 (m, 9H, H_{a,b,l,m}), 7.17-7.09 (m, 4H, H_f), 6.99-6.97 (m, 2H, H_d), 6.04 (s, 2H, H_e), 5.05 (s, 4H, H_g), 4.59 (s, 2H, H_j), 2.54 (t, J = 7.1 Hz, 4H, H_h), 1.41 (tt, J_1 = 7.1 Hz, J_2 = 7.2 Hz, 4H, H_k), 1.24-1.18 (m, 4H, H_h), 0.81 (t, J = 7.3 Hz, 6H, H_i), \]

the spectra was recorded at 100 °C, due to the presence of rotamers, the structure at r.t. was unresolved; \[ ^{13}C\text{-NMR (100 MHz, DMSO-d}_6\text{):} \delta 174.57, 152.68, 135.88, 135.32, 135.18, 128.39, 128.01, 127.57, 127.40, 127.21, 124.00, 105.69, 68.30, 40.45, 38.61, 26.82, 22.10, 14.29; \]

MS (ESI⁺) found for [C\text{27}H\text{25}N\text{3}O\text{6} + Na]\text{+} 646.2888, calc. 646.2877; IR KBr (cm⁻¹): 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)**

![Diagram of molecule](image)

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 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).

\[
\begin{align*}
\delta & = 6.92 \ (s, 2H, H_b), 6.24 \ (s, 2H, H_c), 3.85 \ (s, 6H, H_a), 3.52 \ (t, J = 8.2 Hz, 2H, H_d), 0.86 \ (t, J = 8.2 Hz, 2H, H_e), -0.07 \ (s, 9H, H_f); \\
\delta & = 161.27, 128.19, 117.72, 76.95, 65.99, 51.96, 18.03, -1.29; \\
\text{MS (ESI)} & \text{ found for } [C_{14}H_{23}NO_5Si + Na]^+ 336.1244, \text{ calc. 336.1238}; \\
\text{IR} & \text{ KBr (cm}^{-1}) v: 2953.12, 2865.13, 1733.81, 1712.21, 1528.57, 1436.18, 1375.41, 1295.18, 1233.48, 1195.42, 1169.59, 1106.74, 1075.51, 990.49, 949.70, 859.35, 836.30, 809.49, 757.13, 650.12, 492.05, 467.10, 418.15;
\end{align*}
\]

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

![Diagram of molecule](image)

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; \(^1\)H-NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 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, \(H_f\)); \(^{13}\)C-NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 161.62, 128.57, 117.72, 72.59, 64.56, 17.19, -1.14; MS (ESI) found for [C₁₂H₁₀NO₅Si + Cl]⁻ 284.1243, calc. 284.1250; IR KBr (cm⁻¹): 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,
4-methoxybenzyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1H-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 µl) 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-d₆): δ 8.94 (br, 2H, Hₑ), 7.32 (d, J = 8.2 Hz, 4H, Hᶜ), 6.92 (d, J = 8.2 Hz, 4H, Hᵇ), 5.77 (s, 2H, Hᵧ), 5.00 (s, 4H, Hᵈ), 4.96 (s, 2H, Hᵈ), 3.75 (s, 6H, Hᵃ), 3.28 (t, J = 7.1 Hz, 2H, Hʰ), 0.73 (t, J = 7.1 Hz, 2H, Hᵢ), -0.06 (s, 9H, Hⱼ); ¹³C-NMR (100 MHz, DMSO-d₆): 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 µl, 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-d₆): δ 7.15 (d, J = 8.7 Hz, 4H, Hc), 6.84 (d, J = 8.7 Hz, 4H, Hb), 5.96 (s, 2H, He), 0.86 (s, 4H, Hd), 4.67 (s, 2H, Hj), 3.70 (s, 6H, Ha), 3.25 (t, J = 8.2 Hz, 2H, Hk), 2.66 (t, J = 7.1 Hz, 4H, Hf), 1.48 (tt, J₁ = 7.1 Hz, J₂ = 7.3 Hz, 4H, Hg), 1.29-1.21 (m, 4H, Hh), 0.81 (t, J = 7.3 Hz, 6H, Hi), 0.62 (t, J = 8.2 Hz, 2H, Hl), -0.11 (s, 9H, Hm), the spectra was recorded at 100 °C, due to the presence of rotamers, the structure at r.t. was unresolved; 13H-NMR (100 MHz, DMSO-d₆): 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) v: 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-d₆): δ 9.00 (br, 2H, He), 5.76 (s, 2H, Hf), 4.95
(s, 2H, \(H_2\)), 3.35 (t, \(J = 8.0\) Hz, 2H, \(H_3\)), 2.21-2.18 (m, 4H, \(H_4\)), 1.53 (br, 4H, \(H_5\)), 1.30 (m, 4H, \(H_6\)), 0.86 (m, 6H, \(H_7\)); 1H-NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 15.72 (br, 1H, \(H_2\)), 8.60 (s, 1H, \(H_3\)), 6.35 (s, 2H, \(H_4\)), 3.80 (s, 3H, \(H_5\)); 13C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 161.53, 138.25, 139.03. Spectral data in agreement with those previously reported.\(^8\)

