New Post Condensation Reactions of Biginelli three and Ugi four component products

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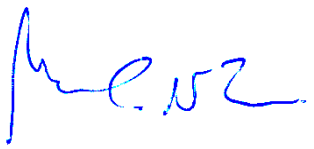
Supervisor and editor of thesis: Prof. Dr. Ludger Wessjohann

Declaration

"I declare that I have completed this dissertation without unauthorized help of a second party and only with the assistance acknowledged therein. I have appropriately acknowledged and referenced all text passages that are derived literally from or based on the content of published or unpublished work of others authors."



Martin Claudio Nin Brauer

1. Gutachter: Prof. Dr. Ludger Wessjohann
2. Gutachter: Prof. Dr. Thomas J. J. Müller
Tag der mündlichen Prüfung: 4. November 2015

Coming Back To Life

Where were you when I was burned and broken?
While the days slipped by from my window watching
Where were you when I was hurt and I was helpless
Because the things you say and the things you do surround me
While you were hanging yourself on someone else's words
Dying to believe in what you heard
I was staring straight into the shining sun

Lost in thought and lost in time
While the seeds of life and the seeds of change were planted
Outside the rain fell dark and slow
While I pondered on this dangerous but irresistible pastime
I took a heavenly ride through our silence
I knew the moment had arrived
For killing the past and coming back to life

I took a heavenly ride through our silence
I knew the waiting had begun
And headed straight into the shining sun

Pink Floyd

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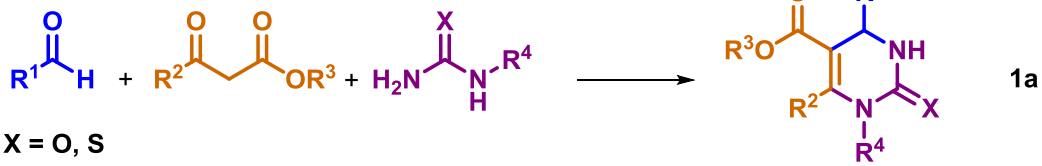
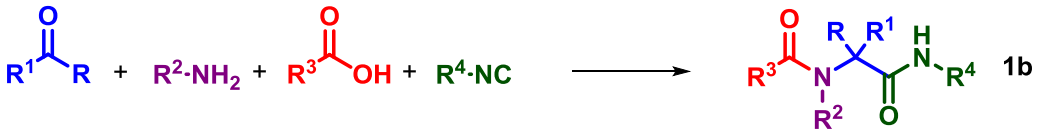
Summary

Currently, multicomponent reactions (MCRs) are seen as powerfull tools in the quest to find new synthetic approaches that accelerate drug discovery, development, as well as increase the efficiency in the synthesis of complex structures. Therefore MCRs play a prominent role in diverse scientific fields such as combinatorial chemistry, medicinal chemistry, and synthesis of natural products. Among the MCRs, there are two reactions that are particularly useful: the Biginelli three component reaction (B-3CR) (**Scheme 1a**) and the Ugi four component reaction (U-4CR) (**Scheme 1b**).

Biginelli three Component Reaction (B-3CR)



Ugi four Component Reaction (U-4CR)



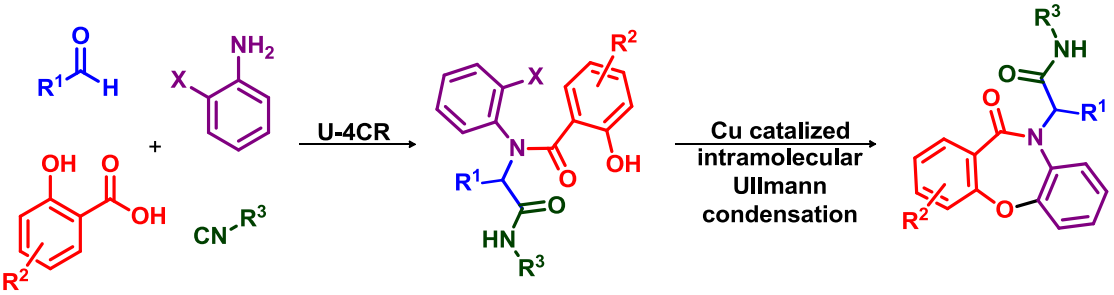
Scheme 1 (a) Biginelli three component reaction (B-3CR); **(b)** Ugi four component reaction (U-4CR).

The importance of B-3CR lies on its basic 3,4-dihydropyrimidin-2(1*H*)-(thi)ones (DHPMs) skeleton, which can appear in products that demonstrate diverse biological activities. The U-4CR is considered the most versatile isocyanide based multicomponent reaction (IMCR) with the main feature of generating a countless variety and diverse range of peptidomimetic compounds with different levels of complexity, through a highly efficient atom economical process.

The main goal of this research was to develop two-step protocols in which primary MCRs (U-4CR or the B-3CR) were coupled with other classical reactions generating compounds with a higher order of complexity.

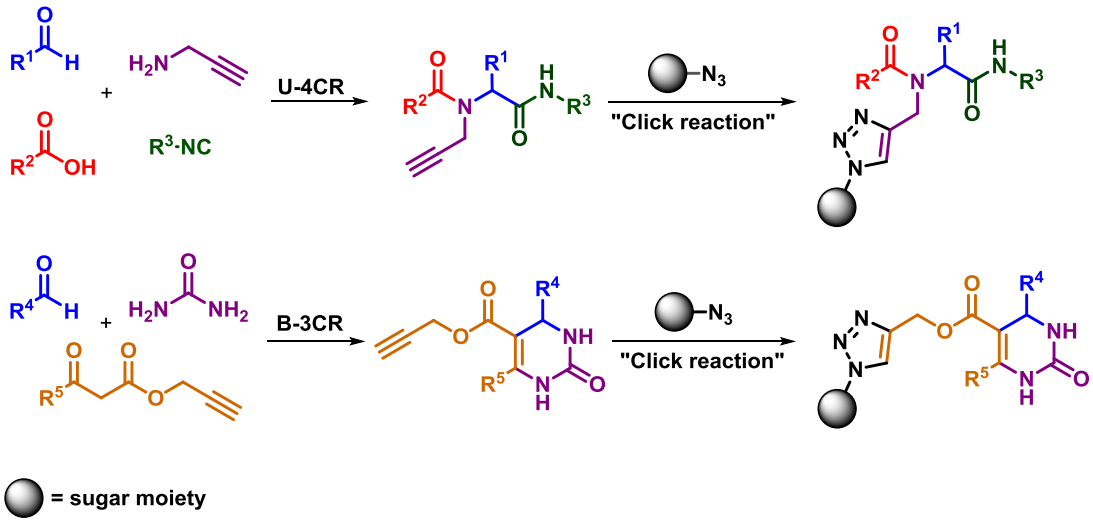
In **Chapter 1** a brief description of the general remarks as well as history of the MCRs is given. Following the general characteristics in the development and study of the B-3CR and U-4CR, an overview of the research completed on them and their applications is also described.

In **Chapter 2**, the development of a new two-step Ugi-Ullmann protocol for the synthesis of *N*-substituted dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-ones that overcomes some limitations of known protocols, is depicted (**Scheme 2**).



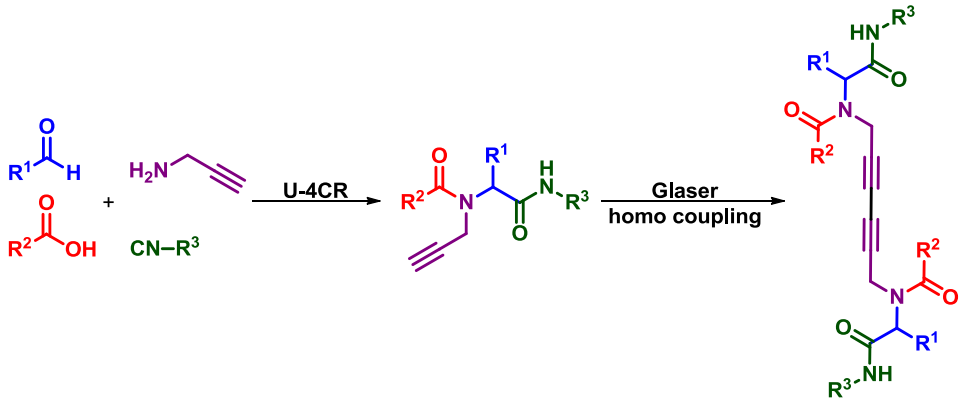
Scheme 2 Synthesis of *N*-substituted dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-ones *via* two-step U-4CR/Ullmann protocol.

In **Chapter 3**, the application of two-step Ugi-Click and Biginelli-Click reactions for the synthesis of new glycoconjugate mimics is presented (**Scheme 3**).



Scheme 3 Synthesis of glycoconjugate mimics *via* two-step U-4CR/Click and B-3CR/Click protocols.

Finally in **Chapter 4** the synthesis of new 1,3-diyne-linked dimeric peptoids employing a newly developed Ugi-Glaser coupling reaction protocol is described. (**Scheme 4**)

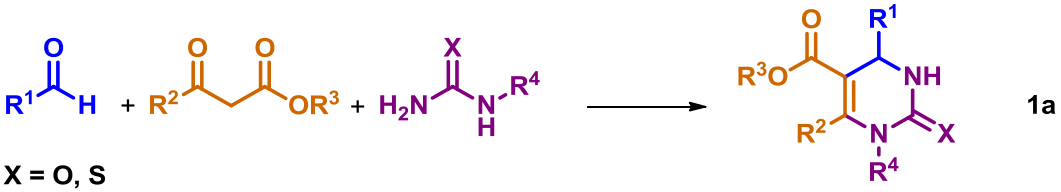


Scheme 4 Synthesis of 1,3-diyne-linked dimeric peptoids *via* new developed U-4CR/Glaser protocol.

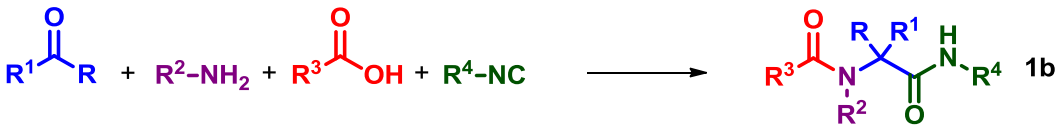
Zusammenfassung

Heutzutage werden Mehrkomponentenreaktionen (*englisch Multi Component Reactions*) (MCRs) als leistungsfähiges Werkzeug bei der Suche nach neuen synthetischen Ansätze, welche die Arzneimittelforschung, die Entwicklung als auch die Effizienz bei der Synthese von komplexen Strukturen beschleunigen, gesehen. Daher spielen sie eine wichtige Rolle in verschiedenen wissenschaftlichen Bereichen wie der kombinatorischen Chemie, der medizinischen Chemie und der Synthese von Naturstoffen. Unter den MCRs gibt es zwei Reaktionen, die besonders nützlich sind: die Biginelli Drei-Komponenten-Reaktion (*englisch Biginelli three Component Reaction*) (B-3CR) (**Schema 1a**) und die Ugi Vier-Komponenten-Reaktion (*englisch Ugi four Component Reaction*) (U-4CR) (**Schema 1b**).

Biginelli Drei-Komponenten-Reaktion (B-3CR)



Ugi Vier-Komponenten-Reaktion (U-4CR)



Schema 1 (a) Biginelli Drei-Komponenten-Reaktion (B-3CR); **(b)** Ugi Vier-Komponenten-Reaktion (U-4CR).

Die Bedeutung von B-3CR liegt im Wesentlichen in der Grundstruktur des 3,4-dihydropyrimidin-2(1*H*)-(thi)one (DHPMs), Produkte die vielfältige biologische Aktivitäten zeigen.

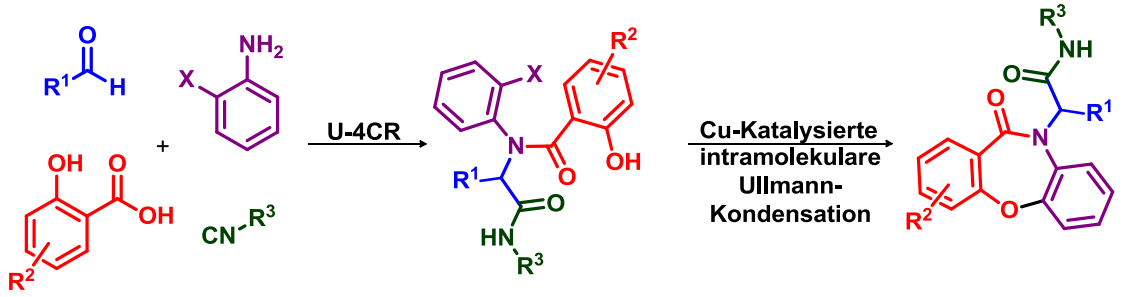
Die U-4CR wird als bedeutendste Isocyanid-basierte Mehrkomponenten-Reaktion (IMCR) angesehen. Hauptmerkmale sind die Erzeugung einer Vielfalt peptidomimetische Verbindungen mit teils hoher Strukturkomplexität, hohe Effizienz und Atomökonomie.

Das Hauptziel dieser Forschung war es, neue Zwei-Schritt-Protokolle zu entwickeln, in welchen hauptsächlich MCRs (U-4CR oder B-3CR) mit anderen klassischen Reaktionen gekoppelt worden sind, wodurch Verbindungen mit einer höheren Komplexität und idealerweise Funktionalität erzeugt werden können.

Kapitel 1 beinhaltet allgemeine Bemerkungen sowie die Geschichte der MCRs. Im Anschluss an die allgemeinen Merkmale in der Entwicklung und der Untersuchung

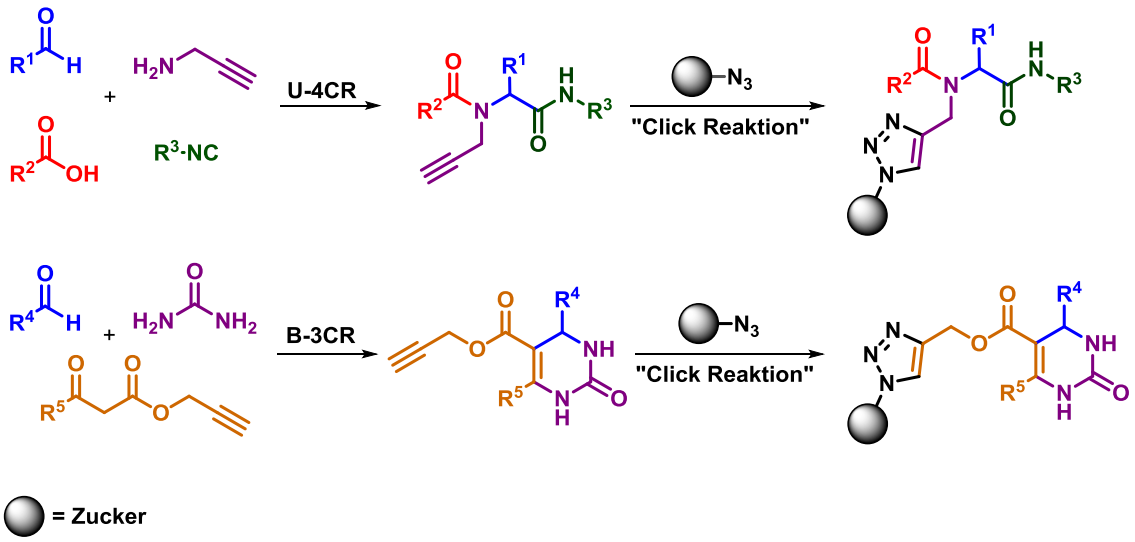
der B-3CR und U-4CR, wird ein Überblick über die Forschung an ihnen und ihren Anwendungen beschrieben.

Kapitel 2 stellt die Entwicklung eines neuen Zwei-Schritte-Ugi-Ullmann-Protokolls dar, das Einschränkungen der bekannten Protokolle für die Synthese von *N*-substituierten Dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-onen überwindet (**Schema 2**).



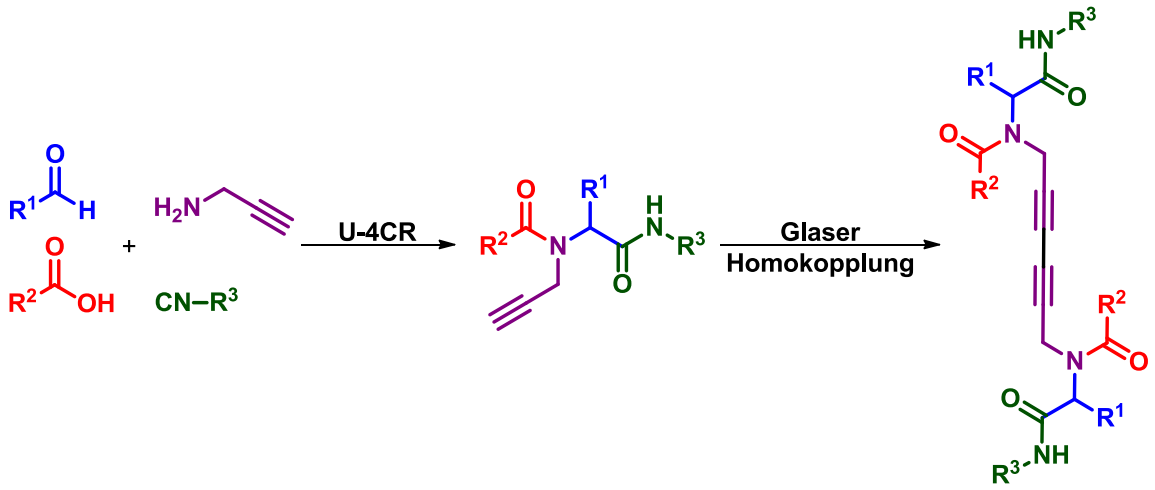
Schema 2 Synthese von *N*-substituierten Dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-onen *via* Zwei-Schritte-U-4CR-Ullmann-Protokoll.

Im **Kapitel 3** wird die Anwendung der Zwei-Schritte-Ugi-Click und Biginelli-Click-Reaktionen zur Synthese neuer Glycoconjugat-Mimetika vorgestellt (**Schema 3**).



Schema 3 Synthese von Glycoconjugat-Mimetika *via* Zwei-Schritte-U-4CR-Click und B-3CR-Click Protokolle.

Schließlich wird im **Kapitel 4** die Synthese neuer 1,3-diinverknüpfter dimerer Peptoide unter Einsatz eines neu entwickelten Ugi-Glaser-Kopplungs-Protokolls beschrieben. (**Schema 4**).



Schema 4 Neu entwickelten U-4CR-Glaser-Homokopplung Protokoll.

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Table of Abbreviations

μW	microwave irradiation	h	hour(s)
Ac	acetyl	HRMS	high resolution mass spectrum
B-3CR	Biginelli three component reaction	Hz	Hertz
Bn	benzyl	*i*-	*iso*-
Boc	*tert*-butoxycarbonyl	IC_{50}	median inhibitory concentration
brs	broad singlet (in NMR)	i.e.	*id est* (that is)
^{o}C	degrees Celcius (centigrade)	IMCR	isocyanide multicomponent reaction
calcd	calculated	*J*	coupling constant (in NMR)
CAN	cerium (IV) nitrate	m	multiplet (in NMR)
Cbz	benzyloxycarbonyl	m	milli
CuTC	copper(I)-thiophene-2-carboxylate	M	molar
d	doublet in NMR	M-3CR	Mannich three component reaction
DCM	dichloromethane	MCR	multicomponent reaction
DFT	density functional theory	Me	methyl
DHPM	3,4-dihydropyrimidin-2(1*H*)-(thio)one	min	minute(s)
DMAP	4-dimethylaminopyridine	mp	melting point
DMF	*N*,*N*-dimethylformamide	MS	mass spectrometry
DMSO	dimethylsulfoxide	NMR	nuclear magnetic resonance
e.g.	*exempli gratia* (for example)	Nu	nucleophile
equiv	equivalent	*p*-	*para*-
ESI	electronspray ionization	Ph	phenyl
Et	ethyl	ppm	parts per milion
et al.	*et alia* (and others)	PS-TBD	(7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene)
FT-ICR	Fourier transformation ion cyclotron resonance	*p*-TSA	*para*-toluenesulfonic acid
g	gram(s)	q	quartet (in NMR)

R_f	retention factor
r.t.	room temperature
s	singlet (in NMR)
S-3CR	Strecker three component reaction
t-	*tert*-
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
U-4CR	Ugi four component reaction

Chapter 1

The Biginelli three component and the Ugi four component reactions*

Abstract

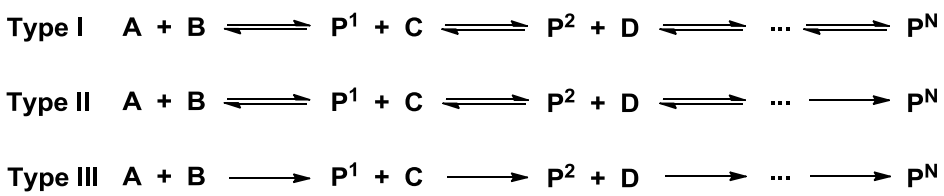
For decades, organic synthetic chemists have dealt with the difficulties surrounding one goal: obtaining highly functionalized complex molecules that could be produced efficiently in a shorter time and manner. Such an aim, which seemed to be almost impossible, could finally be achieved through the multicomponent reactions (MCRs). Among the MCRs, there are two reactions that are particularly useful: the Biginelli three component reaction (B-3CR) and the Ugi four component reaction (U-4CR). The importance of B-3CR remains principally on its products, 3,4-dihydropyrimidin-2(1*H*)-(thio)ones (DHPMs), which present a large range of biological activities. In turn, the U-4CR is the most versatile isocyanide based multicomponent reaction (IMCR). Its main feature is the generation of a countless variety and diverse range of peptidomimetic compounds with applications in the fields of synthesis, pharmacology and materials science. The aim of this chapter is to give a brief overview of the main aspects of these two MCRs.

* Part of this chapter has been published in: Neves Filho, R. A. R.; Brauer, M. C. N.; Palm-Forster, M. A. T.; de Oliveira, R. N.; Wessjohann, L. A. *Recent Patents on Catalysis* **2012**, *1*, 51.

1.1 Multicomponent Reaction: definition, short history and overview

Multicomponent reactions (MCRs) are chemical transformations that start with three or more different materials and react in a one-pot process. In MCRs, such differentiated starting materials, are converted into a new product that contains the majority of the atoms of the educts. One of the consequences is that at least two new chemical bonds are formed.[1,2] The MCRs (principally the types II and III see **Scheme 1.1.1**) are highly convergent processes that can lead to high structural diversity and molecular complexity, high overall yields, short reaction times, and ideally are easy to carry out. The fact that they take place in one-pot means that the cost and time invested in the MCRs are drastically reduced in comparison to other kinds of reactions. At the same time, many MCRs are also considered to be environmentally friendly.

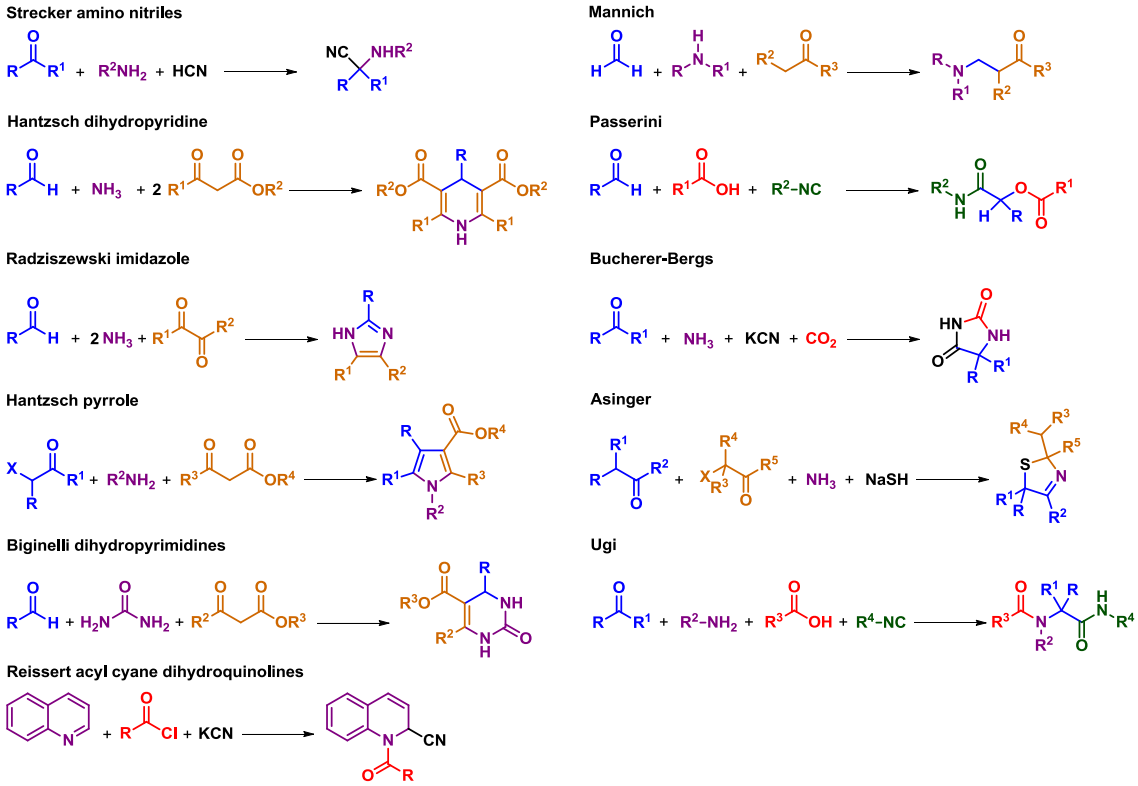
In this type of chemical transformation, the product formation does not occur in a simultaneous single step. It is rather the result of partial two-component-reactions. Based on the reversibility or irreversibility of these bimolecular events occurring in the MCR, Ugi has suggested classifying them in three general types shown in **Scheme 1.1.1**.[1,3,4]



Scheme 1.1.1 Three general MCR types suggested by Ugi.[1,3,4]

In the MCR of type I there is a mobile equilibrium between the partial reactions of educts, intermediates and final products. One example of this kind of MCR is the classical α-aminoalkylation of nucleophiles. In the processes of type I the yield may vary depending on the nature of the products, formed intermadiates and/or their stability. In the vast majority of the cases, the results are a complex mixture of products, intermediates and starting materials that are difficult to isolate. In turn, the MCRs of type II show equilibria between the starting materials and the intermediates and the partial reaction to the final product is an irreversible process. The formation of heterocycle products and the isocyanide-based MCRs (IMCRs) are examples of type II reactions. Finally, MCRs of type III are sequences of irreversible sub-reactions that proceed from educts to final products. While MCRs of type III in preparative chemistry are rare, most of the biochemical transformations in nature are usually of type III.

Reports of MCRs can be traced back to more than one and a half centuries ago, the first reaction being of bitter almond oil, ammonia and hydrogen cyanide that formed cyanohydrin imines as poorly soluble products as published by Laurent and Gerhardt in 1838.[5] Despite the existence of this early publication the preparative chemistry of MCRs is considered to officially have been started in 1850 with the Strecker synthesis of α-cyano amines.[6] A number of classical MCRs were reported in the late nineteenth and early twentieth centuries such the Hantzsch dihydropyridine synthesis (1882),[7] the Radziszewski imidazole synthesis (1882),[8] the Hantzsch pyrrole synthesis (1890),[9] the Biginelli dihydropyrimidine reaction (1891),[10] the Reissert reaction (1905),[11] the Mannich reaction (1912),[12] the Bucherer-Bergs hydantoin synthesis (1929),[13] and the Asinger reaction (1956)[14] (see **Scheme 1.1.2**).



Scheme 1.1.2 Classical MCRs.

Among the MCRs, there are two that are particularly important: the Passerini three-component reaction (P-3CR) and the Ugi four-component reaction (U-4CR). Both reactions include isocyanides. Isocyanides are compounds whose main feature is the reactivity similar to carbenes, i.e. they can react with nucleophiles and electrophiles at the same time.

The synthesis of α-acyloxycarboxamides from carboxylic acids, carbonyl compounds and isocyanides, introduced by Passerini (P-3CR) in 1921, was the first

isocyanide based multicomponent reaction (IMCR) reported.[15] At this time, only a few isocyanides and methods for their preparation where known.[16] In 1958, Ugi reported a preparation of isocyanides by dehydration of *N*-formylamines.[17] One year later, in 1959, Ugi and his co-workers introduced the four component condensation of the isocyanides, carboxylic acids, amines and aldehydes, later named Ugi four component reaction (U-4CR),[18-20] which nowadays is considered a milestone of MCR chemistry.

In the three decades following Ugi's 1958 report, the research on MCRs took place mainly in an academic setting. Since then, some developments such as the diastereoselective MCRs (S-3CR, B-3CR, M-3CR), the isolation and investigation of isocyano natural products, the general approaches for synthesis of isocyanides (included chiral ones), as well as the application of MCRs for the synthesis of natural products, had yet to be studied.

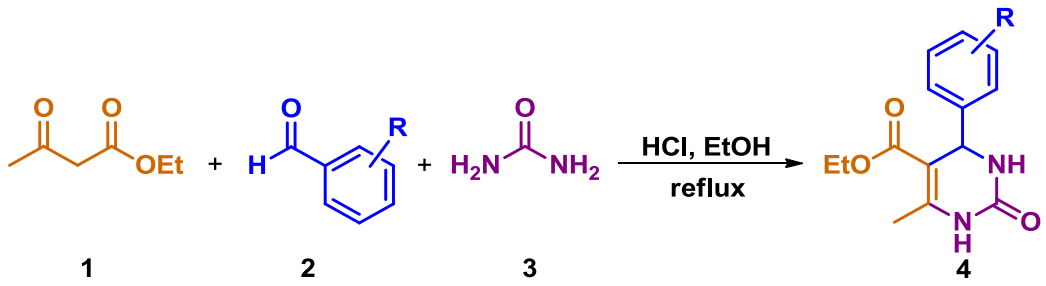
Since the early 1990s the pharmaceutical industry realized that MCRs are a powerful tool in the quest to find new synthetic approaches that accelerate drug discovery, and that it can increase the efficiency of the synthesis of complex structures. The advantages of MCRs, when compared with other, traditional approaches, are the reduced reaction times, high overall yield, simplicity of performance, low cost, safety, and environmental acceptability. All the listed advantages, together with the emergence of new analytical methods and the combinatorial chemistry, have as consequence led to an exponential growth in the interest around the research both in academic and in industrial settings for this kind of reactions.

In the following two sections, the focus will be on the Biginelli three component reaction (B-3CR) and the Ugi four component reaction (U-4CR) in terms of mechanism, scope and application.

1.2 The Biginelli three component reaction (B-3CR)

1.2.1 Mechanistic aspects

In 1893, Pietro Biginelli reported the acid catalyzed reaction between ethyl acetoacetate (**1**), aromatic aldehydes **2**, and urea (**3**) in ethanol at reflux furnishing as products 3,4-dihydropyrimidin-2(*1H*)-ones (DHPM) **4** that were easy to isolate as they precipitate after the reaction is cooled down. Later these reactions became known as the Biginelli three component reactions (B-3CR) (**Scheme 1.2.1**).[10]



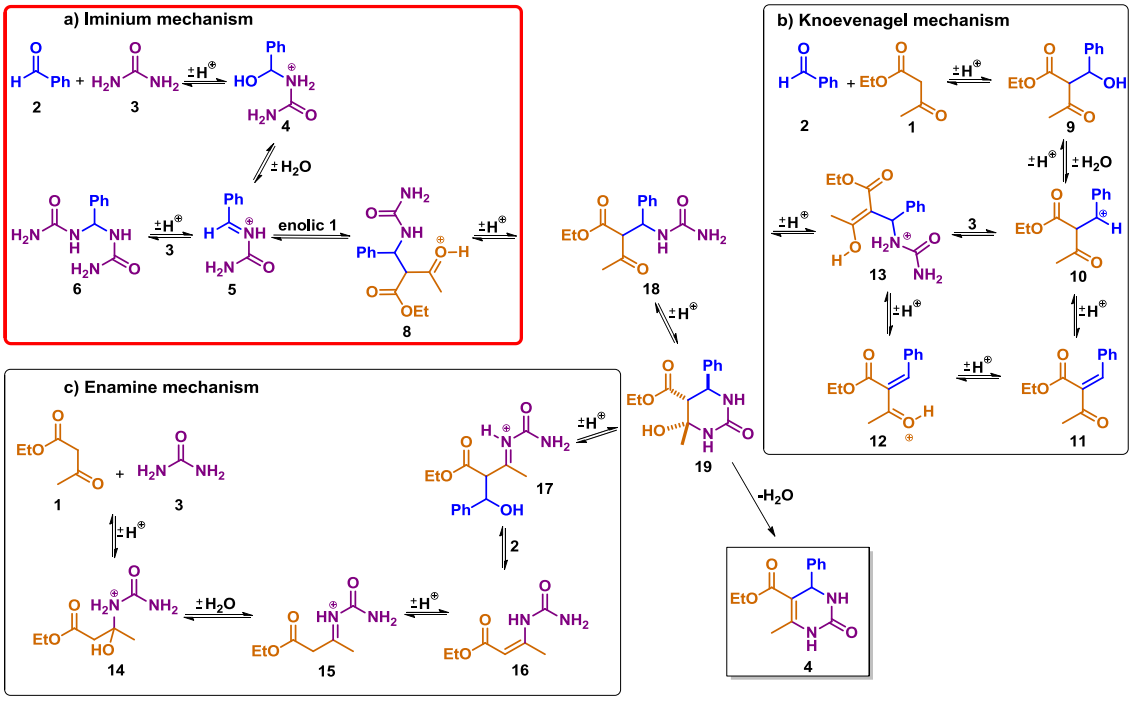
Scheme 1.2.1 The classical Biginelli three component reaction (B-3CR) and its products 3,4-dihydropyrimidin-2(*1H*)-ones (DHPM).

The B-3CR was neglected for decades because it had a narrow scope of educts (variations were only possible for the aldehyde moiety) to furnish the DHPM products in low to moderate yields.[10]

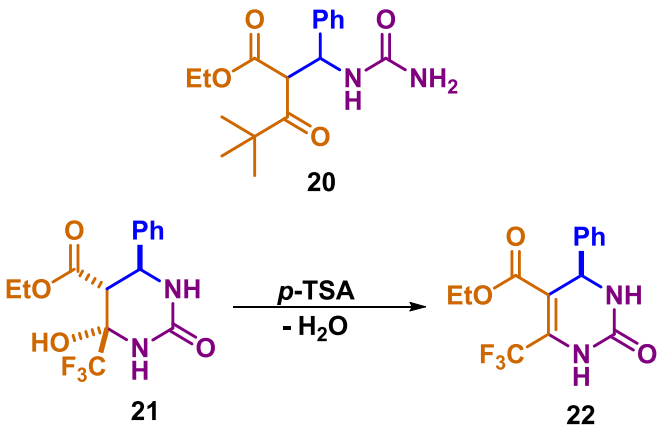
In the early 1930s, Folkers and Johnson[21] suggested that the bisureide **6** (**Scheme 1.2.2a**) furnished by the bimolecular condensation of benzaldehyde (**2**) and urea (**3**), is the first intermediate in this reaction. By early 1970s, Sweet and Fissekis[22] presented a more detailed interpretation of the mechanism. The authors postulated that the formation of key intermediate carbenium ion **10** (**Scheme 1.2.2b**) is the first and rate limiting step of B-3CR.

Around the end of the 1990s, Kappe,[23] using ^{1}H and ^{13}C NMR spectroscopy and trapping experiments, re-examined the mechanism reported by Sweet and Fissekis[22] and proposed a new one, in which the nucleophilic addition of urea (**3**) to benzaldehyde (**2**) resulted in intermediate **4** as a rate-determining (slow) step of the process (**Scheme 1.2.2a**). Later, employing bulky or electron-deficient acetoacetates, Kappe was able to isolate intermediates **20** and **21**, and obtained the DHPM **22** by dehydration with *p*-toluenesulfonic acid (**Scheme 1.2.3**). Further studies employing DFT calculations, such as the one by Zhuo et al.,[24] supported the mechanism proposed by Kappe. Of special interest are the ESI-MS, ESI-MS/MS experiments and additional DFT calculations carried out by De Souza et al.,[25] which provided a detailed picture of the mechanism of the B-3CR. In this study, the authors examined the Biginelli reaction under three and two-component conditions. With this they detected the intermediates **9** and **12** (**Scheme 1.2.2b**) which Kappe was not able to observe in his previous NMR based studies. Moreover, De Souza showed that the Knoevenagel pathways are too slow and, as a consequence, such pathway is not especially significant in the Biginelli reaction. Furthermore, De Souza et al. observed only a single early intermediate **14** associated with the enamine mechanism (**Scheme 1.2.2c**), confirming Kappe´s suggestion that the enamine mechanism pathway is dormant in the B-3CR and that **14** reverts to reagents during the course of the B-3CR reaction. The most accepted mechanism for the B-3CR

under Brønsted acid catalyzed conditions is the following: nucleophilic addition of urea (**3**) to benzaldehyde (**2**) resulting in intermediate **4** as a rate-determining step (slow). The intermediate **4** undergoes rapid dehydration under acidic conditions to form *N*-acyliminium ion **5** (fast). A second addition of urea (**3**) to iminium ion **5** can take place. The 1,3-dicarbonyl compound (**1**) is intercepted by iminium ion **5** in its enolic form furnishing the open chain ureide **18** that cyclized to the hexahydropyrimidine **19**. Subsequent elimination of water from **19** leads to DHPM **4** (**Scheme 1.2.2a**).

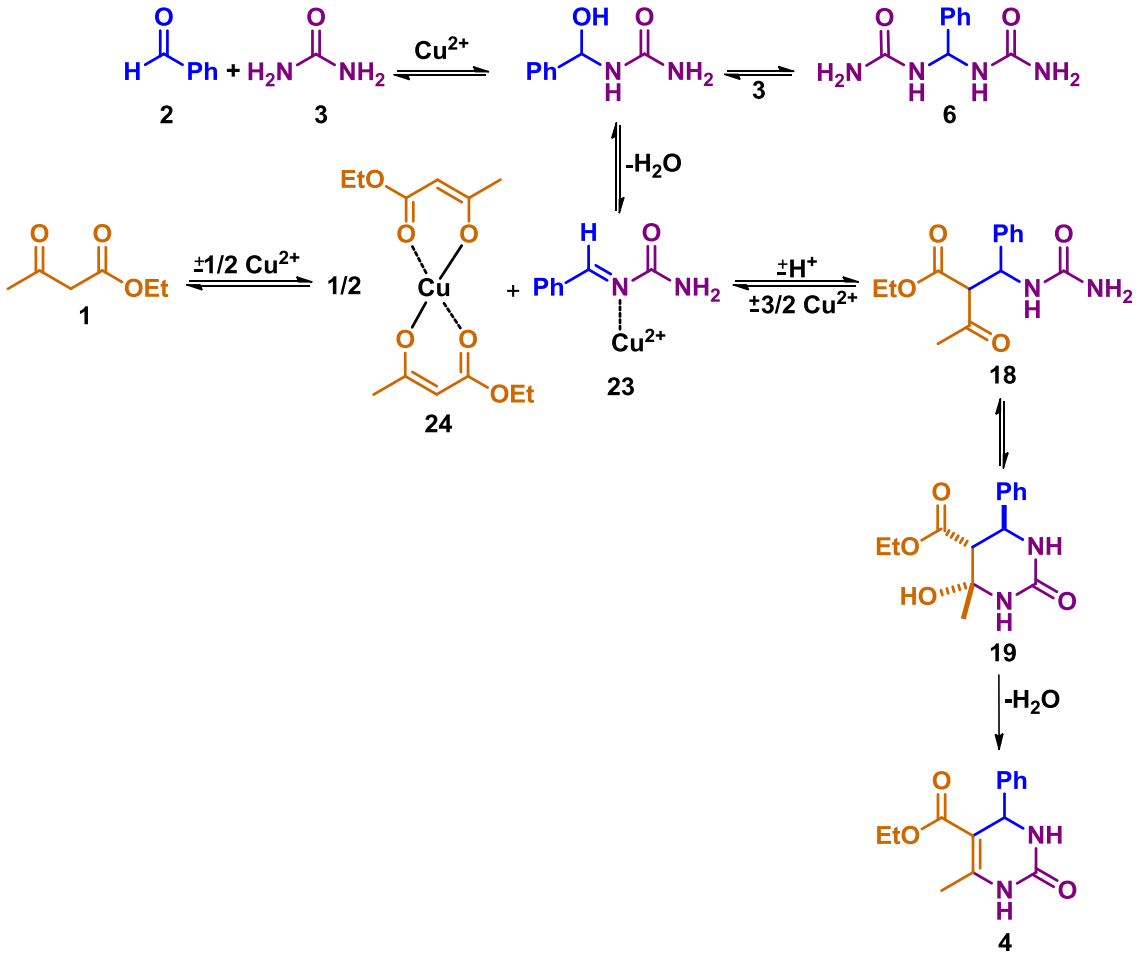


Scheme 1.2.2 B-3CR under Brønsted acid catalysis: **(a)** most accepted iminium mechanism proposed by Kappe, **(b)** Knoevenagel mechanism proposed by Folkers and Johnson, **(c)** Enamine mechanism.



Scheme 1.2.3 Intermediates **20**, **21** isolated by Kappe when sterically bulky or electron-deficient acetoacetates are employed.

Nowadays, Lewis acid catalysts such as $CuCl_2$, are extensively used in B-3CR. Many authors sustain a very similar mechanism to the one proposed by Kappe.[23] The only difference is that the metal complexed with imine and ß-ketoester results in the formation of a metal-acylimine and metal-ß-keto ester enolate complex intermediate such **23** and **24,** respectively (**Scheme 1.2.4**).[26,27]

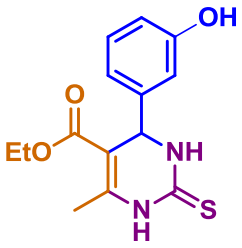


Scheme 1.2.4 Proposed mechanism of B-3CR Lewis acid catalyzed.

However, more recent works show that an understanding of the mechanism of the Lewis acid B-3CR is still pending. Kolosov et al.[28], for example, presented new data that re-opened the debate around the mechanism of B-3CR. These authors argue that Kappe´s mechanism is plausible only for Brønsted acid catalyzed B-3CRs and is no longer valid in the case of Lewis acid catalyzed, or uncatalyzed reactions. In turn, Ramos et al.[29] in NMR spectroscopy and ESI-MS based studies suggested that the mechanism of Lewis acid catalyzed B-3CR is more complex than it was believed until now. The B-3CR can be both Brønsted base catalyzed[30] and organo catalyzed.[31] In these cases, other types of mechanisms are proposed but will not be discussed herein.

1.2.2 Scope, methods and catalysts in B-3CR

As mentioned above, the B-3CR was limited to a narrow scope for a long time after its discovery. The educts were restricted to aromatic aldehydes substituted with eletron-withdrawing groups in *m-, p*-positions, *C-H* acidic acetoacetates, and (thio)urea, catalyzed by strong Brønsted acids such as HCl and H_2SO_4 in protic solvents such as methanol and ethanol under reflux conditions.[28] During the 1970s, the interest in the B-3CR started increasing slowly. This scenario changed in 1999 after the discovery of the biological activity of simple DHPMs like Monastrol (**Figure 1.2.1**).[32] This triggered an increasing interest in the Biginelli reaction which continues until today.

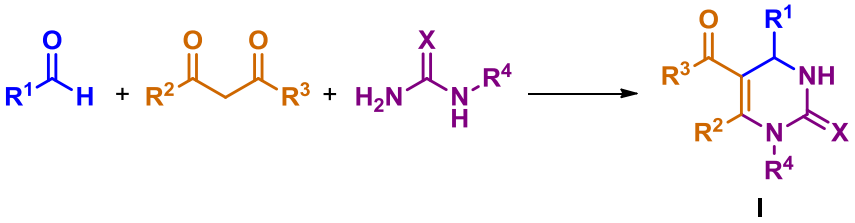


Monastrol

Figure 1.2.1 Structure of the inhibitor of kinesin Eg5, Monastrol.

Recent reviews list new catalysts for the B-3CR from the last two decades. Lewis acids catalyst in form of their halides, methanesulfonates, perchlorates, nitrates, acetates and other salts of internal and external transition metals, solid acid catalysts (clays), Brønsted acids, achiral and chiral organocatalysts and biocatalyst were used.[28,33-35]

The modifications were not only in catalystis, but also reaction conditions (e.g. by using aprotic solvents such as acetonitrile, DMF, THF, dioxane, dichlorethene, dichloromethane, and toluene). Depending on the catalyst, the reaction can be carried out at room temperature, in solvent-free conditions, on solid-phase or fluorous-phase. In addition, protocols that employ microwave or ultrasound irradiation as the energy source for reagent activation have been developed.[33-35] All these improvements provide an enhancement of the yields and dramatic reduction of the reaction times of the classical Biginelli reaction (**Scheme 1.2.5**).[7]

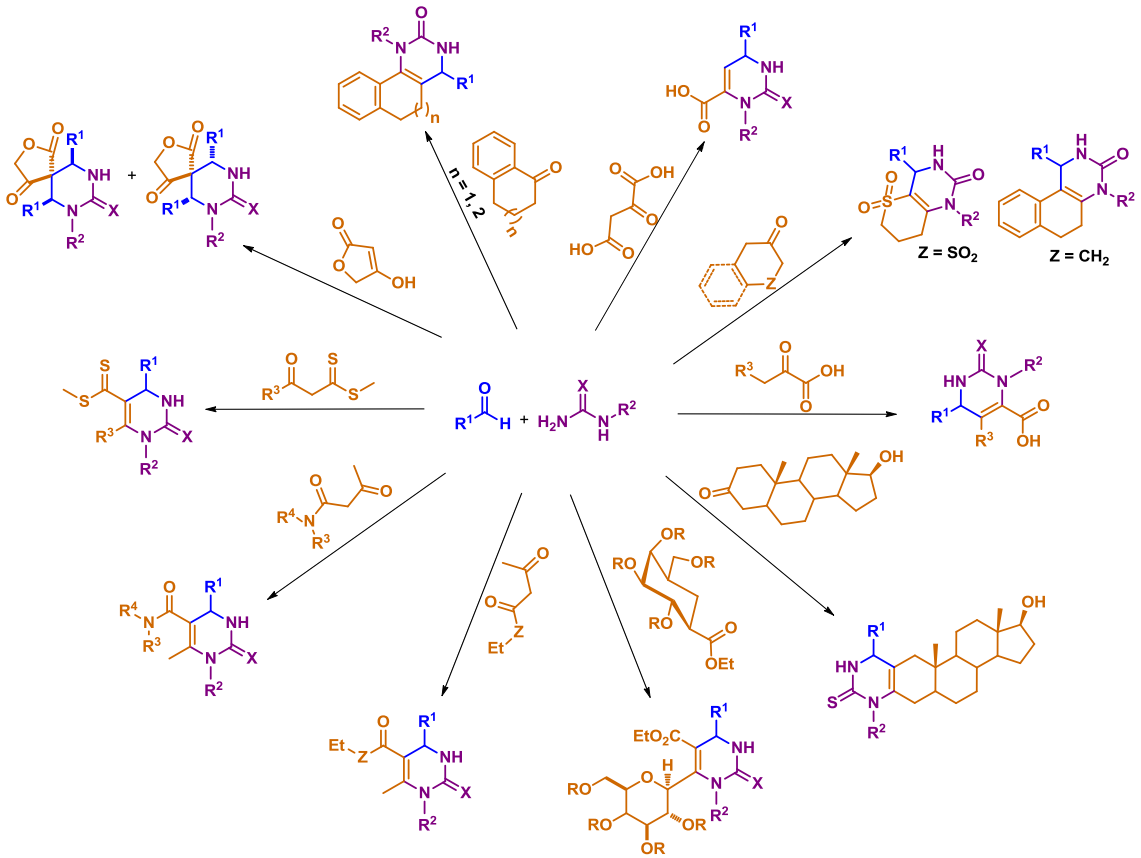


I

R^1 = aryl, alkyl
R^2 = aryl, alkyl
R^3 = aryl, alkoxy
R^4 = H, aryl, alkyl
X = O, S

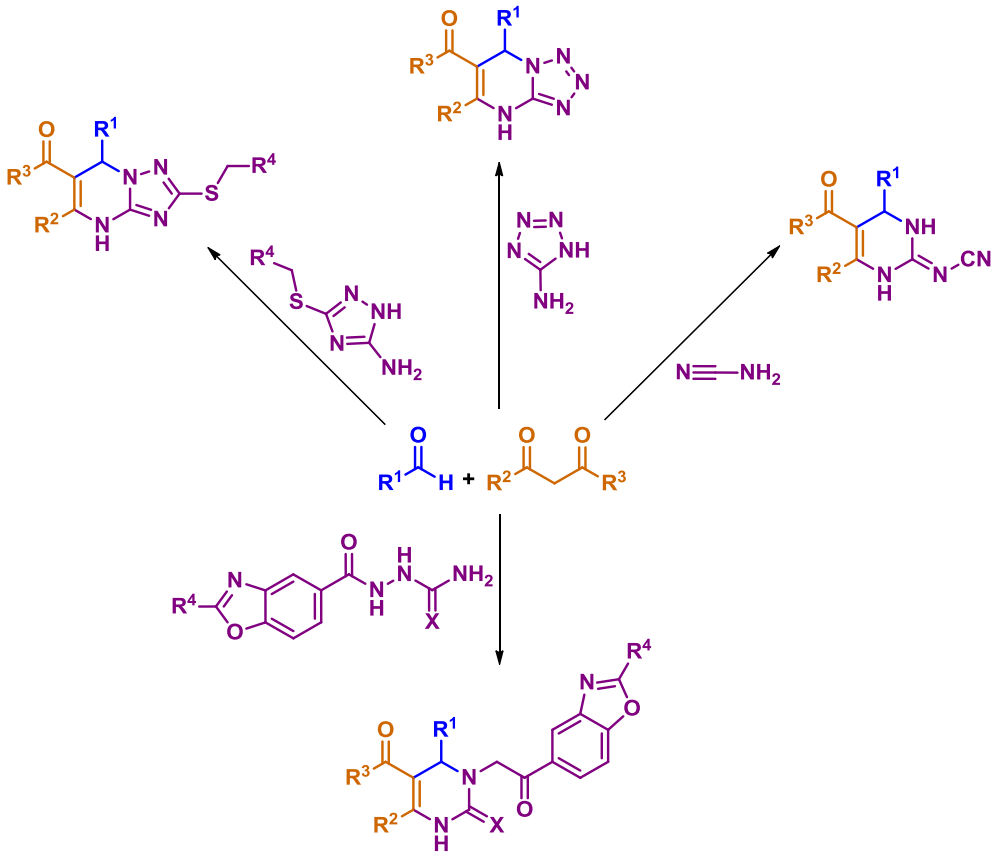
Scheme 1.2.5 Scope of classical B-3CR.

Moreover, the discovery of new 3CRs, in which one or more starting materials differ from the classical ones (the so-called Biginelli-like reactions) enables the generation of DHPM derivatives possessing new substitution motifs that also differ from the classical DHPM motif **I** (**Scheme 1.2.6**).[33-35] The component that displays highest variability is the dicarbonylic one.

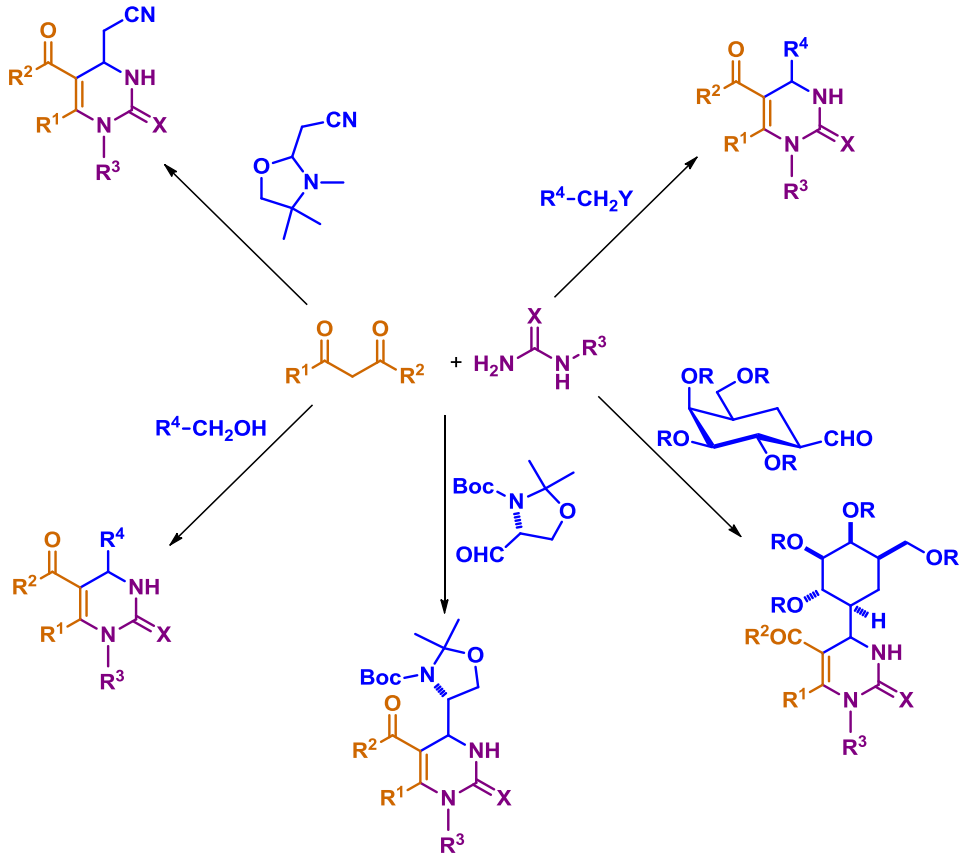


Scheme 1.2.6 DHPM derivatives generated with dicarbonylic components alternative as educts in B-3CR.

Also, urea can be substituted by thiourea compounds (**Scheme 1.2.7**), as well as aldehydes alternative and even ketones can be used (**Scheme 1.2.8**).[33-36]

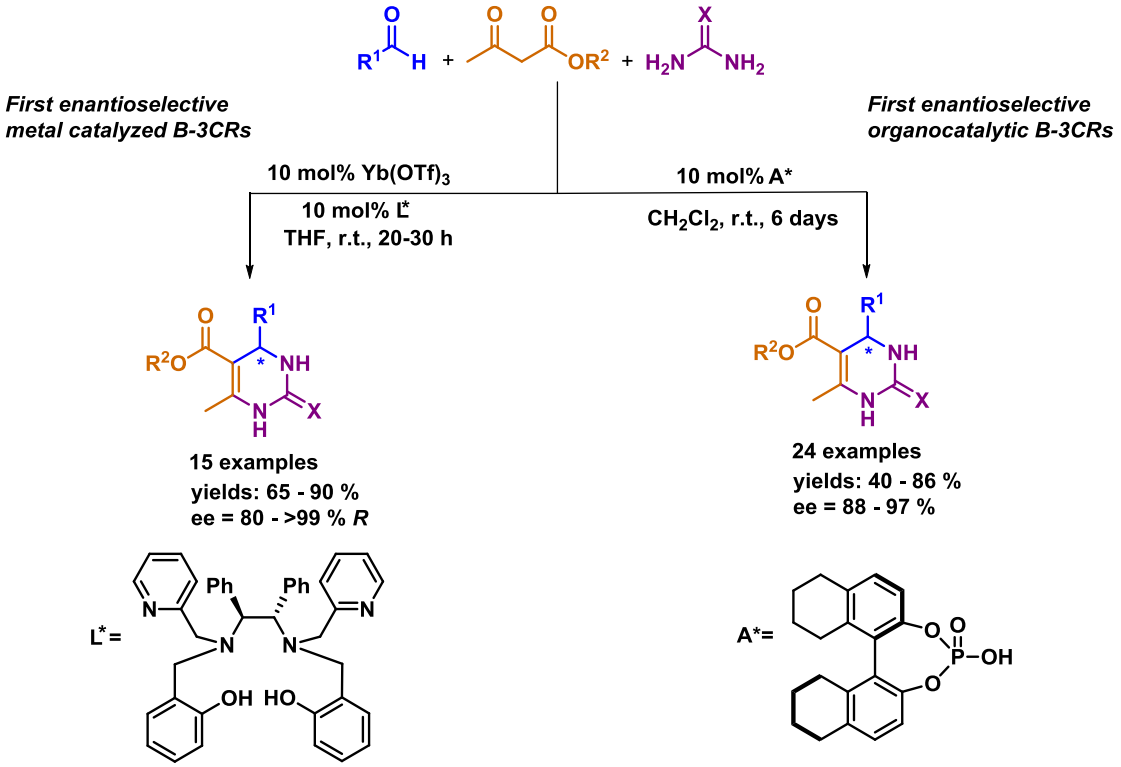


Scheme 1.2.7 DHPM derivatives generated with urea or thiourea as educts in B-3CR.



Scheme 1.2.8 DHPM derivatives generated with aldehydes alternative as educts in B-3CR.

Studies have shown that biological activities of the DHPMs are dependent on the absolute configuration at position *C*-4 (see **Scheme 1.2.10**).[37] In former times, obtaining the enantiopure Biginelli compounds relied only on enzymatic and chemical resolution, and chiral auxiliary-assisted asymmetric synthesis protocols. This has recently changed with the report of the first enantioselectively catalyzed reactions by asymmetric metal complexes[38] (**Scheme 1.2.9 left**) followed by an organocatalytic[39] B-3CRs (**Scheme 1.2.9 right**).



Scheme 1.2.9 First enantioselective metal ion catalyzed and first enantioselective organocatalytic B-3CR.

To date, several organocatalysts have been reported for asymmetric B-3CRs.[40,41] Examples of organocatalysts are depicted in **Figure 1.2.2**.

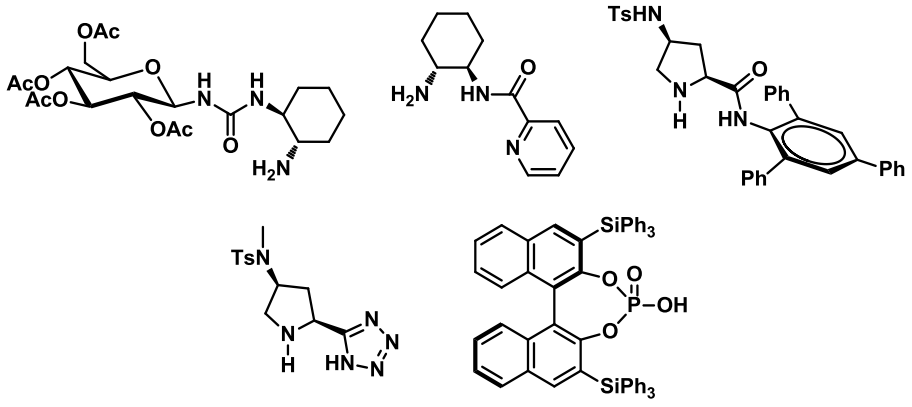
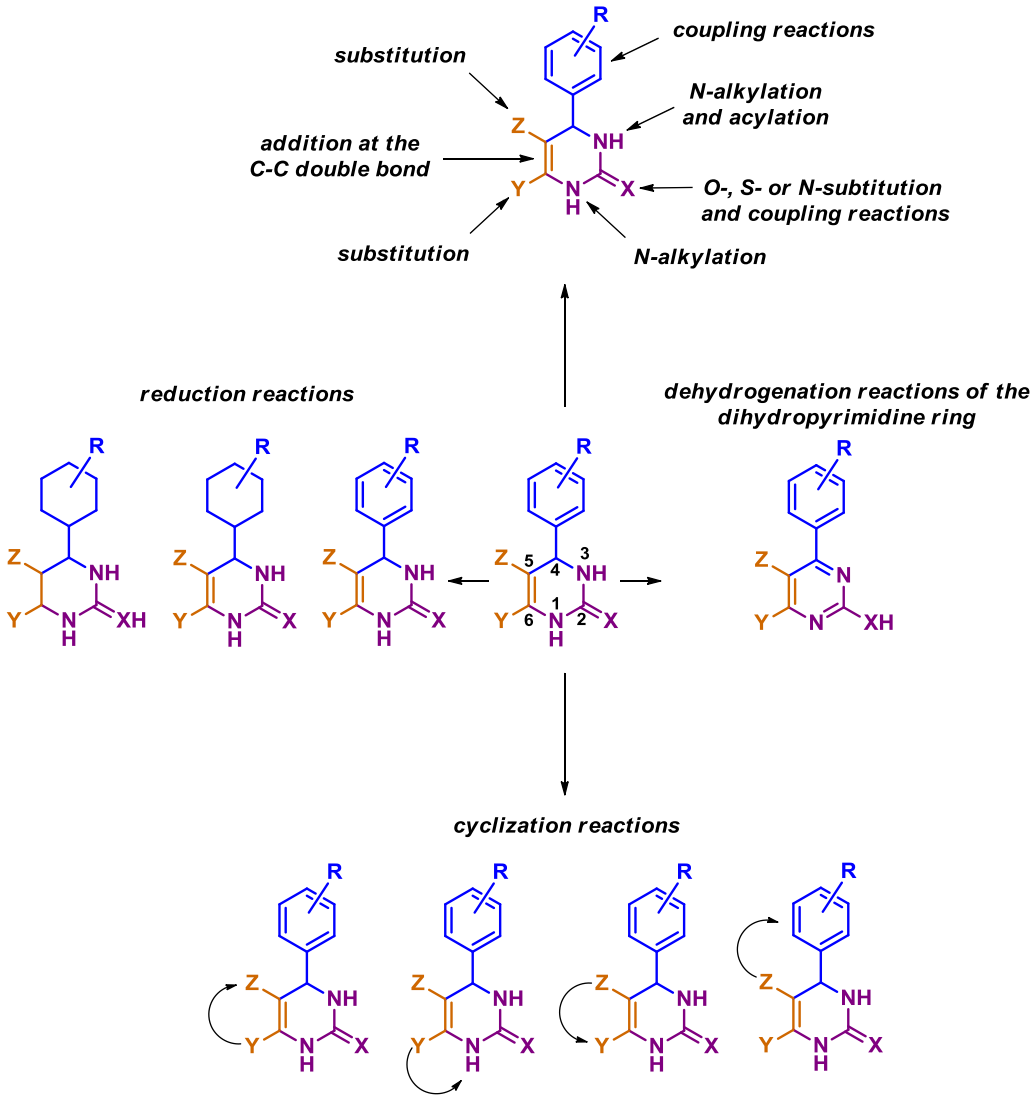


Figure 1.2.2 Examples of organocatalysts used in B-3CR.

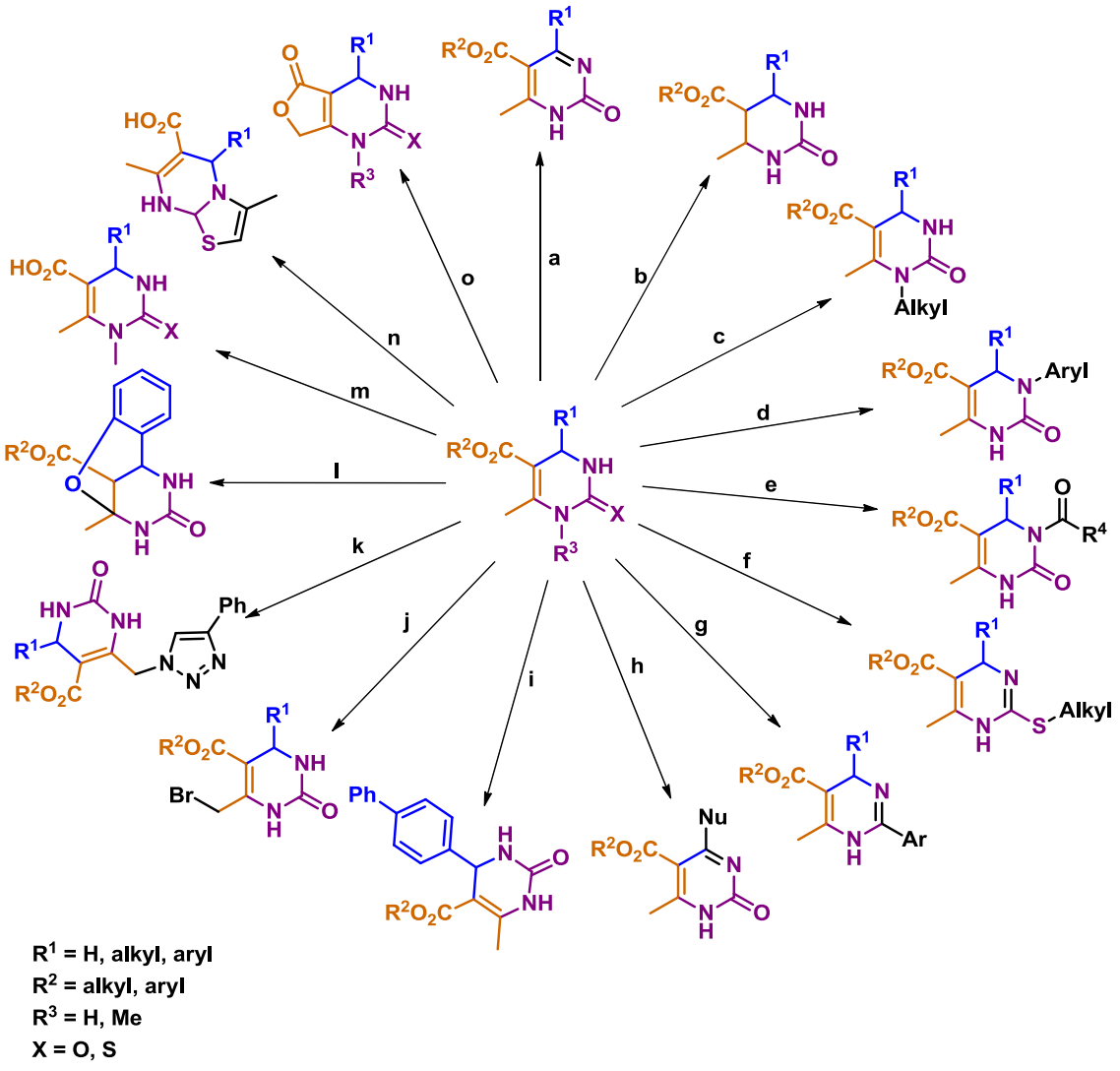
1.2.3 Post modification in Biginelli compounds

A recent review[40] showed that the DHPMs provide multiple possibilities of transformation not only of its heterocyclic core, but also of the substituents on the dihydropyrimidine ring (**Scheme 1.2.10**).



Scheme 1.2.10 Reactive sites used to further transformations (post modifications) of the DHPMs.

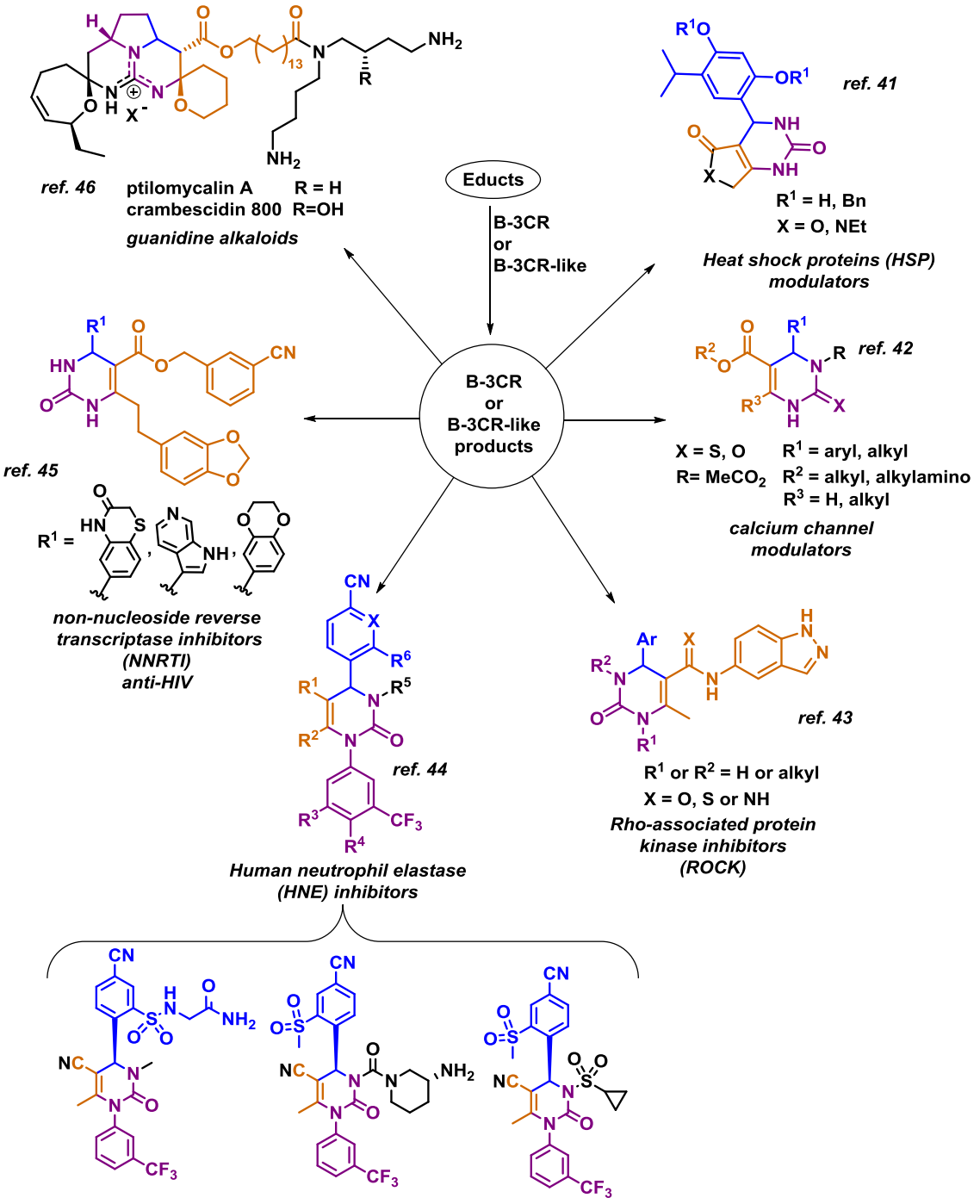
Examples of the approaches used for these post modifications in the DHPM are shown in **Scheme 1.2.11**.[40]



Scheme 1.2.11 Selected post modifications of DHPMs. For **(a)** HNO_3 50-60%, 0 ºC or CAN (3 equiv.), $NaHCO_3$ (5 equiv.), acetone; **(b)** CuBaCrO; **(c)** primary alkyl halide; **(d)** ArI, CuI, Cs_2CO_3, DMF, μW; **(e)** DMF, $POCl_3$ or $(RCO)_2O$, TEA, DMAP, MeCN, μW; **(f)** AlkylX; **(g)** $ArB(OH)_2$, $Pd(PPh_3)_4$, CuTC, THF; **(h)** *i)* HNO_3, *ii)* base, low temp., N_2, *C*-Nucleophile; **(i)** $B(OH)_2Ph$, Pd/C, Na_2CO_3, NMP/H_2O/μW; **(j)** Br_2, $CHCl_3$, r.t.; **(k)** *i)* Br_2, $CHCl_3$, r.t., *ii)* NaN_3, *iii)* PhCHCH, $CuSO_4$, sodium ascorbate; **(l)** when R^1 = 2-OH-C_6H_{11}; **(m)** KOH/EtOH; **(n)** $BrCH_2COCH_3$, H_2O, heating; **(o)** *i)* Br_2, $CHCl_3$, r.t., *ii)* heating.

1.2.4 Application of B-3CR in the synthesis of bioactive compounds

All the efforts done by synthetic chemist´s in order to develop new catalysts for the B-3CRs extending the reaction's scope are directly related to the highly valuable pharmacological properties of the DHPM heterocyclic scaffold. The interest is also connected to total synthesis approaches toward natural products, e.g. for HSP modulators, calcium channel modulators, Rho kinase inhibitors, non-nucleoside reverse transcriptase inhibitors (Anti-HIV agents), and melanine-concentrating hormone receptors, just to mention few of them (**Scheme 1.2.12**).



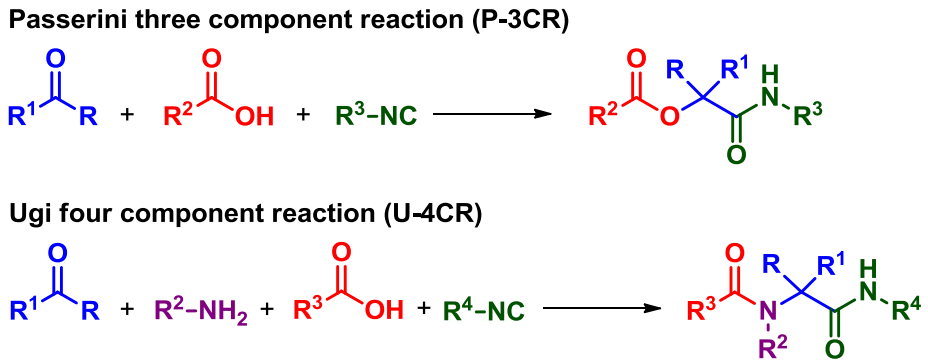
Scheme 1.2.12 Examples of biologicaly active compounds synthesized *via* B-3CRs.[41-46]

1.3 The Ugi four component reaction (U-4CR)

1.3.1 The U-4CR and its proposed mechanism

The U-4CR is undoubtedly the most used reaction in the field of IMCRs. The reaction provides one of the most versatile tools for generating a peptoid backbone (Ugi-products), peptidomimetic structures. These peptoid-like structures are an integral part of many compounds that occur in natural products, or heterocycles with biological activities that sometimes can be accessed directly by this reaction. Moreover, owing to the wide diversity available for each of their components, this reaction is by far one of the most employed in combinatorial chemistry for the design and development of new drugs. [1,2,47]

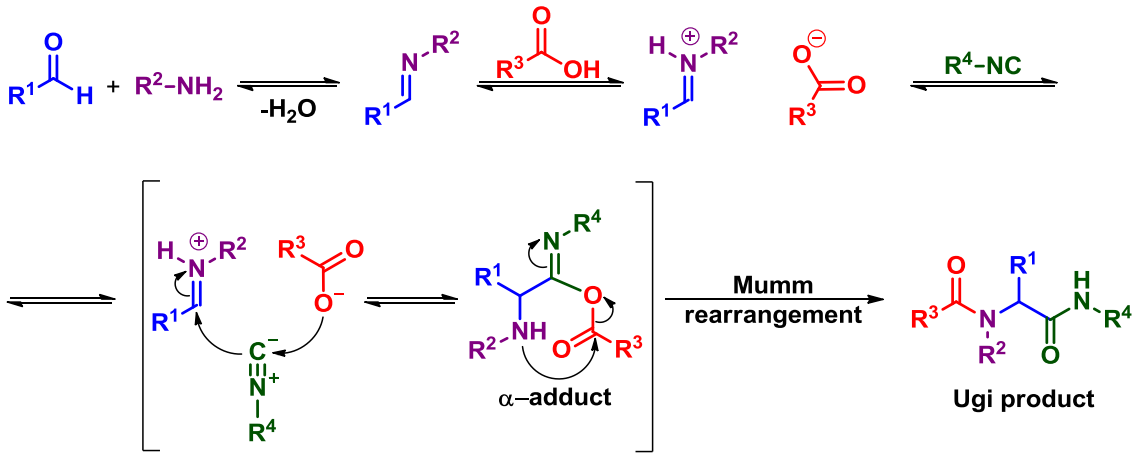
The classical U-4CR is a one-pot condensation reaction between an amine, a carbonyl compound, a carboxylic acid and an isocyanide furnishing normally a *N*-mono alkylated dipeptide (α-*N*-acylaminocarboxamides) as final product (**Scheme 1.3.1**).[19] The Ugi reaction is seen as an aza variation of the P-3CR, in which the imine is generated *in situ* from amine and oxo-components (**Scheme 1.3.1**).



Scheme 1.3.1 The Passerini three component reaction (P-3CR) and the Ugi four component reaction (U-4CR).

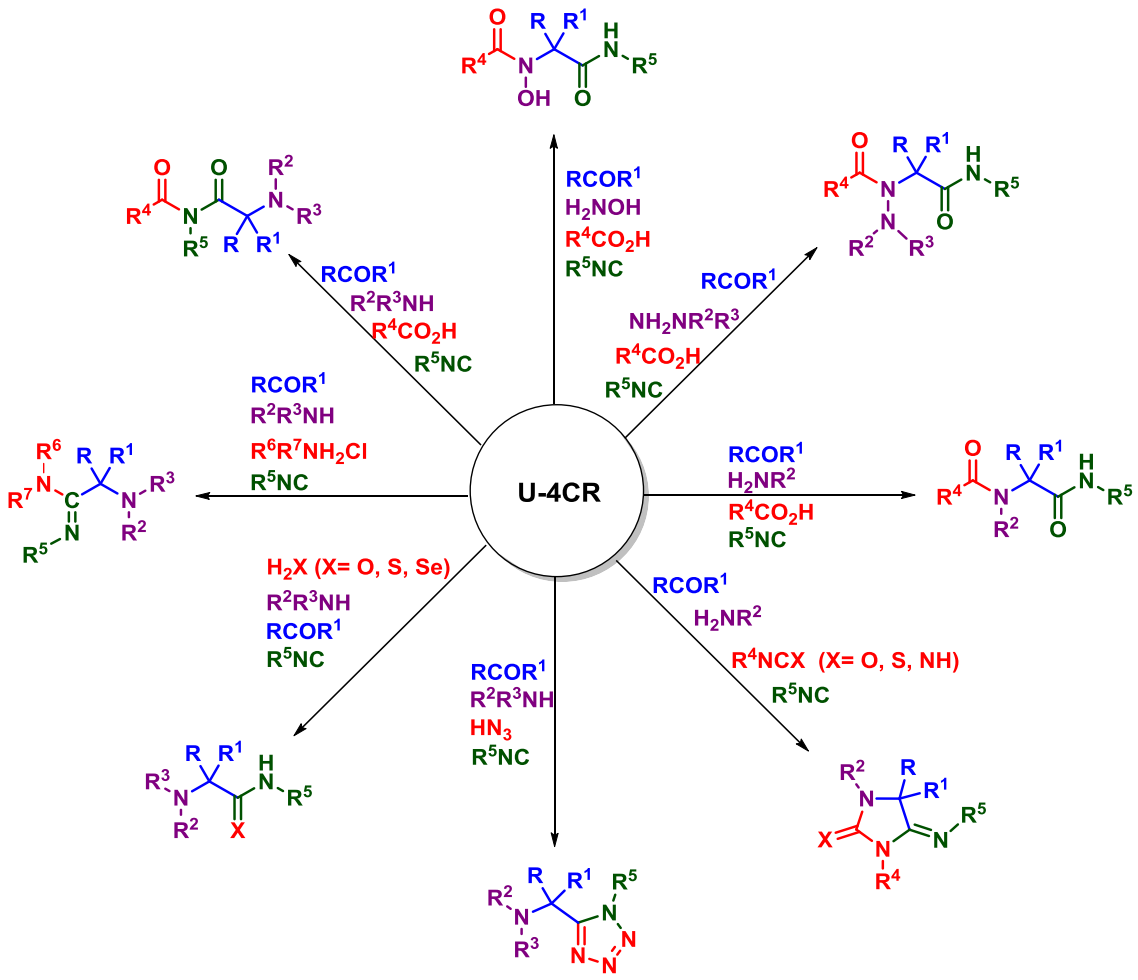
The most accepted mechanism for the U-4CR is outlined in **Scheme 1.3.2**. The first step consists of a sequence involving a condensation of the oxo compound and the amine to generate imine. The imine is protonated by the acid furnishing the iminium ion. Next, an α-addition of the electrophilic iminium cation and the nucleophilic carboxylate anion to the carbine-like carbon of the isocyanide group with the generation of the so-called *α*-adduct with sequential intramolecular acyl transfer (Mumm like rearrangement) takes place to afford the final Ugi-product (**Scheme 1.3.2**).[1-4,48-50] All elementary reactions are supposed to be in equilibrium, except for the final rearrangement step to form the *α*-acylaminoamide (MCR of type II). The driving force for the U-4CR relies on the oxidation of the isocyanide carbon formally C^{II} to the amide carbon C^{IV}. Every time

that an unsymmetrical carbonylic compound is employed in the reaction, a new stereogenic carbon is formed in the product.



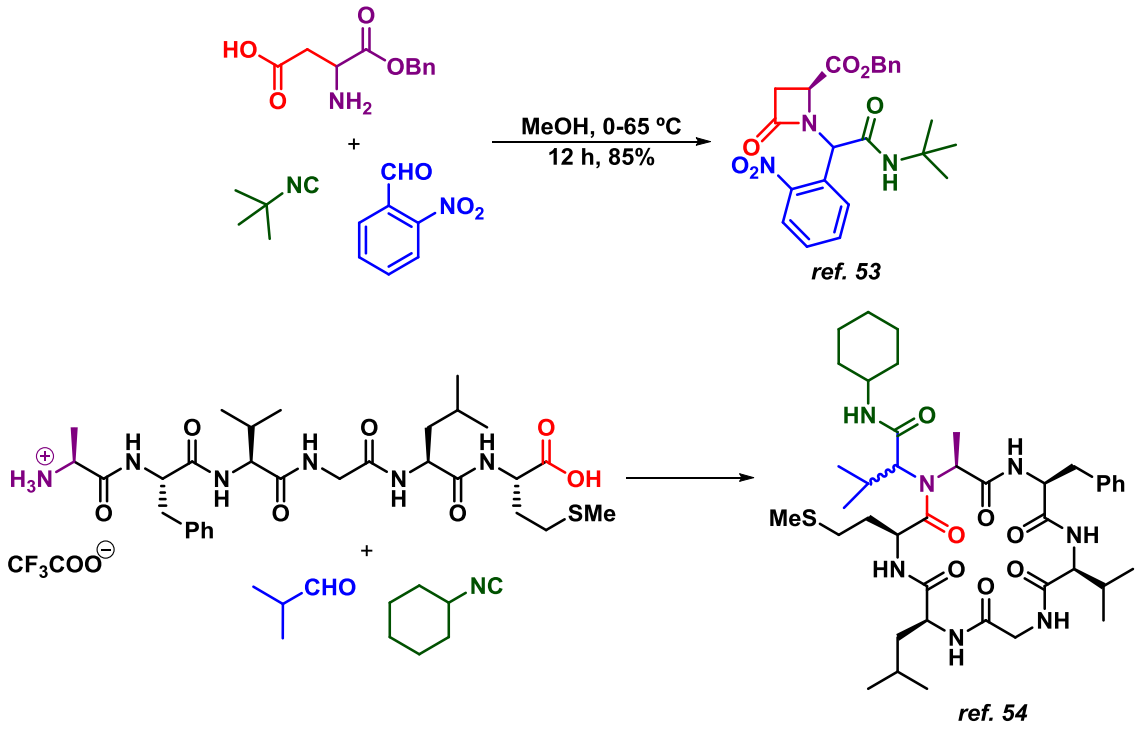
Scheme 1.3.2 Postulated mechanism for the U-4CR.

Usually, the Ugi reaction proceeds well when the amine and carbonyl compound are pre-condensed before the addition of the others educts. Sometimes, the addition of Lewis acid is needed to activate the imine intermediate. The reactivity in the U-4CR is widely influenced by inductive and mesomeric effects. At the same time, it is little influenced by steric effects, what makes it possible to generate crowded peptide moieties. Another crucial point is the concentration of the reactants. The reactions take place in shorter times with higher yields when the concentration of reactants is high, e.g. 0,5 - 2 M. The U-4CRs can easily be carried out at room temperature and by simple mixing of the reactants in almost any solvent (the most widely used ones are aliphatic alcohols, such as methanol and ethanol). Considering these factors, the U-4CR can be employed for almost all possible combinations of the four components educts. At the same time, such low interference of steric effects on the reactivity of the U-4CR enables easy access to products with high diversity and complex structures. This last feature makes the development of a general catalytic stereoselective (enantio or diastereoselective) approach an arduous task to be achieved. Thus, access to pure diastereo or enantiomerically pure Ugi products relies on ex-chiral-pool synthesis and a few auxiliary controlled approaches with employment of chiral educts.[51] The Ugi reaction can provide access to a wide variety of open chain compounds. At the same time, it produces several heterocycles mimetics by simple variation of edducts (**Scheme 1.3.3**).[52]



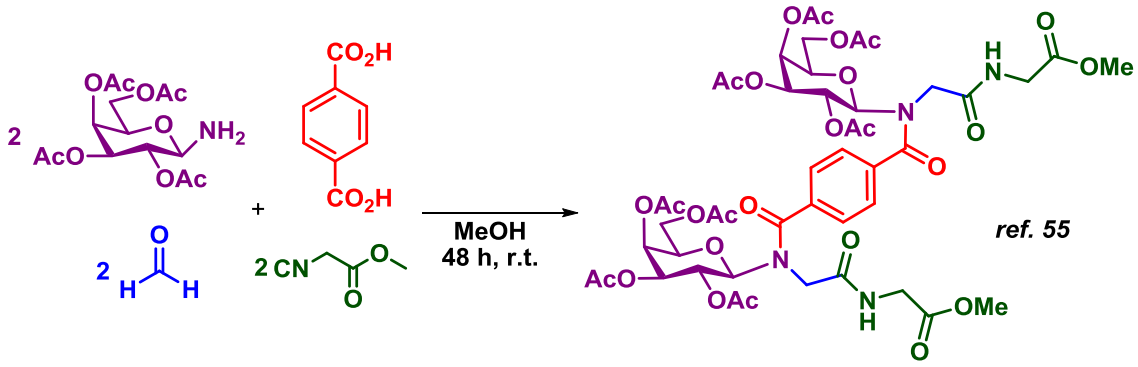
Scheme 1.3.3 Examples of structural diversity generated by U-4CR.

A very simple approach to generate cyclic compounds is the use of building blocks where two different functionalities of the four are employed, resulting in the so-called Ugi-four-center-three-component reactions (U-4CC-3CR), e.g. by the use of natural amino acids or peptides (**Scheme 1.3.4**).[53, 54]



Scheme 1.3.4 Access to heterocycles *via* U-4CC-3CR employing amino acids as bifunctionalized building blocks.[53, 54]

Oligosaccharides and proteins play a big role in cell-cell interactions like immune response, inflammation, cell signaling and infection by pathogens. Due to their design, the synthesis and development of glycoconjugate-based drugs are also of great relevance. U-4CR also could be successfully used to produce libraries of glycoconjugate-based compounds (**Scheme 1.3.5**). [1, 55]



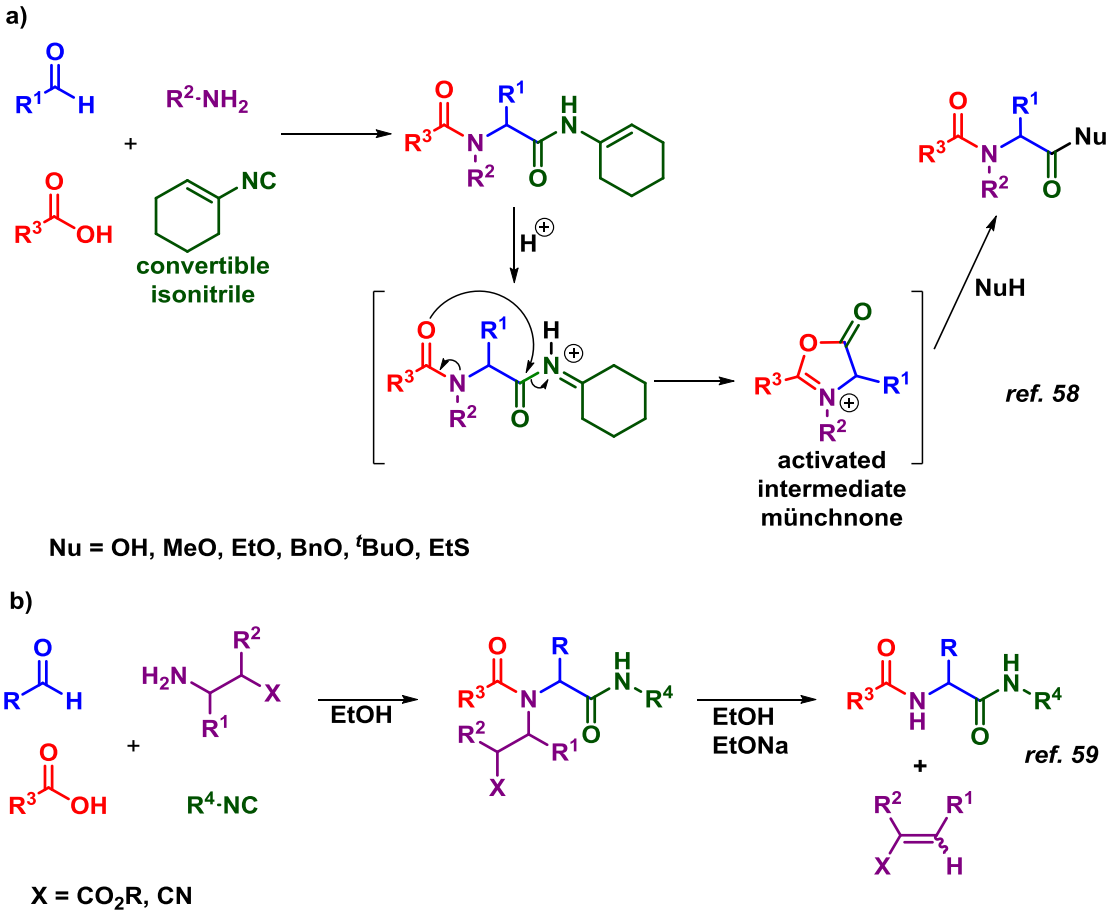
Scheme 1.3.5 An example of synthesis of glycoconjugate-based compound *via* U-4CR.[55]

1.3.2 Post condensation modification of Ugi products

In the beginning of this chapter it was mentionened that MCRs are a powerful synthetic tool to generate structural diversity and complexity. This can be enhanced by producing compounds where the scaffold synthesized by the MCR is able to be part of

a post condensation transformation. This strategy usually consists on the employment of unreactive, convertible (e.g. “convertible isonitriles”) or protected functional Ugi-substrates, which are able to be used for later sequential transformations.[56] These sequential transformations sometimes occur spontaneously or upon treatment with additional reagents.[56] Such further transformations can be either carried out in two step procedures or developed in one-pot processes for those cases when the reaction conditions are suitable.

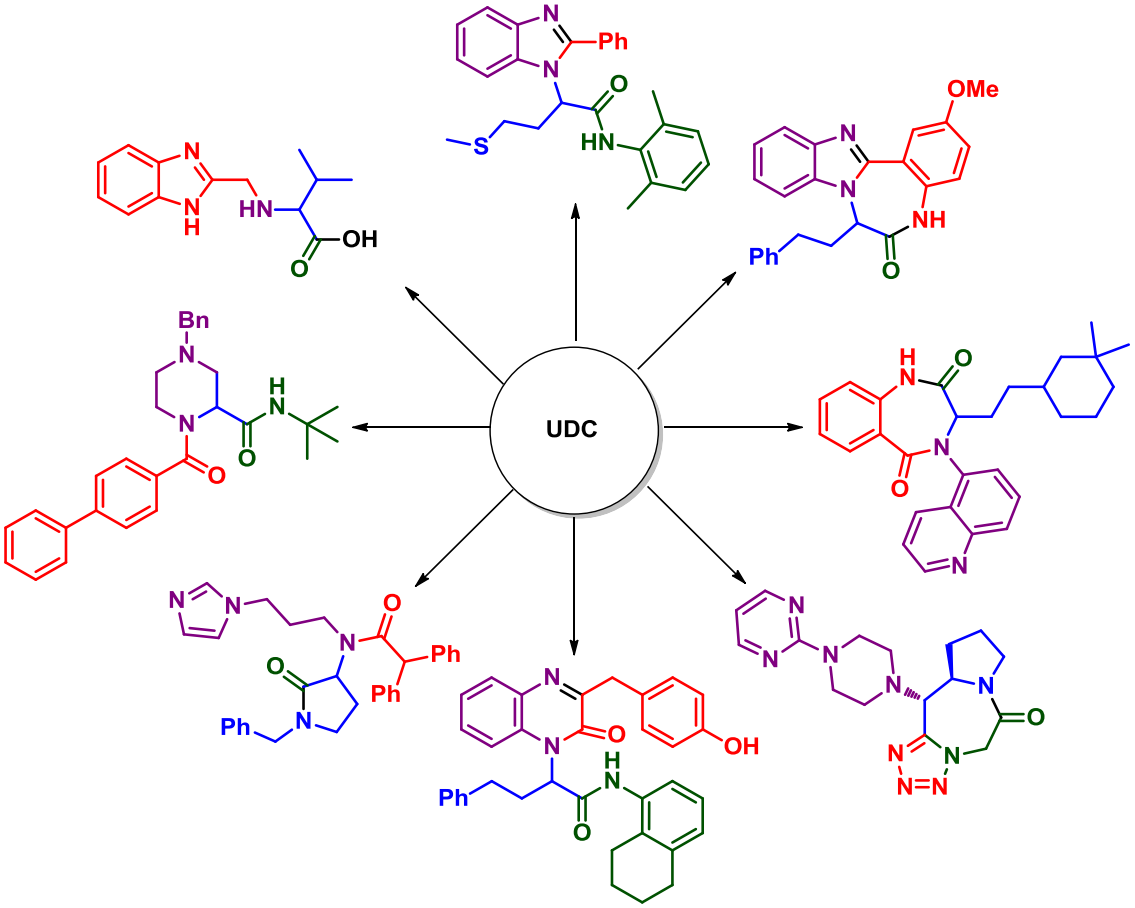
With the post condensation modification, the generation of libraries of higher-ordered structures possessing a multitude of functionalities is possible.[57] The potential of post condensation modifications in U-4CRs are countless. For example, the generation of linear peptides and peptide-like compounds by the application of varied synthetic strategies, e.g. the use of “convertible isonitriles”,[58] *β*-aminoesters or nitriles as the amino input,[59] respectively (**Scheme 1.3.6**).



Scheme 1.3.6 a) Use of Armstrong convertible isocyanide and **b)** *β*-aminoesters or nitriles as post modification strategies.[58, 59]

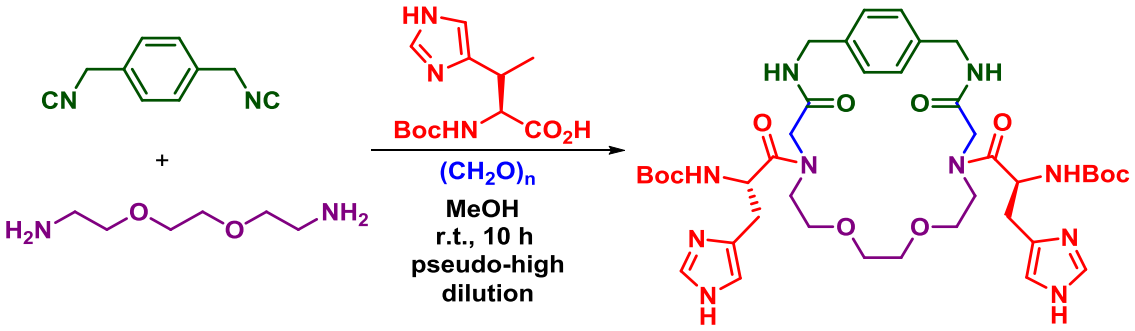
Also, a wide spectrum of cyclic peptidomimetic derivatives can be synthesized by use of post cyclization strategies *via* the introduction of bifunctional substracts by the first IMCR. The bifunctional groups such *N*-protected amino acids, convertible isocyanides

or Ugi educts that bear an additional alkene, alkyne or azide moiety that can be cyclized *via* either the Ugi/deprotections/cyclization (UDC), Ugi/activation/cyclization (UAC) and the Ugi/deprotection/activation/cyclization (UDAC), respectively. The UDC strategy consists in using nucleophile protected building blocks in the Ugi reaction with subsequent deprotection of the Ugi product that allows the intramolecular cyclization, generating a variety of different scaffolds (**Scheme 1.3.7**). In the UDC, "convertible isocyanides", like the one in the **Scheme 1.3.6 a**, are employed as Ugi substrates in the initial transformation, followed by activation and cleavage of the moiety delivered by the isocyanide component and sequential cyclization. A combination of deprotection and activation is possible in the UDAC. [56, 58, 60]



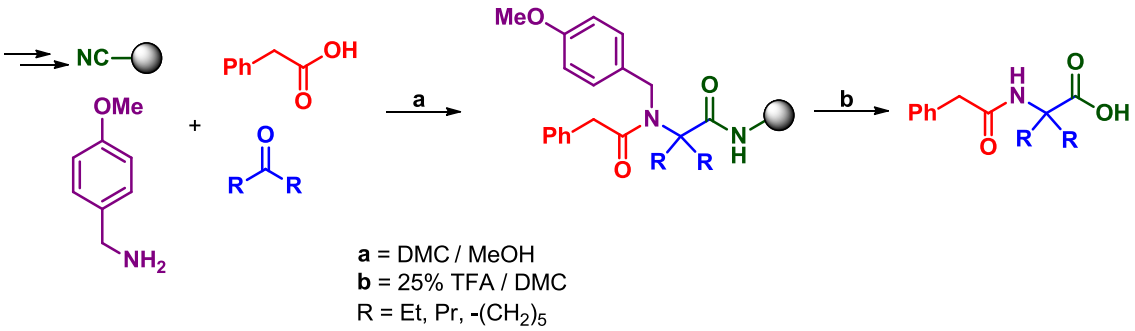
Scheme 1.3.7 Examples of structural diversity employing the UDC strategy.[60]

Complex macrocycles can also be synthesized with the use of multiple multicomponent reactions including bifunctional building blocks (MiBis)[61] (**Scheme 1.3.8**).



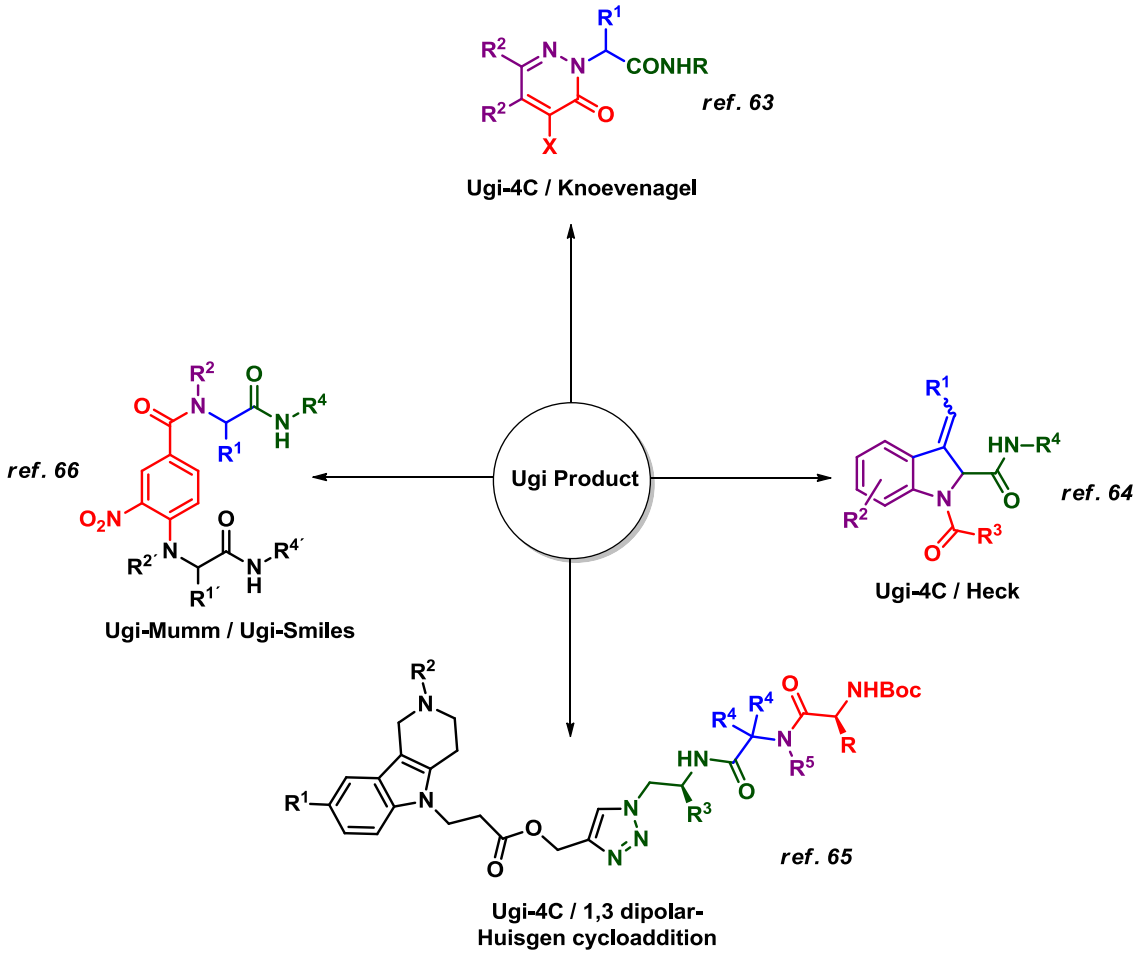
Scheme 1.3.8 Access to macrocycles natural product-like with the employment of multiple multicomponent reactions including bifunctional building blocks (MiBis) strategy.

The access to highly substituted acyclic peptides, such as *α,α*-dialkylglycine derivatives *via* classical solid-phase organic synthesis (SPOS) approaches, is difficult to achieve due to the sterical hindrance. The access to such types of peptides is possible through the accomplishment of SPOS with the U-4CR. The peptides were synthesized by immobilising one of the Ugi educts on the resin, following the U-4CR and posterior release from the solid support (**Scheme 1.3.9**).[62]



Scheme 1.3.9 Synthesis of highly substituted acyclic peptides by SPOS and U-4CR. For (**a**) DMC / MeOH and (**b**) 25% TFA / DMC

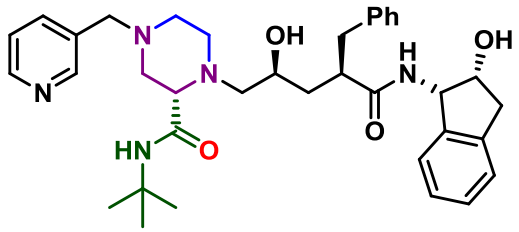
Furthermore, the combination of the U-4CRs with other classical reactions is described, such as with the Knoevenagel condensation, the Heck reaction, the 1,3 dipolar-Huisgen cycloaddition reaction (as discussed in Chapter 4), the Ugi-Smiles reaction, and several others (**Scheme 1.3.10**).[63-66]



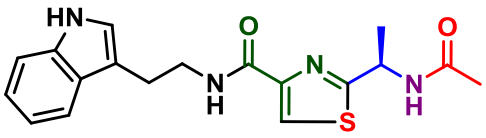
Scheme 1.3.10 Combination of U-4CR with classical reactions.[63-66]

1.3.3 Application of U-4CRs

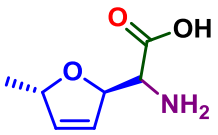
The applications of the highly versatile U-4CR are not restricted to the design and generation of large combinatorial libraries of high complexity and diversity for screening. The positive traits of Ugi-4CR have become a powerfull tool for organic synthesis in the last few years. To date, there are many reports on its use to access or assemble complex building blocks for total synthesis of natural products. Furthermore, the U-4CR has shown great value in generating new materials in the fields of polymer science and for protein profiling (**Figure 1.3.1**). There is no doubt that in the coming years, the applicability of the MCRs will be extended to other scientific fields too.



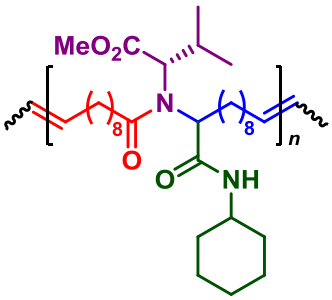
Crixivan (Indinavir)
ref. 67



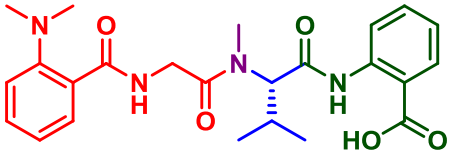
(-)-Bacillamide C
ref. 68



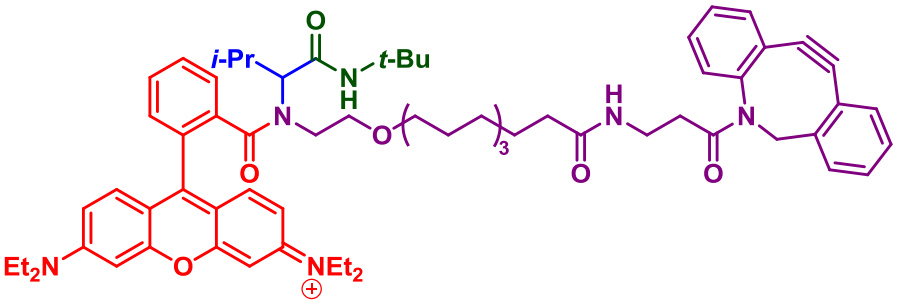
(+)-Furanomycin
ref. 69



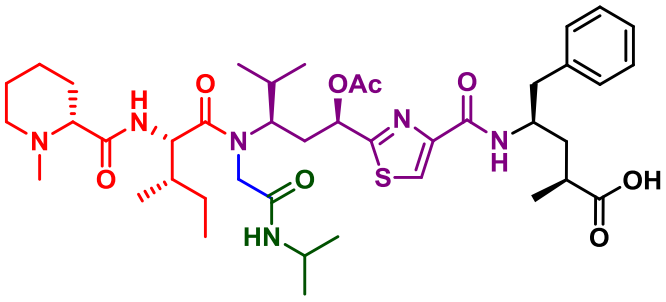
Polymer
ref. 70



(-)-Viridic acid
ref. 71



Rhodamine clickable probes for protein labeling
ref. 72



Tubugi, highly active cytotoxin
ref. 73

Figure 1.3.1 Application of U-4CR in different areas of chemistry.[67-73]

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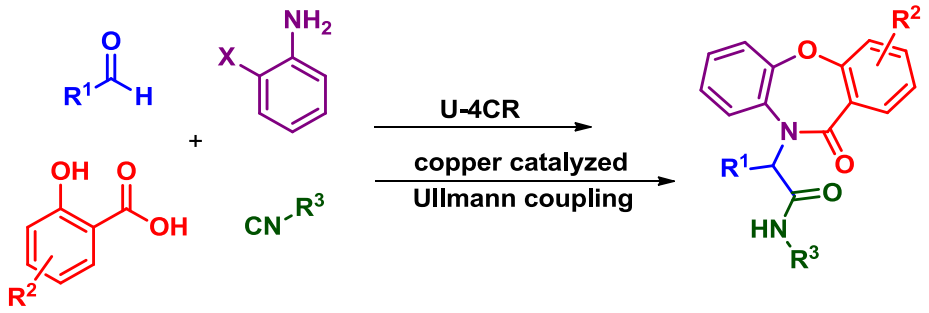
Chapter 2

Synthesis of *N*-substituted dibenz[*b,f*][1,4]oxazepin-11(10*H*)-ones *via* U-4CR/copper catalyzed Ullmann-type coupling reaction

Abstract



In this chapter the synthesis of *N*-substituted dibenz[*b,f*][1,4]oxazepin-11(10*H*)-ones *via* sequential U-4CR/copper catalyzed Ullmann *C-O* cross coupling reaction is described. Also the antibiotic activity on *Bacillus subtilis* was evaluated.