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

\[\text{TMS-N}_3 (5.0 \text{ g}, 43.4 \text{ mmol}) \text{ and methyl propiolate (1.74 g, 20.7 mmol) were subsequently charged into a resealable Schlenck 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\(_3\)): \(\delta\) 15.72 (br, 1H, \(H_2\)), 8.60 (s, 1H, \(H_3\)), 6.35 (s, 2H, \(H_4\)), 3.80 (s, 3H, \(H_5\)); 13C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 161.53, 138.25, 139.03. Spectral data in agreement with those previously reported.\(^8\)**

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

\[\text{NH}_2\text{NH}_2 (64\% \text{ in H}_2\text{O}) (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 \(\text{H}_2\text{O, MeOH, Et}_2\text{O. White solid, 92}\%\) yield (920 mg, 36.8 mmol). m.p. 250-251 °C; 1H-NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 15.42 (br, 1H, \(H_2\)), 9.68 (br, 1H, \(H_3\)), 8.27 (s, 1H, \(H_4\)), 4.44 (br, 2H, \(H_5\)); 3.80; 13C-NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 162.17, 139.89, 130.75. Spectral data in agreement with those previously reported.\(^6\)**

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

\[\text{NH}_2\text{NH}_2 (64\% \text{ in H}_2\text{O}) (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 \(\text{H}_2\text{O, MeOH, Et}_2\text{O. White solid, 92}\%\) yield (920 mg, 36.8 mmol). m.p. 250-251 °C; 1H-NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 15.42 (br, 1H, \(H_2\)), 9.68 (br, 1H, \(H_3\)), 8.27 (s, 1H, \(H_4\)), 4.44 (br, 2H, \(H_5\)); 3.80; 13C-NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 162.17, 139.89, 130.75. Spectral data in agreement with those previously reported.\(^6\)**
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, Hα), 8.68 (s, 1H, Hc);
13C-NMR (100 MHz, CDCl3): δ 166.23, 139.64, 131.84. Spectral data in agreement with those previously reported.[6]

1-phenethyl-3-(1H-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-d6): δ 14.13 (s, 1H, Hα), 9.01 (s, 1H, Hc), 7.71 (s, 1H, Hb), 7.27-7.25 (m, 3H, Habc), 7.20-7.17 (m, 2H, Hg), 6.25 (br, 1H, Hδ), 3.37-3.31 (m, 2H, He), 2.73 (t, J = 7.1 Hz, 2H, Hf); 13C-NMR (100 MHz, DMSO-d6): 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, Haba), 4.33 (s, 2H, Hδ); 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]
Experimental Part

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

CuSO₄ x 5 H₂O (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/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 x 40 ml), H₂O, dried over MgSO₄, filtered and concentrated in vacuo. Precipitation from CH₂Cl₂/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, DMSO-d₆): δ 13.07 (br, 1H, Hf), 8.74 (s, 1H, He), 7.33-7.31 (m, 5H, Ha,b,c) 5.60 (s, 2H, Hd); ¹³C-NMR (100 MHz, DMSO-d₆): 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 (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 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. White solid, 90% yield (510 mg, 2.7 mmol). m.p. 102-103°C; ¹H-NMR (400 MHz, CDCl₃): 8.67 (s, 1H, He), 7.34-7.30 (m, 5H, Ha,b,c) 5.80 (s, 2H, Hd); ¹³C-NMR (100 MHz, CDCl₃): δ 165.83, 141.23, 133.40, 129.52, 129.44, 128.46, 127.91, 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-d6): δ 9.01 (s, 1H, Hc), 7.71 (s, 1H, He), 7.33-7.28 (m, 10H, Ha,b,c,j,k,l), 6.25 (br, 1H, Hd), 5.58 (s, 2H, Hd), 3.37-3.31 (m, 2H, Hh), 2.73 (t, J = 7.1 Hz, 2H, Hi); (100 MHz, DMSO-d6): δ 154.33, 139.4, 134.01, 133.75, 130.66, 128.66, 127.81, 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, Ha), 3.40 (t, J = 8.3 Hz, 2H, Hb), 0.79 (t, J = 8.3 Hz, 2H, Hc), 0.01 (s, 9H, Hd); 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 x 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 x 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, Hf), 8.35 (s, 1H, He), 5.75 (s, 2H, Hd), 3.62 (t, J = 8.5 Hz, 2H, Hc), 0.93 (t, J = 8.5 Hz, 2H,
Experimental Part