2.1 Introduction

The benzoxazepin scaffold is an important motif in medicinal chemistry. It is found in many biologically active compounds, including natural products.[1-4] From these classes of compounds, the dibenz[*b,f*][1,4]oxazepinones systems and derivatives are of special interest because they exhibit a wide range of biological activities. These compounds can act as PGE_2 antagonists and analgesics,[2,5] antidepressants,[6] calcium antagonists,[7] non-nucleoside inhibitor of HIV-1 reverse transcriptase,[8] to mention a few (**Figure 2.1.1**).

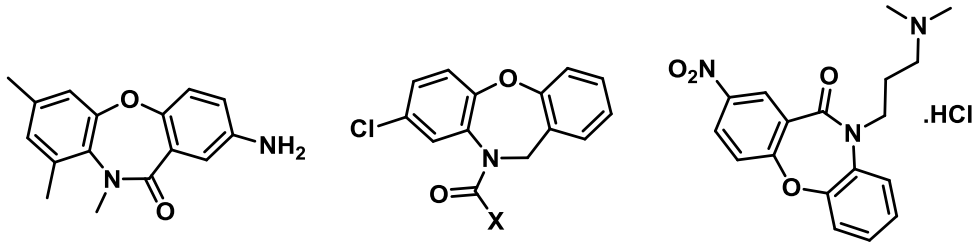
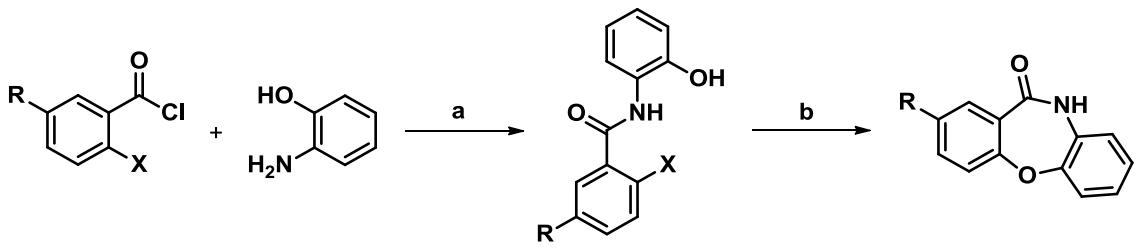


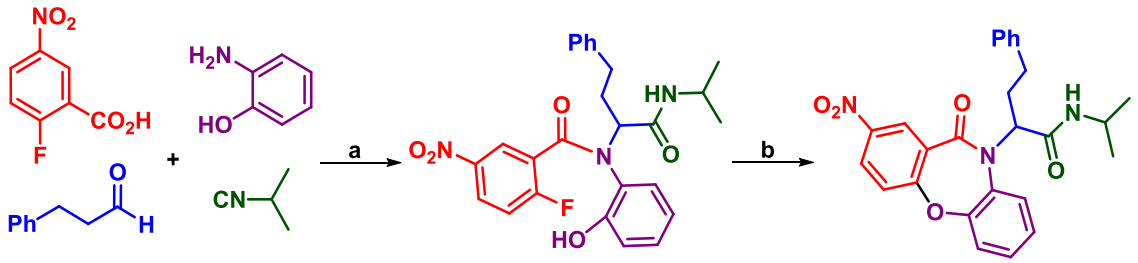
Figure 2.1.1 Examples of biologically active dibenz[*b,f*][1,4]oxazepinones and derivatives

A common method to access dibenz[*b,f*][1,4]oxazepin-11(10*H*)-ones derivatives is the intramolecular cyclization *via* nucleophilic aromatic substitution (S_NAr) starting from 2-aminophenols and 2-fluoro or 2-chloro-5-nitrobenzoyl chlorides (**Scheme 2.1.1**).[9]



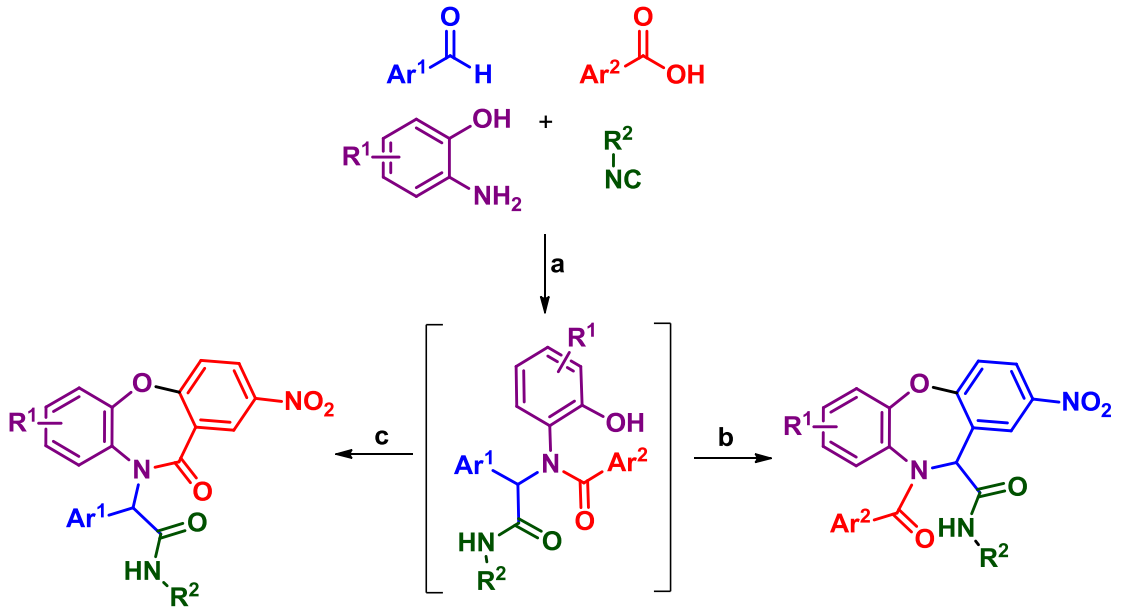
Scheme 2.1.1 Common method to synthesized dibenz[*b,f*][1,4]oxazepin-11(10*H*)-ones. For **a)** 1 equiv. aq. NaOH; **b)** *i)* 2 equiv. aq. NaOH; *ii*) DMF, heating; *iii*) H_3O^+

In 2001, Hulme et al.[10] reported the synthesis of indazolinones, benzazepines, benzoxazepines *via* a novel U-4CR-S_NAr methodology. Herein, only a single *N*-substituted dibenz[*b,f*][1,4]oxazepin-11(10*H*)-one was synthesized starting from 2-fluoro-5-nitrobenzoic acid as the acid component of the U-4CR, with only 25% yields (**Scheme 2.1.2**).



Scheme 2.1.2 Hulme´s U-4CR-S_NAr methodology to benzoxazepines. For **a)** MeOH, 48 h; **b)** DMF, 5 equiv. PS-TBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene), 36 h, r.t.

In a later study, Dai et al.[11b] reported the microwave assisted U-4CR-S_NAr for the synthesis of dibenz[*b,f*][1,4]oxazepin-11(10*H*)-ones (**Scheme 2.1.3** *via* **a,c**) and dibenz[*b,f*][1,4]oxazepine-11(10*H*)-carboxamides (**Scheme 2.1.3** *via* **a,b**) using 2-chloro-5-nitro-benzoic acid as starting material in the U-4CR (**Scheme 2.1.3** *via* **a,c**). When the 2-chloro-5-nitrobenzaldehyde was employed as edduct, the U-4CR did not take place efficiently. Dai et al. assumed that the electron-deficient imine formed might be difficult to be protonated by the acid (**Scheme 2.1.3** *via* **a,b**).

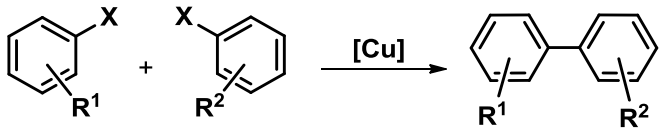


Scheme 2.1.3 Dai´s µW assisted U-4CR-S_NAr reaction. For **a)** MeOH, 80 ºC, 20 min; **b)** Ar^1 = 2-Cl-5-NO_2-C_6H_3, addition of aq. K_2CO_3, 120 ºC, 10 min; **c)** Ar^2 = 2-Cl-5-NO_2-C_6H_3, addition of aq. K_2CO_3, 100 ºC, 10 min.

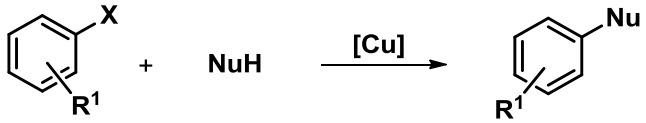
The principal limitation of all the synthetic approaches discussed above is the indispensable presence of an strong electron withdrawing group (normally a nitro group) in *ortho* or *para* position to the halogen atom in the aromatic ring of the starting material in which the nucleophilic oxygen atom of the amino phenol ring will be added *via* S_NAr

cyclization affording the dibenz[*b,f*][1,4]oxazepine with an electron withdrawing group in the position two of the tricyclic structure.

The classical Ullmann reaction is a copper catalyzed cross coupling of aryl halides to give (symmetrical) biarylic compounds (**Scheme 2.1.4**).[12]



Ullmann reaction



X = Hal

Ullmann-type reaction

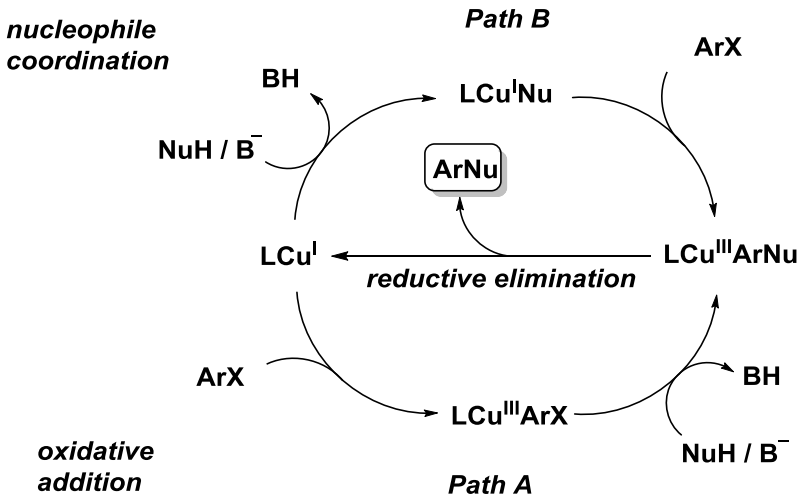
Scheme 2.1.4 Classical Ullmann reaction and Ullmann-type reactions

The Ullmann(-type) reactions are a powerful tool to generate *C(aryl)-C*, *C(aryl)-N* and *C(aryl)-O* bonds with several applications in academic research and industrial processes.[13] However, the potential of these reactions have not been explored to its full extent due to many drawbacks, such as the high temperatures required for the reaction, long reaction times, a high metal ion loading, and a narrow scope.[12-14]

In 1987, Paine[15] reported that the catalytically active species in the Ullmann reaction is a soluble cuprous ion. Employing soluble copper complex with additives and base, Buchwald[16] demonstrated cross-coupling of phenols with aryl bromides in toluene at 110 ºC. Finally, in 2001, a new versatile and very efficient copper/ligand system for the Ullmann reaction was developed. This new protocol enabled the use of only catalytic amounts of metal under mild conditions (90-110 ºC compared with above 200 ºC for the classical methods).

The mechanism of copper catalysis in the Ullmann reaction with addition of ligand in the presence of base is still not well understood. There are two proposals (**Scheme 2.1.5**). In the first proposed pathway, a putative oxidative addition of the aryl halide (ArX) proceeds before the nucleophilic substitution of NuH, which itself precedes the formation of the coupling product (ArNu) and the regeneration of the catalytic copper species (**Pathway A, Scheme 2.1.5**). In the second proposed pathway, a nucleophilic substitution occurs in the first step (**Pathway B, Scheme 2.1.5**). Regarding the oxidation

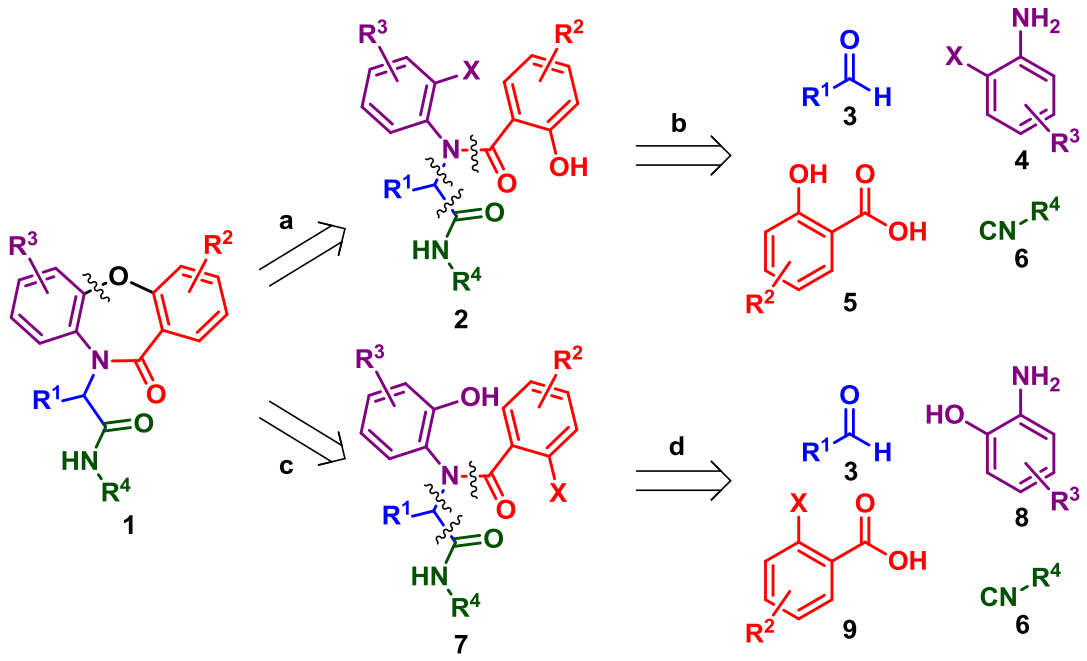
state of the copper, these types of reaction are supposed to proceed *via* Cu^{I} and Cu^{III} intermediates.[13, 14, 17]



Scheme 2.1.5 Two possible pathways for the copper-catalyzed arylation of nucleophiles.

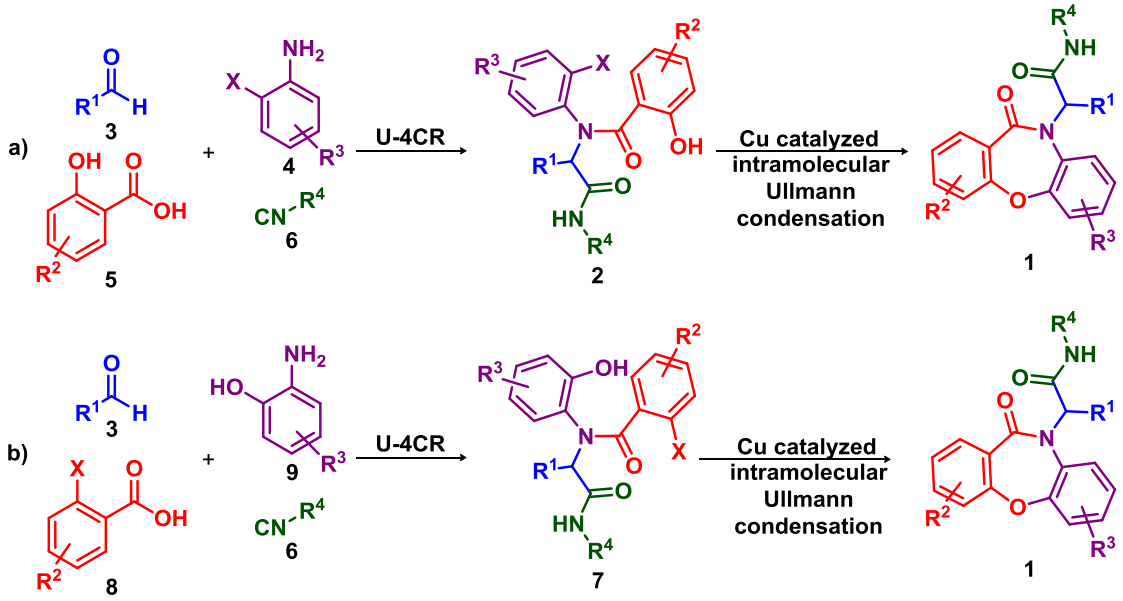
2.2 Synthetic strategies

Our goal was to develop a new synthetic strategy in which the presence of an electron withdrawing group would not be necessary, directly accessing dibenz[*b,f*][1,4]oxazepin-11(10*H*)-ones without substitution in position 2 of the tricyclic compound. In order to achieve this goal, two different strategies were proposed (**Scheme 2.2.1**). The first disconnection was made at the oxygen atom of the core heterocycle, resulting in the fragments **2** or **7** (**Scheme 2.2.1**)**.** These were planned to be assembled through the respective U-4CRs (**Scheme 2.2.1**). In the forward reaction (**Scheme 2.2.2**) the U-4CRs will be followed by Ullmann couplings.



Scheme 2.2.1 Retrosynthetic analysis of *N*-substituted dibenz[*b,f*][1,4]oxazepin-11(10*H*)-ones.

The copper catalyzed Ullmann condensation was chosen because in an earlier report,[12] it was shown that palladium catalysts (Buchwald-type *O*-arylation) are inefficient to promote intramolecular cross coupling to form *C-O* bonds in compounds with similar structures to **1**. Moreover, the new versatile and very efficient copper/ligand systems are mild enough for Ugi-peptoids.[13, 14] Third, copper salts are less toxic when compared to the normally employed palladium compounds, and have a lower cost.[13, 14]



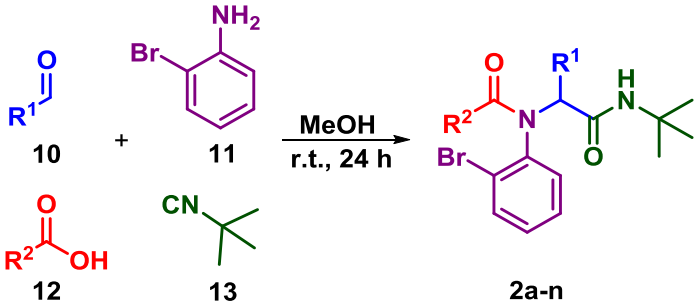
Scheme 2.2.2 Synthetic strategies for synthesis of *N*-substituted dibenz[*b,f*][1,4]oxazepin-11(10*H*)-ones *via* U-4CR/Cu catalyzed Ullmann reaction.

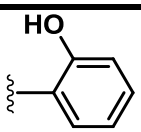
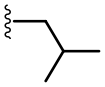
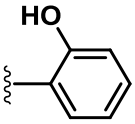
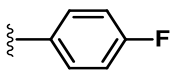
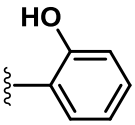
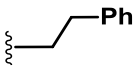
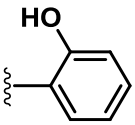
2.3 Synthesis of *N*-substituted dibenz[*b,f*][1,4]oxazepin-11(10*H*)-ones *via* two step sequential U-4CR/copper catalyzed Ullmann *C-O* cross coupling condensation

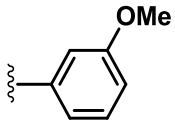
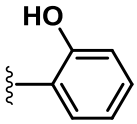
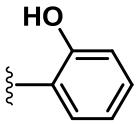
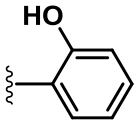
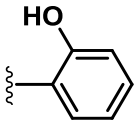
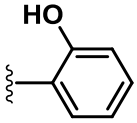
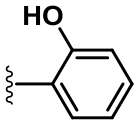
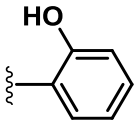
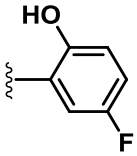
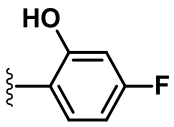
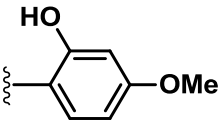
N-Substituted peptoids of type **2** were obtained by reacting equimolar quantities of aldehydes (**10**), 2-bromoaniline (**11**), salicylic and related acids (**12**) and *tert*-butylisocyanide (**13**) in methanol (1M) at room temperature for 24 hours (**Table 2.3.1**). The products **2a-n** were isolated in good yield and high purity.

Following a recent protocol for Ullmann reaction[17], we envisaged this protocol modified for an intramolecular cyclization condensation of **2a**. Reacting **2a** in the presence of 10 mol% of CuI, *N,N*-dimethylglycine hydrochloride as ligand (30 mol%) and Cs_2CO_3 as base in dioxane at 105 ºC under nitrogen atmosphere for 24 hours, gave **1a** in good yield (**Table 2.3.2, entry a**).

Table 2.3.1 Synthesis of *N*-substituted peptoids **2a-n** by U-4CR.



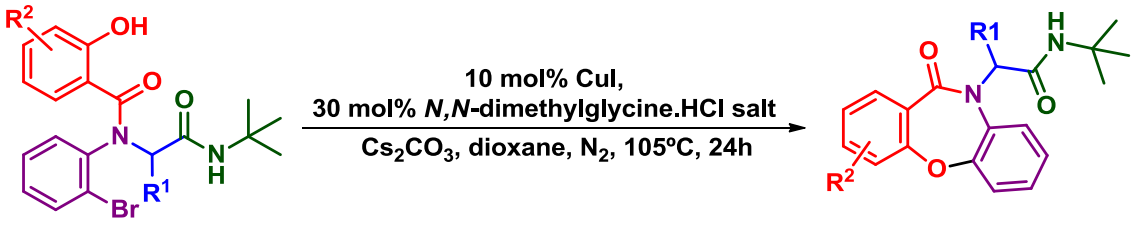
Entry	R^1	R^2	Compound Yield (%)[a]
a			**2a** 90
b			**2b** 82
c			**2c** 78
d			**2d** 85

e			**2e** 88
f	**Et**		**2f** 75
g	***n*-Bu**		**2g** 91
h	***n*-octyl**		**2h** 75
i	**H**		**2i** 87
j			**2j** 92
k	**Me**		**2k** 85
l			**2l** 84
m			**2m** 80
n			**2n** 71

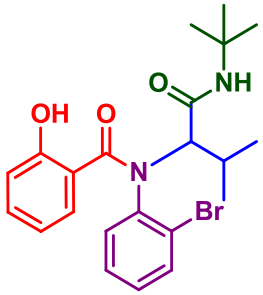
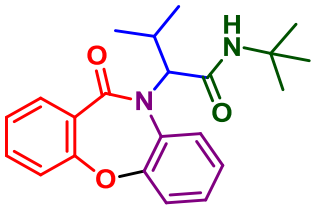
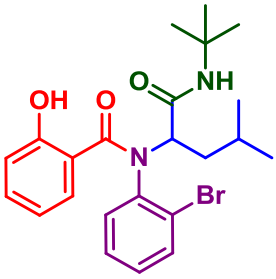
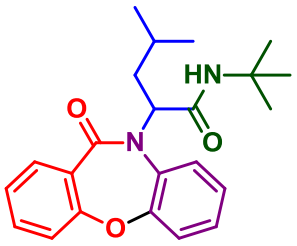
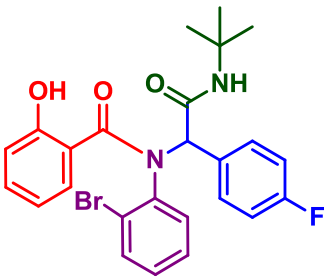
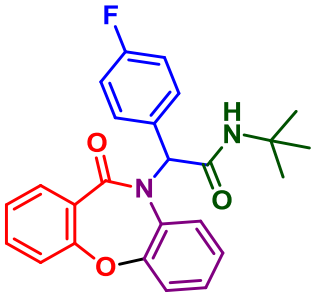
[a] Isolated and purified by column chromatography.

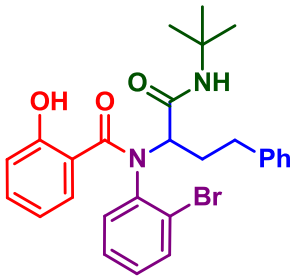
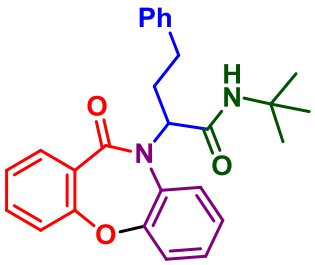
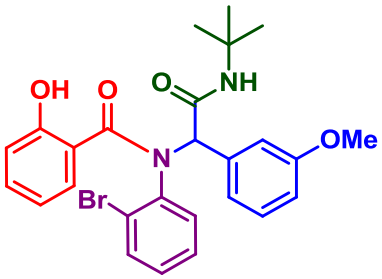
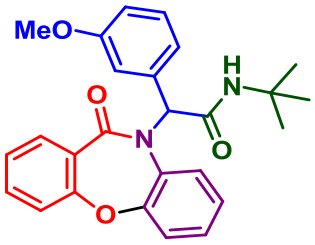
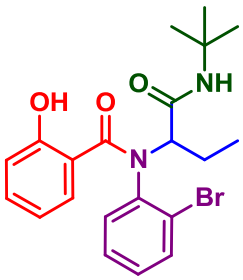
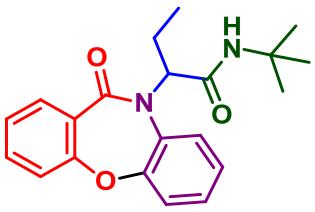
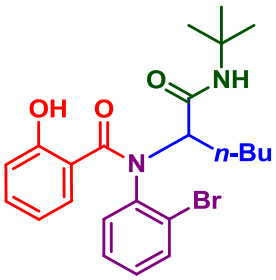
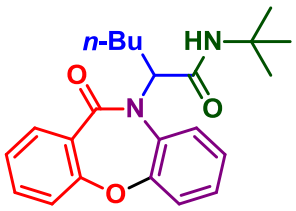
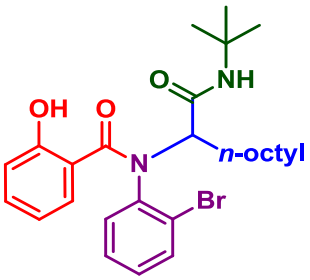
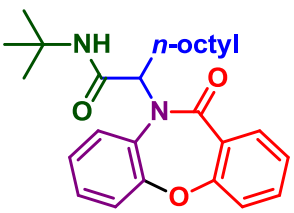
The Ugi products **2b-n** accordingly were subjected to the same conditions (**Table 2.3.2**). The *N*-substituted dibenz[*b,f*][1,4]oxazepin-11(10*H*)-ones of type **1**, were obtained in moderate to good yields (**Table 2.3.2**).

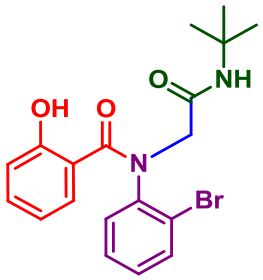
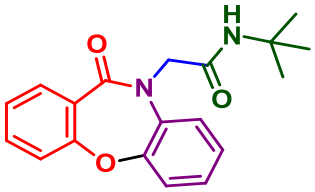
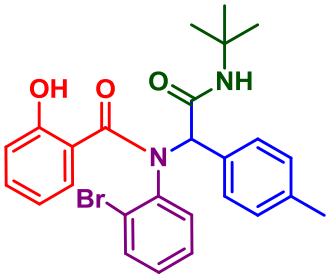
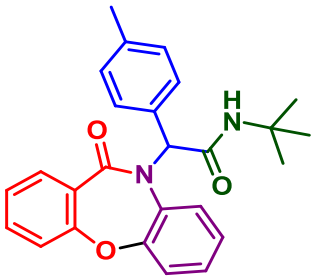
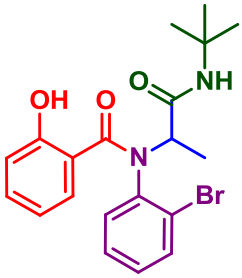
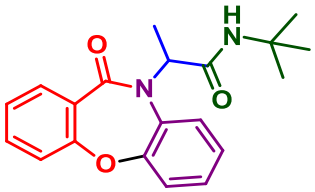
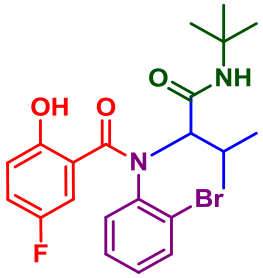
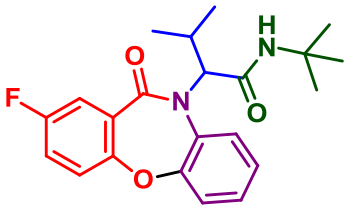
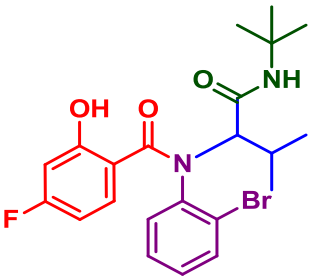
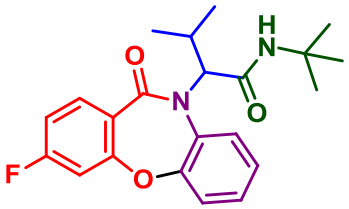
Table 2.3.2 Ullmann *C-O* coupling reaction of the compounds **2a-n** under the catalysis of CuI.

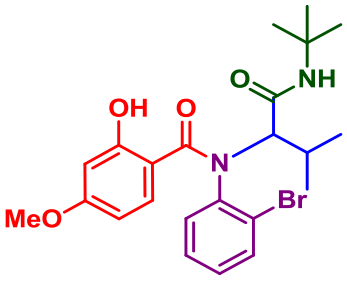
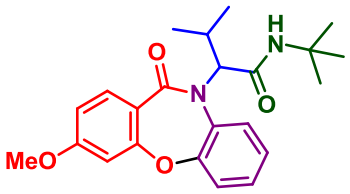


2a-n **1a-n**

Entry	*N*-substituted peptoid	Product	Yield (%)[a]
a	 **2a**	 **1a**	70
b	 **2b**	 **1b**	85
c	 **2c**	 **1c**	78

d	 **2d**	 **1d**	76
e	 **2e**	 **1e**	81
f	 **2f**	 **1f**	73
g	 **2g**	 **1g**	65
h	 **2h**	 **1h**	45

i	 **2i**	 **1i**	80
j	 **2j**	 **1j**	68
k	 **2k**	 **1k**	81
l	 **2l**	 **1l**	12
m	 **2m**	 **1m**	74

n			85
	2n	**1n**	

[a] Yields after purification with flash column chromatography.

Interestingly, a drastic variation of the yields was observed when the position of halogen substituent at the aromatic moiety of the phenol partner was exchanged (**entries l and m**, **Table 2.3.2**). This indicates that the formation of the copper intermediate is highly affected by the inductive effect and acidity of the nucleophile employed. Using the alternative strategy, exchanging the functionalities of acid and amine (**Strategy b Scheme 2.2.2**), did not afford compounds **1a-n** efficiently.

2.4 Antibacterial activity studies[a]

As mentioned in **Section 2.1**, *N*-substituted dibenz[*b,f*][1,4]oxazepin-11(10*H*)-ones are known for displaying diverse biological activities. In spite of many reports on the properties of these compounds, their antibacterial effects have not been evaluated so far. Threrefore, it was decided to test the compounds **1a-n** against the gram-positive bacterium *Bacillus subtilis* strain 168 using a fluorescence based assay.[18-20] The compounds showed low to moderated growth inhibition when compared to the standard erythromycin (grown inhibition 70.8 ± 4.5 % at 1 µM, **Table 2.4.1**). It is important to observe that the antibacterial activity increases with the introduction of a halide substituent on the aromatic ring at the *para* position in relation to the carbonyl group of the tricycle (**compound 1m**, **Table 2.4.1**). Also, something that should be taken into account is the effect of the variation of the substituents on the α position of the nitrogen participant of the tricycle (exocyclic chain). As for the alkyl series, we can see that all the compounds presented the antibacterial activity in the same range. Interestingly, an increment in the size of the alkyl chain leds to a decrease of activity. A replacement of the alkyl exocyclic group for aromatic rings increases the antibacterial activity, being **1j** (**compound 1j**, **Table 2.4.1**) the most active compound. Among all assayed susbtances, the best values were found for compounds **1m** (44.6 ± 7.5) at 1 µM and **1j** (65.1 ± 7.5) at 10 µM.

[a] The antibacterial activity assay was performed by Dr. R. Heinke.

Table 2.4.1 Result of the antibacterial activity tests against *Bacillus subtilis*

Compound	Growth inhibition[a] in % at 1 µM[d]	Standard Deviation[d]	Growth inhibition in % at 10 µM[d]	Standard Deviation[d]
1a	inactive	-	24.6	11.9
1b	inactive	-	34.0	17.1
1c	inactive	-	**64.5**	**4.7**
1d	inactive	-	29.0	12.3
1e	24.0	7.5	41.1	14.7
1f	32.9	13.6	36.7	13.6
1g	33.0	10.3	36.6	4.8
1h	inactive	-	34.9	6.7
1i	25.5	12.5	30.2	14.6
1j	35.2	2.6	**65.1**	**7.5**
1k	29.7	13.1	**52.8**	**17.3**
1l	inactive	-	32.4	12.0
1m	**44.6**	**7.5**	**47.7**	**5.2**
1n	31.3	10.6	45.2	15.2
Std.[b]	70.8	4.5	NP[c]	NP[c]

[a] Measured after 15h
[b] Erythromycin
[c] Not performed.
[d] Mean values of two trials involving 3 replicates

2.5 Conclusions

We developed a new and efficient protocol for rapid access to *N*-substituted dibenz[*b,f*][1,4]oxazepin-11(10*H*)-ones through a two-step sequential U-4CR/copper promoted Ullmann *C*-*O* cross coupling intramolecular condensation employing cheap and available starting materials. Moreover, the developed U-4CR/Ullmann protocol allowed us to overcome the limitations to electron poor aryl electrophiles of earlier approaches, enabling us to synthesize the heterocyclic compounds of type **1**. Further the compounds **1** display low to moderated antibacterial activity against bacterium *Bacillus subtilis*, using a fluorescence based assay. Also from the results of the antibacterial assay it was possible to get a first insight into the structure/activity relationships of this series, which may be used in further studies, torwards the development of more active compounds.

2.6 Experimental part

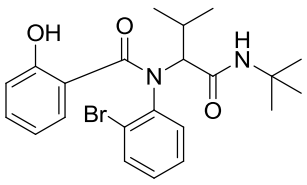
General remarks

All reagents were commercially available and were not subjected to further purifications. The solvents were purified by standard procedures. The dioxane used in the experiments was purchased from Sigma-Aldrich in dry form. The TLC was performed using Merck silica gel 60 F254 aluminum sheets. The flash column chromatography was performed using silica gel (0.040- 0.063 mm) Merck. ^{1}H and ^{13}C NMR spectra were recorded in solutions on a NMR spectrometer at 400 MHz and 100 MHz (in some cases 75 MHz). Chemical shifts (δ) are reported in ppm relative to the TMS (^{1}H NMR) and to the solvent signal (^{13}C NMR). HRMS spectra were obtained from a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer equipped with an Infinity™ cell, a 7.0 Tesla superconducting magnet, a RF-only hexapole ion guide and an external electrospray ion source (off axis spray). Melting points were measured in a Leica DM LS2 microscope and is uncorrected.

General procedure for U-4CR

Suitable amine (1 mmol) was added to a stirring solution of suitable aldehyde (1 mmol) in methanol (10 ml). The mixture was stirred at room temperature for 30 minutes. Later, carboxylic acid (1 mmol), followed by the isocyanide (1 mmol) were added. The solution was stirred at room temperature for 24 hours. The solvent was removed under reduced pressure in a rotavap and crude material purified by silica gel column chromatography to afford the desired products. NMR-data: Please note that these may show *s-cis* and *s-trans* isomeric mixtures.

***N*-(2-Bromophenyl)-*N*-[1-(*tert*-butylamino)-3-methyl-1-oxobutan-2-yl]-2-hydroxy benzamide (2a)**

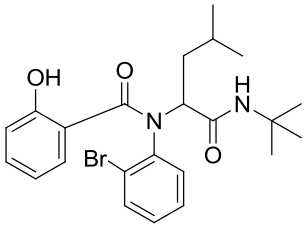


2a

Purified by silica gel column chromatography. R_f 0.39 (EtOAc / hexane 1:3). White solid. M.p.: 202.8-203.7 ºC. Yield: 90%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 10.29 and 10.03 (2s, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.48-7.26 (m, 3H), 7.20-7.07 (2m, 2H), 6.93-6.87 (m, 1H), 6.70 (d, *J* = 6.8 Hz, 1H), 6.44-6.37 (m, 1H), 4.61 and 4.03 (2d, *J* = 10.8 Hz, 1H), 2.77-2.59 (m, 1H), 1.39 (s, 5H), 1.25-1.21 (m, 5H), 1.06-1.04 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 173.60, 172.79, 169.16, 160.37, 160.02, 142.10, 134.15, 133.98, 133.28, 133.08, 130.16, 129.95, 129.29, 129.20, 128.99,

128.96, 128.64, 128.33, 124.26, 118.02, 117.96, 117.82, 117.78, 117.42, 51.32, 51.22, 29.63, 28.62, 28.37, 27.05, 20.62, 20.06, 19.81, 19.29. HRMS *m/z* calcd for $C_{22}H_{27}BrN_2NaO_3$ $(M+Na)^+$ 469.1103, Found 469.1097.

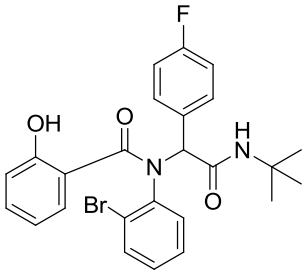
_N_-(2-Bromophenyl)-_N_-[1-(*tert*-butylamino)-4-methyl-1-oxopentan-2-yl]-2-hydroxy benzamide (2b)



2b

Purified by silica gel column chromatography. R_f 0.56 (EtOAc / hexane 1:3). White solid. M.p.: 191.7-192.3 ºC. Yield: 82%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 10.26 and 9.98 (2s, 1H), 7.82 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.47-7.30 (m, 2H), 7.18-7.10 (m, 2H), 6.90 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.76 and 6.63 (2d, *J* = 8.0 Hz, 1H), 6.51-6.37 (m, 2H), 5.12-5.08 and 4.83-4.79 (2m, 1H), 1.85-1.53 (m, 2H), 1.40 and 1.25 (2s, 9H), 1.03-0.96 (m, 1H), 0.88-0.86 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 172.52, 171.53, 170.20, 167.75, 159.93, 159.18, 140.92, 139.09, 133.39, 133.08, 132.58, 131.58, 130.64, 129.60, 129.41, 128.98, 128.52, 128.39, 128.25, 125.09, 124.13, 118.25, 117.94, 117.81, 117.79, 117.51, 58.92, 51.50, 51.33, 40.40, 37.31, 28.66, 28.42, 25.74, 25.13, 22.16, 21.95. HRMS *m/z* calcd for $C_{23}H_{29}BrN_2NaO_3$ $(M+Na)^+$ 483.1259, Found 483.1251.

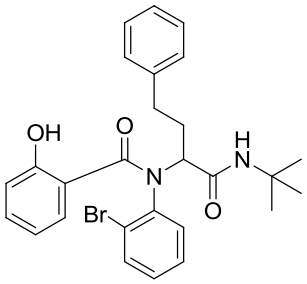
_N_-(2-Bromophenyl)-_N_-[2-(*tert*-butylamino)-1-(4-fluorophenyl)-2-oxoethyl]-2-hydro xybenzamide (2c)



2c

Purified by silica gel column chromatography. R_f 0.40 (EtOAc / hexane 1:3). White solid. M.p.:191.5-192.3 ºC. Yield: 78%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.90 (s, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.61-7.56 and 7.47-7.43 (2t, *J* = 7.8 Hz, 1H), 7.25-7.07 (m, 4H), 7.05-6.91 (m, 2H), 6.90-6.80 (m, 3H), 6.49-6.45 (m, 1H), 6.25 and 6.15 (2s, 1H), 5.71 and 5.35 (2s, 1H), 1.39 and 1.32 (2s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.05, 169.12, 163.92, 161.45, 157.30, 138.44, 132.87, 132.67, 132.59, 132.33, 132.25, 129.59, 128.52, 128.03, 127.64, 125.61, 119.56, 118.18, 117.10, 115.31, 115.09, 65.12, 52.22, 28.58, 28.49. HRMS *m/z* calcd for $C_{25}H_{24}BrFN_2NaO_3$ $(M+Na)^+$ 521.0852, Found 521.0847.

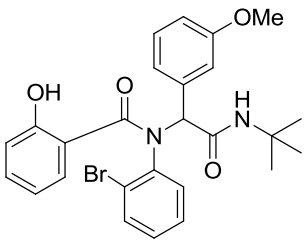
_N_-(2-Bromophenyl)-_N_-[1-(*tert*-butylamino)-1-oxo-4-phenylbutan-2-yl]-2-hydroxy benzamide (2d)



2d

Purified by silica gel column chromatography. R_f 0.44 (EtOAc / hexane 1:3). Yellowish semisolid. Yield: 85%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.97 (s, 1H), 7.82 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.42-7.35 (m, 2H), 7.31-7.25 (m, 3H), 7.21-7.10 (m, 5H), 6.92-6.90 (m, 1H), 6.78 and 6.66 (2d, *J* = 7.8 Hz, 1H), 6.45 (s, 1H), 5.01-4.97 and 4.77-4.73 (2m, 1H), 2.77-2.70 and 2.60-2.53 (2m, 2H), 2.07-1.97 and 1.67-1.58 (2m, 2H), 1.43 and 1.29 (2s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.52, 169.88, 167.57, 159.09, 140.60, 139.03, 133.51, 132.67, 131.67, 130.75, 129.79, 129.55, 128.58, 128.53, 128.48, 128.42, 128.38, 126.23, 125.06, 118.22, 118.06, 117.91, 117.77, 117.54, 60.41, 51.65, 32.51, 30.18, 28.71, 28.50. HRMS *m/z* calcd for $C_{27}H_{29}BrN_2NaO_3$ $(M+Na)^+$ 531.1259, Found 531.1254.

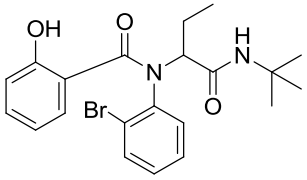
_N_-(2-Bromophenyl)-_N_-[2-(*tert*-butylamino)-1-(3-methoxyphenyl)-2-oxoethyl]-2-hy droxybenzamide (2e)



2e

Purified by silica gel column chromatography. R_f 0.31 (EtOAc / hexane 1:3). Yellowish oil. Yield: 88%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.87 (s, 1H), 7.78 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.12-6.99 (m, 5H), 6.85-6.73 (m, 4H), 6.65 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.45 (t, *J* = 6.8 Hz, 1H), 6.27 (s, 1H), 6.00 (s, 1H), 3.62 and 3.38 (2s, 3H), 1.36 and 1.29 (2s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 170.84, 169.24, 158.91, 156.52, 138.23, 133.95, 132.47, 132.00, 131.86, 129.25, 129.00, 127.81, 127.22, 125.54, 122.80, 120.09, 118.05, 116.73, 115.58, 114.76, 65.72, 55.08, 55.03, 51.98, 51.66, 28.38, 28.30. HRMS *m/z* calcd for $C_{26}H_{27}BrN_2NaO_4$ $(M+Na)^+$ 533.1052, Found 533.1046.

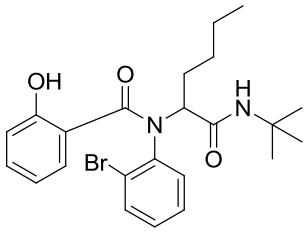
_N_-(2-Bromophenyl)-_N_-[1-(_tert_-butylamino)-1-oxobutan-2-yl]-2-hydroxybenzamide (2f)



2f

Purified by silica gel column chromatography. R_f 0.28 (EtOAc / hexane 1:3). Reddish semisolid. Yield: 75%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.98, (s, 1H), 7.87 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.43-7.37 (m, 2H), 7.18-7.13 (m, 2H), 6.90-6.88 (m, 1H), 6.63 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.41-6.36 (m, 2H), 4.87-4.86 and 4.64-4.90 (2m, 1H), 1.63-1.60 (m, 2H), 1.40 and 1.27 (2s, 9H), 1.07 and 0.93 (2t, *J* = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.10, 169.94, 158.69, 138.92, 133.78, 133.08, 132.30, 131.81, 129.50, 128.39, 128.20, 128.02, 125.08, 118.35, 117.69, 117.23, 62.38, 51.40, 28.53, 28.32, 22.06, 10.89. HRMS *m/z* calcd for $C_{21}H_{25}BrN_2NaO_3$ $(M+Na)^+$ 455.0946, Found 455.0941.

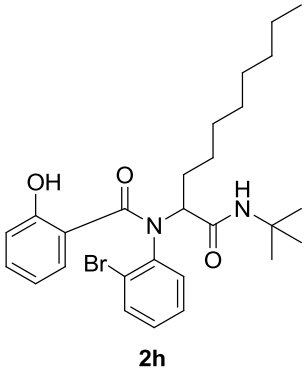
_N_-(2-Bromophenyl)-_N_-[1-(_tert_-butylamino)-1-oxohexan-2-yl]-2-hydroxybenzamide (2g)



2g

Purified by silica gel column chromatography. R_f 0.43 (EtOAc / hexane 1:4). Slightly yellow crystalline solid. M.p.: 170.6-171.1 ºC. Yield: 91%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 10.27 and 9.98 (2s, 1H), 7.84 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.49-7.37 (m, 2H), 7.18-7.10 (m, 2H), 6.92-6.89 (m, 1H), 6.62 (d, *J* = 6.8 Hz, 1H), 6.43-6.38 (m, 2H), 4.97- 4.94 and 4.70-4.60 (2m, 1H), 2.34-2.28, 2.04-1.97 and 1.67-1.53 (3m, 2H), 1.43-1.36 (m, 9H), 1.32-1.22 (m, 3H), 1.08-1.01 (m, 1H), 0.84-0.80 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.47, 170.11, 159.28, 139.17, 133.38, 132.61, 131.67, 129.62, 128.50, 128.26, 125.10, 118.14, 117.79, 117.53, 61.05, 51.54, 28.68, 28.58, 28.46, 28.22, 22.43, 13.83. HRMS *m/z* calcd for $C_{23}H_{29}BrN_2NaO_3$ $(M+Na)^+$ 483.1259, Found 483.1254.

_N_-(2-Bromophenyl)-_N_-[1-(_tert_-butylamino)-1-oxodecan-2-yl]-2-hydroxybenzamide (2h)

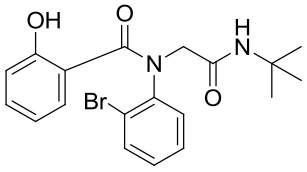


2h

Purified by silica gel column chromatography. R_f 0.49 (EtOAc / hexane 1:4). Slightly yellow cristaline solid. M.p.: 101.9-102.3 ºC. Yield: 75%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 10.00 (s, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.39-7.20 (m, 2H), 7.08-7.00 (m, 2H), 6.83-6.77 (m, 1H), 6.72 (s, 1H), 6.66 (d, *J* = 7.2 Hz, 1H), 6.38-6.32 (m, 1H), 4.99-4.96 and 4.70-4.66 (2m, 1H), 2.29-2.22, 2.00-1.93 and 1.59-1.51 (3m, 2H), 1.49-1.04 (m, 21H), 0.81-0.76 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 172.19, 170.98, 170.17, 167.69, 158.32, 140.65, 138.77, 133.60, 132.93, 132.61, 132.06, 131.78, 130.50, 129.36, 129.15, 128.66, 128.35, 128.07, 127.86, 125.05, 123.85, 118.60, 117.78, 117.62, 117.31, 117.03, 60.72, 51.26, 51.03,

31.57, 31.49, 31.29, 29.14, 29.17, 29.06, 29.04, 28.97, 28.83, 28.70, 28.45, 28.22, 26.49, 26.13, 22.42, 22.37, 13.88. HRMS *m/z* calcd for $C_{27}H_{37}BrN_2NaO_3$ $(M+Na)^+$ 539.1885, Found 539.1880.

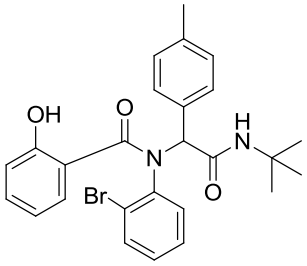
_N_-(2-Bromophenyl)-_N_-[2-(*tert*-butylamino)-2-oxoethyl]-2-hydroxybenzamide (2i)



2i

Purified by silica gel column chromatography. R_f 0.41 (EtOAc / hexane 1:3). Slightly pink cristaline solid. M.p.: 214.5-215.3 ºC. Yield: 87%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 10.37 (s, 1H), 7.58 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.44 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.31-7.26 (m, 1H), 7.21-7.14 (m, 2H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.74-6.72 (m, 1H), 6.46-6.43 (m, 1H), 6.14 (s, 1H), 4.70 and 3.91 (2d, *J* = 15.7 Hz, 2H), 1.37 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.88, 166.95, 133.84, 133.24, 130.67, 129.66, 128.93, 128.81, 122.31, 118.15, 117.77, 55.18, 51.64, 28.72. HRMS *m/z* calcd for $C_{19}H_{21}BrN_2NaO_3$ $(M+Na)^+$ 427.0633, Found 427.0628.

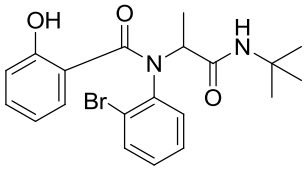
_N_-(2-Bromophenyl)-_N_-[2-(*tert*-butylamino)-1-(4-methylphenyl)-2-oxoethyl]-2-hydroxybenzamide (2j)



2j

Purified by silica gel column chromatography. R_f 0.38 (EtOAc / hexane 1:3). Yellowish semi solid. Yield: 92%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.90 (s, 1H), 7.77 (dd, *J* = 9.6, 1.4 Hz, 1H), 7.48-7.46 and 7.42-7.40 (2m, 1H), 7.17-7.05 (m, 4H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.87-6.83 (m, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.46 (t, *J* = 7.2 Hz, 1H), 6.26 (s, 1H), 5.74 and 5.30 (2s, 1H), 2.34 and 2.19 (2s, 3H), 1.37 and 1.31 (2s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 170.89, 169.52, 156.72, 138.49, 138.42, 132.56, 132.04, 131.90, 130.52, 129.45, 129.25, 128.97, 128.80, 127.84, 127.32, 125.59, 120.10, 118.06, 116.83, 52.05, 28.50, 21.02. HRMS *m/z* calcd for $C_{26}H_{27}BrN_2NaO_3$ $(M+Na)^+$ 517.1103, Found 517.1097.

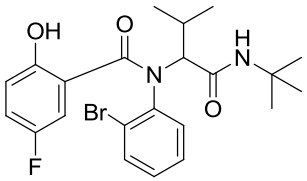
_N_-(2-Bromophenyl)-_N_-[1-(*tert*-butylamino)-1-oxopropan-2-yl]-2-hydroxybenzamide (2k)



2k

Purified by silica gel column chromatography. R_f 0.43 (EtOAc / hexane 1:3). Brownish powder. M.p.: 167.7-168.0 ºC. Yield: 85%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 10.26 and 10.01 (2s, 1H), 7.65 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.54-7.48 (m, 1H), 7.41-7.31 (m, 1H), 7.19-7.13 (m, 2H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.76-6.68 (m, 1H), 6.43 (t, *J* = 8.0 Hz, 1H), 6.27 (s, 1H), 5.08 (q, *J* = 7.2 Hz, 1H), 1.40 and 1.32 (2s, 9H), 1.15 (d, *J* = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.41, 170.65, 158.86, 139.01, 133.52, 132.61, 131.59, 129.85, 128.42, 128.23, 124.90, 118.00, 117.51, 56.42, 51.50, 28.68, 13.88. HRMS *m/z* calcd for $C_{20}H_{23}BrN_2NaO_3$ $(M+Na)^+$ 441.0790, Found 441.0784.

_N_-(2-Bromophenyl)-_N_-[1-(*tert*-butylamino)-3-methyl-1-oxobutan-2-yl]-5-fluoro-2-hydroxybenzamide (2l)

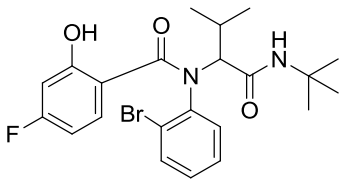


2l

Purified by silica gel column chromatography. R_f 0.40 (EtOAc / hexane 1:3). White crystalline solid. M.p.: 216.6-218.1 ºC. Yield: 84%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 10.06 and 9.79 (2s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.48-7.34 (m, 2H), 7.22-7.12 (m, 1H), 6.94-6.83 (m, 2H), 6.55-6.52 and 6.39-6.36 (2m, 1H), 6.23 (s, 1H), 4.64 and 4.07 (2d, *J* = 11.2 Hz, 1H), 2.75-2.66 and 2.60-2.51 (2m, 1H), 1.39 (s, 6H), 1.25-1.21 (m, 5H), 1.06-1.01 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.54, 169.07, 155.33, 134.28, 134.09, 129.98, 129.73, 129.49, 128.84, 128.54,

124.27, 120.32, 120.09, 118.86, 118.76, 118.69, 114.75, 114.50, 51.42, 29.61, 28.62, 28.34, 27.01, 20.68, 19.96, 19.76, 19.24. HRMS *m/z* calcd for $C_{22}H_{26}BrFN_2NaO_3$ $(M+Na)^+$ 487.1009, Found 487.1003.

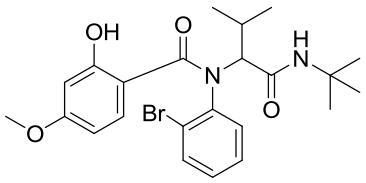
_N_-(2-Bromophenyl)-_N_-[1-(_tert_-butylamino)-3-methyl-1-oxobutan-2-yl]-4-fluoro-2-hydroxybenzamide (2m)



2m

Purified by silica gel column chromatography. R_f 0.46 (EtOAc / hexane 1:3). White crystalline solid. M.p.: 171.1-172.7 ºC. Yield: 80%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 10.65 and 10.42 (2s, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.41-7.26 (m, 2H), 7.09-7.03 (m, 1H), 6.87-6.83 and 6.71-6.67 (2m, 1H), 6.56-6.51 (m, 1H), 6.42 (s, 1H), 6.13-6.05 (m, 1H), 4.63 and 4.12 (2d, *J* = 11.2 Hz, 1H), 2.70-2.54 (m, 1H), 1.35 (s, 5H), 1.21-1.17 (m, 5H), 1.01-0.98 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 172.59, 171.86, 169.15, 166.96, 166.20, 166.08, 163.68, 163.57, 162.36, 162.22, 161.88, 161.74, 141.59, 140.17, 134.00, 133.82, 130.92, 130.81, 130.64, 130.54, 129.95, 129.88, 129.30, 129.03, 128.56, 128.23, 124.00, 114.69, 114.08, 105.71, 105.59, 105.49, 105.37, 104.65, 104.60, 104.41, 104.37, 51.18, 51.09, 29.51, 28.45, 28.17, 26.93, 20.48, 19.80, 19.63, 19.10. HRMS *m/z* calcd for $C_{22}H_{26}BrFN_2NaO_3$ $(M+Na)^+$ 487.1009, Found 487.1003.

_N_-(2-Bromophenyl)-_N_-[1-(_tert_-butylamino)-3-methyl-1-oxobutan-2-yl]-2-hydroxy-4-methoxybenzamide (2n)



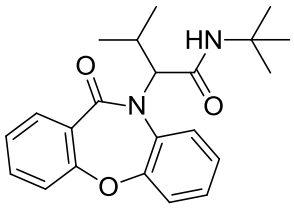
2n

Purified by silica gel column chromatography. R_f 0.46 (EtOAc / hexane 1:3). White solid. M.p.: 83.7-85.0 ºC. Yield: 71%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 11.03 and 10.80 (2s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.48-7.40 (m, 2H), 7.39-7.28 (m, 1H), 7.13-7.08 (m, 1H), 6.78 and 6.59 (2d, *J* = 9.0 Hz, 1H), 6.42-6.41 (m, 1H), 4.52-4.50 and 3.94-3.92 (2m, 1H), 3.73 (s, 3H), 2.77-2.66 (m, 1H), 1.58 (s, 1H), 1.38 and 1.25 (2s, 9H), 1.22-1.20 and 1.06-1.03 (2m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 173.83, 172.87, 169.16, 167.51, 163.62, 163.46, 163.41, 163.26, 142.89, 134.31, 134.21, 130.74, 130.47, 130.13, 129.68, 129.14, 128.80, 128.77, 128.42, 123.99, 105.94, 105.70, 101.41, 101.36, 55.28, 51.21, 29.55, 28.62, 28.40, 20.61, 20.11, 19.81, 19.35. HRMS *m/z* calcd for $C_{23}H_{29}BrN_2NaO_4$ $(M+Na)^+$ 499.1208, Found 499.1203.

General procedure for Ullmann intramolecular cyclization

A mixture of *N*-substituted peptoid **2** (0.5 mmol), CuI (0.05 mmol, 10 mol %), *N,N*-dimethylglycine hydrochloride (0.15 mmol, 30 mol%), Cs_2CO_3 (1 mmol), dry 1,4-dioxane (2mL) in a sealed tube under nitrogen was heated at 105 ºC for 24 h. The consumption of the starting material was monitored by TLC. The mixture was put to cool down to room temperature. The mixture was partitioned between EtOAc (10 ml) and water (3 ml). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 10 ml). The organic layers were washed with brine (2 x 5 ml), dried over Na_2SO_4, filtered and concentrated by the removal of solvent under reduced pressure in a rotavap. The crude material was purified by silica gel column chromatography to afford the desired products.

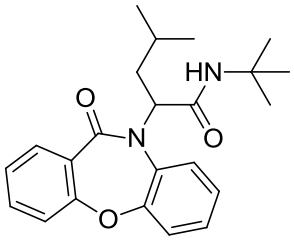
***N-tert*-Butyl-3-methyl-2-(11-oxodibenzo[*b*,*f*][1,4]oxazepin-10(11*H*)-yl)butanamide (1a)**



1a

Purified by silica gel column chromatography. R_f 0.41 (EtOAc / hexane 1:9). White crystalline solid. M.p.: 180.2-180.7 ºC. Yield: 70%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.98 (brs, 1H), 7.88 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.47 (m, 2H), 7.27-7.16 (m, 5H), 4.75 (brs, 1H), 2.17 (brs, 1H), 1.40 (s, 9H), 1.05 (d, *J* = 6.0 Hz, 3H), 0.76 (brs, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.25, 168.47 (br), 161.09, 154.97 (br), 133.92, 132.51, 127.42, 126.11, 125.73 (br), 125.20, 121.14, 119.72, 66.51 (br), 51.05, 28.65, 25.57 (br), 20.07, 18.73 (br). HRMS *m/z* calcd for $C_{22}H_{26}N_2NaO_3$ $(M+Na)^+$ 389.1841, Found 389.1836.

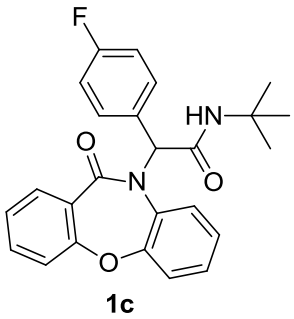
N-tert-Butyl-4-methyl-2-(11-oxodibenzo[*b*,*f*][1,4]oxazepin-10(11*H*)-yl)pentanamide (1b)



1b

Purified by silica gel column chromatography. R_f 0.37 (EtOAc / hexane 1:9). White crystalline solid. M.p.: 166.7-167.3 ºC. Yield: 85%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.91 (d, *J* = 8.0 Hz, 1H), 7.50-7.44 (m, 2H), 7.26-7.13 (m, 6H), 5.32 (brs, 1H), 1.74-1.34 (m, 12H), 0.83 (d, *J* = 6.4 Hz, 4H), 0.73 (brs, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 171.10, 168.32 (br), 161.10, 155.24, 134.03, 132.54, 131.51 (br), 127.52, 125.73, 125.20, 121.27, 119.81, 57.71 (br), 50.99, 35.87 (br), 28.57, 28.37, 24.12 (br), 23.13, 21.50. HRMS *m/z* calcd for $C_{23}H_{28}N_2NaO_3$ $(M+Na)^+$ 403.1998, Found 403.1992.

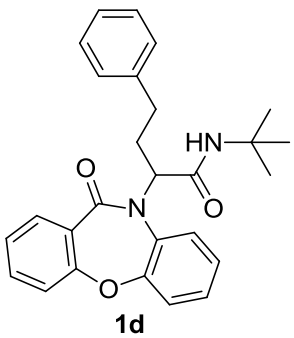
N-tert-Butyl-2-(4-fluorophenyl)-2-(11-oxodibenzo[*b*,*f*][1,4]oxazepin-10(11*H*)-yl)acetamide (1c)



1c

Purified by silica gel column chromatography. R_f 0.32 (EtOAc / hexane 1:4). White crystalline solid. M.p.: 153.9-154.1 ºC. Yield: 78%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.84 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.54 (d, *J* = 5.2 Hz, 1H), 7.46-7.41 (m, 1H), 7.36-7.32 (m, 2H), 7.20-7.16 (m, 3H), 7.06-6.91 (m, 4H), 6.72 (brs, 1H), 5.97 (brs, 1H), 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.99, 168.49, 167.18, 163.56, 160.99, 160.29, 155.07 (br), 133.84, 132.40, 130.54, 129.98 (br), 127.22, 125.82, 125.52, 125.19, 120.74, 119.75, 115.33, 115.04, 51.57, 29.57, 28.47. HRMS *m/z* calcd for $C_{25}H_{23}FN_2NaO_3$ $(M+Na)^+$ 441.1590, Found 441.1585.

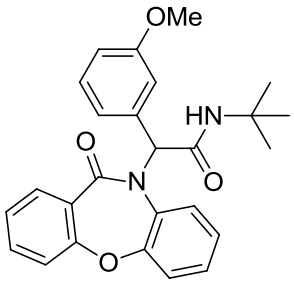
N-tert-Butyl-2-(11-oxodibenzo[*b*,*f*][1,4]oxazepin-10(11*H*)-yl)-4-phenylbutanamide (1d)



1d

Purified by silica gel column chromatography. R_f 0.27 (EtOAc / hexane 1:9). White crystalline solid. M.p.: 143.5-144.2 ºC. Yield: 76%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.96-7.94 (m, 1H), 7.55-7.49 (m, 2H), 7.34-7.12 (m, 10H), 7.03 (d, *J* = 7.6 Hz, 1H), 5.18 (brs, 1H), 2.67-2.46 (m, 2H), 2.30-2.19 and 2.00-1.86 (2m, 2H), 1.41 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.68, 168.37 (br), 161.10, 155.35 (br), 140.78, 134.12, 132.62, 128.38, 128.26, 127.68, 125.89, 125.83, 125.66, 125.27, 121.42, 119.89, 58.89 (br), 51.02, 31.61 (br), 28.56. HRMS *m/z* calcd for $C_{27}H_{28}N_2O_3$ $(M+Na)^+$ 451.1998, Found 451.1992.

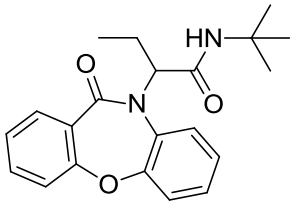
N-tert-Butyl-2-(3-methoxyphenyl)-2-(11-oxodibenzo[*b*,*f*][1,4]oxazepin-10(11*H*)-yl) acetamide (1e)



1e

Purified by silica gel column chromatography. R_f 0.20 (EtOAc / hexane 1:4). Yellowish semi solid. Yield: 81%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.86 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.46-7.41 (m, 1H), 7.20-7.15 (m, 4H), 7.09-6.93 (m, 4H), 6.75-6.73 (m, 1H), 6.54 (brs, very weak, 1H), 5.92 (brs, 1H), 3.71 (s, 3H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 168.68, 167.28, 161.16, 159.57, 155.15, 136.45, 133.85, 132.57, 129.43, 127.19, 126.14, 125.59, 125.26, 120.76, 119.87, 113.63, 55.15, 51.68, 28.62. HRMS *m/z* calcd for $C_{26}H_{26}N_2NaO_4$ $(M+Na)^+$ 453.1790, Found 453.1785.

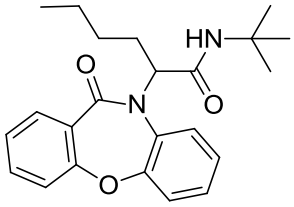
***N-tert*-Butyl-2-(11-oxodibenzo[*b*,*f*][1,4]oxazepin-10(11*H*)-yl)butanamide (1f)**



1f

Purified by silica gel column chromatography. R_f 0.28 (EtOAc / hexane 1:9). White crystalline solid. M.p.: 168.7-169.0 ºC. Yield: 73%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.91-7.89 (m, 1H), 7.51-7.44 (m, 2H), 7.29-7.12 (m, 6H), 5.11 (brs, 1H), 1.94 and 1.54 (2brs, 2H), 1.38 (s, 9H), 0.88-0.78 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.79, 168.40 (br), 161.12, 155.26, 134.01, 132.54, 127.51, 125.76, 125.68, 125.32, 125.18, 121.30, 119.80, 61.89, 50.98, 28.58, 20.45 (br), 10.30. HRMS *m/z* calcd for $C_{21}H_{24}N_2NaO_3$ $(M+Na)^+$ 375.1685, Found 375.1679.

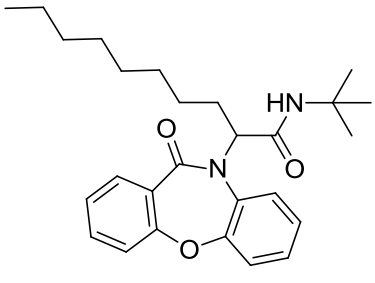
***N-tert*-Butyl-2-(11-oxodibenzo[*b*,*f*][1,4]oxazepin-10(11*H*)-yl)hexanamide (1g)**



1g

Purified by silica gel column chromatography. R_f 0.51 (EtOAc / hexane 1:9). Yellowish crystalline solid. M.p.: 164.8-165.6 ºC. Yield: 65%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.91 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.52-7.44 (m, 2H), 7.29-7.13 (m, 6H), 5.20 (brs, 1H), 1.89 and 1.54 (2brs, 2H), 1.38 (s, 9H), 1.28-1.13 (m, 4H), 0.77-0.71 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 171.02, 168.45, 161.21, 155.39, 134.08, 132.61, 127.59, 125.86, 125.76, 125.39, 125.26, 121.35, 119.88, 60.14 (br), 51.06, 28.65, 27.71, 26.82 (br), 22.14, 13.74. HRMS *m/z* calcd for $C_{23}H_{28}N_2NaO_3$ $(M+Na)^+$ 403.1998, Found 403.1992.

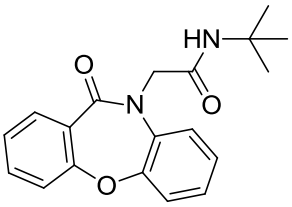
***N-tert*-Butyl-2-(11-oxodibenzo[*b*,*f*][1,4]oxazepin-10(11*H*)-yl)decanamide (1h)**



1h

Purified by silica gel column chromatography. R_f 0.39 (EtOAc / hexane 1:9). Dense colorless oil. Yield: 45%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.94-7.90 (m, 1H), 7.54-7.46 (m, 2H), 7.32 (brs, 1H), 7.29-7.15 (m, 5H), 5.22 (brs, 1H), 1.89 and 1.56 (2brs, 2H), 1.40 (s, 9H), 1.28-1.10 (m, 12H), 0.84 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.94, 168.31 (br), 161.12, 155.29, 133.96, 132.51, 127.47, 125.76, 125.64, 125.30, 125.14, 121.26, 119.78, 60.10 (br), 50.94, 31.62, 29.59 (br), 28.97, 28.90, 28.56, 27.00 (br), 25.64, 22.50, 13.98. HRMS *m/z* calcd for $C_{27}H_{36}N_2NaO_3$ $(M+Na)^+$ 459.2624, Found 459.2618.

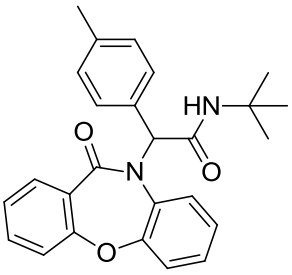
N-tert-Butyl-2-(11-oxodibenzo[*b*,*f*][1,4]oxazepin-10(11*H*)-yl)acetamide (1i)



1i

Purified by silica gel column chromatography. R_f 0.29 (EtOAc / hexane 1:4). White crystalline solid. M.p.: 168.5-169.1 ºC. Yield: 80%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.85 (m, 1H), 7.50-7.43 (m, 2H), 7.26-7.13 (m, 5H), 6.53 (s, 1H), 4.54 (s, 2H), 1.31 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 167.65, 166.87, 160.60, 153.69, 134.78, 133.97, 132.19, 127.04, 126.26, 125.65, 125.36, 123.38, 121.17, 119.85, 54.57, 51.24, 28.47. HRMS *m/z* calcd for $C_{19}H_{20}N_2NaO_3$ $(M+Na)^+$ 347.1372, Found 347.1366.

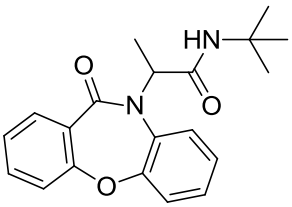
N-tert-Butyl-2-(4-methylphenyl)-2-(11-oxodibenzo[*b*,*f*][1,4]oxazepin-10(11*H*)-yl)acetamide (1j)



1j

Purified by silica gel column chromatography. R_f 0.35 (EtOAc / hexane 1:4). White crystalline solid. M.p.: 170.9-171.6 ºC. Yield: 68%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.87 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.46-7.42 (m, 1H), 7.27 (d, *J* = 7.6 Hz, 2H), 7.21-7.17 (m, 3H), 7.09-6.99 (m, 4H), 6.53 (brs, very weak, 1H), 5.92 (brs, 1H), 2.27 (s, 3H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 168.94, 167.19, 161.16, 155.13, 137.54, 133.80, 132.60, 131.88, 129.18, 128.20, 127.10 (br), 126.19, 125.57 (br), 125.24, 120.80, 119.84, 51.52, 28.52, 20.97. HRMS *m/z* calcd for $C_{26}H_{26}N_2NaO_3$ $(M+Na)^+$ 437.1841, Found 437.1836.

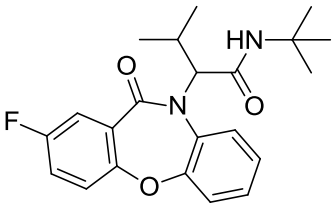
N-tert-Butyl-2-(11-oxodibenzo[*b*,*f*][1,4]oxazepin-10(11*H*)-yl)propanamide (1k)



1k

Purified by silica gel column chromatography. R_f 0.41 (EtOAc / hexane 1:4). Slightly orange crystalline solid. M.p.: 173.7-174.3 ºC. Yield: 81%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.89 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.48-7.39 (m, 2H), 7.26-7.13 (m, 6H), 5.34 (s, 1H), 1.35 (s, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.77, 167.84, 161.03, 155.48, 133.99, 132.48, 127.49, 125.75, 125.22, 125.03, 121.30, 119.79, 50.98, 28.52, 14.21. HRMS *m/z* calcd for $C_{20}H_{22}N_2NaO_3$ $(M+Na)^+$ 361.1528, Found 361.1523.

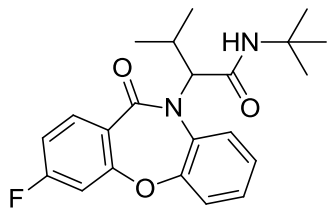
N-tert-Butyl-2-(2-fluoro-11-oxodibenzo[*b*,*f*][1,4]oxazepin-10(11*H*)-yl)-3-methylbutanamide (1l)



1l

Purified by silica gel column chromatography. R_f 0.35 (EtOAc / hexane 1:9). Slightly yellow crystalline solid. M.p.: 149.4-150.2 ºC. Yield: 12%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.05 (brs, 1H), 7.55 (dd, *J* = 8.6, 3.0 Hz, 1 Hz), 7.28-7.12 (m, 6H), 4.73 (brs, 1H), 2.16 (brs, 1H), 1.41 (s, 9H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.73 (brs, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 169.93, 167.30 (br), 160.59, 158.15, 157.45, 157.08, 157.11, 155.04 (br), 131.54 (br), 127.61, 127.45, 125.90 (br), 121.24, 121.16, 120.96, 120.75, 120.51, 119.61, 119.54, 118.61, 118.37, 111.41, 111.17, 66.84 (br), 51.09, 29.34, 28.67, 28.53, 20.03, 19.88. HRMS *m/z* calcd for $C_{22}H_{25}N_2NaO_3$ $(M+Na)^+$ 407.1747, Found 407.1741.

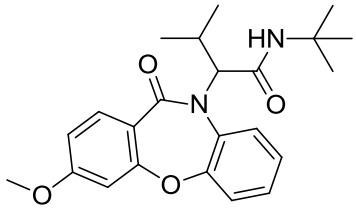
N-tert-Butyl-2-(3-fluoro-11-oxodibenzo[*b*,*f*][1,4]oxazepin-10(11*H*)-yl)-3-methylbutanamide (1m)



1m

Purified by silica gel column chromatography. R_f 0.35 (EtOAc / hexane 1:9). Slightly yellow crystalline solid. M.p.: 165.2-165.7 ºC. Yield: 74%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.00 (brs, very weak, 1H), 7.91-7.88 (m, 1H), 7.28-7.19 (m, 4H), 6.97-6.92 (m, 2H), 4.69 (brs, 1H), 2.19 (brs, 1H), 1.41 (s, 9H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.77 (brs, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 170.11, 167.26 (br), 163.87, 162.27, 162.12, 154.36 (br), 134.44, 134.30, 127.49, 126.07, 125.79, 122.40, 121.06, 112.91, 112.63, 107.49, 107.18, 66.75, 51.04, 28.73, 28.60, 19.98. HRMS *m/z* calcd for $C_{22}H_{25}N_2NaO_3$ $(M+Na)^+$ 407.1747, Found 407.1741.

N-tert-Butyl-2-(3-methoxy-11-oxodibenzo[_b_,_f_][1,4]oxazepin-10(11_H_)-yl)-3-methyl butanamide (1n)



1n

Purified by silica gel column chromatography. R_f 0.40 (EtOAc / hexane 1:4). White crystalline solid. M.p.: 157.3-157.5 ºC. Yield: 85%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.92 (brs, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.48 (brs, 1H), 7.22-7.14 (m, 3H), 6.73 (dd, *J* = 8.4, 2.4 Hz, 1H), 6,69 (d, *J* = 8.0 Hz, 1H), 4.68 (brs, 1H), 3.81 (s, 3H), 2.17 (brs, 1H), 1.37 (s, 9H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.75 (brs, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.44, 168.06 (br), 164.14, 162.38, 154.35 (br), 133.72, 127.16, 125.74 (br), 125.45 (br), 121.04, 118.12, 111.56, 104.32, 66.38 (br), 55.60, 50.88, 28.57, 25.68 (br), 20.03, 18.71 (br). HRMS *m/z* calcd for $C_{23}H_{28}N_2NaO_4$ $(M+Na)^+$ 419.1947, Found 419.1941.

Biological activity assay[18-20]

The antibacterial activity against transgenic *Bacillus subtilis* expressing YFP in the growth phase only was determined with a fluorescence based antibacterial growth inhibition assay. The fluorescence was measured on a microtiter plate reader GENios Pro (Fa. Tecan, excitation, 510 nm; emission, 535 nm). The *Bacillus subtilis* strain 168 (P_{AbrB}-IYFP)[20] was maintained on TY (tryptone-yeast extract) medium supplemented with 1% Bacto-tryptone, 0.5 % Bacto-yeast extract, 1% NaCl and chloramphenicol (5 µg.ml^{-1}). All experiments were conducted in triplicate.

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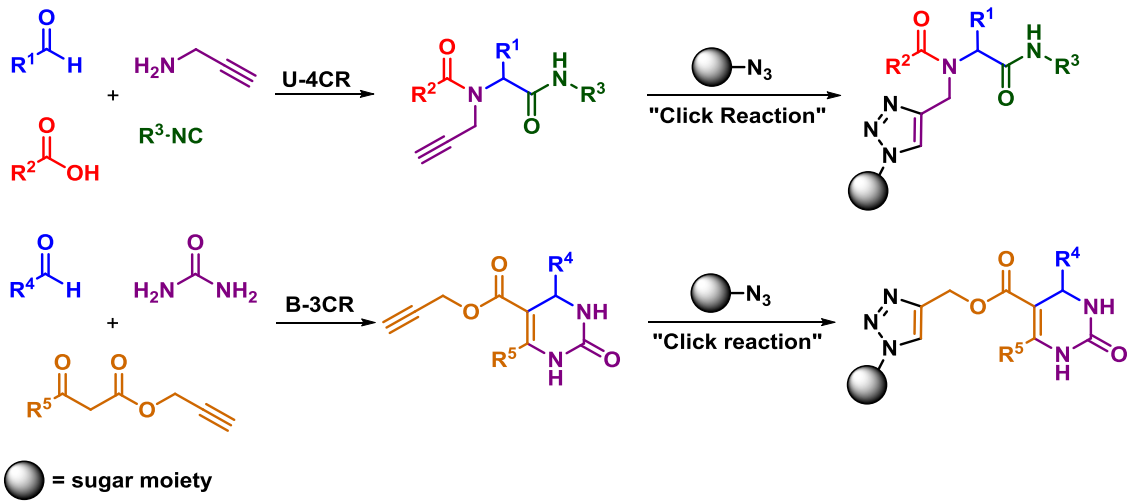
Chapter 3

Synthesis of glycoconjugate mimetics *via* U-4CR/Click and B-3CR/Click reactions*

Abstract



In this chapter, the synthesis of new glycopeptide mimetics are discussed using two step protocols of U-4CR/copper catalyzed Huisgen 1,3-cycloadditions or glyco 3,4-dihydropirimidin-2(1*H*)-ones derivatives by two steps B-3CR/copper catalyzed Huisgen 1,3-cycloadditions generating 1,2,3-triazoles as linkers. The antibacterial activity of the compounds was tested against the bacterium *Bacillus subtilis* in a fluorescence based assay.

* Same compounds synthesized by another synthetic route were published during the compilation of the thesis manuscript by Rao, D. G. B.; Anjaneyulu, B.; Kaushik, M. P. *Tetrahedon Lett.* **2014**, *55*, 19.

3.1 Introduction

Glycoconjugated compounds consist of carbohydrate unit(s) covalently linked to other chemical moieties, e.g. peptides (glycopeptides), lipids (glycolipids), proteins (glycoproteins), among several others, usually via the anomeric oxygen, but also *N*- and *C*- glycosides are known. They are ubiquitous components that are directly involved in the modulation or mediation of a wide variety of events in cell-cell and cell-matrix interactions. These components are crucial for the development and function of complex multicellular organisms, such as immune response, inflammation, cell signaling and infection by pathogens. There is a great interest in the application of this kind of compounds in diverse scientific fields such as biology, medical chemistry, biochemistry, and materials science. Applications that seem to be particularly attractive are, for example, the elucidation of active mechanisms in living cell systems, the discovery of new approaches in the treatment of diseases, the design of vaccines, and the development of new materials.[1]

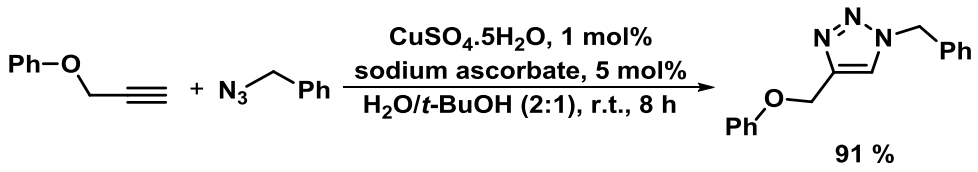
In order to get a better understanding of the structure-activity relation of glycoconjugates, as well as investigating their potential as therapeutic agents, it is necessary to obtain them as pure and homogeneous as possible. This is a challenging task for glycobiology, given the difficulty to extract glycoconjugated compounds from natural sources in significant quantities and purity for practical applications. Moreover, the high complexity of these natural biopolymers makes a difficult challenge to synthetize them. Furthermore, the unavailability of glycoconjugated test compounds is still a breakdown that precludes the possibility for high-throughput screening in the search of new drugs from natural products.[2,3]

An approach to overcome this issue is the synthesis of small molecules containing functionalities, which can mimic the glycoconjugated compounds; these are the so-called neoglycoconjugates. These compounds can be combined with high-throughput screening techniques in the search of new drugs candidates or the development of new therapeutic approaches.[4] In spite of these functionalized small molecules (neoglycoconjugates) being able to mimic glycoconjugated compounds with remarkable results, sometimes they may display poor bioavailability. A strategy to overcome this problem is attaching sugar moieties to these bioactive small molecules what helps to increase its solubility, and therefore their bioavailability.

3.2 Synthetic strategies

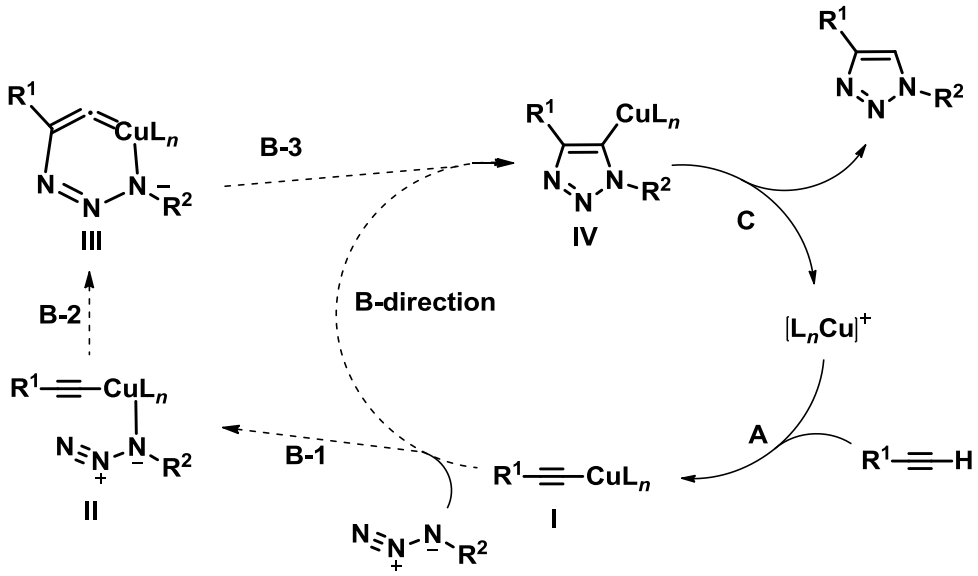
Our goal was developing a strategy to have rapid access to a series of glycoconjugate mimetics employing U-4CR and B-3CR, producing peptoids as well as 3,4-dihydropyrimidin-2(1*H*)-ones respectively, which would be able to be modified later in order to introduce the sugar moiety to MCR products.

Triazoles are well-known heterocyclic scaffolds that have a wide range of biological activities, including anti-tumor, anti-inflammatory, analgesic, anti-fungal, anti-bacterial, and anti-viral ones.[5] Besides that, triazoles also have multiple applications in material science[6] and medical chemistry.[7] The copper catalyzed Huisgen 1,3-cycloaddition reaction, in which azides and terminal acetylenes react to regiospecifically produce 1,4-disubstituted 1,2,3-triazoles (**Scheme 3.2.1**) is a versatile method that constitutes the best example of click reactions to date. [8]



Scheme 3.2.1 Copper catalized 1,3-Huisgen cycloaddition.[8]

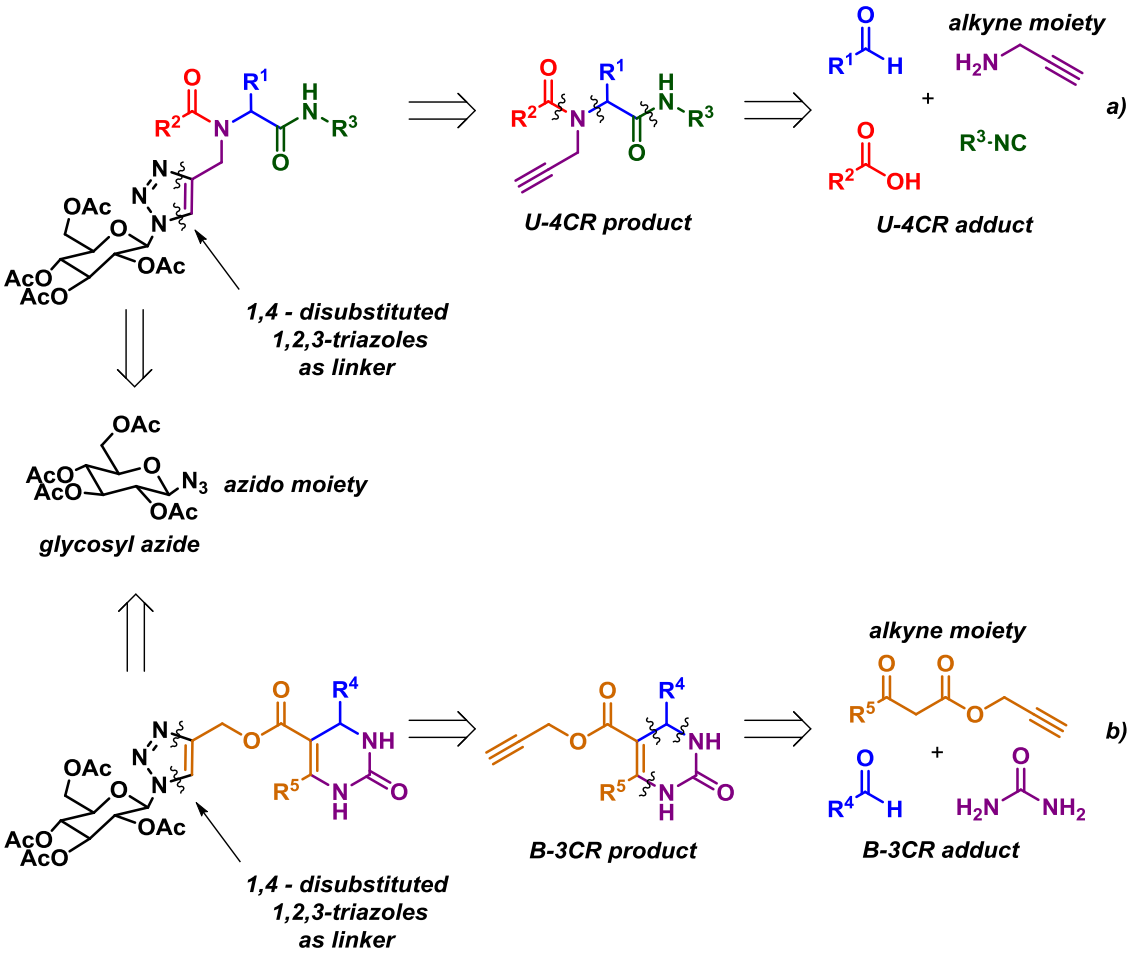
The proposed mechanism is as follows: it begins with formation of the copper (I) acetylide **I**, following to the concerted [2+3] cycloaddition (B-direct) and points to a stepwise, annealing sequence, which proceeds via the six-membered copper-containing intermediate **III** (**Scheme 3.2.2**).[8]



Scheme 3.2.2 Proposed mechanism for the copper catalized 1,3-Huisgen cycloaddition.

Many publications report the strategy of introducing the azide moiety into compound **a** and the terminal alkyne functionality in another compound, **b**, and later to react **a** and **b** *via* copper catalyzed 1,3 Huisgen cycloaddition, to generate 1,4-disubstituted 1,2,3-triazol as linker of these two compounds.[9]

We envisaged the coupling of U-4CR/Click reaction two step sequence to access glycopeptide mimetics, by the introduction of a terminal alkyne moiety as amine educt in the U-4CR and an azido moiety in the sugar compound (**Scheme 3.2.3 a**). We also planed the use of B-3CR/Click reaction in a two step sequence to access DHPM glycoconjugates, by introducing a terminal alkyne in the acyl moiety connected to *C*-5 of the DHPM product (**Scheme 3.2.3 b**).



Scheme 3.2.3 Synthetic strategies for the synthesis of **(a)** glycopeptides mimics, and **(b)** DHPM glycoconjugated.

3.3 Synthesis of glycopeptide mimetics and DHPM glycoconjugates

The precursors azido sugars **1** and **2** and the β-keto ester **3** were prepared employing reported procedures (**Figure 3.3.1**).[10,11]

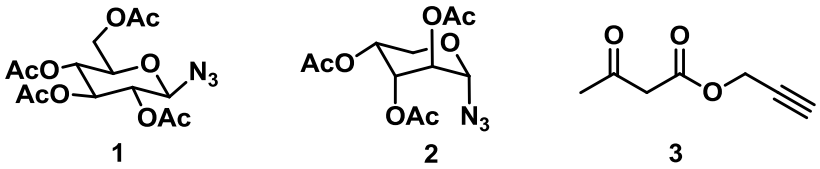
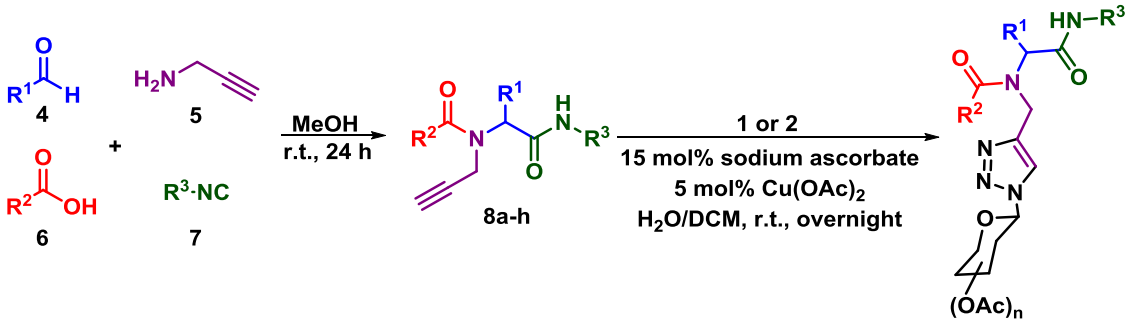
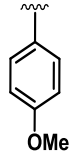


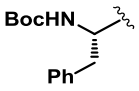
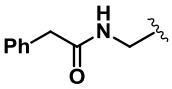
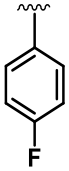
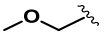
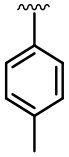
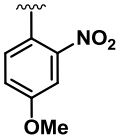
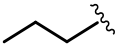
Figure 3.3.1 Synthetized precursors: tetra-*O*-acetyl-β-D-glucosyl azide (**1**), tri-*O*-acetyl-α-D-arabinosyl azide (**2**) and propargyl acetoacetate (**3**).

For the U-4CR, aldehydes **4**, propargylamine (**5**), carboxylic acids **6**, and isocyanides **7** were reacted in equimolar quantities in methanol at room temperature for 24 hours. After isolation and purification by column chromathography, a small library of peptoids **8a-h** with the terminal alkyne moiety installed at the nitrogen of the tertiary amide was obtained in high purity and good yields. The second step, the copper catalyzed 1,3-Huisgen cycloaddition reaction of the *N*-propargylic peptoids **8a-h** with azides **1** and **2**, permitted access to the glycopeptide mimetics **9a-h** in high yield and purity.[12] The compounds were consecutively deprotected, generating the final compounds **10a-h** (**Table 3.3.1**).[13]

Table 3.3.1 Synthesis of glycopeptide mimetics **10a-h**.



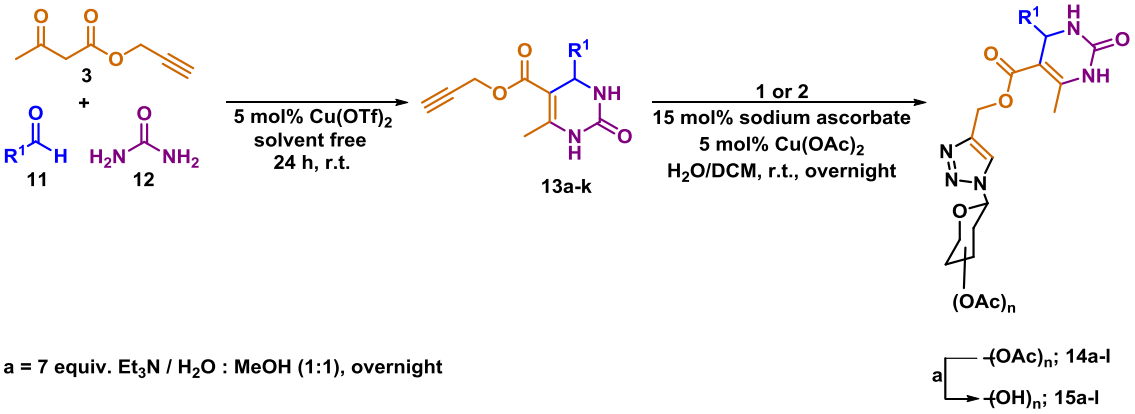
Entry	R^1	R^2	R^3	Product Yield (%)[a]	Azide	Product Yield (%)[a]	
a		Me		**8a** 99	**1**	**9a** 95	**10a** 86
b		Me		**8b** 97	**1**	**9b** 60	**10b** 96

c	H			**8c** 98	**1**	**9c** 95	**10c** 67
d				**8d** 82	**1**	**9d** 70	**10d** 89
e				**8e** 98	**1**	**9e** 72	**10e** 92
f		Pr		**8f** 91	**1**	**9f** 90	**10f** 91
g		Me		**8g** 96	**1**	**9g** 91	**10g** 89
h	H			**8h** 70	**2**	**9h** 90	**10h** 78

[a] Yields after purification with silica gel column chromatography.

Following with our synthetic strategy, aldehydes **11**, propargyl acetoacetate (**3**), and urea (**12**) were reacted in presence of catalytic (5 mol%) copper(II)triflate at room temperature for 24 hours under solvent-free conditions. The B-3CR products **13a-k** were purified by recrystallization from ethanol in good yields. The DHPMs **13** were reacted with the sugar azides **1** and **2** in click reactions enabling access to DHPM glycoconjugate **14a-l** in good yields.[12] These were consecutively deprotected, resulting in compounds **15a-l** (**Table 3.3.2**).[13]

Table 3.3.2 Synthesis of DHPM glycoconjugated.



Entry	R^1	Product Yield (%)	Azide	Product Yield (%)[a]	
a	2-$CF_3C_6H_4$	**13a** 86	**1**	**14a** 90	**15a** 81
b	3-BrC_6H_4	**13b** 83	**1**	**14b** 99	**15b** 68
c	4-FC_6H_4	**13c** 90	**1**	**14c** 99	**15c** 85
d	1-naphthyl	**13d** 78	**1**	**14d** 91	**15d** 90
e	4-$CH_3C_6H_4$	**13e** 88	**1**	**14e** 98	**15e** 95
f	2-ClC_6H_4	**13f** 82	**1**	**14f** 96	**15f** 91
g	4-OHC_6H_4	**13g** 78	**1**	**14g** 95	**15g** 89
h	4-$NO_2C_6H_4$	**13h** 89	**1**	**14h** 99	**15h** 93
i	2-naphtyl	**13i** 81	**1**	**14i** 99	**15i** 73
j	4-BrC_6H_4	**13j** 90	**1**	**14j** 99	**15j** 92
k	4-ClC_6H_4	**13k** 87	**1**	**14k** 94	**15k** 92
l	4-BrC_6H_4	**13j** 90	**2**	**14l** 99	**15l** 98

[a] Yields after purification with silica gel column chromatography.

3.4 Biological studies[a]

As discussed above and in chapters 1 and 2 the 1,2,3-triazoles, peptoids and the DHPM moieties are present in several compounds displaying biological activity. We tested compounds **8a-h**, **9a-h**, **10a-h, 13a-k, 14a-l** and **15a-l** against Gram-positive bacterium *Bacillus subtilis* strain 168 in a fluorescence based assay.[14-16] Unfortunately, the compounds showed only low to moderate growth inhibition when compared to the standard erythromycin (grown inhibition 70.8 ± 4.5 % at 1 µM). Surprisingly, the glycopeptide mimetics **9a-h**, **10a-h** were less active than their peptoids precursors **8a-h**. On the other hand, into the DHPM **13a-k** and DHPM glycoconjugated series **14a-l** and **15a-l**, an increment of activity was observed after the attachment of the sugar moiety to the DHPM scaffold. Interestingly, the acetylated compounds were more active than the deprotected ones. The moderate values are marked in bold in **Table 3.4.1**.

Table 3.4.1 Result of the antibacterial activity tests.

Compound	Growth inhibition[a] in % at 1 µM[d]	Standard Deviation[d]	Growth inhibition in % at 10 µM[d]	Standard Deviation[d]
8a	**45.9**	**15.2**	**42.5**	**15.9**
8b	**45.3**	**11.1**	**41.2**	**12.3**
8c	**42.8**	**14.2**	**46.6**	**10.8**
8d	inactive	-	36.4	17.2
8e	**36.7**	**23.5**	**41.4**	**22.0**
8f	inactive	-	inactive	-
8g	**44.6**	**13.1**	**48.7**	**11.1**
8h	**50.6**	**24.8**	**52.5**	**22.6**
9a	inactive	-	inactive	-
9b	inactive	-	inactive	-
9c	19.5	5.7	20.0	9.0
9d	17.0	5.8	14.7	4.4
9e	inactive	-	inactive	-
9f	inactive	-	inactive	-
9g	**35.6**	**12.9**	**40.5**	**9.5**
9h	33.8	10.8	32.1	12.2
10a	13.6	6.4	25.4	13.7
10b	21.7	10.2	24.5	12.1
10c	23.6	13.6	26.3	14.1

[a] The antibacterial activity assay was performed by Dr. R. Heinke.

10d	**27.0**	**11.5**	**42.1**	**13.7**
10e	**32.8**	**10.9**	**47.3**	**11.8**
10f	18.4	8.7	24.9	9.3
10g	19.1	10.0	29.8	7.7
10h	inactive	-	inactive	-
13a	**41.5**	**15.8**	**47.7**	**28.7**
13b	**45.7**	**18.9**	**42.5**	**15.9**
13c	15.9	8.5	18.5	10.2
13d	inactive	-	inactive	-
13e	inactive	-	inactive	-
13f	25.7	14.5	27.0	16.2
13g	28.1	16.6	31.9	14.1
13h	inactive	-	inactive	-
13i	27.5	14.2	30.6	14.3
13j	31.1	10.3	28.1	10.8
13k	inactive	-	inactive	-
14a	27.3	7.0	27.5	9.6
14b	32.2	10.0	28.6	9.8
14c	20.5	5.5	30.0	9.6
14d	**35.0**	**3.9**	**38.4**	**6.0**
14e	**48.2**	**6.9**	**42.6**	**7.3**
14f	**46.9**	**5.6**	**40.2**	**8.4**
14g	inactive	-	inactive	-
14h	25.8	7.1	32.6	8.1
14i	28.6	7.7	32.4	7.6
14j	30.1	8.9	23.4	3.9
14k	inactive	-	inactive	-
14l	23.9	12.7	31.6	11.0
15a	14.3	8.2	18.0	10.4
15b	inactive	-	16.3	11.7
15c	23.0	11.4	25.4	14.9
15d	inactive	-	inactive	-
15e	24.4	14.0	28.5	9.8
15f	inactive	-	inactive	-
15g	inactive	-	inactive	-
15h	13.8	7.3	21.8	6.6
15i	19.2	10.7	19.4	10.1
15j	inactive	-	26.8	7.3
15k	18.6	9.4	21.3	9.5
15l	18.2	8.2	19.1	11.9

Std.[b]	70.8	4.5	NP[c]	NP[c]

[a] Measured after 15h
[b] Erythromycin
[c] Not performed.
[d] Mean values of two trials involving 3 replicates

3.5 Conclusions

The efficient and short two step sequence of coupling, U-4CR and B-3CR with Huisgen-type Click reactions gave access to small libraries of glycoconjugate mimics. In these, the sugar moiety was triazole-linked to Ugi-peptoids by the nitrogen of the tertiary amide and in DHPMs by the ester moiety connected to position *C*-5 of the heterocycle. Almost all compounds were obtained in good to excellent yields. From the biological assays, it was observed that the glycopeptide mimetics had no significant antibiotic effect on *Bacillus subtilis* strain 168.[14-16] In turn, DHPM glycoconjugated series, in particular **14d-f**, presented satisfactory results in this first assay.

3.6 Experimental part

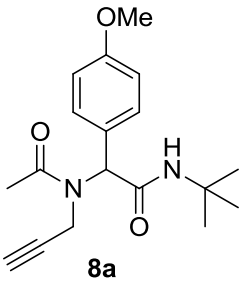
General remarks

All commercially available reagents were used without further purification. Solvents were purified by standard procedures. The dioxane used was purchased from Sigma-Aldrich in dry form. The TLC was performed using Merck silica gel 60 F254 aluminum sheets. Flash column chromatography was performed using silica gel (0.040-0.063 mm) Merck. ^{1}H and ^{13}C NMR spectra were recorded in solutions on a NMR spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the TMS (^{1}H NMR) and to the solvent signal (^{13}C NMR). Please note that some peptoids show double signals (*s-cis* / *s-trans* isomers). HRMS spectra were obtained from a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer equipped with an Infinity™ cell, a 7.0 Tesla superconducting magnet, an RF-only hexapole ion guide and an external electrospray ion source (off axis spray). Melting point was measured in a Leica DM LS2 microscope and is uncorrected.

General procedure for the synthesis of compounds 8a-h

To a stirred solution of aldehyde **4** (2.5 mmol) in methanol (2.5 mL), propargylamine (**5**) (0.14 g, 0.16 mL, 2.5 mmol) was added. After 30 minutes, carboxylic acid **6** (2.5 mmol) and isocyanide **7** (2.5 mmol) were added. The mixture was stirred for 24 hours. The solvent was concentrated under reduced pressure in a rotavap. The crude material was purified by column chromatography on silica gel to afford the pure products.

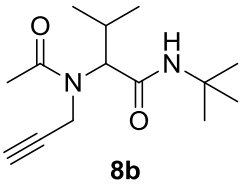
2-[Acetyl(prop-2-yn-1-yl)amino]-*N*-*tert*-butyl-2-(4-methoxyphenyl)acetamide (8a).



8a

Purified by silica gel column chromatography. R_f 0.23 (EtOAc / hexane 1:1). Yellowish solid. Yield: 99%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.29 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.15 (s, 1H), 6.00 (brs, 1H), 4.08 (d, *J* = 2.4 Hz, 2H), 3.81 (s, 3H), 2.26 (s, 3H), 2.02 (t, *J* = 2.4 Hz, 1H), 1.36 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.50, 169.09, 159.45, 130.65, 126.97, 113.93, 79.49, 71.21, 59.70, 55.10, 51.48, 35.51, 28.46, 22.01. HRMS (ESI-pos) m/z calcd for $C_{18}H_{24}N_2NaO_3$ $(M+Na)^+$ 339.1685, found 339.1679.

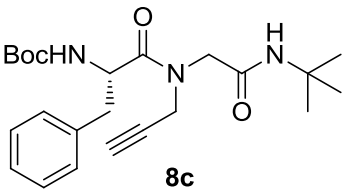
N^2-Acetyl-*N*-*tert*-butyl-N^2-prop-2-yn-1-ylvalinamide (8b).