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Hb, 0.01 (s, 9H, Hα), 13C-NMR (100 MHz, CDCl3): δ 164.20, 140.09, 128.28, 79.05, 68.27, 17.83, -1.40; MS (APCI) found for [C9H17N3O3Si + 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 (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 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. White solid, 88% yield (1.4 g, 5.4 mmol). m.p. 102-103°C; 1H-NMR (400 MHz, CDCl₃): 8.30 (s, 1H, He), 5.71 (s, 2H, Hd), 3.57 (t, J = 8.5 Hz, 2H, Hc), 0.88 (t, J = 8.5 Hz, 2H, Hb), -0.01 (s, 9H, Hα); 13C-NMR (100 MHz, CDCl₃): δ 165.74, 141.68, 127.90, 79.02, 68.23, 17.80, -1.43; MS (APCI⁺) found for [C₉H₁₆N₆O₂Si + 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, CDCl₃): δ 9.55 (s, 1H, Hf), 7.77 (s, 1H, He), 7.29-7.20 (m, 3H, Hk,l), 7.19-7.17 (m, 2H, Hj), 6.07 (br, 1H, Hg), 5.55 (s, 2H, Hβ), 3.62 (t, J = 8.5 Hz, 2H, HΔ), 3.32-3.27 (m, 2H, Hβ), 2.27 (t, J = 7.2 Hz, 2H, Hδ), 0.93 (t, J = 8.5 Hz, 2H, Hδ), 0.01 (s,
9H, H<sub>d</sub>; <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): 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<sup>+</sup>) found for [C<sub>17</sub>H<sub>27</sub>N<sub>5</sub>O<sub>2</sub>Si + Na]<sup>+</sup> 384.1836, calc. 384.1826; IR KBr (cm<sup>-1</sup>) 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)

CuSO<sub>4</sub> x 5 H<sub>2</sub>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<sub>2</sub>O mixture (10 ml). The mixture was stirred at r.t. for 12 hrs then was diluted with CHCl<sub>3</sub> (50 ml) washed with sat. NH<sub>4</sub>Cl aq. (2 x 40 ml), H<sub>2</sub>O, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. Precipitation from CH<sub>2</sub>Cl<sub>2</sub>/pentane afforded 206 as a white solid in 82% yield (2.6 g, 11.7 mmol). m.p. 149-150° C, <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 9.85 (br, 1H, H<sub>d</sub>), 8.45 (s, 1H, H<sub>c</sub>), 6.29 (s, 2H, H<sub>b</sub>), 1.19 (s, 9H, H<sub>a</sub>), <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ 177.87, 163.92, 139.71, 130.12, 69.87, 38.92, 26.86; Spectral data in agreement with those previously reported.<sup>12</sup>

(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 (COCl)<sub>2</sub> (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<sub>3</sub> aq. solution (4 ml), stirred for 30’, diluted with Et<sub>2</sub>O (50 ml), and then washed with sat. NaHCO<sub>3</sub> aq. (50 ml), H<sub>2</sub>O (2 x 50ml), dried over MgSO<sub>4</sub>, and concentrated in vacuo. White solid, 90% yield (2.1 g, 8.5 mmol). decomposition before melting; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 8.40 (s, 1H, H<sub>c</sub>), 6.26 (s, 2H, H<sub>b</sub>), 1.18 (s, 9H, H<sub>a</sub>), <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ 177.94, 165.62, 141.42, 129.82, 69.82, 38.91, 26.84; MS (APCI<sup>+</sup>) found for [C<sub>9</sub>H<sub>12</sub>N<sub>6</sub>O<sub>3</sub> + H]<sup>+</sup> 253.0982, calc. 253.1044; IR KBr (cm<sup>-1</sup>) ν: 3126.42, 2982.03, 2165.12, 1743.45, 1701.25, 1544.87, 1344.93, 1229.71, 1137.83, 1001.54, 954.65.
Experimental Part

(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-d₆): δ 9.14 (s, 1H, Hₜ), 7.90 (s, 1H, Hₜ), 7.27-7.21 (m, 3H, Hₕ, Hₖ), 7.20-7.17 (m, 2H, Hₗ, Hₘ), 6.24 (br, 1H, Hₜ), 3.32-3.27 (m, 2H, Hₜ), 2.27 (t, J = 6.9 Hz, 2H, Hₗ), 1.09 (s, 9H, Hₐ), ¹³C-NMR (100 MHz, DMSO-d₆): 177.88, 154.43, 138.56, 133.34, 131.7, 126.98, 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, Hₜ), 7.48 (s, 1H, Hₜ), 6.21 (s, 2H, Hₕ, Hₖ), 5.90 (br, 1H, Hₗ), 3.32-3.29 (m, 2H, Hₗ), 1.38-1.35 (m, 2H, Hₗ), 1.29-1.20 (m, 8H, Hₘ, Hₙ), 1.09 (s, 9H, Hₐ), 0.80 (t, J = 7.1 Hz, 3H, Hₗ); 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,
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3331.44, 2961.66, 2930.22, 2858.47, 1755.48, 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-(1H-1,2,3-triazol-4-yl)urea (210)

![Structural formula of 1-heptyl-3-(1H-1,2,3-triazol-4-yl)urea (210)]

1N 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-d₆): 14.23 (br, 1H, Hₐ), 8.90 (s, 1H, H₇), 7.62 (s, 1H, H₈), 6.25 (br, 1H, H₉), 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-d₆): 154.90, 130.42, 127.01, 31.80, 31.23, 30.26, 28.95, 26.83, 22.58, 14.48; MS (APCI⁺) found for [C₁₀H₁₀N₅O + H]⁺ 226.1626, calc. 226.1616; IR KBr (cm⁻¹) v: 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.

3.4 References


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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).