8b

Purified by silica gel column chromatography. R_f 0.59 (EtOAc / hexane 3:7). White solid. Yield: 97%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.26 (s, 1H), 4.36-4.30 (m, 2H), 3.85 and 3.82 (2d, *J* = 2.4 Hz, 1H), 2.15 (t, *J* = 2.4 Hz, 1H), 2.06 (s, 3H), 2.04-1.95 (m, 1H), 1.10 (s, 9H), 0.74 (d, *J* = 4.4 Hz, 3H), 0.69 (d, *J* = 4.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.49, 169.10, 79.18, 72.02, 62.14, 50.76, 33.73, 28.11, 26.82, 21.65, 18.94. HRMS (ESI-pos) m/z calcd for $C_{14}H_{24}N_2NaO_2$ $(M+Na)^+$ 275.1735, found 275.1729.

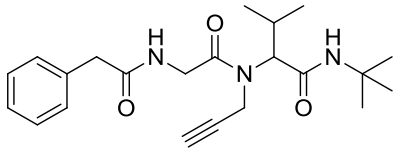
***N*-(*tert*-Butoxycarbonyl)-L-phenylalanyl-*N*-*tert*-butyl-N^2-prop-2-yn-1-ylglycinamide (8c).**



8c

Purified by silica gel column chromatography. R_f 0.34 (EtOAc / hexane 3:7). Yellowish solid. Yield: 98%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.18-7.09 (m, 5H), 6.87 and 6.28 (2s, 1H), 5.80 and 5.55 (2d, *J* = 8.0 Hz, 1H), 4.72 and 4.47 (2q, *J* = 6.4 Hz, 1H), 4.35-3.58 (set of signals, 4H), 3.07-2.77 (m, 2H), 2.31 and 2.17 (2s, 1H), 1.26-1.21 (m, 18H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 172.06, 171.86, 166.93, 166.45, 155.17, 154.96, 135.87, 135.65, 129.05, 128.12, 128.05, 126.58, 126.48, 79.28, 79.22, 77.68, 77.42, 73.65, 72.48, 51.69, 51.47, 51.15, 50.83, 50.21, 49.87, 38.08, 37.84, 35.52, 28.23, 28.16, 27.84. HRMS (ESI-pos) m/z calcd for $C_{23}H_{33}N_3O_4$ $(M+Na)^+$ 438.2369, found 438.2363.

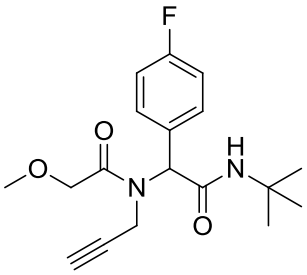
***N*-(Phenylacetyl)glycyl-*N*-*tert*-butyl-N^2-prop-2-yn-1-ylvalinamide (8d).**



8d

Purified by silica gel column chromatography. R_f 0.30 (EtOAc / hexane 2:3). Slightly yellow solid. Yield: 82%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.77 and 6.77 (2t, *J* = 4.4 Hz,1H), 7.36-7.23 (m, 5H), 6.01 (s, 1H), 4.53 and 4.05 (2d, *J* = 2.4 Hz, 2H), 4.49-3.76 (m, 3H), 3.61 and 3.55 (2s, 2H), 2.35 and 2.14 (2t, *J* = 2.4 Hz, 1H), 2.30-2.21 (m, 1H), 1.29 and 1.27 (2s, 9H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.36, 170.56, 169.57, 168.65, 168.31, 167.76, 134.37, 134.23, 128.98, 128.88, 128.44, 126.82, 126.80, 79.48, 78.20, 73.08, 70.26, 65.86, 62.97, 51.03, 50.97, 42.93, 42.63, 41.40, 41.14, 32.34, 31.86, 28.09, 28.02, 26.74, 19.15, 18.96, 18.88. HRMS (ESI-pos) m/z calcd for $C_{22}H_{31}N_3NaO_3$ $(M+Na)^+$ 408.2263, found 408.2258.

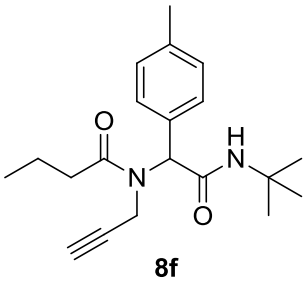
***N*-[2-(*tert*-Butylamino)-1-(4-fluorophenyl)-2-oxoethyl]-2-methoxy-*N*-(prop-2-yn-1-yl)acetamide (8e).**



8e

Purified by silica gel column chromatography. R_f 0.25 (EtOAc / hexane 1:1). Yellowish crystalline solid. Yield: 98%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.36 (dd, J_{H-H} = 6.8 Hz, J_{H-F} = 5.2 Hz, 2H), 7.07-7.03 (m, 2H), 6.26-6.15 (m, 2H), 4.30 (s, 2H), 4.20-4.06 (m, 2H), 3.42 (s, 3H), 2.07 (t, J = 2.4 Hz, 1H), 1.36 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 169.99, 168.18, 164.05, 160.77, 131.15, 131.05, 130.35, 130.32, 115.56, 115.27, 78.62, 71.82, 70.76, 59.45, 58.90, 51.48, 33.73, 28.26. HRMS (ESI-pos) m/z calcd for $C_{18}H_{23}FN_2NaO_3$ $(M+Na)^+$ 357.1590, found 357.1585.

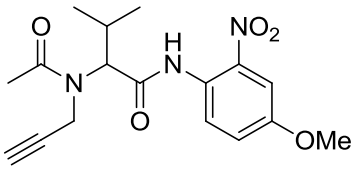
_N_-[2-(_tert_-Butylamino)-1-(4-methylphenyl)-2-oxoethyl]-_N_-(prop-2-yn-1-yl)butanamide (8f).



8f

Purified by silica gel column chromatography. R_f 0.16 (EtOAc / hexane 1:4). Yellowish solid. Yield: 91%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.17 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 6.07 (s, 1H), 6.06 (s, 1H), 3.98 (s, 2H), 2.41 (t, J = 6.4 Hz, 2H), 2.26 (s, 3H), 1.96 (s, 1H), 1.67-1.54 (m, J = 6.4 Hz, 2H), 1.27 (s, 9H), 0.86 (t, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 173.40, 168.99, 137.36, 131.85, 128.94, 128.78, 79.55, 70.93, 60.15, 50.85, 34.93, 34.62, 28.11, 20.65, 17.87, 13.28. HRMS (ESI-pos) m/z calcd for $C_{20}H_{28}N_2NaO_2$ $(M+Na)^+$ 351.2048, found 351.2042.

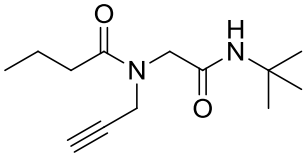
N^2-Acetyl-_N_-(4-methoxy-2-nitrophenyl)-N^2-prop-2-yn-1-ylvalinamide (8g)



8g

Purified by silica gel column chromatography. R_f 0.41 (EtOAc / hexane 1:3). Redish crystalline solid. Yield: 96%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 10.12 (s, 1H), 8.41 (d, J = 8.8 Hz, 1H), 7.62 (d, J = 3.2 Hz, 1H), 7.20 (dd, J = 9.2, 2.8 Hz, 1H), 4.28 and 4.04 (2dd, J = 19.0, 2.4 Hz, 2H), 3.86 (s, 3H), 2.47-2.36 (m, 1H), 2.33 (s, 3H), 2.28 (t, J = 2.4 Hz, 1H), 1.05 and 0.97 (2d, J = 6.4 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 172.02, 168.72, 155.21, 138.20, 126.89, 124.59, 122.27, 108.45, 78.59, 72.54, 63.28, 55.69, 34.30, 26.23, 21.63, 19.59, 18.84. HRMS (ESI-pos) m/z calcd for $C_{17}H_{21}N_3NaO_5$ $(M+Na)^+$ 370.1379, found 370.1373.

_N_-[2-(_tert_-Butylamino)-2-oxoethyl]-_N_-(prop-2-yn-1-yl)butanamide (8h).



8h

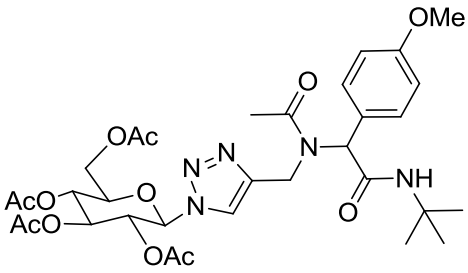
Purified by silica gel column chromatography. R_f 0.34 (EtOAc / hexane 1:1). Yellowish crystalline solid. Yield: 70%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.10 and 6.06 (2s, 1H), 4.29 and 4.19 (2s, 2H), 3.98 (s, 2H), 2.45 and 2.25 (2t, J = 6.4 Hz, 2H), 2.43 and 2.31 (2t, J = 2.4 Hz, 1H), 1.64-1.51 (m, 2H), 1.24 and 1.20 (2s, 9H), 0.88-0.82 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 173.27, 173.14, 167.71, 166.96, 78.81, 77.88, 73.02, 72.60, 51.42, 50.94, 50.42, 38.59, 36.05, 34.68, 34.55, 28.37, 18.15, 18.03, 13.57, 13.54. HRMS (ESI-pos) m/z calcdfor $C_{13}H_{22}N_2NaO_2$ $(M+Na)^+$ 261.1579, found 261.1573.

General procedure for the synthesis of compounds 9a-h

A solution of sodium ascorbate (3.7 mg, 0.018 mmol) and copper (II) acetate (1 mg, 6 µmol, 5 mol%) in water (1.5 mL) was added individually to a mixture of a *N*-propargylic peptoid **8** (0.125 mmol) and azidosugar **1** or **2** (0.125 mmol) in dichloromethane (1.5 mL). The contents were stirred for 24 h at room temperature. The progress of the reaction was monitored by TLC. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were

washed with aqueous $NaHCO_3$, saturated brine solution and water. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The solvent was concentrated under reduced pressure in a rotavap. The crude material was purified by column chromatography on silica gel to afford the pure products, as mixture of diastereomers.

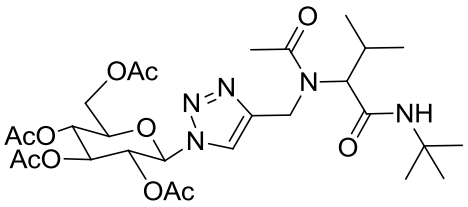
4-({Acetyl[2-(*tert*-butylamino)-1-(4-methoxyphenyl)-2-oxoethyl]amino}methyl)-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazole (9a) (mixture of diastereomers)



9a

Purified by silica gel column chromatography. R_f 0.34 (EtOAc / hexane 1:1). Yield: 95%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.10-6.85 (set of signals and $CHCl_3$ residual, >10H), 6.38, 6.10, 6.01 (3s, 2H), 5.84-5.68 (m, 3H), 5.52-5.09 (m, 6H), 4.72-3.79 (set of signals, 17H), 2.30 (s, 3H), 2.20-1.84 (m, 27H), 1.42-1.34 (m, 18H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 172.30, 172.23, 169.83, 169.77, 169.31, 169.17, 169.05, 168.70, 168.53, 159.75, 146.00, 145.66, 131.16, 127.92, 127.59, 120.61, 120.35, 114.54, 114.39, 85.52, 85.14, 74.93, 74.85, 72.61, 72.36, 70.53, 69.93, 67.52, 67.43, 61.46, 60.32, 60.16, 55.28, 55.21, 51.60, 51.55, 28.54, 28.44, 22.48, 22.32, 20.66, 20.61, 20.47, 20.45, 20.42, 20.08, 20.02. HRMS (ESI-pos) m/z calcd. for $C_{32}H_{43}N_5NaO_{12}$ $(M+Na)^+$ 712.2806, found 712.2800.

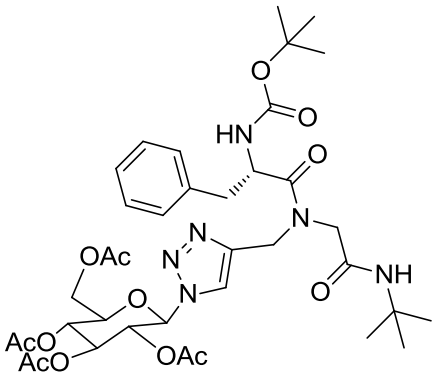
4-({Acetyl[1-(*tert*-butylamino)-3-methyl-1-oxobutan-2-yl]amino}methyl)-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazole (9b) (mixture of diastereomers)



9b

Purified by silica gel column chromatography. R_f 0.16 (EtOAc / hexane 1:1). Yield: 60%.^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.83-7.70 (set of signals, 2H), 6.28 (brs, 1H), 6.17 (brs, 1H), 5.81-5.76 (m, 2H), 5.44-5.24 (m, 4H), 5.20-5.11 (m, 2H), 4.75-4.47 (m, 4H), 4.40-4.03 (set of signals, 6H), 3.97-3.94 (m, 2H), 2.35-2.14 (m, 8H), 2.04-1.96 (m, 18H), 1.81-1.77 (m, 6H), 1.23 and 1.16 (2s, 18H), 0.90 (d, J = 6 Hz, 6H), 0.72 (d, J = 6 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 173.19, 172.98, 170.45, 170.44, 169.90, 169.87, 169.75, 169.59, 169.28, 169.25, 168.64, 168.61, 145.77, 145.02, 122.04, 121.23, 85.68, 85.66, 74.95, 72.45, 72.34, 70.46, 70.24, 67.58, 61.55, 61.49, 60.33, 51.16, 51.04, 40.78 (br), 39.81 (br), 28.51, 28.49, 28.42, 28.38, 26.99, 26.59, 22.74, 22.39, 20.63, 20.49, 20.08, 20.07, 19.44, 18.62, 18.51. HRMS (ESI-pos) m/z calcd. for $C_{28}H_{43}N_5NaO_{11}$ $(M+Na)^+$ 648.2857, found 648.2851.

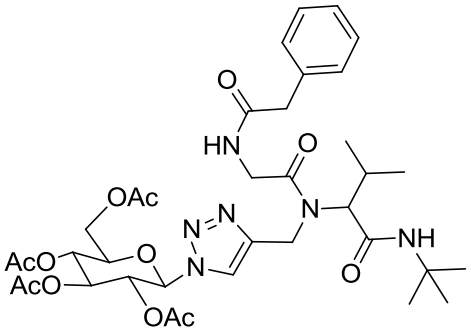
4-[({(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-phenylpropanoyl}[2-(*tert*-butylamino)-2-oxoethyl]amino)methyl]-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazole (9c)



9c

Purified by silica gel column chromatography. R_f 0.14 (EtOAc / hexane 1:1). Yield: 95%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.83 and 7.78 (2s, 1H), 7.31-7.19 and 7.13-7.11 (2m, >5H), 6.58 and 6.32 (2s, 1H), 5.92-5.85 (m, 1H), 5.47-5.36 (m, 2H), 5.29-5.20 (m, 2H), 4.96-3.61 (set of signals, 8H), 3.13-2.97 and 2.92-2.83 (2m, 2H), 2.08-2.03 and 1.86-1.80 (2m, 12H), 1.35-1.21 (s, 18H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 172.89, 172.56, 170.41, 169.86, 169.80, 169.24, 168.74, 168.68, 167.25, 166.47, 155.37, 155.25, 143.81, 143.56, 136.30, 135.95, 129.34, 129.19, 128.52, 128.48, 127.01, 126.83, 121.93, 121.19, 85.67, 85.55, 79.87, 79.80, 75.02, 74.94, 72.55, 72.37, 70.37, 70.16, 67.52, 61.44, 60.30, 51.95, 51.62, 51.20, 43.85, 42.27, 38.66, 38.43, 28.54, 28.43, 28.16, 20.60, 20.46, 20.44, 20.12, 20.00. HRMS (ESI-pos) m/z calcd. for $C_{37}H_{52}N_6NaO_{13}$ $(M+Na)^+$ 811.3490, found 811.3485.

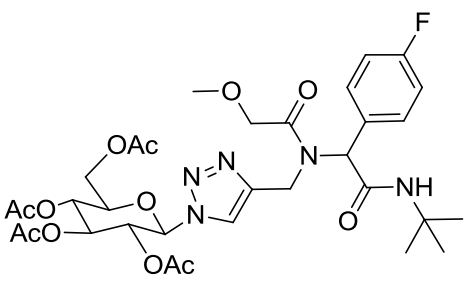
4-[([1-(*tert*-Butylamino)-3-methyl-1-oxobutan-2-yl]{[(phenylacetyl)amino]acetyl} amino)methyl]-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazole (9d) (mixture of diastereomers)



9d

Purified by silica gel column chromatography. R_f 0.26 (EtOAc / hexane 7:3). Yield: 70%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.81-6.44 (set of signals, >14H), 6.05 (s, 1H), 5.90 (s, 1H), 5.85-5.80 (m, 2H), 5.47-5.33 and 5.26-5.17 (2m, 6H), 4.91-4.23 (set of signals, 9H), 4.15-3.96 (m, 6H), 3.85-3.69 (m, 1H), 3.63-3.60 (m, 4H), 2.54-2.47 and 2.36-2.26 (2m, 2H), 2.09-1.77 (set of signals, 24H), 1.29-1.14 (set of signals, 18H), 0.98-0.57 (set of signals, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.52, 170.67, 170.65, 170.60, 170.50, 170.41, 170.40, 169.89, 169.83, 169.80, 169.77, 169.24, 169.21, 168.90, 168.77, 168.73, 168.42, 143.97, 134.65, 134.61, 129.39, 129.36, 129.31, 128.84, 128.78, 127.31, 127.21, 127.14, 122.09, 121.57, 121.09, 85.57, 85.47, 74.86, 72.47, 72.38, 70.17, 67.54, 67.51, 61.46, 51.55, 51.27, 51.14, 43.48, 43.44, 42.13, 42.00, 39.12 (br), 38.28 (br), 28.36, 28.26, 26.96, 26.63, 20.59, 20.45, 20.43, 20.09, 20.00, 19.37, 19.33, 18.49, 18.34. HRMS (ESI-pos) m/z calcd. for $C_{36}H_{50}N_6NaO_{12}$ $(M+Na)^+$ 781.3384, found 781.3379.

4-({[2-(*tert*-Butylamino)-1-(4-fluorophenyl)-2-oxoethyl](methoxyacetyl)amino} methyl)-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazole (9e) (mixture of diastereomers)

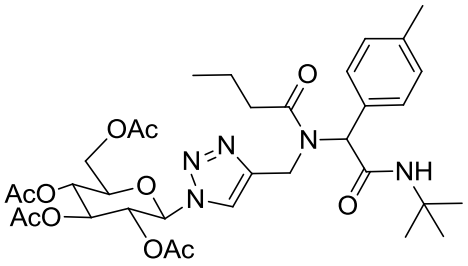


9e

Purified by silica gel column chromatography. R_f 0.13 (EtOAc / hexane 7:3). Yield: 72%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.66-5.59 (set of signals, >16H), 5.43-5.37 and 5.27-5.18 (2m, 6H), 4.67-4.09 (set of signals, 12H), 4.00-3.97 (m, 2H), 3.45 (d, J = 12.0 Hz, 6H), 2.12-1.86 (set of signals, 24H), 1.35-1.30 (m, 18H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 170.69, 170.45, 170.43, 169.81, 169.24, 168.69, 168.61, 168.37, 168.14, 163.79, 161.32, 145.20, 145.06, 131.56 (br), 130.86 (br), 120.56, 119.77, 115.89, 115.79, 115.68, 115.58, 85.51, 75.01, 72.41, 72.29, 71.28, 70.41, 70.16, 67.50, 67.47, 61.47, 61.40, 61.13 (br), 60.73 (br), 59.12, 51.66, 40.40,

39.99, 28.47, 20.61, 20.60, 20.46, 20.44, 20.42, 20.08, 20.06. HRMS (ESI-pos) m/z calcd. for $C_{32}H_{42}FN_5NaO_{12}$ $(M+Na)^+$ 730.2712, found 730.2706.

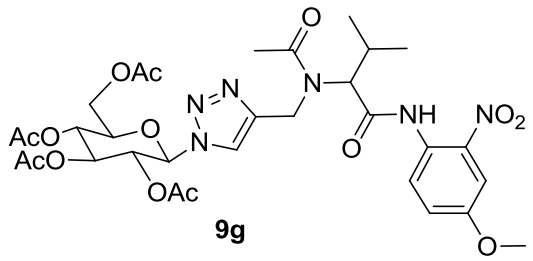
(4-({Butanoyl[2-(*tert*-butylamino)-1-(4-methylphenyl)-2-oxoethyl]amino}methyl)-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazole (9f) (mixture of diastereomers)



9f

Purified by silica gel column chromatography. R_f 0.31 (EtOAc / hexane 1:1). Yield: 90%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.17-6.70 (set of signals, >12H), 6.01-5.89 (set of signals, 2H), 5.84-5.74 (m, 2H), 5.53-5.36 and 5.26-5.16 (2m, 6H), 4.70-4.09 (set of signals, 8H), 3.99-3.92 (m, 2H), 2.50-2.35 (m, 10H), 2.12-2.03 and 1.87-1.84 (2m, 24H), 1.71-1.57 (m, 4H), 1.42-1.34 (m,18H), 0.95-0.88 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 174.59, 174.56, 170.36, 169.82, 169.80, 169.26, 169.08, 169.01, 168.49, 168.48, 168.40, 146.17, 146.11, 138.31, 138.27, 132.78, 132.66, 129.69, 129.62, 129.58, 129.17, 120.71, 120.44, 85.52, 85.37, 74.90, 74.82, 72.52, 72.42, 70.41, 70.18, 67.49, 61.75, 61.49, 51.46, 41.32, 35.52, 35.44, 28.51, 21.05, 20.62, 20.45, 20.42, 20.04, 19.98, 18.45, 13.65, 13.62. HRMS (ESI-pos) m/z calcd. for $C_{34}H_{47}N_5NaO_{11}$ $(M+Na)^+$ 724.3170, found 724.3164.

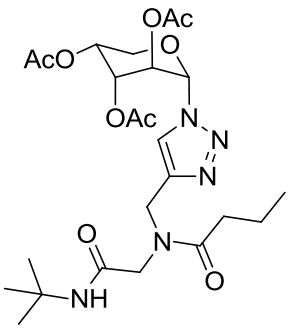
4-[(Acetyl{1-[(4-methoxy-2-nitrophenyl)amino]-3-methyl-1-oxobutan-2-yl}amino) methyl]-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazole (9g) (mixture of diastereomers)



9g

Purified by silica gel column chromatography. R_f 0.11 (EtOAc / hexane 1:1). Yield: 91%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 10.41-10.32 (set of signals, 2H), 8.60-8.32 (set of signals, 2H), 7.69-7.64 (m, 4H), 7.27-7.18 (m, 2H), 5.79-5.74 (m, 2H), 5.42-4.92 (set of signals, 6H), 4.81-4.73 and 4.68-4.60 (2m, 6H), 4.31-4.21 and 4.15-4.04 (2m, 4H), 3.99-3.93 (m, 2H), 3.87 (d, J = 4.8 Hz, 6H), 2.72-2.65 and 2.57-2.46 (2m, 2H), 2.33-2.27 (m, 6H), 2.11-2.02 (m, 18H), 1.86-1.79 (m, 6H), 1.11-0.98 and 0.94-0.81 (2m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 172.93, 172.78, 169.82, 169.79, 169.44, 169.32, 169.26, 168.84, 168.61, 155.38, 155.35, 144.92, 144.65, 138.57, 138.41, 127.32, 127.23, 124.69, 124.26, 123.17, 122.57, 121.82, 120.86, 120.58, 109.08, 108.75, 108.51, 85.68, 85.60, 75.13, 75.06, 72.42, 72.17, 70.36, 70.24, 67.63, 61.53, 55.89, 55.86, 40.96, 26.43, 26.29, 22.38, 22.20, 20.66, 20.52, 20.47, 20.42, 20.10, 19.97, 18.74, 18.64. HRMS (ESI-pos) m/z calcd. for $C_{31}H_{40}N_6NaO_{14}$ $(M+Na)^+$ 743.2500, found 743.2495.

4-({Butanoyl[2-(*tert*-butylamino)-2-oxoethyl]amino}methyl)-1-(2,3,4-tri-*O*-acetyl-α-D-arabinopyranosyl)-1*H*-1,2,3-triazole (9h)



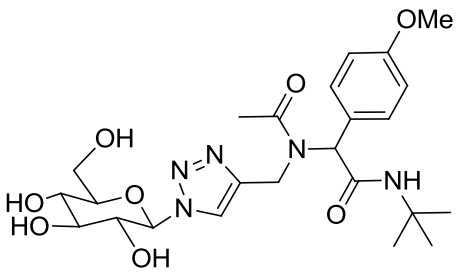
9h

Purified by silica gel column chromatography. R_f 0.15 (EtOAc / hexane 7:3). Yield: 90%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.80 and 7.78 (2s overlapped, 1H), 6.73 and 6.25 (2s, 1H), 5.72-5.69 (m, 1H), 5.50-5.41 (m, 1H), 5.37-5.35 (m, 1H), 5.20 (td, *J* = 9.6, 3.6 Hz, 1H), 4.72-4.58 and 4.44-4.40 (2m, 2H), 4.13-3.73 (set of signals, 4H), 2.46 (t, *J* = 7.4 Hz, 1H), 2.21-2.15 (m, 4H), 1.95 (s, 3H), 1.82 (s, 3H), 1.66-1.55 (m, 2H), 1.27 and 1.22 (2s, 9H), 0.91-0.83 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 174.02, 173.94, 170.14, 170.09, 169.83, 169.78, 169.08, 168.96, 168.17, 167.39, 144.47, 143.99, 121.53, 120.88, 86.63, 86.57, 70.39, 70.25, 68.33, 68.19, 67.62, 67.25, 67.16, 53.31, 51.58, 51.21, 51.06, 44.36, 43.00, 34.91, 34.89, 28.54, 28.50, 20.90, 20.52, 20.22, 18.51, 18.24, 13.77, 13.74. HRMS (ESI-pos) m/z calcd. for $C_{24}H_{37}N_5NaO_9$ $(M+Na)^+$ 532.2489, found 532.2483.

General procedure for the deprotection of compounds 9a-h

Compound **9** (0.050 mmol) was added to a solution of triethylamine (0.031g, 43 µl, 0.350 mmol, 7 equiv.), methanol (0.5 mL), and water (0.5 mL). The mixture was stirred for 12 hours at room temperature. The solvent was concentrated under reduced pressure in a rotavap. The crude material was purified by short column chromatography on silica gel (EtOAc / MeOH 9:1) to afford the desired product.

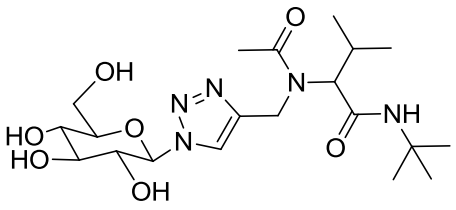
4-({Acetyl[2-(*tert*-butylamino)-1-(4-methoxyphenyl)-2-oxoethyl]amino}methyl)-1-(β-D-glucopyranosyl)-1*H*-1,2,3-triazole (10a) (mixture of diastereomers)



10a

R_f 0.24. Yield: 86%. ^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 7.61 (s, 1H), 7.57 (s, 1H), 7.23-7.19 (m, 4H), 6.90-6.86 (m, 4H), 5.91 and 5.63 (2s, 2H), 5.46 (dd, *J* = 9.2, 1.6 Hz, 2H), 4.74-4.54 (m, 4H), 3.90-3.42 (set of signals, 18H), 2.25-2.21 (m, 6H), 1.34-1.29 (m, 18H). ^{13}C NMR (CD_3OD, 100 MHz): δ (ppm) 174.74, 174.26, 172.06, 171.30 161.41, 161.38, 146.22, 132.56, 132.54, 131.87, 131.84, 128.31, 128.29, 122.99, 122.80, 122.61, 115.32, 115.28, 89.45, 89.35, 81.11, 78.42, 74.12, 73.99, 70.93, 70.84, 66.38, 63.42, 63.40, 62.44, 62.38, 55.91, 55.83, 52.63, 52.32, 42.86, 42.83, 28.82, 28.11, 22.59, 22.30. HRMS (ESI-pos) m/z calcd. for $C_{24}H_{35}N_5NaO_8$ $(M+Na)^+$ 544,2383, found 544.2378.

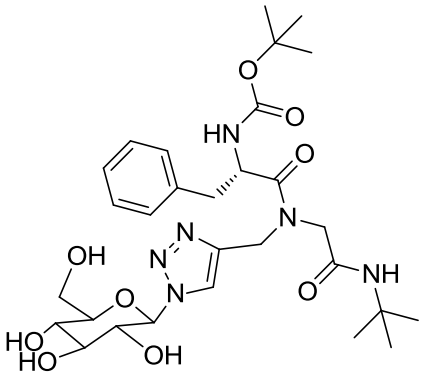
4-({Acetyl[1-(*tert*-butylamino)-3-methyl-1-oxobutan-2-yl]amino}methyl)-1-(β-D-glucopyranosyl)-1*H*-1,2,3-triazole (10b) (mixture of diastereomers)



10b

R_f 0.35. Yield: 96%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 7.98, 7.91, 7.79, 7.75 (4s, 2H), 5.50-5.43 (m, 2H), 4.83-4.52 (set of signals, 6H), 3.84-3.14 (set of signals, >12H), 2.33-1.95 (set of signals, 8H), 1.25-1.21 (m, 18H), 0.94-0.83 and 0.69-0.62 (2m, 12H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 171.41, 171.36, 170.52, 169.79, 169.64, 169.18, 169.07, 145.21, 144.95, 144.93, 144.83, 122.51, 122.43, 122.01, 121.62, 87.47, 87.37, 87.30, 87.27, 79.91, 79.87, 79.85, 76.82, 76.63, 76.58, 72.39, 72.30, 72.18, 72.09, 69.55, 69.49, 69.42, 69.39, 66.60, 66.53, 61.91, 61.88, 61.84, 60.75, 60.73, 60.67, 60.64, 50.40, 50.24, 50.20, 28.29, 28.27, 28.25, 28.15, 22.46, 22.43, 22.41, 22.33, 19.20, 19.16, 19.04, 18.90. HRMS (ESI-pos) m/z calcd. for $C_{20}H_{35}N_5NaO_7$ $(M+Na)^+$ 480.2434, found 480.2429.

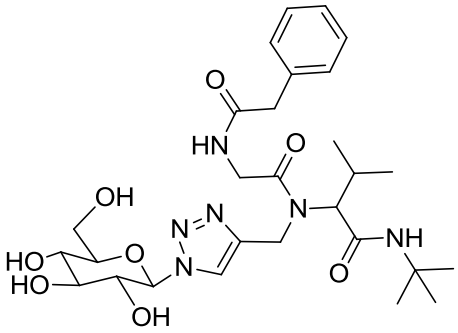
4-[({(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-phenylpropanoyl}[2-(*tert*-butylamino)-2-oxoethyl]amino)methyl]-1-(β-D-glucopyranosyl)-1*H*-1,2,3-triazole (10c)



10c

R_f 0.46. Yield: 67%. ^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 8.10 and 8.00 (2s, 1H), 7.27-7.17 (m, 5H), 5.58 (d, *J* = 8.8 Hz, 1H), 4.81-4.52 (m, 3H), 4.04-3.47 (set of signals, 8H), 3.13-2.84 (set of signals, 2H), 1.38-1.26 (m, 18H). ^{13}C NMR (CD_3OD, 100 MHz): δ (ppm) 174.90, 174.38, 169.56, 169.01, 157.38, 157.31, 144.47, 138.30, 138.04, 130.53, 130.38, 129.37, 127.75, 127.66, 124.22, 123.67, 89.57, 81.02, 80.57, 78.25, 78.17, 74.05, 73.91, 70.77, 62.32, 53.46, 53.34, 52.45, 52.21, 51.89, 51.20, 45.13, 43.42, 39.15, 28.90, 28.70, 28.30. HRMS (ESI-pos) m/z calcd. for $C_{29}H_{44}N_6NaO_9$ $(M+Na)^+$ 643.3067, found 643.3062.

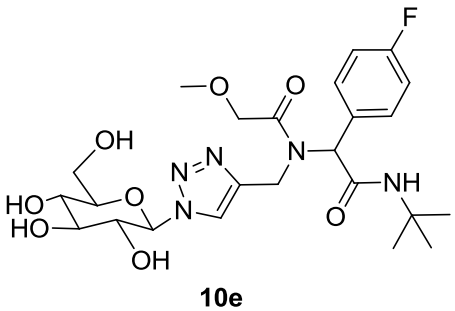
4-[([1-(*tert*-Butylamino)-3-methyl-1-oxobutan-2-yl]{[(phenylacetyl)amino]acetyl}amino)methyl]-1-(β-D-glucopyranosyl)-1*H*-1,2,3-triazole (10d) (mixture of diastereomers)



10d

R_f 0.61. Yield: 89%. ^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 8.04-7.22 (set of signals, 12H), 5.55-5.48 (m, 2H), 4.96-3.41 (set of signals, >30H), 2.47-2.22 (m, 2H), 1.29-1.23 (m, 18H), 0.97-0.91 (m, 6H), 0.80-0.74 (m, 6H). ^{13}C NMR (CD_3OD, 100 MHz): δ (ppm) 174.48, 174.39, 172.43, 171.42, 171.29, 171.26, 171.18, 171.11, 170.67, 170.48, 146.01, 145.81, 136.67, 136.64, 136.62, 130.31, 129.63, 129.58, 127.99, 127.92, 123.64, 123.41, 89.69, 89.64, 89.57, 81.11, 81.08, 81.03, 78.39, 78.36, 78.31, 78.25, 74.31, 74.19, 74.16, 74.04, 70.96, 70.94, 70.82, 62.49, 62.33, 52.60, 52.58, 52.38, 52.27, 43.55, 43.02, 42.95, 42.75, 40.74, 39.93, 29.62, 29.57, 28.87, 28.85, 28.79, 28.75, 19.80, 19.58, 19.53, 19.20, 19.17. HRMS (ESI-pos) m/z calcd. for $C_{28}H_{42}N_6NaO_8$ $(M+Na)^+$ 613.2962, found 613.2956.

4-({[2-(*tert*-Butylamino)-1-(4-fluorophenyl)-2-oxoethyl](methoxyacetyl)amino}methyl)-1-(β-D-glucopyranosyl)-1*H*-1,2,3-triazole (10e) (mixture of diastereomers)

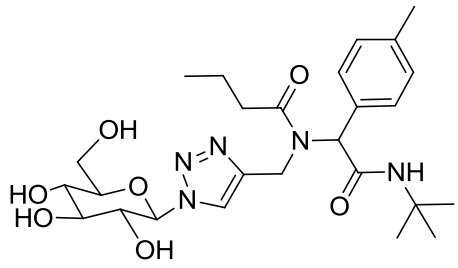


10e

R_f 0.25. Yield: 92%. ^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 7.66-7.01 (set of signals, 10H), 5.89 and 5.69 (2s, 2H), 5.47-5.44 (m, 2H), 4.63-4.25 (set of signals, 8 H), 3.89-3.41 (set of signals, 18H), 1.42-1.27 (m, 18H). ^{13}C NMR (CD_3OD, 100 MHz): δ (ppm) 173.07, 171.31, 165.40, 162.94, 145.73, 133.26, 133.18, 132.61, 132.03, 130.87, 130.79, 116.77, 116.72, 116.55, 116.50, 89.44, 89.35, 81.13, 81.03, 78.45, 74.04, 73.94, 71.93, 70.99, 70.77, 63.52, 63.40, 62.47, 62.28, 59.53, 52.41, 36.53, 28.79. HRMS (ESI-pos) m/z calcd. for $C_{24}H_{34}FN_5NaO_8$ $(M+Na)^+$ 562.2289, found 562.2283.

4-({Butanoyl[2-(*tert*-butylamino)-1-(4-methylphenyl)-2-oxoethyl]amino}methyl)-1-(β-D-glucopyranosyl)-1*H*-1,2,3-triazole (10f) (mixture of diastereomers)

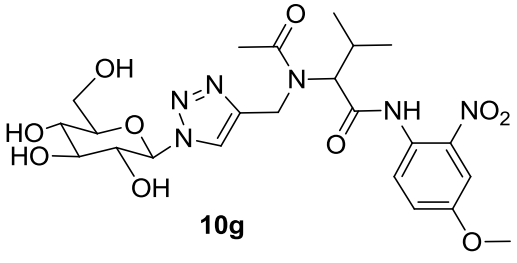
R_f 0.45. Yield: 91%. ^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 7.61-6.86 (set of signals, 10H), 5.91 and 5.63 (2s, 2H), 5.46-5.44 (m, 2H), 4.66-4.54 (m, 4H), 3.90-3.42 (set of singlets, 12H), 2.30-2.17 (m, 10H), 1.38-1.29 (m, 22H), 0.97-0.85 (m, 6H). 13C NMR (CD3OD,



10f

100 MHz): δ (ppm) 174.75, 174.74, 174.27, 174.24, 172.06, 172.05, 171.30, 171.28, 161.41, 161.38, 146.68, 146.64, 146.22, 132.56, 132.54, 131.87, 131.84, 130.87, 130.79, 128.31, 128.29, 127.87, 127.83, 123.00, 122.80, 122.61, 115.32, 115.28, 89.54, 89.46, 89.35, 81.11, 81.05, 78.42, 78.36, 74.12, 73.99, 70.93, 70.85, 63.42, 63.40, 62.44, 62.38, 55.91, 55.83, 52.63, 52.32, 42.86, 42.83, 36.53, 28.82, 28.79, 22.59, 18.47, 18.45, 14.47, 14.45. HRMS (ESI-pos) m/z calcd. for $C_{26}H_{39}N_5NaO_7$ $(M+Na)^+$ 556.2747, found 556.2742.

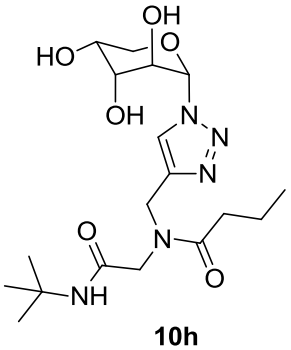
4-[(Acetyl{1-[(4-methoxy-2-nitrophenyl)amino]-3-methyl-1-oxobutan-2-yl}amino) methyl]-1-(β-D-glucopyranosyl)-1*H*-1,2,3-triazole (10g) (mixture of diastereomers)



10g

R_f 0.31. Yield: 89%. ^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 8.01-7.24 (set of signals, 8H), 5.52-5.50 (m, 2H), 4.84-4.15 (set of signals, 6H), 3.88-3.45 (set of signals, 18H), 2.57-2.42 (m, 2H), 2.33-2.29 (m, 6H), 1.10-1.03 (m, 6H), 0.96-0.83 (m, 6H). ^{13}C NMR (CD_3OD, 100 MHz): δ (ppm) 175.36, 175.32, 174.09, 174.01, 170.78, 170.71, 170.31, 170.21, 158.90, 158.87, 158.17, 158.15, 146.10, 146.06, 145.42, 145.38, 144.69, 144.63, 143.16, 143.06, 130.86, 130.78, 129.17, 129.14, 128.21, 127.98, 125.85, 125.80, 124.86, 124.81, 124.23, 123.51, 123.40, 122.00, 121.56, 121.53, 110.61, 110.57, 110.40, 110.30, 89.57, 89.53, 81.13, 78.40, 78.36, 78.33, 74.15, 74.11, 74.03, 73.99, 70.87, 70.83, 70.80, 69.34, 69.32, 65.66, 65.48, 62.66, 62.42, 62.35, 62.31, 56.59, 56.54, 56.53, 42.33, 42.24, 39.58, 29.62, 29.58, 28.11, 22.43, 22.39, 22.37, 20.22, 20.20, 19.70, 19.43, 19.39, 19.11. HRMS (ESI-pos) m/z calcd. for $C_{23}H_{32}N_6NaO_{10}$ $(M+Na)^+$ 575.2078, found 575.2072.

1-(α-D-Arabinopyranosyl)-4-({butanoyl[2-(*tert*-butylamino)-2-oxoethyl]amino}me thyl)-1*H*-1,2,3-triazole (10h)



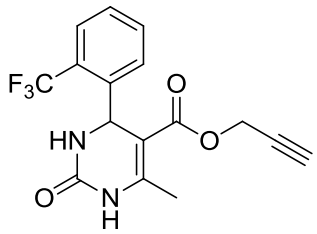
10h

R_f 0.29. Yield: 78%. ^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 8.22 and 8.08 (2s, 1H), 5.51-5.45 (m, 1H), 4.73 and 4.65 (2s, 2H), 4.16-3.69 (set of signals, 7H), 2.57 and 2.30 (2t, J = 8 Hz, 2H), 1.71-1.59 (m, 2H), 1.33-1.32 (m, 9H), 0.99-0.93 (m, 3H). ^{13}C NMR (CD_3OD, 100 MHz): δ (ppm) 176.31, 176.12, 170.11, 169.57, 145.27, 144.98, 123.46, 123.11, 90.51, 90.48, 74.74, 71.44, 71.38, 70.72, 70.20, 52.36, 52.22, 52.16, 50.72, 45.40, 43.33, 35.88, 35.85, 28.88, 28.84, 19.58, 19.48, 14.18, 14.15. HRMS (ESI-pos) m/z calcd. for $C_{18}H_{31}N_5NaO_6$ $(M+Na)^+$ 436.2172, found 436.2167.

General procedure for the synthesis of compounds 13a-k

A 25 mL round-bottom flask was charged with aldehyde **11** (2 mmol), propargyl acetoacetate (**3**) (0.28 g, 2 mmol), urea (**12**) (0.150 g, 2.5 mmol), and copper(II) triflate (0.036 g, 0.10 mmol). The mixture was stirred for 24 hours at room temperature. Afterwards water containing crushed ice (10 mL) was added and the mixture was stirred for 10 min. The resulting precipitate was filtered under vacuum and washed with cold water (3 x 2.5 mL). The precipitate was recrystallized from hot ethanol, to afford the pure products.

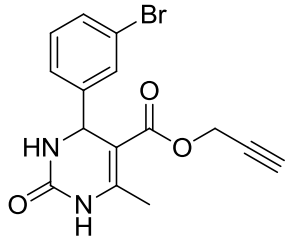
Prop-2-yn-1-yl 6-methyl-2-oxo-4-[2-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylate (13a)



13a

Yield: 86%. White crystalline solid. M.p.: 223.1-223.8 ºC. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ (ppm) 9.49 (s, 1H), 7.69-7.66 (m, 2H), 7.51-7.45 (m, 3H), 5.55 (d, *J* = 2.4 Hz, 1H), 4.54-4.24 (m, 2H), 3.35-3.32 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ (ppm) 164.43, 151.42, 151.37, 143.38, 133.84, 128.98, 128.58, 126.38, 126.22, 97.85, 78.88, 77.33, 51.20, 50.83, 18.38. HRMS (ESI-pos) m/z calcd. for $C_{16}H_{13}F_3N_2NaO_3$ $(M+Na)^+$ 361.0776, found 361.0770.

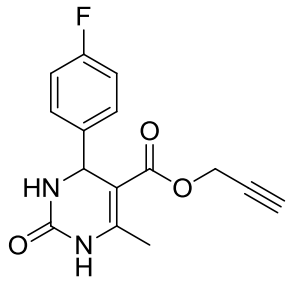
Prop-2-yn-1-yl 4-(3-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (13b)



13b

Yield: 83%. White crystalline solid. M.p.: 198.3-198.7 ºC. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ (ppm) 9.42 (s, 1H), 7.87 (s, 1H), 7.47-7.23 (m, 4H), 5.14 (d, *J* = 3.6 Hz, 1H), 4.70-4.60 (m, 2H), 3.48 (t, *J* = 2.4 Hz, 1H), 2.27 (s, 3H). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ (ppm) 164.32, 151.84, 150.44, 147.13, 130.87, 130.29, 129.06, 125.19, 121.68, 97.70, 78.71, 77.36, 53.27, 51.10, 18.00. HRMS (ESI-pos) m/z calcd. for $C_{15}H_{13}BrN_2NaO_3$ $(M+Na)^+$ 371.0007, found 371.0002.

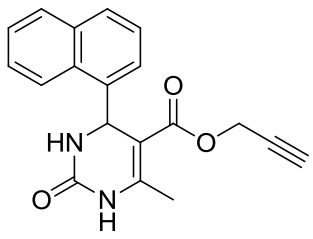
Prop-2-yn-1-yl 4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (13c)



13c

Yield: 90%. White crystalline solid. M.p.: 194.8-195.3 ºC. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ (ppm) 9.38 (s, 1H), 7.83 (s, 1H), 7.28-7.24 (m, 2H), 7.18-7.12 (m, 2H), 5.14 (d, *J* = 3.2 Hz, 1H), 4.63 (d, *J* = 2.4 Hz, 2H), 3.47 (t, *J* = 2.4 Hz, 1H), 2.27 (s, 3H). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ (ppm) 164.40, 162.59, 160.17, 151.91, 150.03, 140.82, 140.79, 128.24, 128.16, 115.32, 115.11, 98.22, 78.79, 77.29, 53.07, 51.01, 17.97. HRMS (ESI-pos) m/z calcd. for $C_{15}H_{13}FN_2NaO_3$ $(M+Na)^+$ 311.0808, found 311.0802.

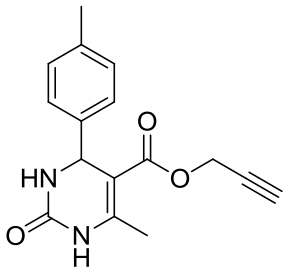
Prop-2-yn-1-yl 6-methyl-4-(1-naphthyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-car boxylate (13d)



13d

Yield: 78%. Yellowish crystallline solid. M.p.: 237.1-237.8 ºC. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ (ppm) 9.40 (s, 1H), 8.3 (d, *J* = 8.4 Hz, 1H), 7.96-7.93 (m, 1 H), 7.86-7.83 (m, 2H), 7.61-7.52 (m, 2H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 1H), 6.03 (d, *J* = 3.2 Hz, 1H), 4.56-4.41 (m, 2H), 3.36-3.34 (m, >1H), 2.39 (s, 3H). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz): δ (ppm) 164.49, 151.65, 150.41, 139.56, 133.61, 130.04, 128.52, 128.08, 126.20, 125.70, 123.96, 123.64, 98.03, 78.69, 77.14, 50.96, 49.62, 18.05. HRMS (ESI-pos) m/z calcd. for $C_{19}H_{16}N_2NaO_3$ $(M+Na)^+$ 343.1059, found 343.1053.

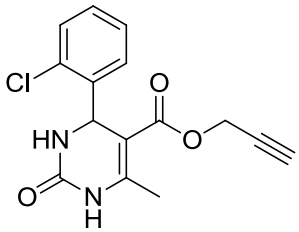
Prop-2-yn-1-yl 6-methyl-4-(4-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (13e)



13e

Yield: 88%. White crystalline solid. M.p.: 196.2-196.5 ºC. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.31 (s, 1H), 7.77 (s, 1H), 7.12 (s, 4H), 5.10 (d, *J* = 3.6 Hz, 1H), 4.63 (d, *J* = 2.4 Hz, 2H), 3.48 (t, *J* = 2.4 Hz, 1H), 2.26-2.25 (m, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 164.50, 152.12, 149.69, 141.63, 136.49, 128.98, 126.07, 98.50, 78.85, 77.28, 53.32, 50.99, 20.68, 17.94. HRMS (ESI-pos) m/z calcd. for $C_{16}H_{16}N_2NaO_3$ $(M+Na)^+$ 307.1059, found 307.1053.

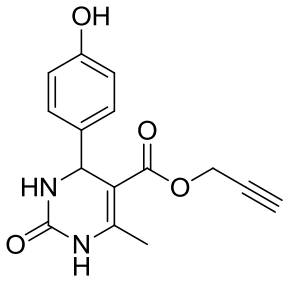
Prop-2-yn-1-yl 4-(2-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (13f)



13f

Yield: 82%. White crystalline solid. M.p.: 221.7-221.9 ºC. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.42 (s, 1H), 7.78 (s, 1H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.31-7.25 (m, 3H), 5.61 (d, *J* = 2.8 Hz, 1H), 4.60-4.49 (m, 2H), 3.40 (t, *J* = 2.4 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 164.21, 151.30, 150.68, 141.30, 131.75, 129.52, 129.20, 128.72, 127.77, 97.03, 78.64, 77.13, 51.36, 50.95, 17.94. HRMS (ESI-pos) m/z calcd. for $C_{15}H_{13}ClN_2NaO_3$ $(M+Na)^+$ 327.0512, found 327.0506.

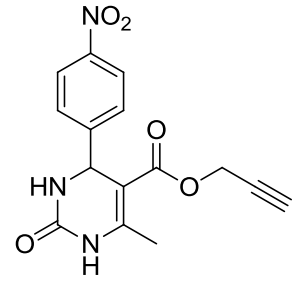
Prop-2-yn-1-yl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (13g)



13g

Yield: 78%. Yellowish crystallline solid. M.p.: 186.7-187.8 ºC. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.34 (s, 1H), 9.26 (s, 1H), 7.70 (s, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 5.03 (d, *J* = 3.2 Hz, 1H), 4.67-4.58 (m, 2H), 3.48 (t, *J* = 2.4 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 164.58, 156.63, 152.15, 149.33, 135.11, 127.35, 115.06, 98.83, 78.88, 77.23, 53.13, 50.95, 17.93. HRMS (ESI-pos) m/z calcd. for $C_{15}H_{14}N_2NaO_4$ $(M+Na)^+$ 309.0851, found 309.0846.

Prop-2-yn-1-yl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (13h)

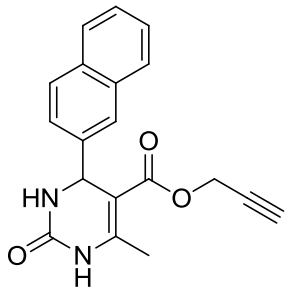


13h

Yield: 89%. Yellowish crystallline solid. M.p.: 211.2-211.4 ºC. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.50 (s, 1H), 8.21 (d, *J* = 8.8 Hz, 2H), 7.97 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 5.27 (d, *J* = 3.6 Hz, 1H), 4.63 (d, *J* = 2.4 Hz, 2H), 3.48 (t, *J* = 2.4 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 164.21, 151.65, 150.82, 146.77, 127.63, 123.88, 97.27, 78.68, 77.38, 53.45, 51.11, 18.04. HRMS (ESI-pos) m/z calcd. for $C_{15}H_{13}ClN_2NaO_3$ $(M+Na)^+$ 338.0753, found 338.0747.

Prop-2-yn-1-yl 6-methyl-4-(2-naphthyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-car boxylate (13i)

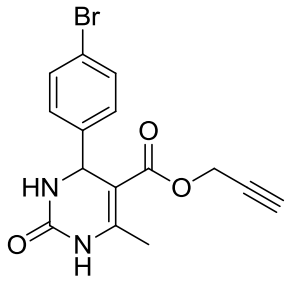
Yield: 81%. White crystalline solid. M.p.: 229.7-230.1 ºC. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.43 (s, 1H), 7.95-7.87 (m, 4H), 7.71 (s, 1H), 7.52-7.47 (m, 3H), 5.36 (s, 1H),



13i

4.65 (d, *J* = 2.4 Hz, 2H), 3.48 (s, 1H), 2.33 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 164.53, 152.08, 150.10, 141.86, 132.73, 132.40, 128.43, 127.93, 127.51, 126.32, 125.98, 124.82, 124.53, 98.20, 78.85, 77.31, 54.03, 51.07, 18.08. HRMS (ESI-pos) m/z calcd. for $C_{19}H_{16}N_2NaO_3$ $(M+Na)^+$ 343.1059, found 343.1053.

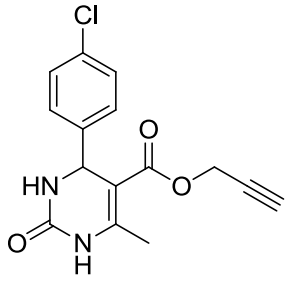
Prop-2-yn-1-yl 4-(4-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (13j)



13j

Yield: 90%. White crystalline solid. M.p.: 207.6-208.1 ºC. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.40 (s, 1H), 7.86 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 5.13 (d, *J* = 2.8 Hz, 1H), 4.64 (d, *J* = 2.4 Hz, 2H), 3.47 (t, *J* = 2.4 Hz, 1H), 2.26 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 164.35, 151.86, 150.22, 143.87, 131.39, 128.49, 120.45, 97.87, 78.77, 77.33, 53.22, 51.05, 17.99. HRMS (ESI-pos) m/z calcd. for $C_{15}H_{13}BrN_2NaO_3$ $(M+Na)^+$ 371.0007, found 371.0002.

Prop-2-yn-1-yl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (13k)



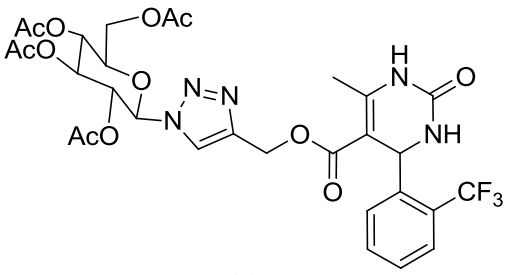
13k

Yield: 87%. White crystalline solid. M.p.: 198.7-199.5 ºC. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.40 (s, 1H), 7.85 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 5.14 (d, *J* = 3.2 Hz, 1H), 4.64 (d, *J* = 2.4 Hz, 2H), 3.47 (t, *J* = 2.4 Hz, 1H), 2.26 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 164.36, 151.87, 150.21, 143.47, 131.90, 128.47, 128.13, 97.93, 78.77, 77.32, 53.15, 51.05, 17.99. HRMS (ESI-pos) m/z calcd. for $C_{15}H_{13}ClN_2NaO_3$ $(M+Na)^+$ 327.0512, found 327.0507.

General procedure for the synthesis of compounds 14a-h

A solution of sodium ascorbate (3.7 mg, 0.018 mmol) and copper (II) acetate (1 mg, 6 µmol, 5 mol%) in water (1.5 mL) was added to a mixture of suitable *N*-propargylic DHMP **13** (0.125 mmol) and azidosugar **1** or **2** (0.125 mmol) in dichloromethane (1.5 mL). The contents were stirred for 24 h at room temperature. The progress of the reaction was monitored by TLC. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, washed with aqueous $NaHCO_3$, saturated brine solution and water. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The solvent was concentrated under reduced pressure in a rotavap. The crude material was purified by column chromatography on silica gel to afford the pure products.

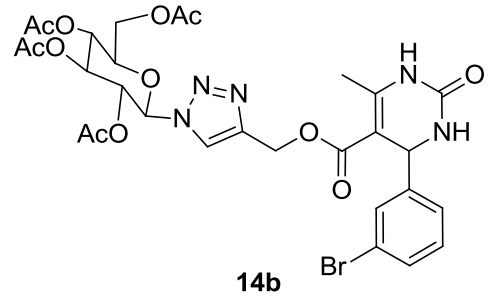
6-Methyl-2-oxo-5-({[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]oxy}carbonyl)-4-[2-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydropyrimidine (14a) (mixture of diastereomers)



14a

Purified by silica gel column chromatography. R_f 0.22 (EtOAc / hexane 7:3). Yield: 90%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.00 (s, 2H), 7.65-7.36 (m, 10H), 5.82-5.75 (m, 4H), 5.45-5.19 (m, 8H), 5.08-4.99 (m, 4H), 4.34-4.28 (m, 2H), 4.15-4.09 (m, 2H), 4.00-3.96 (m, 2H), 2.43 and 2.42 (2s, 6H), 2.08-2.02 (m, 18H), 1.81 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 170.61, 170.58, 170.03, 169.99, 169.52, 169.49, 168.89, 168.84, 164.62, 152.53, 152.49, 149.80, 149.76, 143.70, 143.64, 141.33, 141.17, 133.32, 133.21, 128.58, 128.44, 128.31, 128.28, 127.10, 127.06, 126.80, 126.76, 126.37, 126.36, 126.31, 126.26, 121.73, 121.53, 98.69, 98.65, 85.73, 85.70, 75.19, 72.71, 72.68, 70.32, 70.24, 67.69, 67.65, 61.68, 61.62, 57.08, 56.98, 51.35, 51.34, 20.77, 20.65, 20.63, 20.20, 20.16, 18.59, 18.55. HRMS (ESI-pos) m/z calcd. for $C_{30}H_{32}F_3N_5NaO_{12}$ $(M+Na)^+$ 734.1897, found 734.1892.

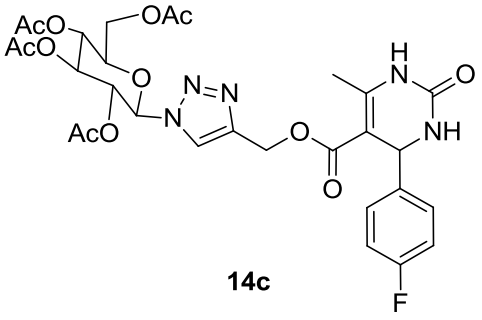
4-(3-Bromophenyl)-6-methyl-2-oxo-5-({[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-1,2,3,4-tetrahydropyrimidine (14b) (mixture of diastereomers)



14b

Purified by silica gel column chromatography. R_f 0.18 (EtOAc / hexane 7:3). Yield: 99%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.67 and 8.66 (2s, 2H), 7.63 (s, 1H), 7.60 (s, 1H), 7.42 (m, 1H), 7.38-7.33 (m, 3H), 7.21-7.09 (m, 4H), 6.35 (s, 1H), 6.30 (s, 1H), 5.88-5.84 (m, 2H), 5.43-5.09 (set of signals, 12H), 4.32-4.26 (m, 2H), 4.15-4.06 (m, 2H), 4.03-3.99 (m, 2H), 2.31 (s, 6H), 2.05-2.00 (m, 18H), 1.81 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 170.65, 170.64, 170.04, 169.48, 168.93, 168.87, 164.92, 153.35, 153.32, 148.48, 148.39, 145.87, 145.84, 143.70, 131.18, 131.15, 130.61, 130.45, 129.77, 125.49, 122.72, 122.08, 122.02, 99.91, 99.85, 85.76, 75.17, 72.60, 72.57, 70.45, 70.36, 67.71, 67.69, 61.65, 57.21, 57.13, 55.00, 54.99, 20.81, 20.63, 20.61, 20.22, 18.83, 18.82. HRMS (ESI-pos) m/z calcd. for $C_{29}H_{32}BrN_5NaO_{12}$ $(M+Na)^+$ 744.1129, found 744.1123.

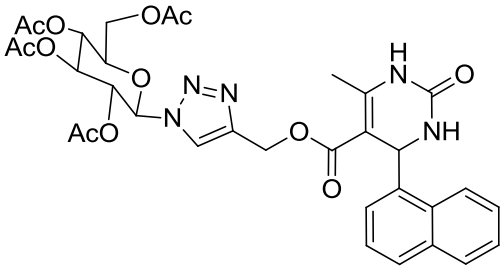
4-(4-Fluorophenyl)-6-methyl-2-oxo-5-({[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-1,2,3,4-tetrahydropyrimidine (14c) (mixture of diastereomers)



14c

Purified by silica gel column chromatography. R_f 0.44 (EtOAc). Yield: 99%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.67 (s, 2 H), 7.49 (s, 2H), 7.24-7.15 (m, 4H), 6.98-6.90 (m, 4H), 6.28 (s, 2H), 5.87-5.82 (m, 2H), 5.43-5.05 (set of signals, 12 H), 4.34-4.27 (m, 2H), 4.15-4.12 (m, 2H), 4.03-3.98 (m, 2H), 2.30 (s, 6H), 2.05-2.00 (m, 18H), 1.81-1.79 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 170.56, 170.54, 169.94, 169.93, 169.37, 168.86, 168.80, 164.89, 164.86, 163.45, 163.43, 161.00, 160.97, 153.33, 153.29, 147.90, 147.79, 143.69, 143.67, 139.52, 139.49, 128.49, 128.44, 128.41, 128.36, 121.79, 121.76, 115.71, 115.61, 115.50, 115.39, 100.34, 100.31, 85.69, 85.66, 75.17, 75.15, 72.52, 72.50, 70.28, 70.25, 67.60, 67.57, 61.53, 61.49, 56.90, 54.78, 54.67, 20.65, 20.53, 20.51, 20.50, 20.09, 18.64, 18.59. HRMS (ESI-pos) m/z calcd. for $C_{29}H_{32}FN_5NaO_{12}$ $(M+Na)^+$ 684.1929, found 684.1924.

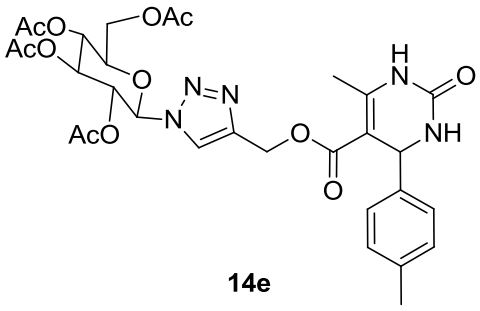
(6-Methyl-4-(1-naphthyl)-2-oxo-5-({[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-1,2,3,4-tetrahydropyrimidine (14d) (mixture of diastereomers)



14d

Purified by silica gel column chromatography. R_f 0.42 (EtOAc). Yield: 91%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.85 and 8.82 (2s, 2H), 8.15-8.13 (m, 1H), 8.05-8.03 (m, 1H), 7.96-7.90 (m, 2H), 7.82-7.80 (m, 2H), 7.63-7.60 (m, 2H), 7.55-7.53 (m, 2H), 7.44-7.38 (m, 4H), 6.90 (s, 1H), 6.79 (s, 1H), 6.27 (s, 1H), 6.21 (s, 1H), 6.04 (s, 1H), 5.99 (s, 1H), 5.69-5.64 (m, 2H), 5.37-5.00 (set of signals, 10H), 4.26-4.18 (m, 2H), 4.13-4.07 (m, 2H), 3.95-3.87 (m, 2H), 2.39 and 2.38 (2s, 6H), 2.08-2.04 (m, 18H), 1.77 and 1.75 (2s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 170.60, 170.57, 170.02, 169.97, 169.60, 169.56, 168.76, 168.63, 165.01, 164.91, 153.22, 149.47, 149.10, 144.17, 144.08, 138.06, 137.93, 134.25, 134.18, 130.14, 129.38, 128.91, 128.85, 127.31, 126.97, 126.21, 126.03, 124.65, 124.42, 122.20, 122.17, 121.17, 120.85, 99.05, 98.71, 85.52, 75.06, 75.02, 72.68, 72.60, 70.31, 70.17, 67.73, 61.87, 61.82, 57.70, 57.40, 50.90, 50.79, 20.80, 20.66, 20.64, 20.16, 18.65, 18.56. HRMS (ESI-pos) m/z calcd. for $C_{33}H_{35}N_5NaO_{12}$ $(M+Na)^+$ 716.2180, found 716.2174.

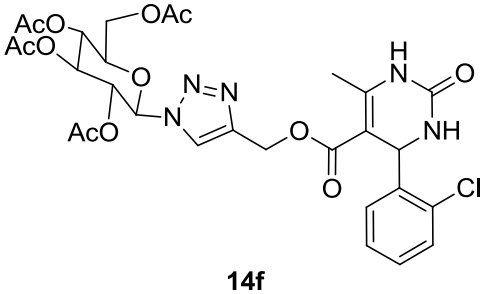
6-Methyl-4-(4-methylphenyl)-2-oxo-5-({[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-1,2,3,4-tetrahydropyrimidine (14e) (mixture of diastereomers)



14e

Purified by silica gel column chromatography. R_f 0.43 (EtOAc). Yield: 98%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.58 (s, 2H), 7.54 (s, 1H), 7.46 (s, 1H), 7.12-7.04 (m, 8H), 6.04 (s, 1H), 6.00 (s, 1H), 5.81-5.78 (m, 2H) 5.39-5.05 (set of signals, 12H), 4.28-4.21 (m, 2H), 4.11-4.05 (m, 2H), 3.98-3.90 (m, 2H), 2.27-2.24 (m, 12H), 2.01-1.96 (m, 18H), 1.76 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 170.62, 170.60, 170.02, 170.01, 169.47, 168.90, 168.84, 165.21, 165.17, 153.61, 153.56, 147.85, 147.77, 144.00, 143.96, 140.71, 140.69, 137.84, 137.81, 129.54, 129.52, 126.62, 126.58, 121.97, 121.85, 100.67, 100.53, 85.76, 75.19, 72.65, 70.38, 70.31, 67.72, 67.68, 61.63, 57.21, 57.11, 55.16, 55.14, 21.23, 21.21, 20.80, 20.79, 20.64, 20.62, 20.61, 20.20, 18.80, 18.78. HRMS (ESI-pos) m/z calcd. for $C_{30}H_{35}N_5NaO_{12}$ $(M+Na)^+$ 680.2180, found 680.2174.

4-(2-Chlorophenyl)-6-methyl-2-oxo-5-({[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-1,2,3,4-tetrahydropyrimidine (14f)

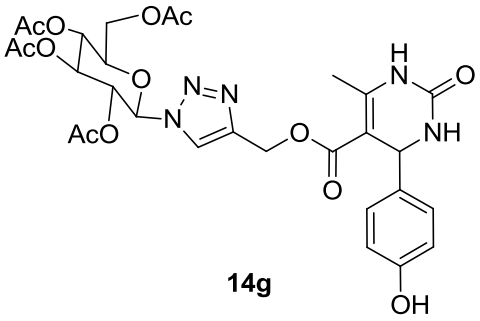


14f

Purified by silica gel column chromatography. R_f 0.42 (EtOAc). Yield: 96%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.96 (s, 2H), 7.44 (s, 1H), 7.39-7.35 (m, 2H), 7.30 (s, 1H), 7.26-7.18 (m, >6H), 5.93-5.91 (m, 2H), 5.85-5.80 (m, 4H), 5.42-5.07 (set of signals, 10H), 4.34-4.29 (m, 2H), 4.15-4.10 (m, 2H), 4.00-3.97 (m, 2H), 2.40 (s, 6H), 2.08-2.01 (set of signals, 18H), 1.82 and 1.80 (2s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 170.58, 170.01, 169.98, 169.49, 168.83, 168.80, 164.77, 164.77, 153.16, 153.13, 149.98, 149.97, 139.43, 139.32, 132.67, 130.06, 129.99, 129.55, 129.52, 128.22, 128.07, 127.83, 127.73, 121.52, 121.40, 97.97, 97.96,

85.74, 85.71, 75.15, 75.12, 72.66, 72.62, 70.42, 70.35, 67.68, 67.63, 61.70, 61.63, 57.37, 57.36, 52.11, 52.08, 20.81, 20.80, 20.63, 20.62, 20.22, 20.19, 18.59, 18.58. HRMS (ESI-pos) m/z calcd. for $C_{29}H_{32}ClN_5NaO_{12}$ $(M+Na)^+$ 700.1634, found 700.1628.

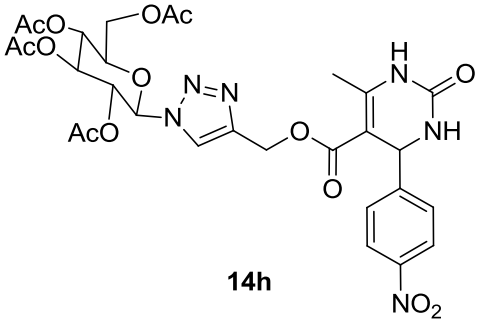
4-(4-Hydroxyphenyl)-6-methyl-2-oxo-5-({[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-1,2,3,4-tetrahydropyrimidine (14g) (mixture of diastereomers)



14g

Purified by silica gel column chromatography. R_f 0.18 (EtOAc). Yield: 95%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 9.33 (s, 2H), 9.20-9.18 (m, 2H), 8.31 and 8.30 (2s, 2H), 7.68-7.64 (m, 2H), 7.01-6.93 (m, 4H), 6.67-6.64 (m, 4H), 6.35 and 6.33 (2s, 2H), 5.67-5.62 (m, 2H), 5.58-5.53 (m, 2H), 5.22-5.17 (m, 2H), 5.12-5.00 (m, 6H), 4.39-4.35 (m, 2H), 4.17-4.07 (m, 4H), 2.21 (s, 6H), 2.03-1.97 (m, 18H), 1.78 and 1.77 (2s, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 170.08, 169.60, 169.39, 168.45, 168.43, 165.01, 156.57, 152.13, 148.82, 148.76, 143.06, 135.29, 135.26, 127.42, 127.36, 115.03, 115.00, 99.18, 99.14, 83.87, 83.84, 73.32, 72.11, 70.10, 67.55, 67.54, 61.85, 61.84, 56.47, 56.45, 54.95, 53.26, 53.25, 20.55, 20.43, 20.30, 19.90, 19.88, 17.95. HRMS (ESI-pos) m/z calcd. for $C_{29}H_{33}N_5NaO_{13}$ $(M+Na)^+$ 682.1973, found 682.1967.

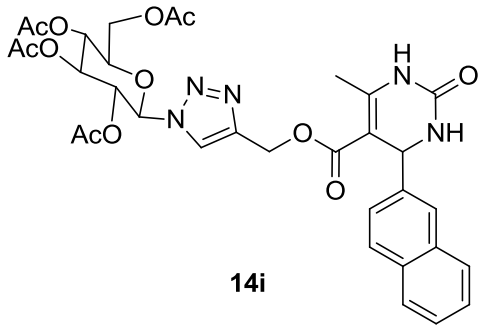
6-Methyl-4-(4-nitrophenyl)-2-oxo-5-({[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-1,2,3,4-tetrahydropyrimidine (14h) (mixture of diastereomers)



14h

Purified by silica gel column chromatography. R_f 0.35 (EtOAc). Yield: 99%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.41 (s, 2H), 8.13-8.07 (m, 4H), 7.75 (s, 1H), 7.68 (s, 1H), 7.45-7.39 (m, 4H), 6.33-6.31 (m, 2H), 5.88-5.84 (m, 2H), 5.47-5.09 (set of signals, 12H), 4.34-4.28 (m, 2H), 4.19-4.15 (m, 2 H), 4.05-4.01 (m, 2H), 2.33 (m, 6H), 2.06-2.02 (m, 18H), 1.84 and 1.83 (2s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 170.65, 170.03, 169.52, 169.05, 169.03, 164.78, 164.76, 153.16, 153.05, 150.28, 150.22, 148.65, 148.53, 147.61, 147.56, 143.34, 127.80, 127.74, 124.20, 124.12, 123.49, 122.24, 122.06, 99.86, 99.79, 85.94, 85.92, 75.40, 75.37, 72.54, 72.49, 70.56, 70.53, 67.74, 67.71, 61.62, 61.58, 57.08, 57.01, 55.05, 54.92, 20.82, 20.68, 20.65, 20.64, 20.26, 19.01, 18.93. HRMS (ESI-pos) m/z calcd. for $C_{29}H_{32}N_6NaO_{14}$ $(M+Na)^+$ 711.1874, found 711.1869.

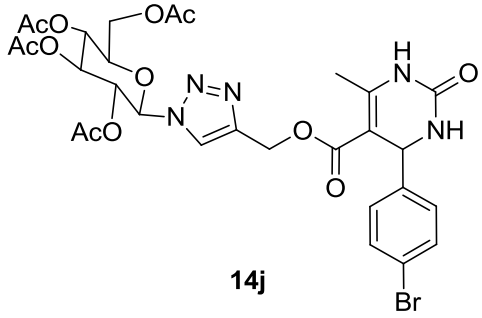
6-Methyl-4-(2-naphthyl)-2-oxo-5-({[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-1,2,3,4-tetrahydropyrimidine (14i) (mixture of diastereomers)



14i

Purified by silica gel column chromatography. R_f 0.16 (EtOAc / hexane 7:3). Yield: 99%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.64 and 8.62 (2s, 2H), 7.78-7.68 (m, 6H), 7.65 (s, 1H), 7.60 (s, 1H), 7.44-7.32 (m, 6H), 7.24-7.20 (m, >2H), 6.25 (s, 1H), 6.19 (s, 1H), 5.63-5.60 (m, 2H), 5.45-5.43 (m, 2H), 5.32-4.99 (set of signals, 10H), 4.20-4.00 (m, 4H), 3.86-3.83 (m, 2H), 2.27 (s, 6H), 2.03-1.95 (m, 18H), 1.72 and 1.70 (2s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 170.62, 170.60, 170.02, 169.49, 168.88, 168.75, 165.06, 165.03, 153.48, 153.44, 148.23, 148.08, 143.98, 140.85, 133.26, 133.21, 133.10, 133.07, 129.05, 128.96, 128.26, 127.79, 127.77, 126.58, 126.49, 126.47, 126.36, 125.50, 124.82, 124.73, 121.68, 121.63, 100.26, 100.17, 85.62, 75.12, 72.65, 72.63, 70.27, 70.16, 67.76, 67.70, 61.73, 61.66, 57.24, 57.17, 55.70, 20.79, 20.78, 20.65, 20.63, 20.62, 20.18, 20.16, 18.81, 18.79. HRMS (ESI-pos) m/z calcd. for $C_{33}H_{35}N_5NaO_{12}$ $(M+Na)^+$ 716.2180, found 716.2174.

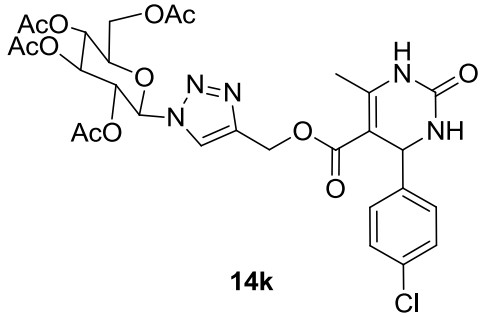
4-(4-Bromophenyl)-6-methyl-2-oxo-5-({[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-1,2,3,4-tetrahydropyrimidine (14j) (mixture of diastereomers)



14j

Purified by silica gel column chromatography. R_f 0.16 (EtOAc / hexane 7:3). Yield: 99%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.55 (s, 2H), 7.56 (s, 1H), 7.54 (s, 1H), 7.42-7.37 (m, 4H), 7.15-7.08 (m, 4H), 6.25 (s, 2H), 5.87-5.84 (m, 2H), 5.44-5.07 (set of signals, 12H), 4.35-4.28 (m, 2H), 4.18-4.13 (m, 2H), 4.05-3.99 (2H), 2.31 (s, 6H), 2.07-2.01 (m, 18H), 1.82 and 1.81 (2s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 170.65, 170.64, 170.05, 169.48, 168.97, 168.92, 164.94, 153.38, 153.31, 148.11, 148.00, 143.68, 143.65, 142.60, 142.57, 131.99, 131.91, 128.58, 128.54, 121.98, 121.94, 100.24, 100.21, 85.86, 85.83, 75.35, 75.31, 72.62, 72.60, 70.41, 67.74, 61.65, 57.06, 55.03, 54.93, 20.86, 20.85, 20.66, 20.64, 20.24, 18.85, 18.78. HRMS (ESI-pos) m/z calcd. for $C_{29}H_{32}BrN_5NaO_{12}$ $(M+Na)^+$ 744.1129, found 744.1123.

4-(4-Chlorophenyl)-6-methyl-2-oxo-5-({[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-1,2,3,4-tetrahydropyrimidine (14k) (mixture of diastereomers)

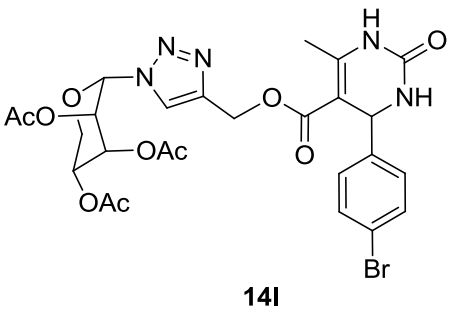


14k

Purified by silica gel column chromatography. R_f 0.18 (EtOAc / hexane 7:3). Yield: 94%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.57 (s, 2H), 7.51 (s, 1H), 7.48 (s, 1H), 7.21-7.09 (m, >8H), 6.27 (s, 2H), 5.83-5.79 (m, 2H), 5.39-5.02 (set of signals, 12H), 4.30-4.23 (m, 2H), 4.12-4.08 (m, 2H), 4.00-3.94 (m, 2H), 2.26 (s, 6H), 2.01-1.96 (m, 18H), 1.77 and 1.76 (2s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 170.65, 170.64, 170.04, 169.48, 168.96, 168.91, 164.94, 164.93, 153.45, 153.39, 153.37, 148.13, 148.03, 143.73, 143.67, 142.12, 133.75, 133.71, 129.01, 128.93, 128.24, 128.19, 121.97, 121.90, 100.24, 85.83, 85.80, 75.31, 75.27, 72.61, 72.59, 70.39, 67.72, 67.72, 61.64, 57.04, 54.91, 54.83, 20.81, 20.64, 20.62, 20.21, 18.80, 18.74. HRMS (ESI-pos) m/z calcd. for $C_{29}H_{32}ClN_5NaO_{12}$ $(M+Na)^+$ 700.1634, found 700.1628.

4-(4-Bromophenyl)-6-methyl-2-oxo-5-({[1-(2,3,4-tri-*O*-acetyl-α-D-arabinopyranosyl)

-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-1,2,3,4-tetrahydropyrimidine (14l) (mixture of diastereomers)



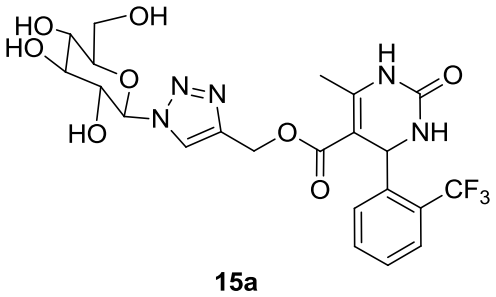
14l

Purified by silica gel column chromatography. R_f 0.43 (EtOAc). Yield: 99%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.61 (s, 2H), 7.68 (s, 1H), 7.62 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.30 (s, 2H), 5.71-5.67 (m, 2H), 5.51-5.41 (m, 2H), 5.39-5.37 (m, 2H), 5.27-5.13 (m, 6H), 5.07-5.00 (m, 2H), 4.17-4.12 (m, 2H), 3.94-3.89 (m, 2H), 2.23 (s, 6H), 2.16 and 2.15 (2s, 6H), 1.97-1.95 (m, 6H), 1.80 and 1.79 (2s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 170.25, 169.98, 169.97, 169.14, 165.04, 164.99, 153.54, 153.44, 147.97, 147.74, 142.63, 142.60, 131.87, 131.77, 128.47, 128.45, 121.90, 121.84, 100.34, 100.31, 86.78, 86.76, 70.48, 70.45, 68.31, 68.27, 67.74, 67.48, 67.46, 60.50, 60.26, 56.97, 56.84, 54.95, 54.80, 21.08, 20.67, 20.33, 18.79, 18.68. HRMS (ESI-pos) m/z calcd. for $C_{26}H_{28}BrN_5NaO_{10}$ $(M+Na)^+$ 672.0917, found 672.0912.

General procedure for the deprotection of compounds 14a-l

To a solution of triethylamine (0.031 g, 43 µl, 0.350 mmol, 7 equiv.), methanol (0.5 mL), and water (0.5 mL) was added compound **14** (0.050 mmol). The mixture was stirred for 12 hours at room temperature. The solvent was concentrated under reduced pressure in a rotavap. The crude material was purified by short column chromatography on silica gel (EtOAc / MeOH 9:1) to afford the desired product.

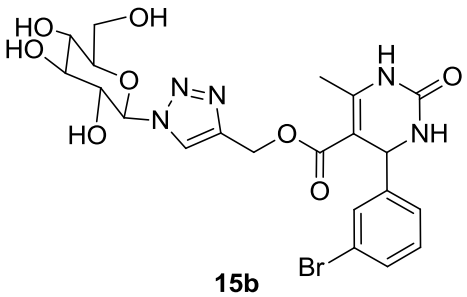
5-({[1-(β-D-Glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-6-methyl-2-oxo-4-[2-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydropyrimidine (15a) (mixture of diastereomers)



15a

R_f 0.33. Yield: 81%. ^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 7.70-7-62 (m, 6H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 5.76 (s, 2H), 5.52 (d, *J* = 8.8 Hz, 2H), 5.12-5.01 (m, 4H), 3.91-3.88 (m, 2H), 3.81-3.70 (m, 4H), 3.59-3.47 (m, 6H), 2.43 (s, 6H). ^{13}C NMR (CD_3OD, 100 MHz): δ (ppm) 166.21, 166.17, 153.68, 151.45, 151.41, 144.23, 144.18, 143.74, 143.73, 143.71, 143.70, 134.38, 134.35, 129.89, 129.69, 129.66, 129.46, 128.49, 128.19, 127.89, 127.30, 127.30, 127.24, 127.21, 127.17, 127.16, 127.12, 127.09, 124.58, 124.55, 124.45, 124.44, 100.06, 100.05, 89.50, 89.49, 81.13, 78.44, 73.91, 70.86, 70.85, 62.36, 57.39, 57.37, 52.41, 52.39, 18.25. HRMS (ESI-pos) m/z calcd. for $C_{22}H_{24}F_3N_5NaO_8$ $(M+Na)^+$ 566.1475, found 566.1469.

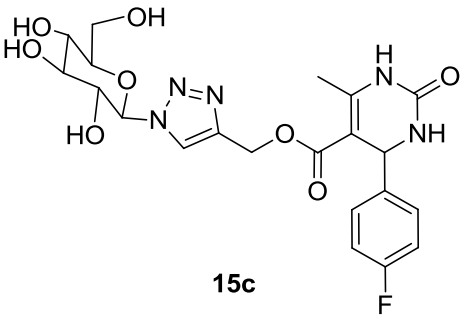
4-(3-Bromophenyl)-5-({[1-(β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (15b) (mixture of diastereomers)



15b

R_f 0.37. Yield: 68%. ^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 8.01 and 8.00 (2s, 2H), 7.44-7.39 (m, 4H), 7.24-7.19 (m, 4H), 5.60 (d, *J* = 2.0 Hz, 1H), 5.58 (d, *J* = 2.0 Hz, 1H), 5.30 (s, 2H), 5.19 (s, 4H), 3.91-3.84 (m, 4H), 3.75-3.70 (m, 2H), 3.60-3.48 (m, 6H), 2.34 (s, 6H). ^{13}C NMR (CD_3OD, 100 MHz): δ (ppm) 166.58, 166.57, 154.66, 150.55, 150.51, 148.05, 144.17, 144.15, 131.88, 131.63, 130.64, 126.56, 124.94, 123.47, 100.82, 100.81, 89.58, 81.17, 81.16, 78.43, 73.96, 70.87, 70.85, 62.37, 62.37, 57.67, 55.64, 18.37. HRMS (ESI-pos) m/z calcd. for $C_{21}H_{24}BrN_5NaO_8$ $(M+Na)^+$ 576.0706, found 576.0700.

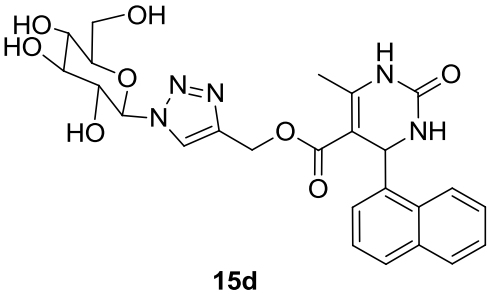
4-(4-Fluorophenyl)-5-({[1-(β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (15c) (mixture of diastereomers)



15c

R_f 0.36. Yield: 85%. ^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 7.98 (s, 2H), 7.29-7.23 (m, 4H), 7.05-6.99 (m, 4H), 5.60 (d, *J* = 2.0 Hz, 1H), 5.58 (d, *J* = 2.0 Hz, 1H), 5.31-5.30 (m, 2H), 5.21-5.13 (m, 4H), 3.91-3.84 (m, 4H), 3.75-3.69 (m, 2H), 3.60-3.48 (m, 6H), 2.34 (s, 6H). ^{13}C NMR (CD_3OD, 100 MHz): δ (ppm) 166.64, 164.81, 162.38, 154.71, 154.70, 150.12, 150.07, 144.19, 144.17, 141.79, 141.76, 141.73, 129.64, 129.62, 129.56, 129.54, 124.93, 116.41, 116.19, 101.29, 101.27, 89.56, 89.55, 81.18, 78.45, 73.96, 73.95, 70.85, 62.35, 57.56, 55.52, 55.48, 18.28, 18.27. HRMS (ESI-pos) m/z calcd. for $C_{21}H_{24}FN_5NaO_8$ $(M+Na)^+$ 516.1507, found 516.1501.

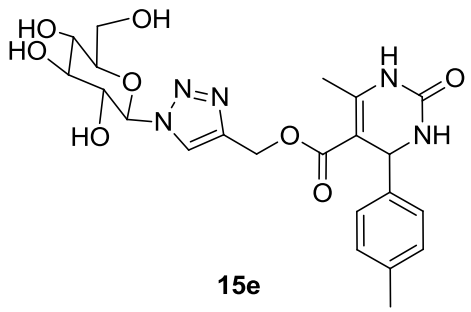
5-({[1-(β-D-Glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-6-methyl-4-(1-naphthyl)-2-oxo-1,2,3,4-tetrahydropyrimidine (15d) (mixture of diastereomers)



15d

R_f 0.28. Yield: 90%. ^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 8.26 and 8.24 (2s, 2H), 7.93-7.90 (m, 2H), 7.84-7.81 (m, 2H), 7.60-7.51 (m, 4H), 7.47-7.42 (m, 4H), 7.36 (s, 1H), 7.28 (s, 1H), 6.25 (s, 2H), 5.44-5.40 (m, 2H), 5.04-4.93 (m, 4H), 3.92 (s, 1H), 3.89 (s, 1H), 3.74-3.69 (m, 4H), 3.59-3.45 (m, 6H), 2.44 (s, 6H). ^{13}C NMR (CD_3OD, 100 MHz): δ (ppm) 166.68, 166.64, 154.50, 150.68, 150.62, 144.31, 144.25, 140.77, 140.73, 135.48, 131.68, 131.67, 129.92, 129.69, 127.71, 126.98, 126.95, 126.81, 126.78, 125.80, 124.26, 124.15, 124.03, 124.02, 100.91, 100.87, 89.49, 81.19, 81.17, 78.41, 73.86, 73.80, 70.89, 70.87, 62.44, 62.42, 57.76, 57.74, 51.74, 51.72, 18.23. HRMS (ESI-pos) m/z calcd. for $C_{25}H_{27}N_5NaO_8$ $(M+Na)^+$ 548.1757, found 548.1752.

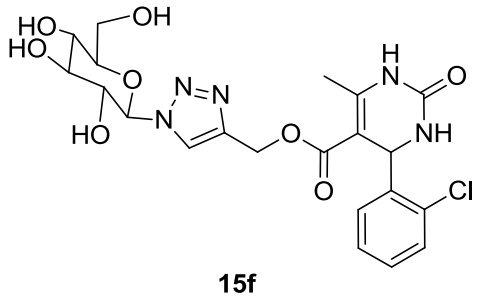
5-({[1-(β-D-Glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-6-methyl-4-(4-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine (15e) (mixture of diastereomers)



15e

R_f 0.29. Yield: 95%. ^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 7.93 (s, 2H), 7.16-7.10 (m, 8H), 5.58 (s, 1H), 5.56 (s, 1H), 5.27 (s, 2H), 5.19-5.13 (m, 4H), 3.92-3.83 (m, 4H), 3.75-3.69 (m, 2H), 3.60-3.47 (m, 6H), 2.33 (s, 6H) 2.30 (s, 6H). ^{13}C NMR (CD_3OD, 100 MHz): δ (ppm) 166.81, 154.93, 154.92, 149.81, 149.78, 144.30, 144.28, 142.66, 142.64, 138.59, 138.58, 130.26, 127.57, 127.55, 124.89, 124.86, 101.52, 101.50, 89.57, 89.56, 81.18, 78.43, 73.95, 73.94, 70.86, 70.85, 62.35, 57.62, 55.82, 55.79, 21.21, 18.26, 18.26. HRMS (ESI-pos) m/z calcd. for $C_{22}H_{27}N_5NaO_8$ $(M+Na)^+$ 512.1757, found 512.1752.

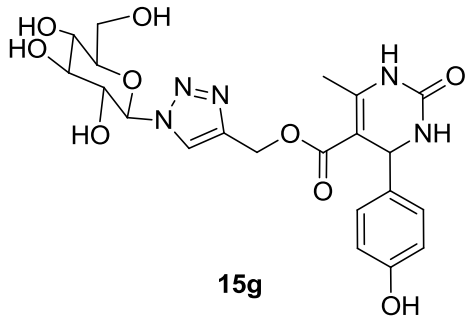
4-(2-Chlorophenyl)-5-({[1-(β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (15f) (mixture of diastereomers)



15f

R_f 0.34. Yield: 91%. ^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 7.78 and 7.76 (2s, 2H), 7.41-7.36 (m, 2H), 7.32-7.23 (m, 6H), 5.83-5.82 (m, 2H), 5.56 (d, *J* = 2.4 Hz, 1H), 5.54 (d, *J* = 2.4 Hz, 1H), 5.15-5.07 (m, 4H), 3.92-3.88 (m, 2H), 3.85-3.79 (m, 2H), 3.75-3.70 (m, 2H), 3.59-3.47 (m, 6H), 2.40 and 2.39 (2s, 6H). ^{13}C NMR (CD_3OD, 100 MHz): δ (ppm) 166.42, 166.39, 154.23, 151.27, 151.24, 141.95, 141.92, 133.81, 133.79, 131.04, 131.02, 130.50, 129.94, 129.93, 128.74, 128.71, 124.61, 124.57, 99.56, 89.54, 81.14, 78.44, 73.96, 70.88, 70.87, 62.39, 57.64, 53.49, 53.45, 18.20. HRMS (ESI-pos) m/z calcd. for $C_{21}H_{24}ClN_5NaO_8$ $(M+Na)^+$ 532.1211, found 532.1206.

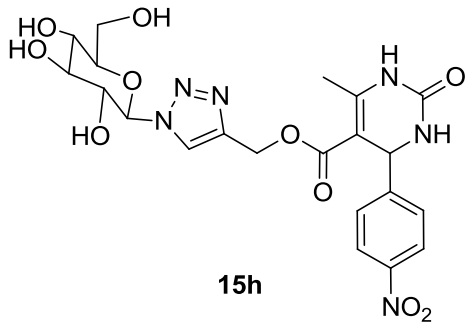
5-({[1-(β-D-Glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (15g) (mixture of diastereomers)



15g

R_f 0.20. Yield: 89%. ^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 7.71 and 7.69 (2s, 2H), 7.09-7.03 (m, 4H), 6.73-6.69 (m, 4H), 5.56-5.52 (m, 2H), 5.27-5.23 (m, 4H), 5.12-5.07 (m, 2H), 3.93-3.81 (m, 4H), 3.76-3.71 (m, 2H), 3.61-3.48 (m, 6H), 2.33 (s, 6H). ^{13}C NMR (CD_3OD, 100 MHz): δ (ppm) 166.79, 166.77, 158.06, 158.04, 154.78, 154.77, 149.53, 149.46, 144.45, 144.41, 136.81, 136.80, 128.97, 124.68, 124.65, 116.34, 101.68, 101.65, 89.58, 89.55, 81.22, 81.21, 78.49, 73.92, 73.90, 70.87, 70.83, 62.44, 62.39, 57.54, 57.52, 55.78, 55.74, 18.17, 18.16. HRMS (ESI-pos) m/z calcd. for $C_{21}H_{25}N_5NaO_9$ $(M+Na)^+$ 514.1550, found 514.1544.

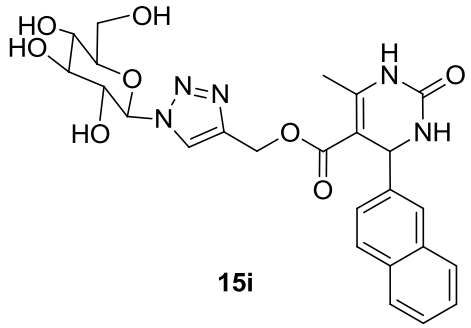
5-({[1-(β-D-Glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine (15h) (mixture of diastereomers)



15h

R_f 0.26. Yield: 93%. ^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 8.17-8.12 (m, 4H), 8.08 and 8.07 (2s, 2H), 7.49-7.44 (m, 4H), 5.62-5.58 (m, 2H), 5.42-5.41 (m, 2H), 5.23-5.11 (m, 4H), 3.92-3.84 (m, 4H), 3.76-3.69 (m, 2H), 3.61-3.48 (m, 6H), 2.35 (s, 6H). ^{13}C NMR (CD_3OD, 100 MHz): δ (ppm) 166.37, 166.35, 154.43, 154.39, 152.60, 152.57, 151.04, 151.01, 148.71, 148.70, 143.94, 128.89, 128.85, 125.18, 125.08, 124.88, 100.28, 89.55, 89.52, 81.17, 81.16, 78.44, 78.44, 73.98, 73.92, 70.82, 62.35, 62.31, 57.52, 55.78, 55.72, 18.35, 18.32. HRMS (ESI-pos) m/z calcd. for $C_{21}H_{24}N_6NaO_{10}$ $(M+Na)^+$ 543.1452, found 543.1446.

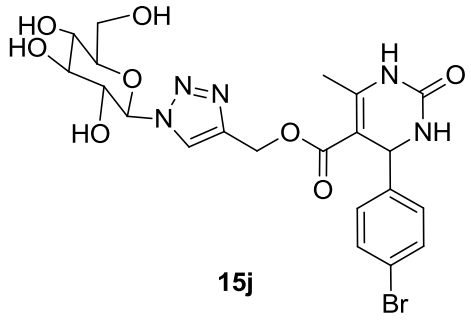
5-({[1-(β-D-Glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-6-methyl-4-(2-naphthyl)-2-oxo-1,2,3,4-tetrahydropyrimidine (15i) (mixture of diastereomers)



15i

R_f 0.35.Yield: 73%. ^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 7.83-7.78 (m, 8H), 7.69-7.67 (m, 2H), 7.50-7.42 (m, 6H), 5.48-5.47 (m, 2H), 5.44 (s, 1H), 5.42 (s, 1H), 5.18-5.11 (m, 4H), 3.89-3.78 (m, 4H), 3.72-3.65 (m, 2H), 3.57-3.44 (m, 6H), 2.37 (s, 6H). ^{13}C NMR (CD_3OD, 100 MHz): δ (ppm) 166.76, 154.88, 154.87, 150.23, 150.17, 144.27, 144.22, 142.81, 134.67, 134.64, 134.39, 129.75, 129.20, 129.17, 128.67, 127.39, 127.36, 127.14, 127.11, 126.38, 126.35, 125.76, 125.74, 124.85, 124.81, 101.22, 101.20, 89.50, 81.16, 81.13, 78.41, 78.40, 73.87, 70.82, 70.80, 62.38, 62.33, 57.70, 57.67, 56.38, 56.34, 18.35, 18.33. HRMS (ESI-pos) m/z calcd. for $C_{25}H_{27}N_5NaO_8$ $(M+Na)^+$ 548.1757, found 548.1752.

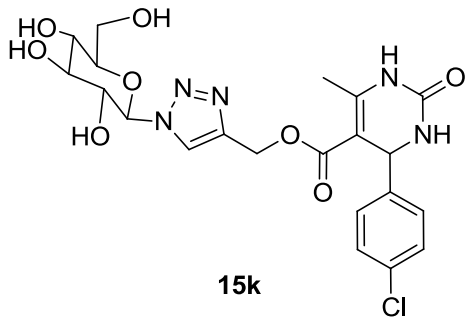
4-(4-Bromophenyl)-5-({[1-(□-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (15j) (mixture of diastereomers)



15j

R_f 0.25. Yield: 92%. ^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 7.99 and 7.98 (2s, 2H), 7.47-7.43 (m, 4H), 7.19-7.15 (m, 4H), 5.60 (d, *J* = 2.0 Hz, 1H), 5.58 (d, *J* = 2.0 Hz, 1H), 5.28 and 5.27 (2s, 2H), 5.21-5.13 (m, 4H), 3.92-3.86 (m, 4H), 3.76-3.71 (m, 2H), 3.62-3.49 (m, 6H), 2.33 (s, 6H). ^{13}C NMR (CD_3OD, 100 MHz): δ (ppm) 166.58, 166.57, 154.67, 154.64, 150.40, 150.34, 144.92, 144.89, 144.15, 144.12, 132.76, 129.69, 129.66, 125.04, 122.42, 122.41, 100.92, 100.90, 89.58, 81.21, 78.47, 73.96, 70.86, 62.38, 57.60, 57.58, 55.66, 55.61, 18.29, 18.27. HRMS (ESI-pos) m/z calcd. for $C_{21}H_{24}BrN_5NaO_8$ $(M+Na)^+$ 576.0706, found 576.0700.

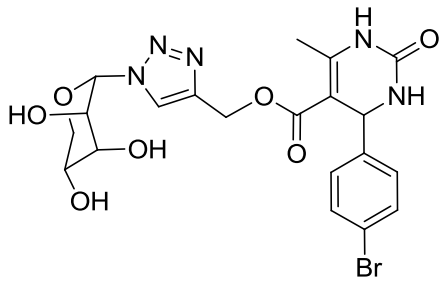
4-(4-Chlorophenyl)-5-({[1-(β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (15k) (mixture of diastereomers)



15k

R_f 0.29. Yield: 92%. ^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 7.99 (s, 2H), 7.31-7.28 (m, 4H), 7.25-7.20 (m, 4H), 5.60 (d, *J* = 2.0 Hz, 1H), 5.58 (d, *J* = 2.0 Hz, 1H), 5.30 and 5.29 (2s, 2H), 5.20-5.13 (m, 4H), 3.92-3.85 (m, 4H), 3.76-3.70 (m, 2H), 3.61-3.49 (m, 6H), 2.33 (s, 6H). ^{13}C NMR (CD_3OD, 100 MHz): δ (ppm) 166.59, 154.69, 154.67, 150.35, 150.30, 144.43, 144.40, 144.15, 144.12, 134.39, 134.38, 129.74, 129.35, 129.33, 125.01, 101.00, 100.97, 89.56, 81.19, 78.45, 73.95, 70.85, 62.36, 57.59, 57.58, 55.57, 55.53, 18.30, 18.28. HRMS (ESI-pos) m/z calcd. for $C_{21}H_{24}ClN_5NaO_8$ $(M+Na)^+$ 532.1211, found 532.1206.

5-({[1-(α-D-Arabinopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-4-(4-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (15l) (mixture of diastereomers)



15l

R_f 0.32. Yield: 98%. ^{1}H NMR (CD_3OD, 400 MHz): δ (ppm) 8.10 (s, 1H), 8.08 (s, 1H), 7.44-7.39 (m, 4H), 7.17-7.11 (m, 4H), 5.50-5.47 (m, 2H), 5.28 and 5.27 (2s, 2H), 5.22-5.12 (m, 4H), 4.19-4.11 (m, 2H), 4.10 (d, *J* = 2.4 Hz, 1H), 4.03 (d, *J* = 2.4 Hz, 1H), 3.96 (s, 2H), 3.90 (s, 1H), 3.86 (s, 1H), 3.74-3.71 (m, 2H), 2.33 (s, 6H). ^{13}C NMR (CD_3OD, 100 MHz): δ (ppm) 166.61, 166.59, 154.71, 154.68, 150.23, 150.16, 144.85, 144.21, 144.19, 132.71, 132.69, 129.58, 124.64, 124.48, 122.40, 122.40, 101.02, 101.01, 90.50, 90.47, 74.83, 74.81, 71.43, 71.37, 70.81, 70.79, 70.22, 57.62, 57.57, 55.64, 55.59, 18.30, 18.25. HRMS (ESI-pos) m/z calcd. for $C_{20}H_{22}BrN_5NaO_7$ $(M+Na)^+$ 546.0600, found 546.0595.

Biological activity assay[14-15]

The antibacterial activity against transgenic *Bacillus subtilis* expressing YFP in the growth phase was only determined with a fluorescence based antibacterial growth inhibition assay. The fluorescence was measured on a microtiter plate reader GENios Pro (Fa. Tecan, excitation, 510 nm; emission, 535 nm). The *Bacillus subtilis* strain 168 (P_{AbrB}-IYFP)[16] was maintained on TY (tryptone-yeast extract) medium supplemented with 1 % Bacto-tryptone, 0.5 % Bacto-yeast extract, 1 % NaCl and chloramphenicol (5 µg ml^{-1}). All experiments were conducted in triplicate.

3.7 References

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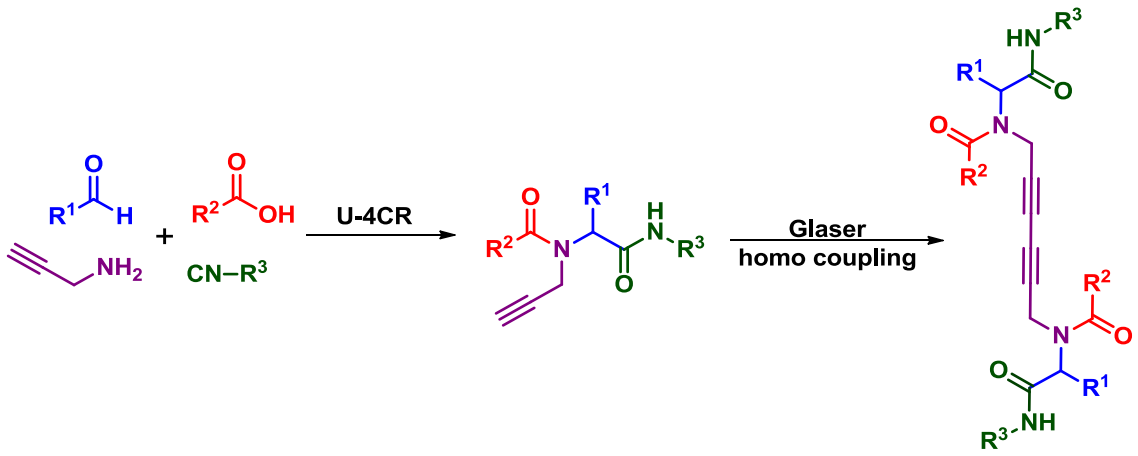
Chapter 4

Synthesis of 1,3-diyne-linked dimeric peptoids by U-4CR/Glaser coupling*

Abstract



In this Chapter a synthesis of a library of ten 1,3-diyne-linked peptoids through an U-4CR followed by a copper-catalysed alkyne homocoupling (Glaser reaction) is described. The short and chemoselective reaction sequence allows generating diverse (pseudo-) dimeric peptoids. A combinatorial version allows the one-pot preparation of six compound libraries of homo- and heterodimers verified by ESI-MS and HPLC. In a preliminary evaluation, some compounds display moderate activity against the Gram-positive bacterium *Bacillus subtilis*.

* Part of this chapter has been published as Brauer, M. C. N.; Neves Filho, R. A. W.; Westermann, B.; Heinke, R.; Wessjohann, L. A. *Beilstein J. Org. Chem.* **2015**, *11*, 25.

4.1 Introduction

Dimerization is a re-occurring principle in nature to mediate or increase biological activity.[1] Many protein receptors dimerize upon activation and recruit their active form by this transformation. This process is mainly initiated by dimeric natural products or symmetric bivalent ligands, which can be of peptidic origin.[2,3] As an example, Harran and co-workers synthesized a low-molecular weight C_2-symmetric 1,3-diyne-linked peptide **1** which was able to mimic the function of Smac (Second mitochondria-derived activator of caspase) protein by triggering caspase 8 activation as well as apoptosis at concentrations as low as 100 *p*M. The higher activity of **1** in comparison to **2** is possibly related to the ability of **1** to interact simultaneously with the adjacent baculovirus inhibitory repeat (Bir) domains in the human X chromosome that encodes IAP (inhibitor of apoptosis)[4] (**Figure 4.1.1**). In another study, Chen and co-workers found a GLP-1R antagonist only because of an unexpected dimerization.[5] The dimer of *S*-adenosylmethionine is up to 13-fold more active than the monomer for promoting the binding of *Escherichia coli* methionine repressor to its operator DNA.[6]

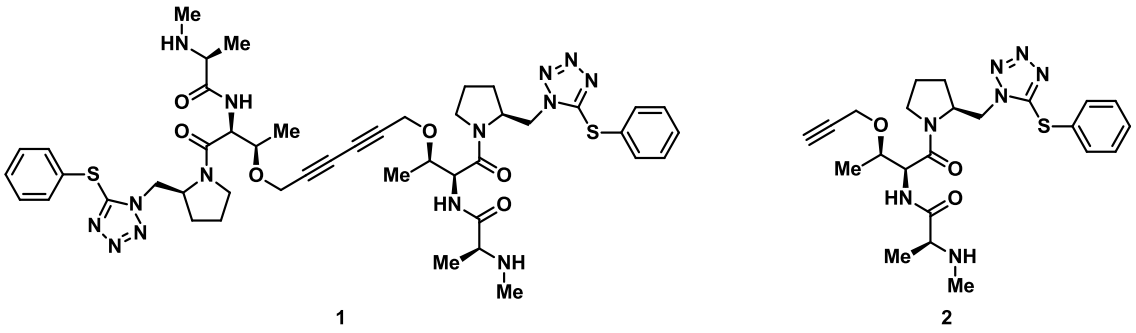
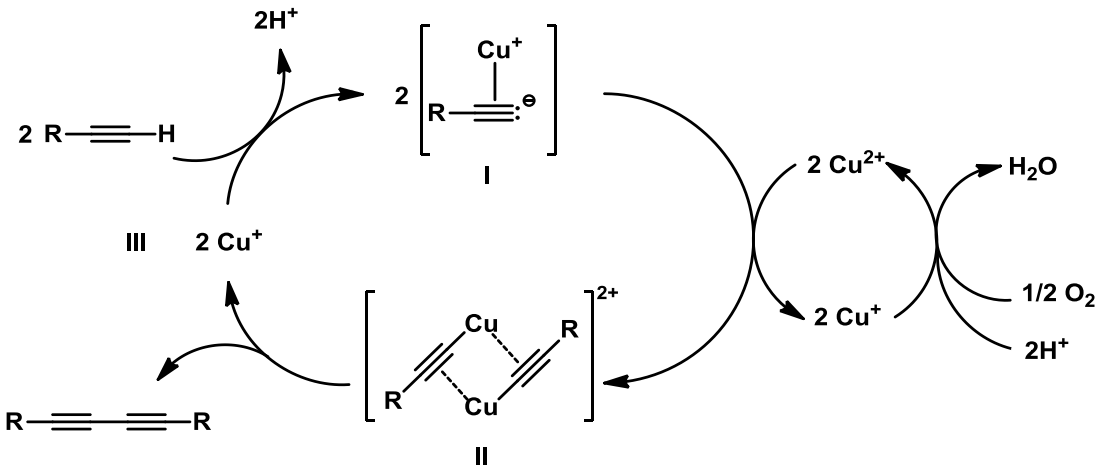


Figure 4.1.1 Apoptosis inducer C_2-symmetric 1,3-diyne-linked peptide **1** and its inactive monomer **2**.

Peptoids are compounds which are able to mimic peptide structures.[7-9] In addition to the mimetic function, these compounds also possess an enhanced resistance to proteolytic enzymes. The fastest method for synthesizing peptoids is the U-4CR.[10-12] In combination with other protocols, this reaction has been used in the synthesis of bioactive peptides and pseudopeptides, e.g., tubulysin mimetics,[13] julocrotine derivatives,[14] architecturally complex peptoid macrocycles,[15,16] building blocks for diversity-oriented synthesis,[17] and heterocyclic compounds.[18] Complex structures as well as simple Ugi products exhibit promising biological profiles, e.g., cytotoxicity,[13,19,20] fungicidal,[21,22] and antibacterial properties,[23-26] or inhibition of histone deacetylases.[27] The Ugi post modification strategy has also been employed in the synthesis of heterocyclic and natural product inspired compounds.[28-32]

4.2 Synthetic strategy

Several protocols of U-4CR followed by transition metal catalysed reactions have been published so far.[33] To the best of our knowledge, there are no reports about U-4CR/Glaser-type (homo-) coupling combinations. The Glaser coupling reaction is an oxidative condensation of mono-substituted acetylenes used to generate corresponding disubstituted butadiyne. It uses oxygen as oxidant in the presence of Cu(I) catalyst. In the proposed mechanism of the Glaser reaction the catalytic cycle begins with the formation of a copper (I) acetylide **I** from a copper salt and a terminal acetylene. Sequential oxidation of the acetylide **I** by a copper (II) salt is proposed to give an unstable dimeric copper (II) acetylide **II**. The decomposition of **II** forms the observed diacetylene product and completes the catalytic cycle by regeneration of copper (I) ions (**III**) (**Scheme 4.2.1**).[34]



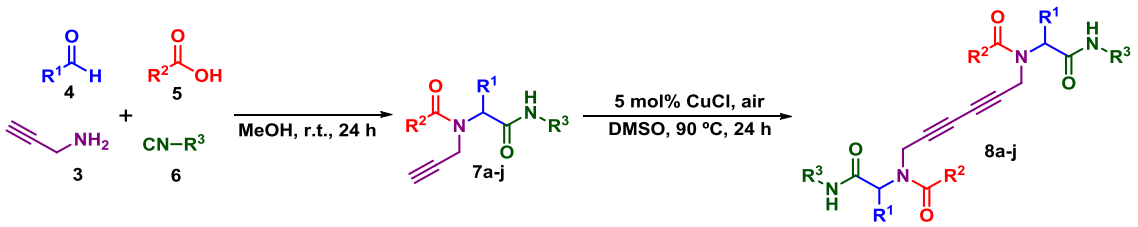
Scheme 4.2.1 Proposed mechanism for the catalytic oxidation coupling of acetylenes.[34]

We set out to develop a strategy based on an U-4CR/Glaser-type homocoupling sequence[35] (**Table 4.3.1**), in order to synthesize dimerized peptidomimetics with pharmacological properties through a step-efficient protocol that allows rapid access to highly diverse dimer libraries. When we compared the Glaser to other popular cross linking reactions, such as click reactions or amide bonds, the Glaser coupling allows the use of truly identical monomers. This decreased the number of steps for appropriate starting materials, and allows access to true homodimers in *sensu strictu*.

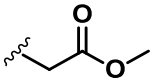
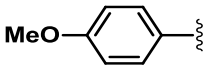
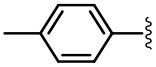
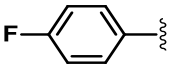
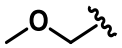
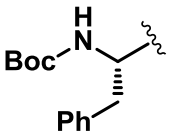
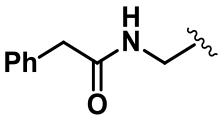
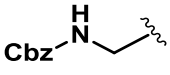
4.3 Synthesis of 1,3-diyne-linked dimeric peptoids by U-4CR/ Glaser couplings

In order to achieve the synthesis of monomers eligible for dimerizations by Glaser coupling, equimolar amounts of propargylamine (**3**), aldehyde **4**, carboxylic acid **5**, and isocyanides **6** were reacted in methanol at room temperature over 24 hours following well established Ugi-protocols.[12] After flash column chromathography, *N*-propargyl peptoids **7a-j** were obtained in good yields. The next step was the copper-catalysed homocoupling (Glaser reaction) of the terminal alkyne functions. Albeit several protocols are reported for this reaction, the CuCl-catalyzed method recently described by Jia and co-workers[35] was used to access the C_2-symmetric 1,3-dyines because it does not require expensive catalysts, ligands or additives (**Table 4.3.1**). The coupling reaction was clean without notable side product formation as confirmed by TLC analysis, and the desired peptoid dimers **8a-j** could be obtained in high to quantitative yields (**Table 4.3.1**). Aromatic, as well as aliphatic carboxylic acids and aldehydes have been successfully employed in both multicomponent and coupling reactions. When performing the reaction with methyl isocyanoacetate (**Table 4.3.1**, **entry b**), the desired products could be obtained in good yields with the ester group remaining untouched. It is important to note that different protecting groups can be used: Boc-, PhAc- and Cbz-protected peptoid derivatives (**Table 4.3.1**, **entries h-j**) reacted to the corresponding dimers **8h-j** without complications. The structure of the compounds **7a-j,** as well as **8a-j**, have been confirmed by ^{1}H, ^{13}C NMR spectra, and HRMS. In addition, HPLC analyses revealed that the adjacent stereocenter (**Table 4.3.1, entry h**, **compounds 7h/8h**) does not racemize under the reaction conditions of both the MCR and the Glaser coupling.

Table 4.3.1 Synthesis of compounds **7a-j** and **8a-j**.

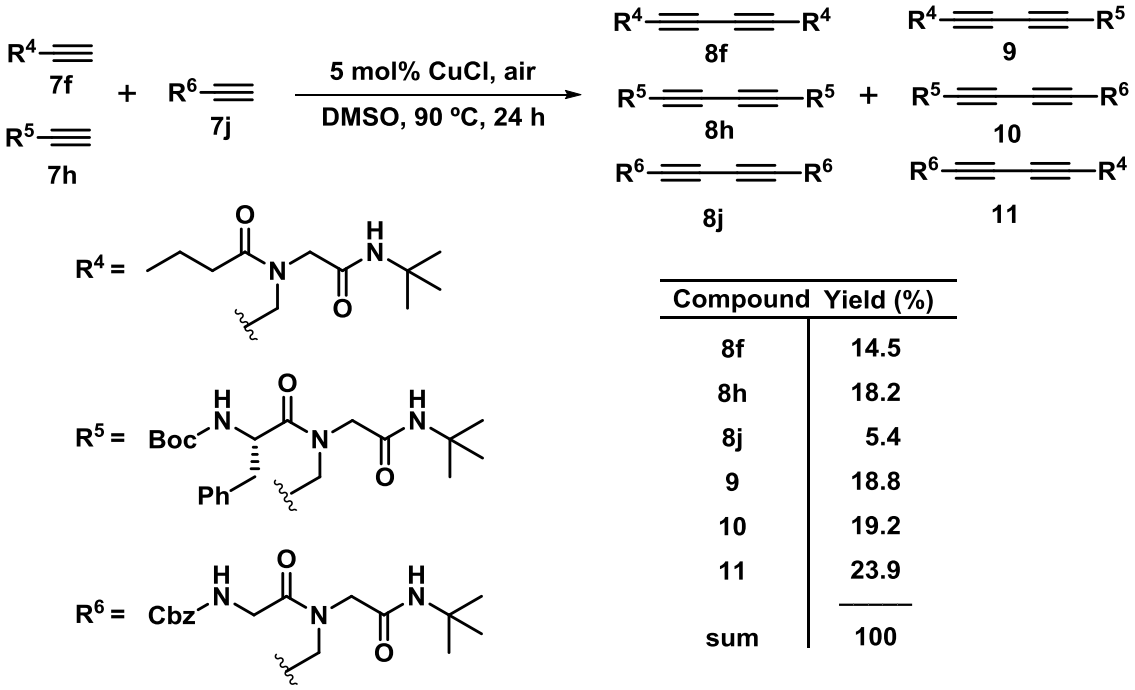


Entry	R^1	R^2	R^3	Monomer 7 Yield (%)	Dimer 8 Yield (%)
a		**Me**		**7a** 97	**8a** 88

b		**Me**		**7b** 95	**8b** 80
c		**Me**		**7c** 99	**8c** 99
d		**Ph**		**7d** 70	**8d** 91
e		***n*-C_3H_7**		**7e** 91	**8e** 99
f	**H**	***n*-C_3H_7**		**7f** 70	**8f** 99
g				**7g** 98	**8g** 97
h	**H**			**7h** 82	**8h** 99
i				**7i** 82	**8i** 96
j	**H**			**7j** 80	**8j** 99

[a] Yields after purification with silica gel column chromatography

Due to the high selectivity and high conversions found in the Glaser coupling step, our attention turned toward the development of a combinatorial version of the copper-catalysed homodimerization. In this strategy, two or more alkyne peptoids should coupled simultaneously in the same reaction vessel in order to generate small libraries of dimers. In contrast to parallel synthesis, the combinatorial approach easily generates non-symmetric dimers **9**, **10** and **11**. Thus, the peptoids **7f**, **7h** and **7j** were pooled to a Glaser reaction as depicted in **Scheme 4.3.1**.



Compound	Yield (%)
8f	14.5
8h	18.2
8j	5.4
9	18.8
10	19.2
11	23.9
sum	100

Scheme 4.3.1 Combinatorial Glaser coupling involving acetylenes **7f**, **7j** and **7h**.

The ESI-MS spectrum of the crude library confirmed the presence of all expected Glaser-coupled products **8f**, **8h**, **8j**, **9**, **10** and **11**. The HPLC-MS analysis of the composition resulted in six peaks with different retention times and intensities identified *via* MS as the six desired components of the library. **Figure 4.3.1** illustrates the expanded region of ESI-MS spectrum (positive mode) and HPLC chromatogram with the respective assignments of the obtained peaks**.** The analysis of the obtained spectra revealed that the non-symmetric dimers **9**, **10** and **11** are formed preferentially. The abundance differences observed are mostly lower than 2-fold, in one case up to ca. 4-fold. This is still acceptable for our initial bioactivity assays, as most screening setups cover several orders of magnitude of concentration anyhow. Therefore no further attempt to optimize for an equal product distribution was deemed necessary.

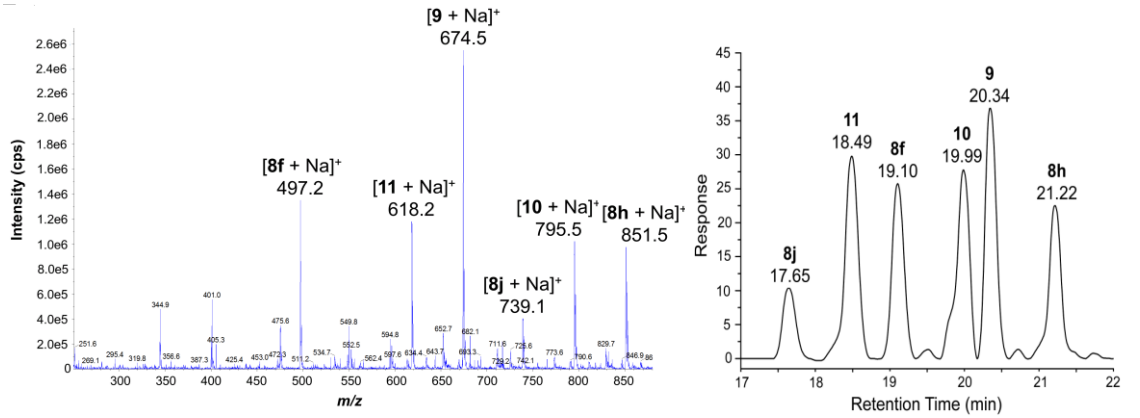


Figure 4.3.1. Expanded region of ESI-MS spectrum (positive mode) and HPLC of crude mixed library of 1,3-dyine peptoids (**8f**, **8h**, **8j**, **9**, **10** and **11**) produced by a combinatorial Glaser coupling of three different monomers (see **Scheme 4.3.1**).

4.4 Biological studies[a]

To gain insight into the antibiotic potential of the products, the single compound dimers **8a-j** were subjected to a preliminary evaluation against *Bacillus subtilis* (**Figure 4.4.1**).[36-38] The active compounds inhibited the bacteria growth in a range from 29 to 44% at 1μM concentration, while erythromycin as the standard led to a growth inhibition of 71% under the same assay conditions. The most active compounds were **8b**, **8d** and **8h** which displayed inhibition rates (%) of 44.0±26.7, 44.0±21.8 and 43.9±23.0. Interestingly, compounds **8c** and **8f** showed almost no effect on bacterial growth, i.e. 1.3± 5.1% and 2.3± 13.5%, respectively. The diyne core fulfils its function as linker and spacer without itself negatively (or positively) influencing the specific activity of the active ligand moieties.

[a] The antibacterial activity assay was performed by Dr. R. Heinke.

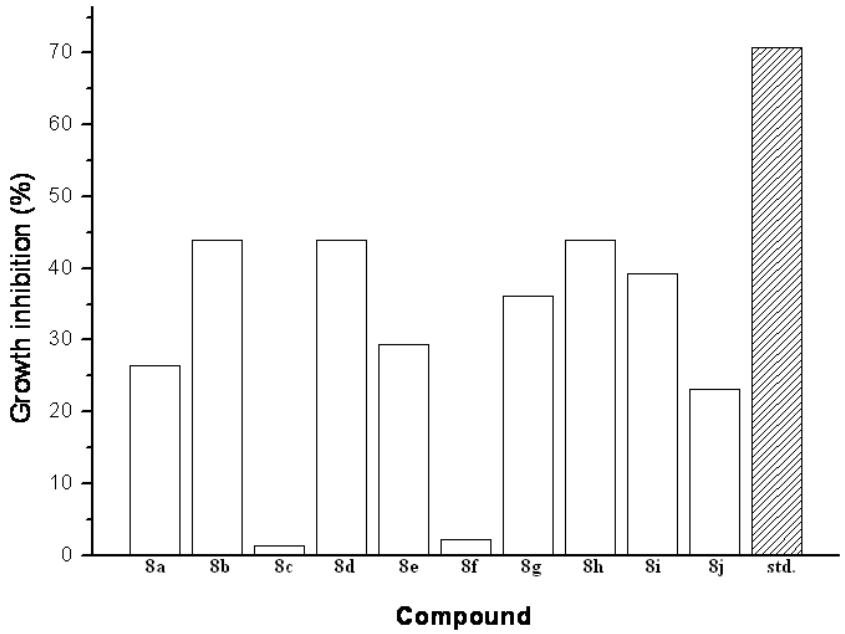


Figure 4.4.1 Growth inhibition of *Bacillus subtilis* by compounds 8a-j at 1 µM (15h), and standard erythromycin at 1 µM (15h).

4.5 Conclusions

In summary, a reliable sequential U-4CR/Glaser coupling approach towards the synthesis of 1,3-diyne-linked peptoids has been developed. The strategy resulted in a library consisting of ten homodimers in good yields. The post-MCR copper-catalysed homocoupling reaction has also been performed in a combinatorial fashion combining three monomers. This procedure resulted in a mixed library containing six 1,3-diyne-linked symmetric and non-symmetric peptoids as confirmed by ESI-MS and HPLC experiments. Some of the synthesized compounds **8a-j** displayed growth inhibition activity against *Bacillus subtilis* in a preliminary assay.

4.6 Experimental part

General remarks

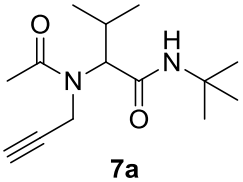
All commercially available chemicals were used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz) spectra were recorded in $CDCl_3$ solutions on a Varian Mercury spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C), respectively. Chemical shifts (δ) are reported in ppm relative to TMS (^{1}H-NMR) and to residual $CDCl_3$ signal (^{13}C-NMR). High resolution ESI mass spectra were obtained from a Bruker Apex III Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer equipped with an Infinity™ cell, a 7.0 Tesla superconducting magnet, an RF-only hexapole ion guide and an external electrospray ion source (Agilent, off axis spray). ESI-MS was recorded on a Finnigan TSQ 7000, LC-Tech Ultra Plus pumps, Linear UV-VIS 200 detector, Sepserve Ultrasep ES RP-18 5µm 1×100 mm column, flow 70µL min^{-1}.

Flash column chromatography was carried out using Merck silica gel 60 (0.040-0.063 mm) and analytical thin layer (TLC) was performed using Merck silica gel 60 F254 aluminium sheets. HPLC experiments were performed in an Agilent 1100 series equipped with a column SNr. 176: YMC pack 150 x 4.6 LD 102 Å 5 µm ODS-A and UV detector (200-600 nm). The employed gradient was MeOH 0.1% formic acid : H_2O 0.1% formic acid 1 mL / min (5 µL), MeOH 2% > 20 min > 100% (5 min) at 25ºC. Please note that spectra of *N*-alkyl-amides (peptoids) like Ugi products display double signal sets in NMR due to interconvertible isomers with *s*-cis and *s*-trans amide bonds. Depending on substitution pattern, solvent and temperature, the equilibrium between these forms is shifted and may lead to broadened or doubled peaks of varied intensity.

General procedure for the synthesis of compounds 7a-j

To a stirred solution of aldehyde **4** (2.5 mmol) in methanol (2.5 mL) propargylamine (**3**) (0.14 g, 0.16 mL, 2.5 mmol) was added. After 30 minutes, carboxylic acid **5** (2.5 mmol) and isocyanide **6** (2.5 mmol) were added. The contents were stirred for 24 hours. The solvent was concentrated under reduced pressure in a rotavap. The crude material was purified by isocratic silica gel column chromatography to afford the pure product. The same solvent system used for R_f value measurements was applied for performing flash column chromatography.

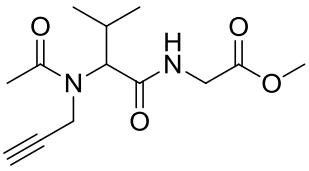
N^2-Acetyl-*N*-*tert*-butyl-N^2-prop-2-yn-1-ylvalinamide (7a).



7a

Purified by silica gel column chromatography. R_f 0.59 (EtOAc / hexane 3:7). White solid. Yield: 97%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.26 (s, 1H), 4.36-4.30 (m, 2H), 3.85 and 3.82 (2d, *J* = 2.4 Hz, 1H), 2.15 (t, *J* = 2.4 Hz, 1H), 2.06 (s, 3H), 2.04-1.95 (m, 1H), 1.10 (s, 9H), 0.74 (d, *J* = 4.4 Hz, 3H), 0.69 (d, *J* = 4.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.49, 169.10, 79.18, 72.02, 62.14, 50.76, 33.73, 28.11, 26.82, 21.65, 18.94. HRMS (ESI-pos) m/z calcd for $C_{14}H_{24}N_2NaO_2$ $(M+Na)^+$ 275.1735, found 275.1729.

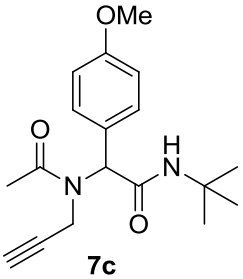
Methyl *N*-acetyl-*N*-(prop-2-yn-1-yl)valylglycinate (7b).



7b

Purified by silica gel column chromatography. R_f 0.15 (EtOAc / hexane 1:1). Yellowish dense oil. Yield: 95%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.37 (brs, 1H), 4.61 and 4.58 (2s, 1H), 4.31 and 3.89 (2d, *J* = 2.4 Hz, 2H), 3.88-3.73 (m, 2H), 3.57 (s, 3H), 2.24 (t, *J* = 2.4 Hz, 1H), 2.14 (m, 4H), 0.80-0.84 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 172.09, 170.50, 169.69, 79.00, 72.35, 61.68, 51.78, 40.54, 34.10, 26.64, 21.69, 19.07, 19.04. HRMS (ESI-pos) m/z calcd for $C_{13}H_{20}N_2NaO_4$ $(M+Na)^+$ 291.1321, found 291.1315.

2-[Acetyl(2-propyn-1-yl)amino]-2-(4-methoxyphenyl)-*N*-(2-methyl-2-propanyl)acetamide (7c).

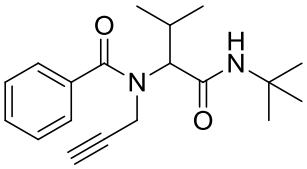


7c

Purified by silica gel column chromatography. R_f 0.23 (EtOAc / hexane 1:1). Yellowish solid. Yield: 99%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.29 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.15 (s, 1H), 6.00 (brs, 1H), 4.08 (d, *J* = 2.4 Hz, 2H), 3.81 (s, 3H), 2.26 (s, 3H), 2.02 (t, *J* = 2.4 Hz, 1H), 1.36 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.50, 169.09, 159.45, 130.65, 126.97, 113.93, 79.49, 71.21, 59.70, 55.10, 51.48, 35.51, 28.46, 22.01. HRMS (ESI-pos) m/z calcd for $C_{18}H_{24}N_2NaO_3$ $(M+Na)^+$ 339.1685, found 339.1679.

***N*-{3-Methyl-1-[(2-methyl-2-propanyl)amino]-1-oxo-2-butanyl}-*N*-(2-propyn-1-yl)**

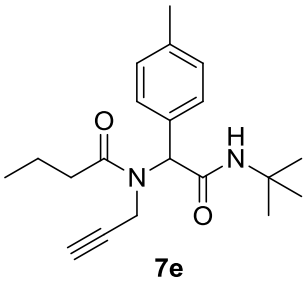
benzamide (7d).



7d

Purified by silica gel column chromatography. R_f 0.56 (EtOAc / hexane 1:4). Yellowish solid. Yield: 70%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.54 (d, *J* = 6.4 Hz, 2H), 7.45-7.37 (m, 3H), 6.58 (brs, 1H), 4.30-4.21 (m, 2H), 3.92 and 3.87 (2s, 1H), 2.63-2.46 (m, 1H), 2.23 and 2.18 (2s, 1H), 1.31 (s, 9H), 1.04-0.99 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 173.08, 169.04, 135.38, 130.15, 128.24, 126.77, 79.57, 72.52, 66.22, 50.87, 37.32, 28.38, 26.50, 19.51. HRMS (ESI-pos) m/z calcd for $C_{19}H_{26}N_2NaO_2$ $(M+Na)^+$ 337.1892, found 337.1886.

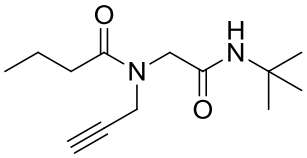
***N*-{1-(4-Methylphenyl)-2-[(2-methyl-2-propanyl)amino]-2-oxoethyl}-*N*-(2-propyn-1-yl)butanamide (7e).**



7e

Purified by silica gel column chromatography. R_f 0.16 (EtOAc / hexane 1:4). Yellowish solid. Yield: 91%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.17 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.07 (s, 1H), 6.06 (s, 1H), 3.98 (s, 2H), 2.41 (t, *J* = 6.4 Hz, 2H), 2.26 (s, 3H), 1.96 (s, 1H), 1.67-1.54 (m, *J* = 6.4 Hz, 2H), 1.27 (s, 9H), 0.86 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 173.40, 168.99, 137.36, 131.85, 128.94, 128.78, 79.55, 70.93, 60.15, 50.85, 34.93, 34.62, 28.11, 20.65, 17.87, 13.28. HRMS (ESI-pos) m/z calcd for $C_{20}H_{28}N_2NaO_2$ $(M+Na)^+$ 351.2048, found 351.2042.

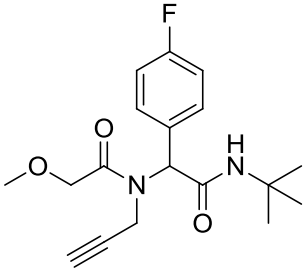
***N*-{2-[(2-Methyl-2-propanyl)amino]-2-oxoethyl}-*N*-(2-propyn-1-yl)butanamide (7f).**



7f

Purified by silica gel column chromatography. R_f 0.34 (EtOAc / hexane 1:1). Yellowish crystalline solid. Yield: 70%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.10 and 6.06 (2s, 1H), 4.29 and 4.19 (2s, 2H), 3.98 (s, 2H), 2.45 and 2.25 (2t, *J* = 6.4 Hz, 2H), 2.43 and 2.31 (2t, *J* = 2.4 Hz, 1H), 1.64-1.51 (m, 2H), 1.24 and 1.20 (2s, 9H), 0.88-0.82 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 173.27, 173.14, 167.71, 166.96, 78.81, 77.88, 73.02, 72.60, 51.42, 50.94, 50.42, 38.59, 36.05, 34.68, 34.55, 28.37, 18.15, 18.03, 13.57, 13.54. HRMS (ESI-pos) m/z calcdfor $C_{13}H_{22}N_2NaO_2$ $(M+Na)^+$ 261.1579, found 261.1573.

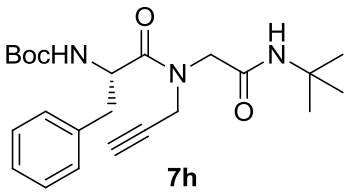
***N*-{1-(4-Fluorophenyl)-2-[(2-methyl-2-propanyl)amino]-2-oxoethyl}-2-methoxy-*N*-(2-propyn-1-yl)acetamide (7g).**



7g

Purified by silica gel column chromatography. R_f 0.25 (EtOAc / hexane 1:1). Yellowish crystalline solid. Yield: 98%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.36 (dd, J_{H-H} = 6.8 Hz, J_{H-F} = 5.2 Hz, 2H), 7.07-7.03 (m, 2H), 6.26-6.15 (m, 2H), 4.30 (s, 2H), 4.20-4.06 (m, 2H), 3.42 (s, 3H), 2.07 (t, *J* = 2.4 Hz, 1H), 1.36 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 169.99, 168.18, 164.05, 160.77, 131.15, 131.05, 130.35, 130.32, 115.56, 115.27, 78.62, 71.82, 70.76, 59.45, 58.90, 51.48, 33.73, 28.26. HRMS (ESI-pos) m/z calcd for $C_{18}H_{23}FN_2NaO_3$ $(M+Na)^+$ 357.1590, found 357.1585.

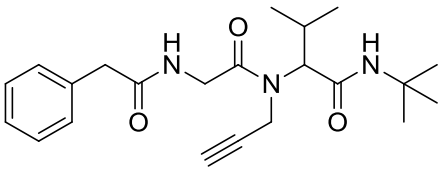
***N*-{[(2-Methyl-2-propanyl)oxy]carbonyl}-L-phenylalanyl-*N*-(2-methyl-2-propanyl)-*N*^{2}-2-propyn-1-ylglycinamide (7h).**



7h

Purified by silica gel column chromatography. R_f 0.34 (EtOAc / hexane 3:7). Yellowish solid. Yield: 98%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.18-7.09 (m, 5H), 6.87 and 6.28 (2s, 1H), 5.80 and 5.55 (2d, *J* = 8.0 Hz, 1H), 4.72 and 4.47 (2q, *J* = 6.4 Hz, 1H), 4.35-3.58 (set of signals, 4H), 3.07-2.77 (m, 2H), 2.31 and 2.17 (2s, 1H), 1.26-1.21 (m, 18H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 172.06, 171.86, 166.93, 166.45, 155.17, 154.96, 135.87, 135.65, 129.05, 128.12, 128.05, 126.58, 126.48, 79.28, 79.22, 77.68, 77.42, 73.65, 72.48, 51.69, 51.47, 51.15, 50.83, 50.21, 49.87, 38.08, 37.84, 35.52, 28.23, 28.16, 27.84. HRMS (ESI-pos) m/z calcd for $C_{23}H_{33}N_3O_4$ $(M+Na)^+$ 438.2369, found 438.2363.

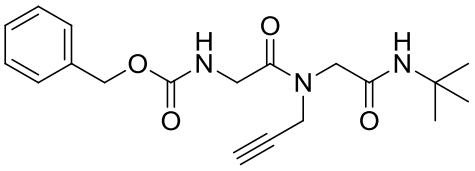
_N_-(Phenylacetyl)glycyl-_N_-(2-methyl-2-propanyl)-_N_^{2}-2-propyn-1-ylvalinamide (7i).



7i

Purified by silica gel column chromatography. R_f 0.30 (EtOAc / hexane 2:3). Slightly yellow solid. Yield: 82%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.77 and 6.77 (2t, *J* = 4.4 Hz,1H), 7.36-7.23 (m, 5H), 6.01 (s, 1H), 4.53 and 4.05 (2d, *J* = 2.4 Hz, 2H), 4.49-3.76 (m, 3H), 3.61 and 3.55 (2s, 2H), 2.35 and 2.14 (2t, *J* = 2.4 Hz, 1H), 2.30-2.21 (m, 1H), 1.29 and 1.27 (2s, 9H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.36, 170.56, 169.57, 168.65, 168.31, 167.76, 134.37, 134.23, 128.98, 128.88, 128.44, 126.82, 126.80, 79.48, 78.20, 73.08, 70.26, 65.86, 62.97, 51.03, 50.97, 42.93, 42.63, 41.40, 41.14, 32.34, 31.86, 28.09, 28.02, 26.74, 19.15, 18.96, 18.88. HRMS (ESI-pos) m/z calcd for $C_{22}H_{31}N_3NaO_3$ $(M+Na)^+$ 408.2263, found 408.2258.

_N_-[(Benzyloxy)carbonyl]glycyl-_N_-(2-methyl-2-propanyl)-_N_^{2}-2-propyn-1-ylglycinamide (7j)



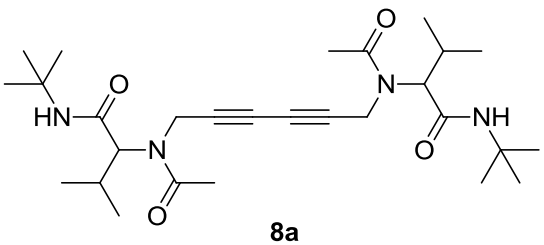
7j

Purified by silica gel column chromatography. R_f 0.19 (EtOAc / hexane 1:1). Yellowish solid. Yield: 80%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.28-7.25 (m, 5H), 6.36 and 6.16 (2s, 1H), 5.95 (s, 1H), 5.04 (d, *J* = 8.0 Hz, 2H), 4.23 and 3.92 (2s, 2H), 4.10 and 3.97 (2s, 2H), 4.05 and 4.03 (2s, 2H), 2.36 and 2.26 (2s, 1H), 1.30 and 1.27 (2s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 169.13, 167.15, 166.25, 156.40, 136.32, 128.49, 128.12, 127.96, 78.22, 74.12, 73.27, 66.89, 51.83, 51.46, 50.26, 49.66, 42.65, 42.58, 37.86, 36.37, 28.63, 28.60. HRMS (ESI-pos) m/z calcd for $C_{19}H_{25}N_3NaO_4$ $(M+Na)^+$ 382.1743, found 382.1737.

General procedure for the synthesis of compounds 8a-j

In a 10 mL round botton flask, to stirred solution of the suitable alkyne **7** (0.25 mmol) in absolute DMSO (0.5 mL), CuCl (1.3 mg, 0,013 mmol / 5 mol%) was added. The contents were stirred at 90 ºC under air atmosphere. After 24 h the reaction mixture was diluted with ethyl acetate (10 mL) and filtered through a Celite plug. The solvent was removed under reduced pressure in a rotavap. The crude material was purified by column chromatography to afford the pure product. The same solvent system used for performing the column chromatography was employed for the R_f values measurements.

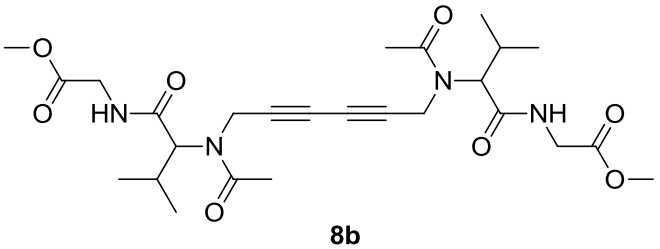
2,2'-[Hexa-2,4-diyne-1,6-diylbis(acetylimino)]bis(_N-tert_-butyl-3-methylbutanamide) (8a) (mixture of diastereoisomers).



8a

Purified by silica gel column chromatography. R_f 0.49 (EtOAc). White solid. Yield: 88%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.91 (s, 4H), 4.54-4.41 (m, 8H), 4.14 and 4.09 (2s, 4H), 2.24 (s, 12H), 2.20-2.15 (m, 4H), 1.31 (s, 36H), 0.94 (d, *J* = 6.8 Hz, 12H), 0.86 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.91, 169.11, 74.36, 68.00, 51.38, 42.63, 34.71, 28.51, 26.95, 22.04, 19.34, 19.01. HRMS (ESI-pos) m/z calcd for $C_{28}H_{46}N_4NaO_4$ $(M+Na)^+$ 525.3417, found 525.3411.

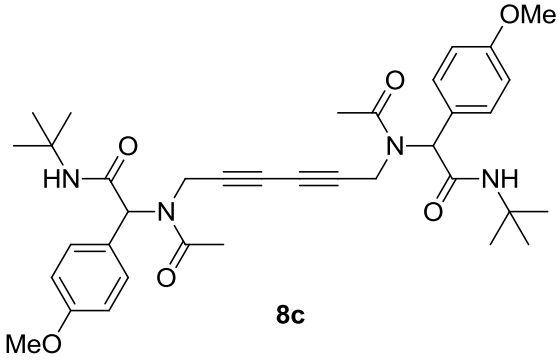
Dimethyl 6,13-diacetyl-4,15-dioxo-5,14-di(propan-2-yl)-3,6,13,16-tetraazaoctadeca-8,10-diyne-1,18-dioate (8b) (mixture of diastereoisomers).



8b

Purified by silica gel column chromatography. R_f 0.29 (EtOAc / MeOH 19:1). Colorless semisolid. Yield: 80%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.79 (t, *J* = 5.2 Hz, 4H), 4.65-4.06 (m, 12H), 3.95 (d, *J* = 5.2 Hz, 8H), 3.73 (s, 12H), 2.27 (m, 16H), 0.99-0.95 (m, 24H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 172.43, 170.56, 169.84, 74.29, 68.17, 68.16, 62.27, 58.27, 52.29, 41.06, 40.87, 35.12, 31.04, 26.70, 26.68, 22.08, 19.38, 19.22. HRMS (ESI-pos) m/z calcd for $C_{26}H_{38}N_4NaO_8$ $(M+Na)^+$ 557.2587, found 557.2581.

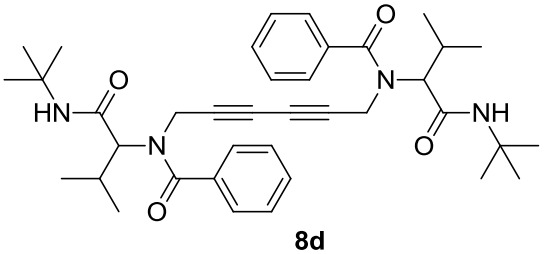
2,2'-[Hexa-2,4-diyne-1,6-diylbis(acetylimino)]bis[*N*-*tert*-butyl-2-(4-methoxyphenyl) acetamide] (8c) (mixture of diastereoisomers)



8c

Purified by silica gel column chromatography. R_f 0.28 (EtOAc). Colorless semisolid. Yield: 99%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.28-7.20 (m, 8H), 6.95-6.81 (m, 8H), 6.08 (s, 4H), 5.83 (brs, 4H), 4.09 (m, 8H), 3.77 and 3.75 (2s, 12H), 2.19-2.16 (m, 12H), 1.34-1.31 (m, 36H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.44, 169.50, 169.31, 169.11, 159.71, 159.28, 130.71, 130.66, 128.41, 126.75, 114.18, 74.25, 67.07, 67.01, 59.28, 56.27, 55.28, 55.23, 51.68, 51.62, 42.62, 36.26, 28.59, 28.52, 23.20, 22.14, 22.12. HRMS (ESI-pos) m/z calcd for $C_{36}H_{46}N_4NaO_6$ $(M+Na)^+$ 653.3315, found 653.3309.

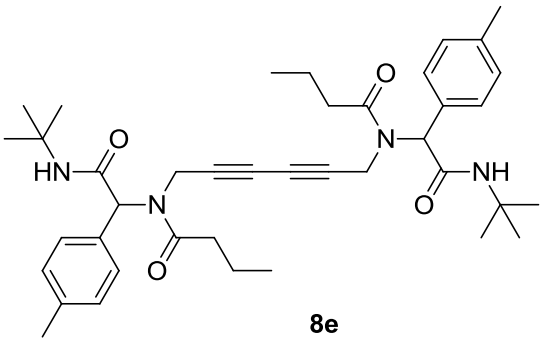
***N*,*N*'-Hexa-2,4-diyne-1,6-diylbis{*N*-[1-(*tert*-butylamino)-3-methyl-1-oxobutan-2-yl] benzamide} (8d) (mixture of diastereoisomers).**



8d

Purified by silica gel column chromatography. R_f 0.34 (EtOAc / hexane 3:7). White solid. Yield: 91%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.53-7.42 (m, 20H), 6.47 (brs, 4H), 4.45-4.32 (m, 8H), 4.03-3.99 (m, 4H), 2.59-2.42 (m, 4H), 1.35 (s, 36H), 1.08-1.04 (m, 24H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 173.35, 169.07, 135.39, 130.51, 128.60, 126.91, 74.85, 68.36, 65.66, 51.28, 37.75, 28.65, 26.78, 19.71, 19.50. HRMS (ESI-pos) m/z calcd for $C_{38}H_{50}N_4NaO_4$ $(M+Na)^+$ 649.3730, found 649.3724.

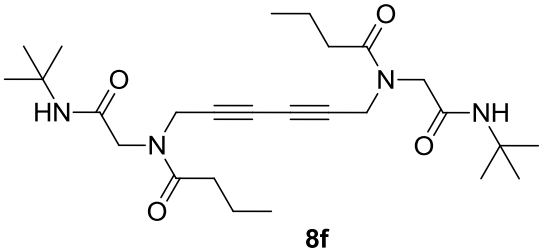
_N_,_N_'-Hexa-2,4-diyne-1,6-diylbis{_N_-[2-(*tert*-butylamino)-1-(4-methylphenyl)-2-oxo ethyl]butanamide} (8e) (mixture of diastereoisomers).



8e

Purified by column chromatography. R_f 0.52 (EtOAc / hexane 1:1). Colorless semisolid. Yield: 99%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.28-7.16 (m, >16H), 6.09 (s, 4H), 5.79 (s, 4H), 4.12 (s, 8H), 2.43 (t, J = 6.4 Hz, 8H), 2.34 and 2.32 (2s, 12H), 1.74-1.69 (m, 8H), 1.34 and 1.28 (2s, 36H), 0.98 and 0.89 (2t, J = 6.4 Hz, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 173.90, 172.28, 169.07, 138.31, 135.85, 131.84, 129.54, 129.43, 129.27, 127.06, 74.44, 67.11, 60.30, 51.67, 35.72, 35.50, 28.60, 28.51, 21.16, 21.12, 18.96, 18.46, 13.85, 13.69. HRMS (ESI-pos) m/z calcd for $C_{40}H_{54}N_4NaO_4$ $(M+Na)^+$ 677.4043, found 677.4037.

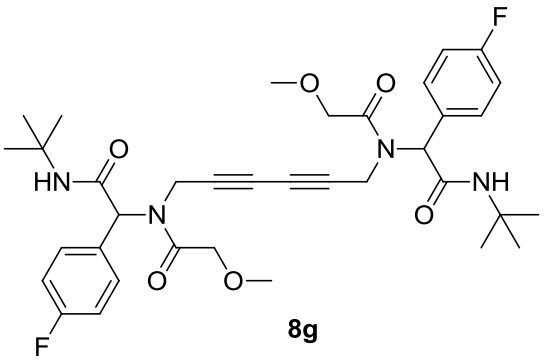
_N_,_N_'-Hexa-2,4-diyne-1,6-diylbis{_N_-[2-(*tert*-butylamino)-2-oxoethyl]butanamide} (8f)



8f

Purified by column chromatography. R_f 0.38 (EtOAc / hexane 4:1). White solid. Yield: 99%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.82 and 6.10 (2s, 2H), 4.29-4.28 (m, 4H), 4.01-3.91 (m, 4H), 2.42-2.39 and 1.72-1.64 (2m, 4H), 2.31-2.22 (m, 4H), 1.37-1.32 (m, 18H), 1.01-0.93 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 173.54, 173.36, 167.78, 166.77, 166.63, 74.53, 73.74, 73.49, 72.95, 68.76, 68.54, 68.18, 67.81, 51.87, 51.69, 51.59, 51.34, 51.27, 50.68, 50.52, 43.75, 39.44, 39.36, 38.22, 36.93, 36.14, 34.84, 34.83, 28.62, 18.41, 18.27, 13.90, 13.82, 13.78, 13.71. HRMS (ESI-pos) m/z calcd for $C_{26}H_{42}N_4NaO_4$ $(M+Na)^+$ 497.3104, found 497.3098.

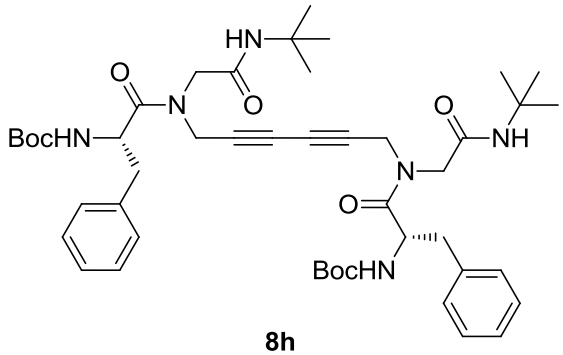
_N_,_N_'-Hexa-2,4-diyne-1,6-diylbis{_N_-[2-(*tert*-butylamino)-1-(4-fluorophenyl)-2-oxo ethyl]-2-methoxyacetamide} (8g) (mixture of diastereoisomers)



8g

Purified by silica gel column chromatography. R_f 0.42 (EtOAc). Colorless semisolid. Yield: 97%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.38-7.29 (m, >8H), 7.08-7.04 (m, 8H), 6.11 (s, 4H), 5.83 (s, 4H), 4.22-4.18 (m, 16H), 3.44 (s, 12H), 1.39-1.29 (m, 36H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 170.03, 168.24, 164.00, 161.53, 131.34, 130.20, 130.17, 115.91, 115.70, 71.18, 59.39, 59.26, 51.86, 42.61, 34.60, 28.53. HRMS (ESI-pos) m/z calcd for $C_{36}H_{44}F_2N_4NaO_6$ $(M+Na)^+$ 689.3127, found 689.3121.

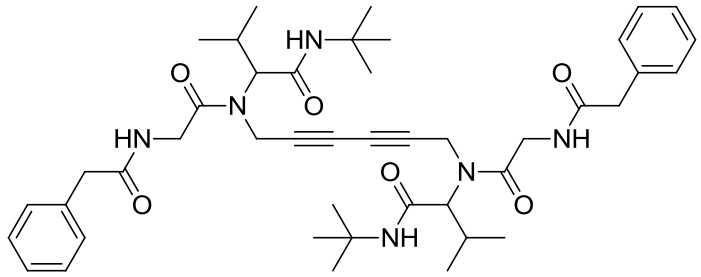
***tert*-Butyl {(6*S*,17*S*)-6-benzyl-8,15-bis[2-(*tert*-butylamino)-2-oxoethyl]-2,2-dimethyl-4,7,16-trioxo-18-phenyl-3-oxa-5,8,15-triazaoctadeca-10,12-diyn-17-yl}carbamate (8h)**



8h

Purified by silica gel column chromatography. R_f 0.34 (EtOAc). Colorless semisolid. Yield: 99%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.32-7.15 (m, >10H), 6.65 and 6.62 (2s, 1H), 6.07 and 6.03 (2s, 1H), 5.40-5.35 and 5.24-5.20 (2m, 2H), 4.77-4.71 (m, 1H), 4.51-4.43 (m, 4H), 4.24-4.07 (m, 2H), 3.74-3.63 (m, 2H), 3.46-3.36 (m, 1H), 3.14-2.85 (m, 4H), 1.38-1.32 (m, 36H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 172.38, 172.21, 167.04, 166.97, 166.41, 166.33, 155.56, 155.28, 135.85, 135.51, 135.48, 129.35, 128.77, 128.74, 128.68, 127.39, 127.17, 80.25, 80.21, 80.06, 74.09, 72.95, 72.03, 69.65, 68.52, 68.03, 51.99, 51.77, 51.41, 50.80, 50.64, 39.02, 38.67, 38.54, 36.42, 28.65, 28.56, 28.22. HRMS (ESI-pos) m/z calcd for $C_{46}H_{64}N_6NaO_8$ $(M+Na)^+$ 851.4683, found 851.4678.

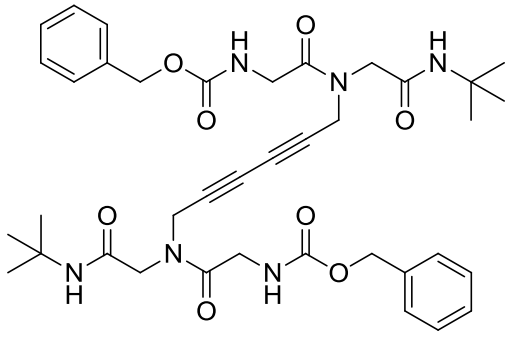
2,2'-[Hexa-2,4-diyne-1,6-diylbis({[(phenylacetyl)amino]acetyl}imino)]bis(*N*-*tert*-butyl-3-methylbutanamide) (8i) (mixture of diastereoisomers)



8i

Purified by silica gel column chromatography. R_f 0.41 (EtOAc / hexane 4:1). Colorless semisolid. Yield: 96%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.68 and 8.42 (2brs, 4H), 7.39-7.20 (m, >20H), 6.45 and 5.66 (2s, 4H), 4.72-4.03 (m, 14H), 4.00-3.75 (m, 2H), 3.63-3.45 (m, 8H), 2.98 (s, 4H), 2.29-2.14 (m, 4H), 1.30-1.25 (m, 36H), 0.96-0.80 (m, 24H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 171.88, 171.68, 170.88, 170.83, 170.13, 169.96, 169.57, 168.63, 168.56, 168.42, 168.06, 168.03, 135.25, 135.13, 134.51, 134.41, 129.50, 129.34, 128.99, 128.91, 128.64, 128.52, 127.41, 127.36, 126.91, 126.89, 75.70, 75.08, 73.82, 72.14, 69.40, 68.66, 66.53, 66.10, 63.26, 51.67, 51.61, 51.53, 51.41, 43.52, 43.24, 43.13, 42.87, 41.92, 41.76, 41.71, 41.65, 33.16, 33.09, 33.00, 32.72, 28.68, 28.52, 28.48, 27.10, 20.01, 19.30, 19.27, 19.18. HRMS (ESI-pos) m/z calcd for $C_{44}H_{60}N_6NaO_6$ $(M+Na)^+$ 791.4472, found 791.4467.

Benzyl {7,14-bis[2-(*tert*-butylamino)-2-oxoethyl]-3,6,15-trioxo-1-phenyl-2-oxa-4,7,14-triazahexadeca-9,11-diyn-16-yl}carbamate (8j)



8j

Purified by silica gel column chromatography. R_f 0.43 (EtOAc). Yellowish semisolid. Yield: 99%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.37-7.28 (m, 10H), 6.36 and 6.11 (2s, 2H), 6.19 and 5.95 (2s, 2H), 5.86-5.80 (m, 2H), 5.11-5.08 (m, 2H), 4.35-3.89 (m, 12H), 1.34-1.31 (m, 18H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 169.25, 169.09, 168.87, 166.87, 165.88, 165.80, 156.34, 136.27, 128.52, 128.20, 128.15, 127.98, 74.40, 73.51, 72.92, 72.01, 69.47, 69.11, 68.39, 68.22, 67.01, 66.96, 51.97, 51.92, 50.08, 49.56, 42.61, 38.37, 36.81, 28.64. HRMS (ESI-pos) m/z calcd for $C_{38}H_{48}N_6NaO_8$ $(M+Na)^+$ 739.3431, found 739.3426.

Combinatorial experiment

In a 10 mL round bottom flask, to stirred solution of the alkynes **7f**, **7j** and **7h** (0.25 mmol each), CuCl (0.07 mmol / 5 mol%) was added. The contents were stirred at 90 ºC under air atmosphere. After 24 h the reaction mixture was diluted with ethyl acetate (10 mL) and filtered through a Celite plug. The solvent was removed under reduced pressure. The crude material analyzed by HPLC.

Biological activity assay[36-38]

The antibacterial activity against *Bacillus subtilis* was determined with a fluorescence based antibacterial growth inhibition assay. The fluorescence was measured on a microtiter plate reader GENios Pro (Fa. Tecan, excitation, 510 nm; emission, 535 nm). The *Bacillus subtilis* strain 168 (P_{AbrB}-IYFP)[34] was maintained on TY (tryptone-yeast extract) medium supplemented with 1 % Bacto-tryptone, 0.5 % Bacto-yeast extract, 1 % NaCl and chloramphenicol (5 µg.ml^{-1}). Details of the assay are published.[36,37]

Table 4.6.1 Result of the antibacterial activity tests

Compound	Growth inhibition[a] in % at 1 µM[d]	Standard Deviation[d]	Growth inhibition in % at 10 µM[d]	Standard Deviation[d]
8a	26.4	18.9	40.9	24.5
8b	44.0	26.7	52.3	27.8
8c	-	-	23.7	12.7
8d	44.0	21.8	54.9	19.1
8e	29.3	11.4	34.1	16.2
8f	inactive	Inactive	Inactive	Inactive
8g	36.2	15.5	41.2	17.1
8h	43.9	23.0	49.9	23.5
8i	39.2	12.6	44.3	10.4
8j	23.2	17.0	57.6	26.5
Std.[b]	70.8	4.5	NP[c]	NP[c]

[a]Measured after 15h
[b] Erythromycin
[c] Not performed.
[d] Mean values of two trials involving 3 replicates

4.7 References

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Attachments

Figure S1 ^{1}H NMR spectrum of *N-tert*-Butyl-3-methyl-2-(11-oxodibenzo[*b*,*f*][1,4]oxazepin-10(11*H*)-yl)butanamide (**1a**, Chapter 2)

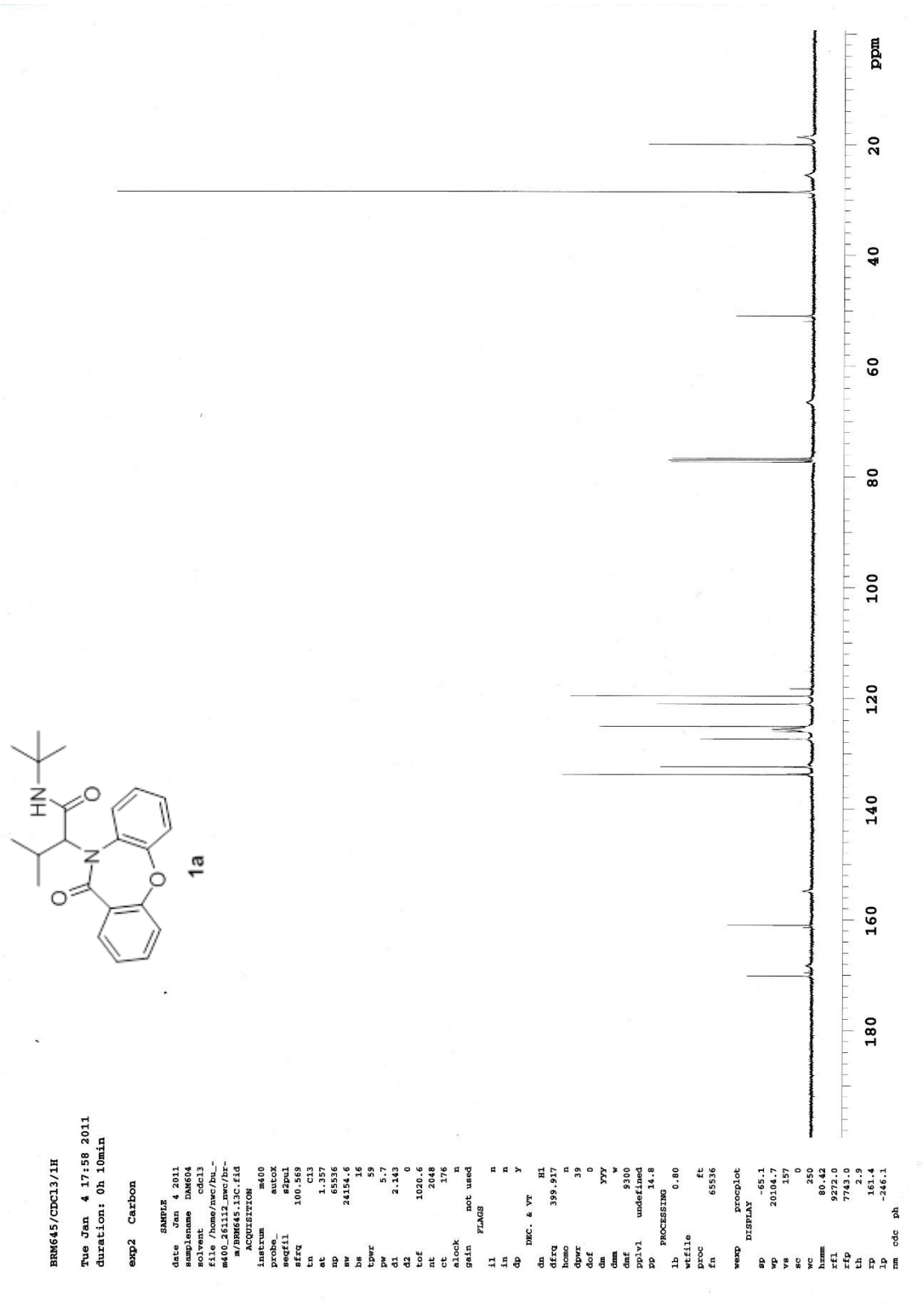

Figure S2 ^{13}C NMR spectrum of *N-tert*-Butyl-3-methyl-2-(11-oxodibenzo[*b*,*f*][1,4]oxazepin-10(11*H*)-yl)butanamide (**1a**, Chapter 2)

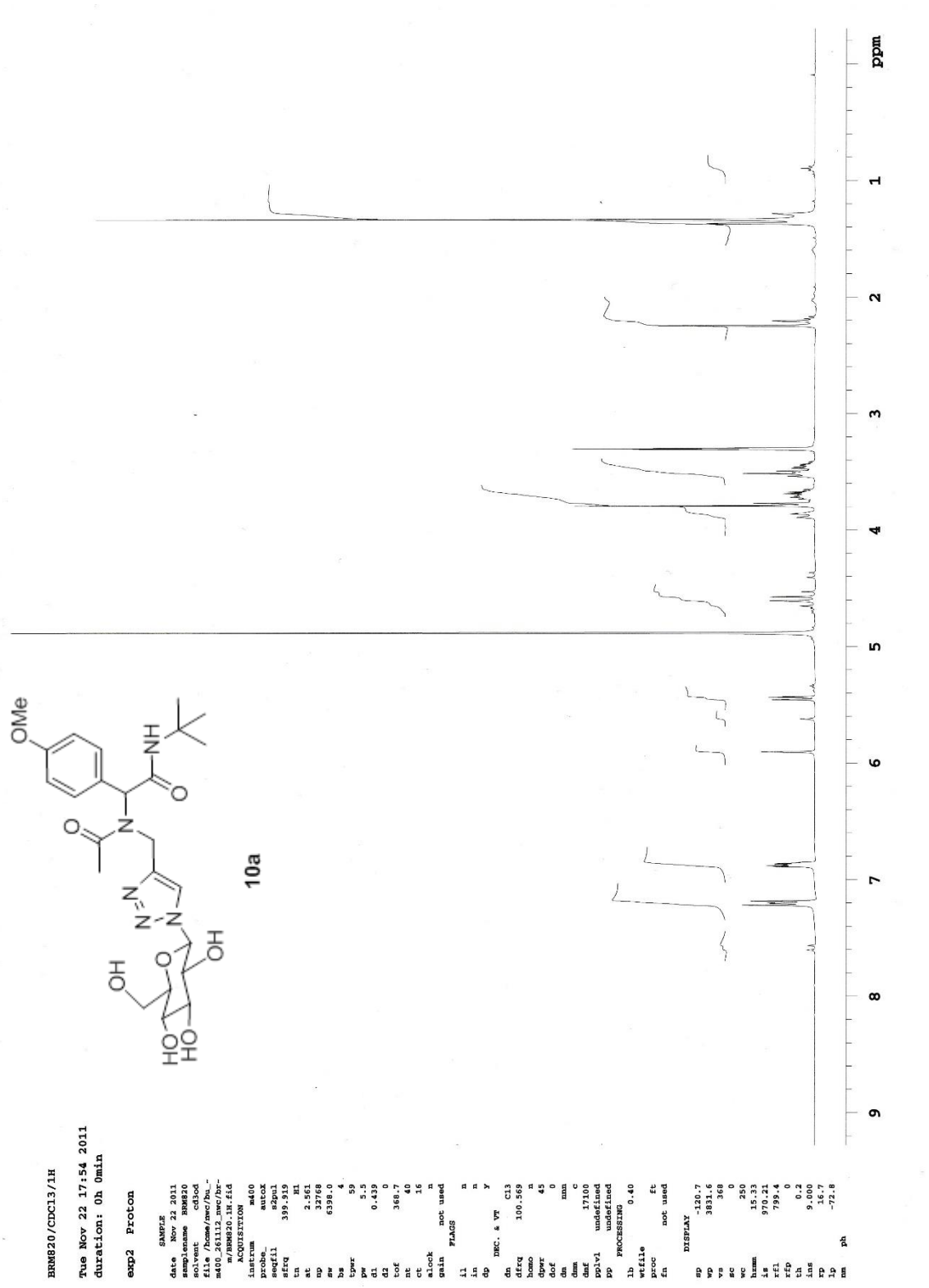

Figure S3 ^{1}H NMR spectrum of 4-({Acetyl[2-(*tert*-butylamino)-1-(4-methoxyphenyl)-2-oxoethyl]amino}methyl)-1-(β-D-glucopyranosyl)-1*H*-1,2,3-triazole (mixture of diastereomers) (**10a**, Chapter 3)

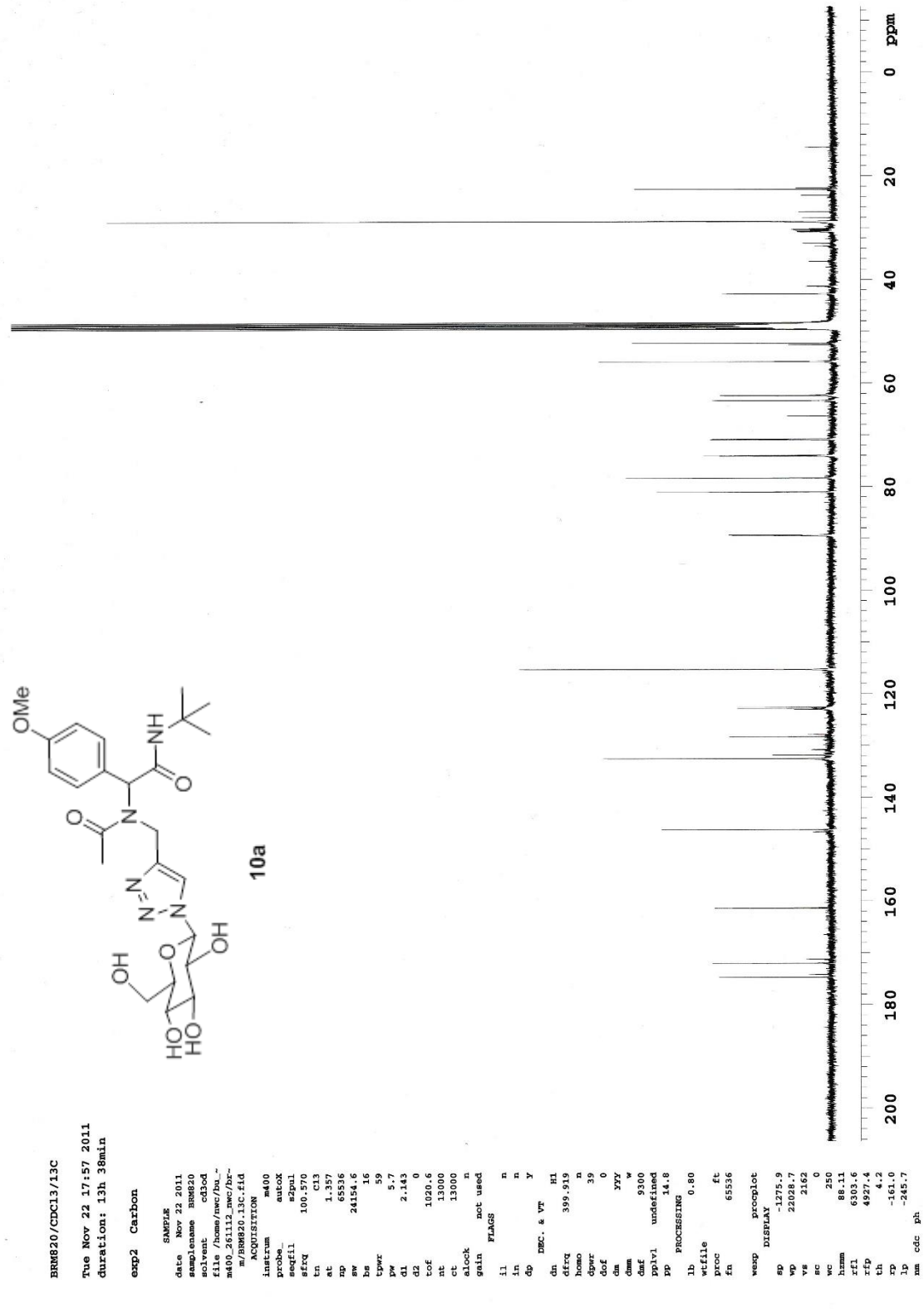

Figure S4 ^{13}C NMR spectrum of 4-({Acetyl[2-(*tert*-butylamino)-1-(4-methoxyphenyl)-2-oxoethyl]amino}methyl)-1-(β-D-glucopyranosyl)-1*H*-1,2,3-triazole (mixture of diastereomers) (**10a**, Chapter 3)

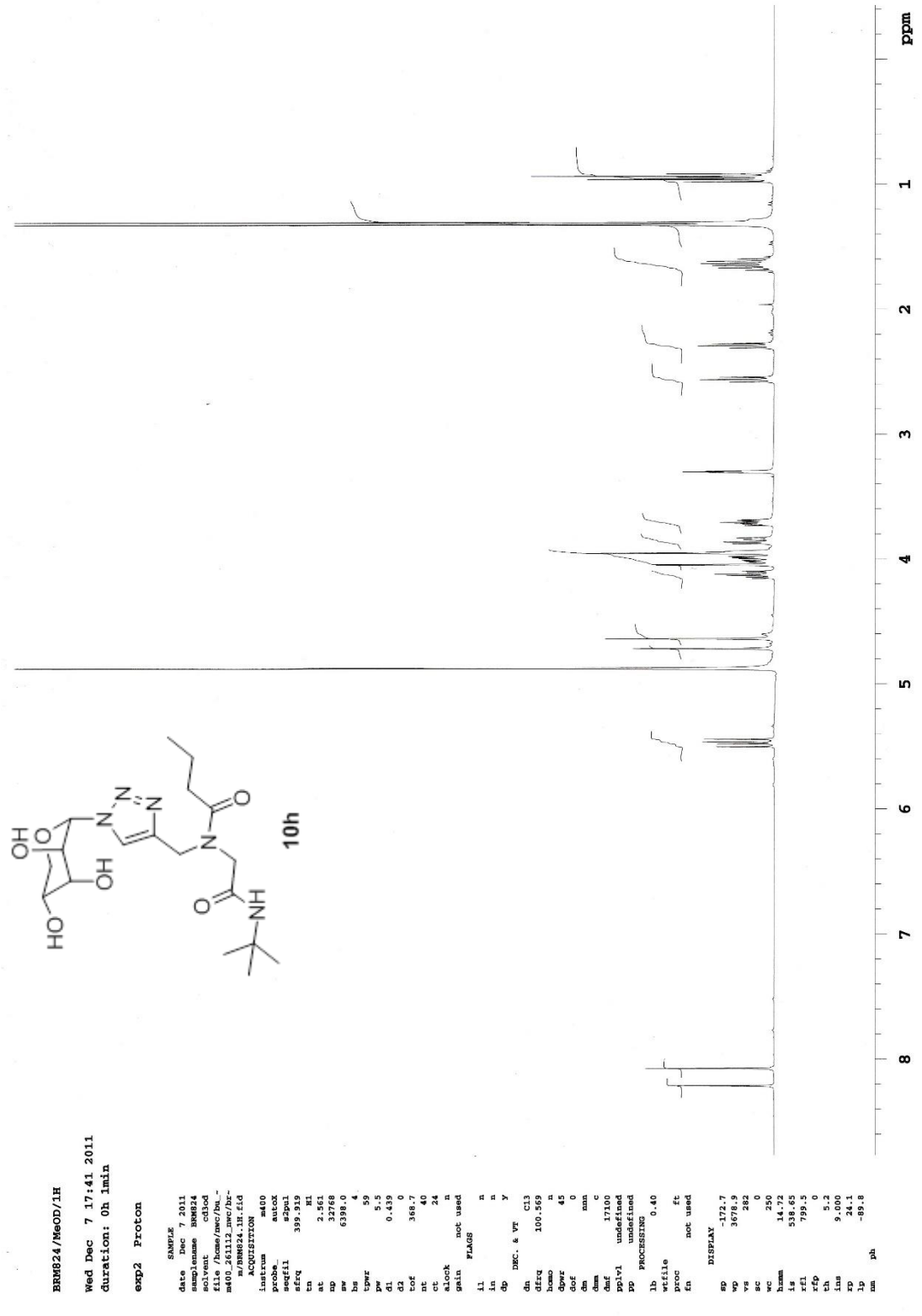

Figure S5 ^{1}H NMR spectrum of 1-(α-D-Arabinopyranosyl)-4-({butanoyl[2-(*tert*-butylamino)-2-oxoethyl]amino}methyl)-1*H*-1,2,3-triazole (**10h**, Chapter 3)

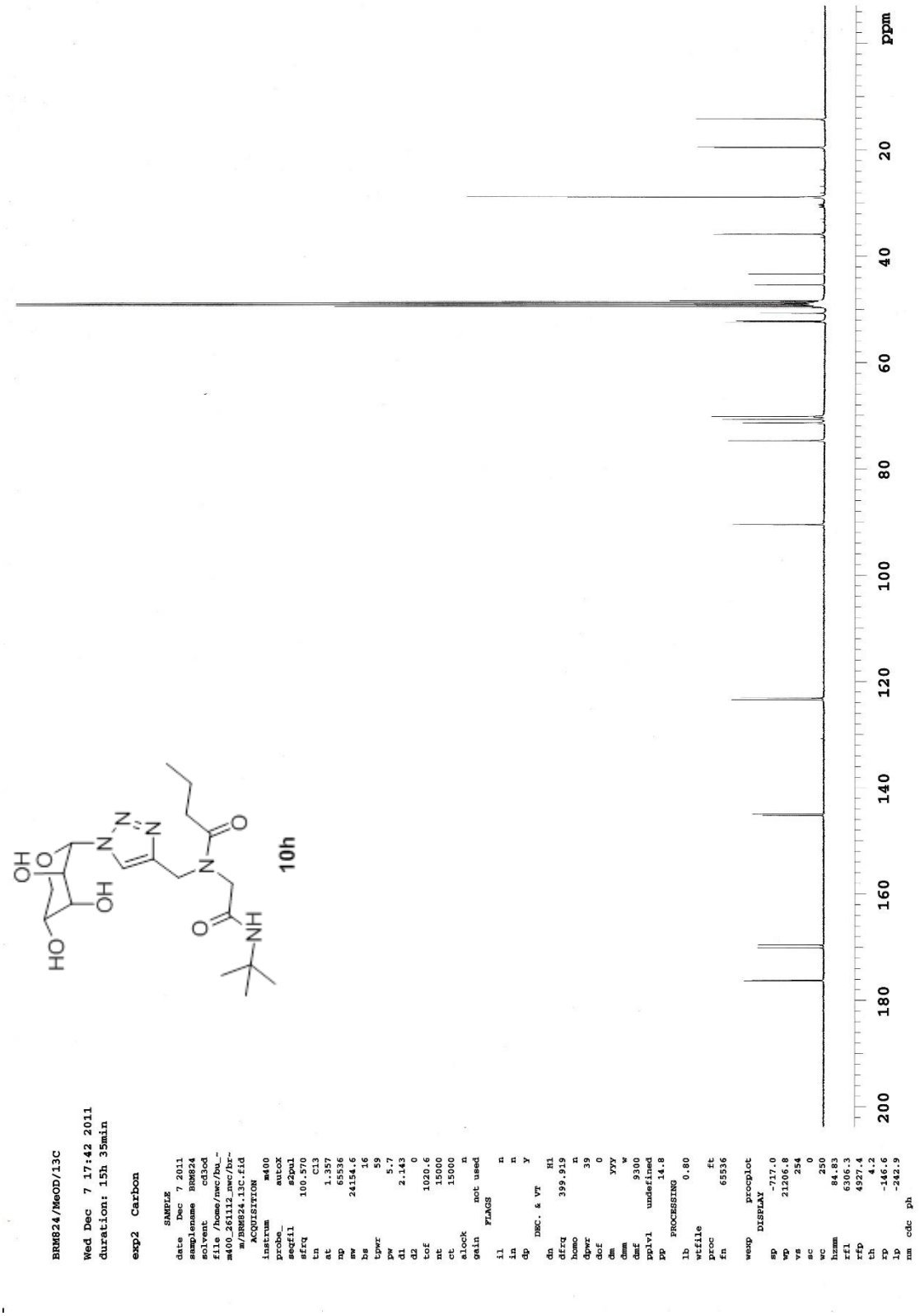

Figure S6 ^{13}C NMR spectrum of 1-(α-D-Arabinopyranosyl)-4-({butanoyl[2-(*tert*-butylamino)-2-oxoethyl]amino}methyl)-1*H*-1,2,3-triazole (**10h**, Chapter 3)

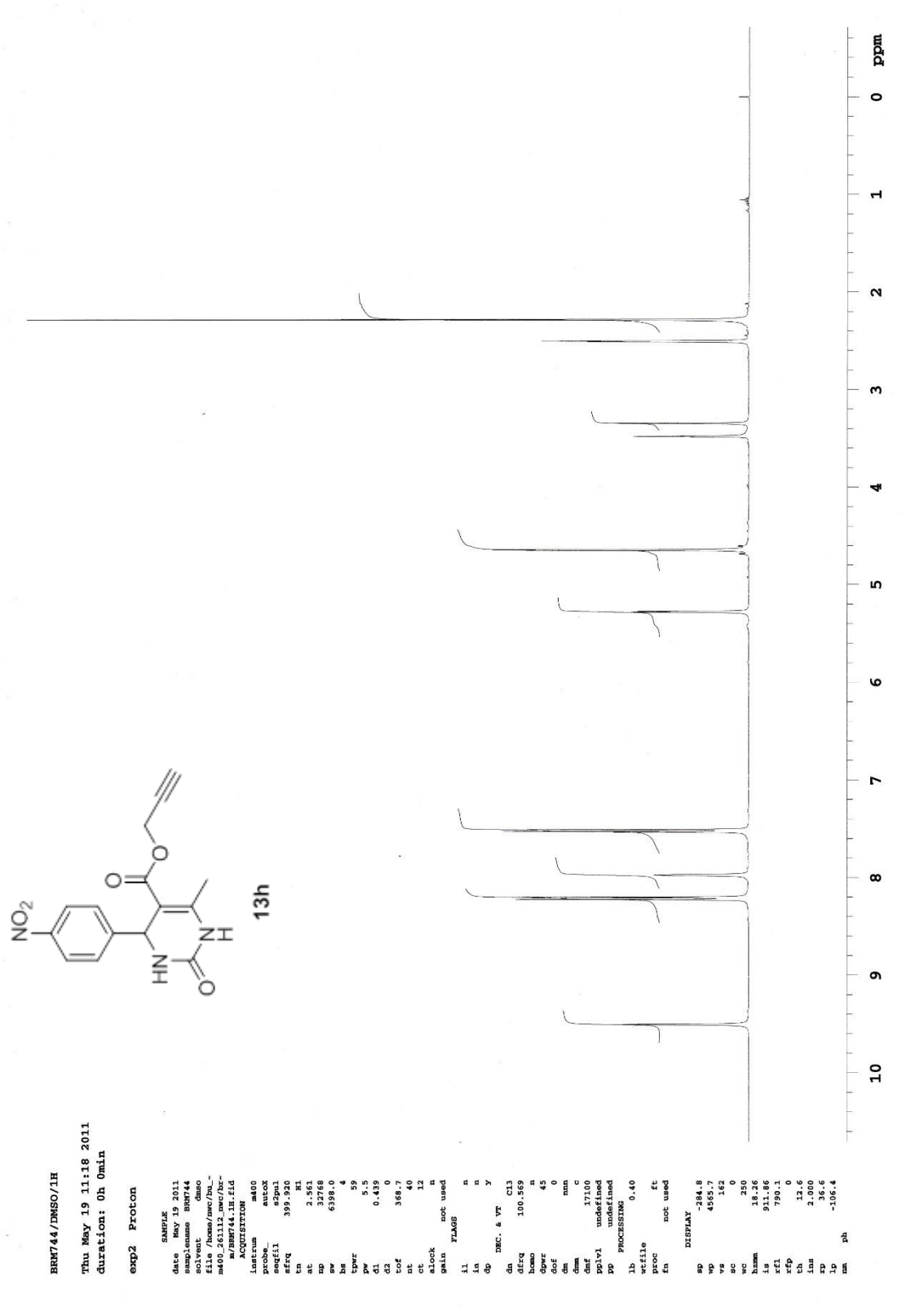

Figure S7 ^{1}H NMR spectrum of Prop-2-yn-1-yl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**13h**, Chapter 3)

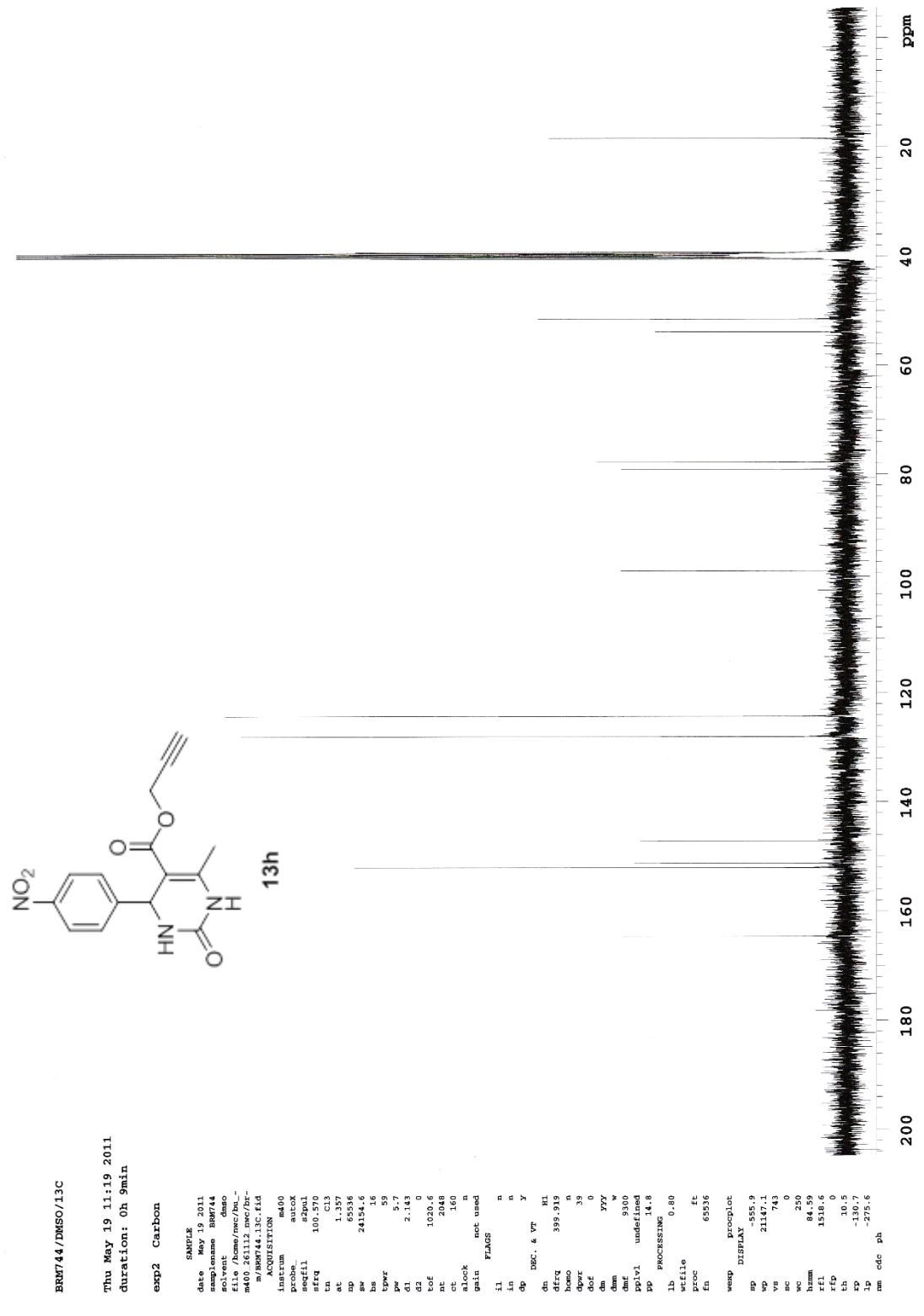

Figure S8 ^{13}C NMR spectrum of Prop-2-yn-1-yl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**13h**, Chapter 3)

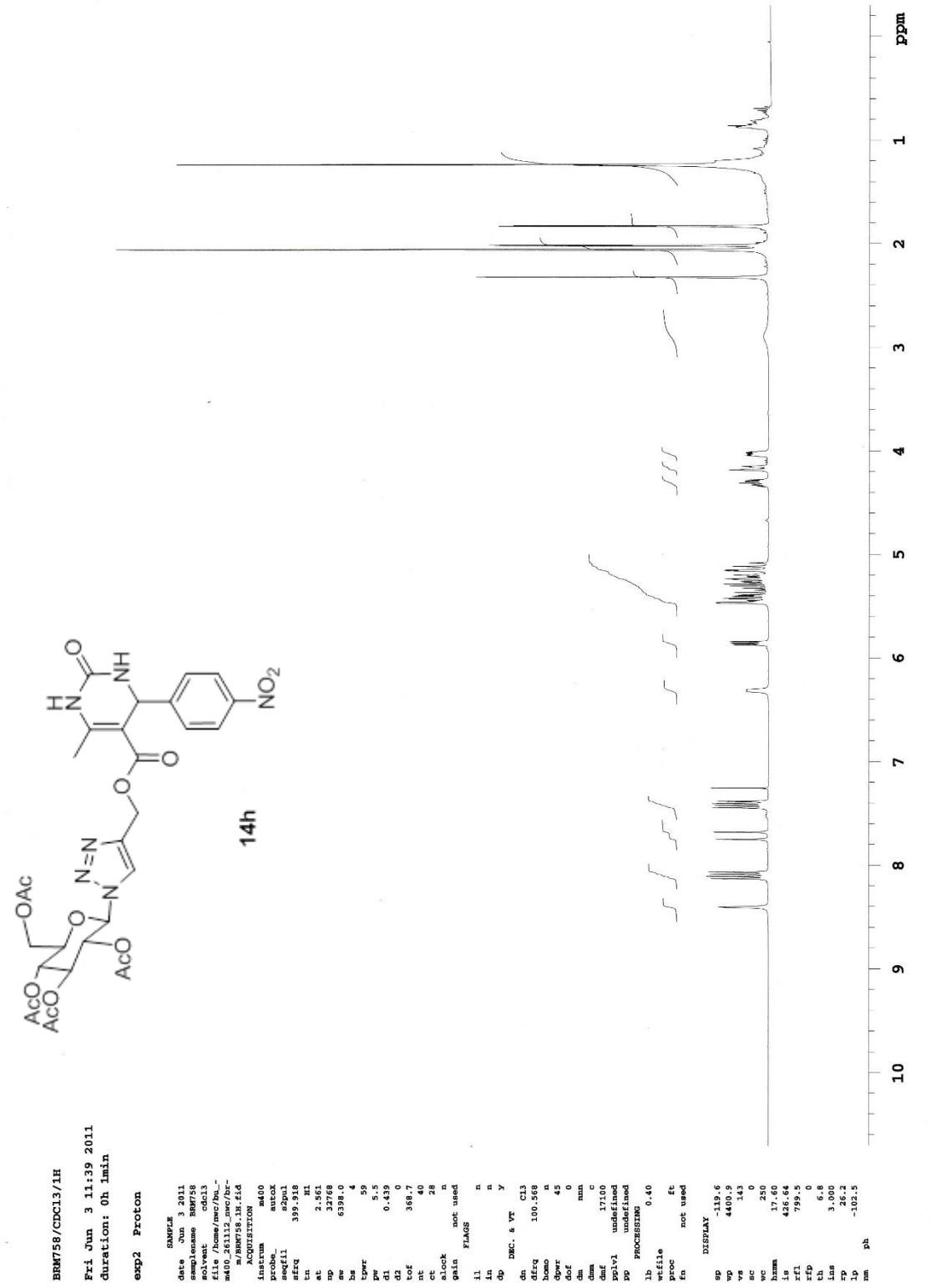

Figure S9 ^{1}H NMR spectrum of 6-Methyl-4-(4-nitrophenyl)-2-oxo-5-({[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-1,2,3,4-tetrahydropyrimidine (mixture of diastereomers) (**14h**, Chapter 3)

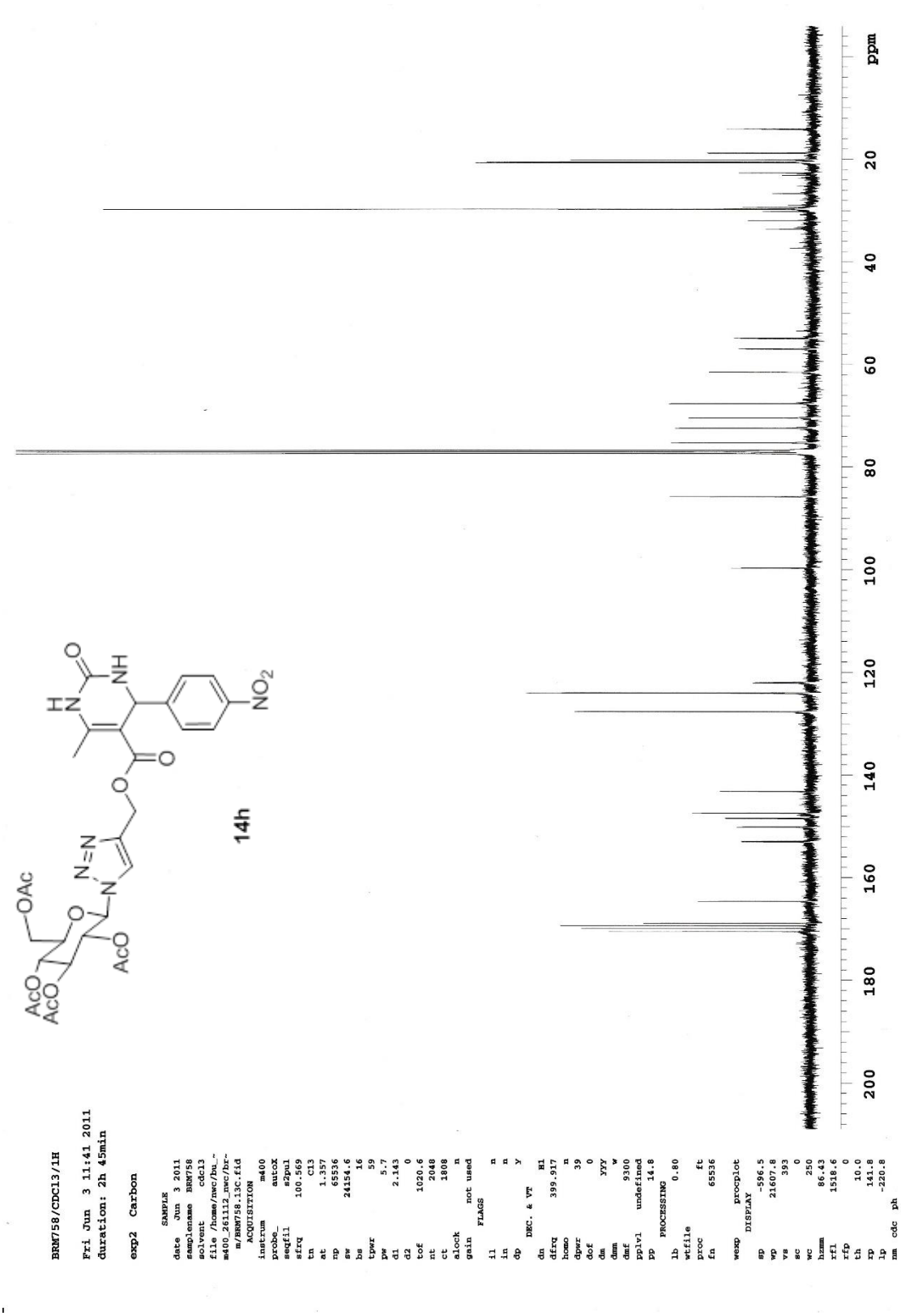

Figure S10 ^{13}C NMR spectrum of 6-Methyl-4-(4-nitrophenyl)-2-oxo-5-({[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-1,2,3,4-tetrahydropyrimidine (mixture of diastereomers) (**14h**, Chapter 3)

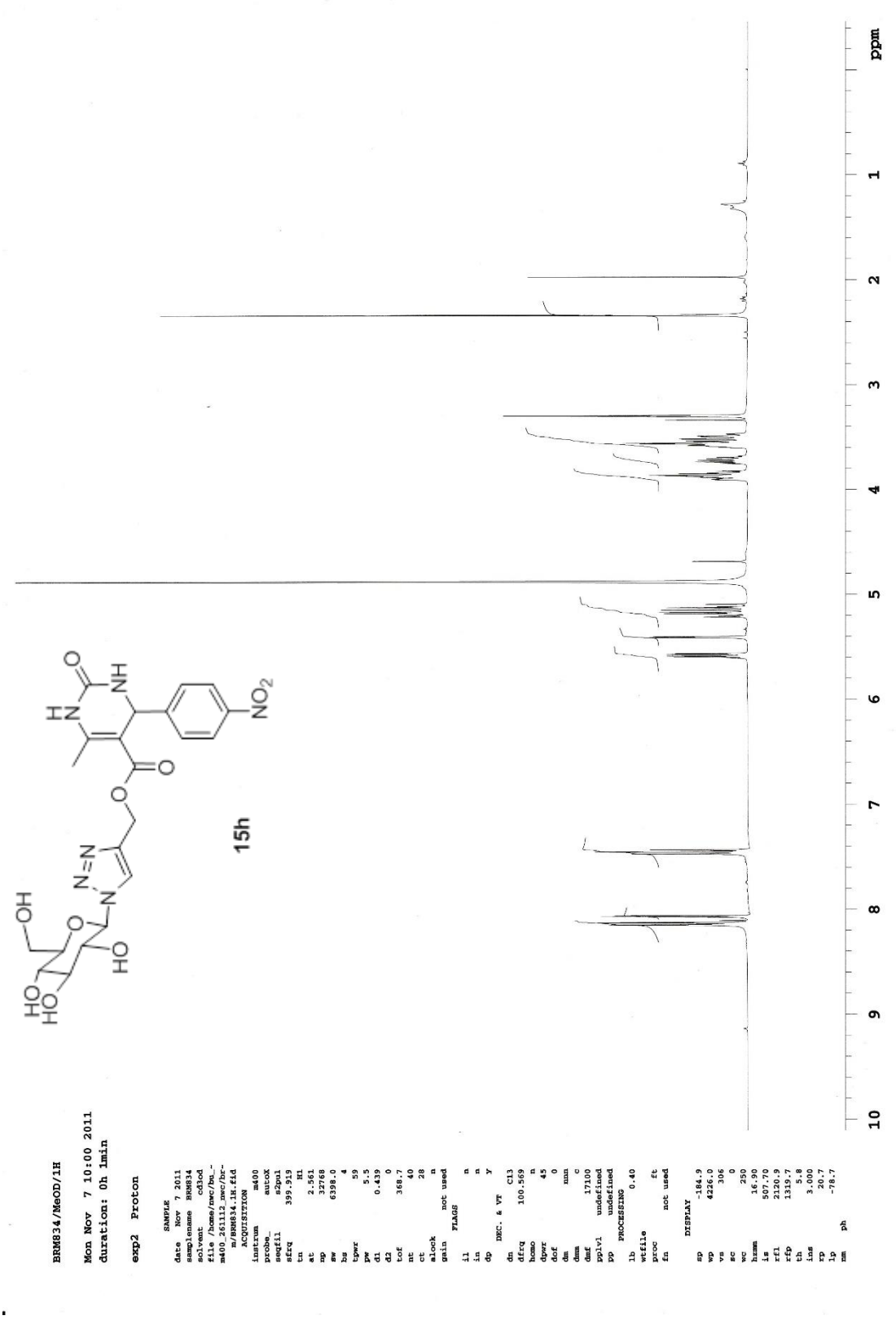

Figure S11 ^{1}H NMR spectrum of 5-({[1-(β-D-Glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine (mixture of diastereomers) (**15h**, Chapter 3)

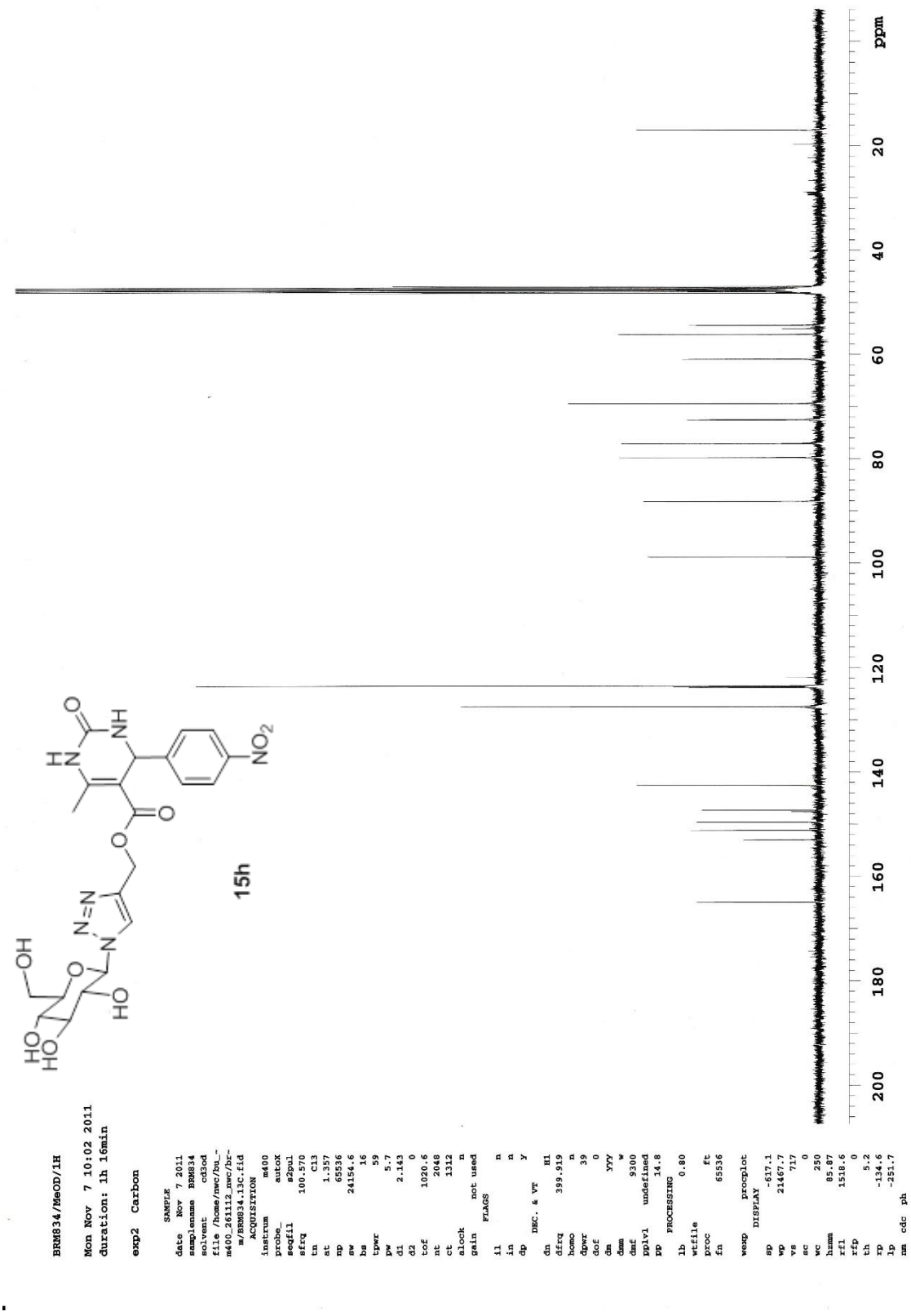

Figure S12 ^{13}C NMR spectrum of 5-({[1-(β-D-Glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methoxy}carbonyl)-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine (mixture of diastereomers) (**15h**, Chapter 3)

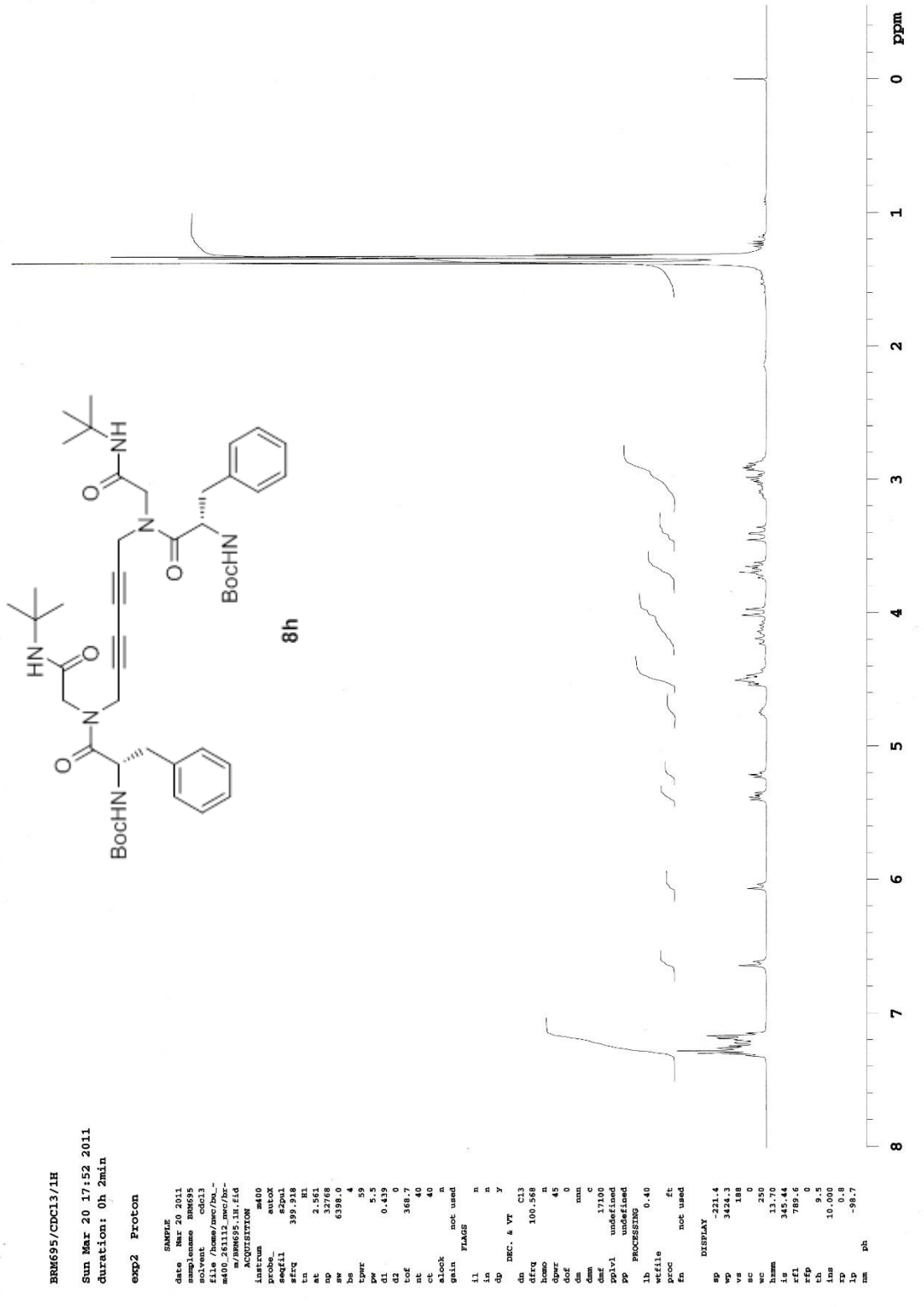

Figure S13 ^{1}H NMR spectrum of *tert*-Butyl {(6*S*,17*S*)-6-benzyl-8,15-bis[2-(*tert*-butylamino)-2-oxoethyl]-2,2-dimethyl-4,7,16-trioxo-18-phenyl-3-oxa-5,8,15-triazaoctadeca-10,12-diyn-17-yl}carbamate (**8h**, Chapter 4)

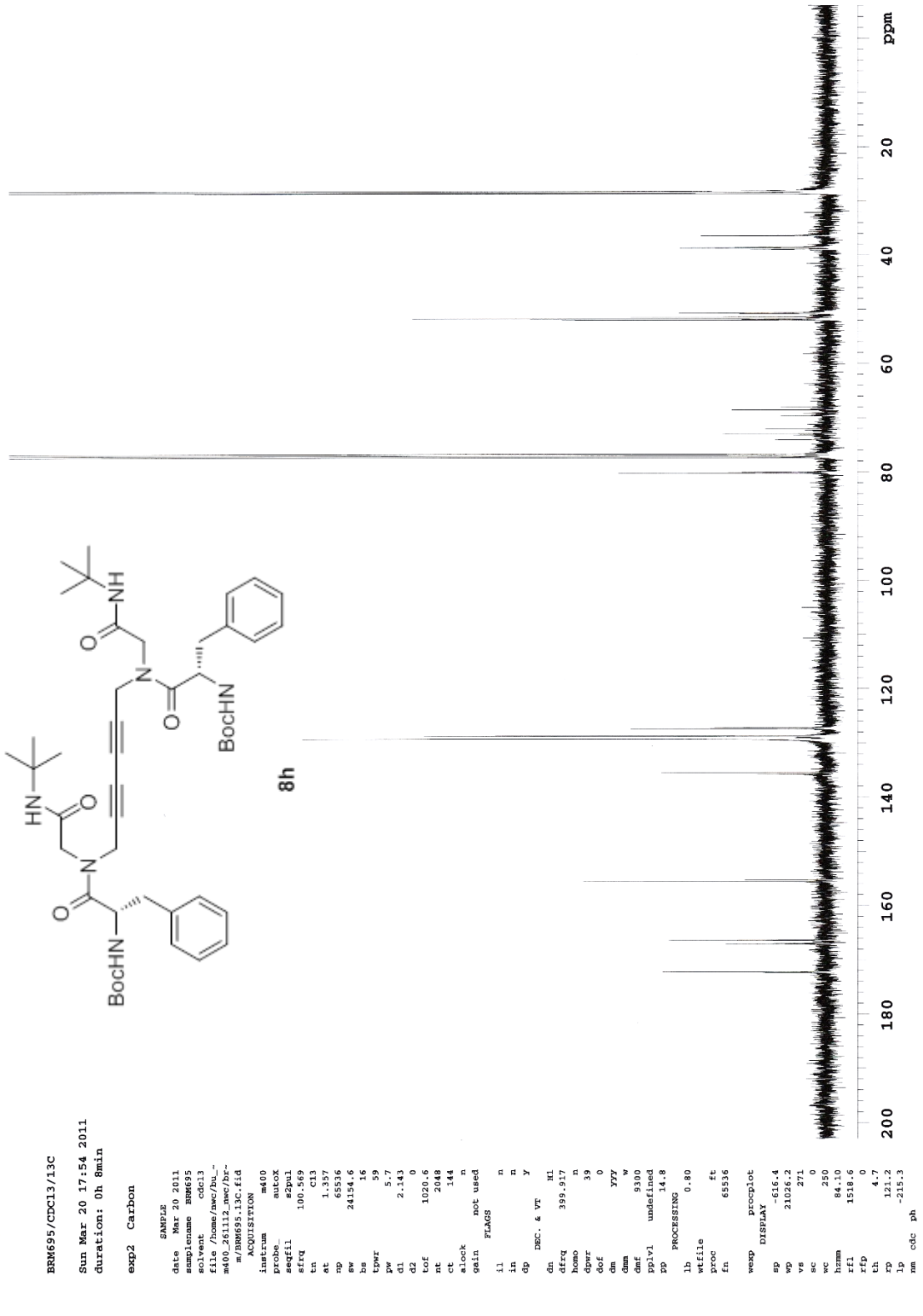

Figure S14 ^{13}C NMR spectrum of *tert*-Butyl {(6*S*,17*S*)-6-benzyl-8,15-bis[2-(*tert*-butylamino)-2-oxoethyl]-2,2-dimethyl-4,7,16-trioxo-18-phenyl-3-oxa-5,8,15-triazaoctadeca-10,12-diyn-17-yl}carbamate (**8h**, Chapter 4)

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2. Academic Curricula

Since 2007	PhD Student at the Leibniz Institute of Plant Biochemistry Department of Bioorganic Chemistry, IPB Halle (Saale), Germany. Recipient of a Ph.D. Fellowship of the CNPq-DAAD program, 2007-2010 Supervisor: Prof. Dr. L.A. Wessjohann
2002-2005	M.S. (Distinction): „*Use of K-10 and Microwave Irradiation for the Transesterification and Synthesis of β-Enamino Esters*" at the Federal University of Santa Maria, UFSM, Santa Maria, RS, Brazil. Recipient of a Master Fellowship of CAPES program, 2003-2004 Supervisor: Prof. Dr. M. E. F. Braibante
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3. Languages

Portuguese, German, English

4. Publications

2015	Brauer, M. C. N.; Neves Filho, R. A. W.; Westermann, B.; Heinke, R.; Wessjohann, L. A. "Synthesis of antibacterial 1,3-diyne-linked peptoids from an Ugi-4CR/ Glaser coupling approach" at *Beilstein J. Org. Chem*. **2015**, *11*, 25-30.
2012	Neves, R. A. W.; Brauer, M.C.N.; Palm-Forster, M.A.T., de Oliveira R.N.; Wessjohann, L.A., Patented Catalysts for the synthesis and biological applications of dihydropyrimidinones: Recent advances of the Biginelli Reaction. *Recent Patents on Catalysis*, **2012**, *1,* 51-73.

Krehl, S.; Loewinger, M.; Florian, S.; Kipp, A.P.; Banning, A.; Wessjohann, L.A.; Brauer, M.N.; Iori, R.; Esworthy, R.S.; Chu, F.F.; Brigelius-Flohe, R., Glutathione peroxidase-2 and selenium decreased inflammation and tumors in a mouse model of inflammation-associated carcinogenesis whereas sulforaphane effects differed with selenium supply. *Carcinogenesis*, **2012**, *33*, 620-628.

2010 Haack, M.; Lowinger, M.; Lippmann, D.; Kipp, A.; Pagnotta, E.; Iori, R.; Monien, B.H.; Glatt, H.; Brauer, M.N.; Wessjohann, L.A.; Brigelius-Flohe, R., Breakdown products of neoglucobrassicin inhibit activation of Nrf2 target genes mediated by myrosinase-derived glucoraphanin hydrolysis products. *Biol. Chem.*, **2010**, *391*, 1281-1293.

1999 Fighera, M.R.; Queiroz, C.M.; Stracke, M.P.; Brauer, M.C.N; Gonzalez-Rodriguez, L.L.; Frussa, R.; Wajner, M.; de Mello, C.F., Ascorbic acid and alpha-tocopherol attenuate methylmalonic acid-induced convultions. *Neuroreport*, **1999**, *10*, 2039-2043.

5. Book Chapters

2011 Wessjohann, L.A.; Brauer, M.C.N.; Brand, K., Chalcogen-Based Organocatalysis. *In Enantioselective Organocatalyzed Reactions I: Enantioselective Oxidation, Reduction, Functionalization and Desymmetrization*, Mahrwald, R., Ed., Springer Science+Business Media B.V., **2011**, pp 209