



HMF in multicomponent reactions: Efficient routes towards novel fine chemicals

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**Utilisation du HMF en réactions
multicomposantes: accès rapide vers de
nouvelles cibles en chimie fine**

**HMF in multicomponent reactions: Efficient
routes towards novel fine chemicals**

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List of Abbreviations

2-MeTHF	2-Methyltetrahydrofuran
5-CMF	5-Chloromethylfurfural
AIBN	Azobisisobutyronitrile
aq	aqueous
BHA	Butylated hydroxyanisole
Boc	<i>tert</i> -Butoxycarbonyl
bp	Boling point
CPME	Cyclopentyl methyl ether
CuAAC	Copper-catalyzed alkyne-azide cycloaddition
DABCO	1,4-Diazabicyclo[2.2.2]octane
DAMF	2,5-Diaminomethylfuran
DAST	Diethylaminosulfur trifluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DHMF	2,5-Dihydroxymethylfurfural
DHPM	3,4-Dihydropyrimidin-2(<i>1H</i>)-one
DIAD	Diisopropyl azodicarboxylate
DIPEA	Diisopropylethylamine
DMAP	<i>N,N</i> -4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide

DMF	2,5-Dimethylfuran
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
DPPA	Diphenylphosphoryl azide
dr	Diastereomeric ratio
EMF	5-Ethoxymethylfurfural
ESI	Electrospray ionization
FDCA	2,5-Furandicarboxylic acid
GMF	Glucosyloxymethylfurfural
HCPN	3-Hydroxymethyl cyclopentanone
HCPL	3-Hydroxymethylcyclopentanol
HD	2,5-Hexanedione
HFIP	Hexafluoroisopropanol
HHCPN	4-Hydroxy-4-(hydroxymethyl)cyclopent-2-en-1-one
HHD	1-Hydroxy-2,5-hexanedione
HLB	Hydrophile-lipophile balance
HMBC	Heteronuclear multiple bond correlation
HMF	5-Hydroxymethylfurfural
HMFA	5-Hydroxymethyl furanoic acid
HMVF	5-Hydroxymethyl-2-vinylfuran
HOBt	1-Hydroxybenzotriazole
HRMS	High resolution mass spectroscopy
HSQC	Heteronuclear single quantum correlation
IL	Ionic liquid
IMDA	Intramolecular Diels-Alder reaction

IPA	Isopropyl alcohol
LA	Levulinic acid
MCO	3-Methyl-2-cyclopenten-1-one
MCP	2-Hydroxy-3-methylcyclopent-2-enone
<i>m</i>-CPBA	<i>Meta</i> -Chloroperoxybenzoic acid
MCR	Multicomponent reaction
MIBK	Methyl isobutyl ketone
MPEG	Methoxy poly(ethylene glycol)
MW	Microwave
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NHC	<i>N</i> -heterocyclic carbene
NMR	Nuclear magnetic resonance
OBMF	5,5'-[Oxybis(methylene)]bis-2-furfural
<i>p</i>-ABSA	4-Acetamidobenzenesulfonyl azide
PEF	Polyethylene furandioate
PET	Polyethylene terephthalate
<i>p</i>-TSA	<i>p</i> -Toluenesulfonic acid
rt	Room temperature
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TBAI	Tetra- <i>n</i> -butylammonium iodide
TBDMS	<i>tert</i> -Butyldimethylsilyl
TBHP	<i>tert</i> -Butyl hydroperoxide
TEA	Triethylamine
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy free radical

TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TPT	1,3,4-Triphenyl-4,5-dihydro-1H-1,2,4-triazol-5-ylidene

Abstract

Recently, the production of chemicals, either bulk or fine chemicals, from renewable biomass has attracted growing interests due to the dwindling reserve of fossil resources and the increasing awareness of environmental concerns. Some chemicals with a structure able to generate a number of derivatives, and able to be directly produced from biomass, are referred to as bio-based “platform chemicals”, and constitute the bridge between biomass and down-stream chemicals. Among these chemicals, 5-hydroxymethylfurfural (HMF), bearing an aldehyde group, a hydroxymethyl group, and a furan moiety, is the most popular one. However, its limited stability obstructs its applications in organic synthesis. Thus, developing mild and efficient synthetic routes towards existing or novel fine chemicals from HMF is still a challenging task.

Multicomponent reactions (MCRs) are powerful synthetic tools allowing the straightforward formation of elaborated molecules from simple starting materials in a time- and step-saving manner. Among MCRs, many involve the aldehyde as one of the reactive components, making HMF as a potential interesting substrate in such strategies. This thesis aims at exploring the use of HMF in MCRs to provide novel fine chemicals, focusing on two reactions, namely the Biginelli and Kabachnik-Fields reactions.

The Biginelli reaction is a condensation of an aldehyde, a 1,3-dicarbonyl compound and urea. Although it is an old reaction, it is still showing thriving vitality, as many of its products, namely dihydropyrimidinones, exhibit various biological properties. We have investigated the reaction by choosing proper conditions to adapt to HMF, notably with respect to acidic conditions. The best conditions found for the reaction are the use of ZnCl_2 as a mild Lewis acid catalyst without any solvent, giving access to new dihydropyrimidinones in modest to good yields.

The Kabachnik-Fields reaction is a one-pot condensation of aldehydes, amines and dialkyl phosphites, and is considered as the most efficient and convenient approach to α -aminophosphonates. For the specific case of HMF, we could establish that the best conditions were the use of iodine as a catalyst in the bio-based solvent 2-MeTHF and room or moderately elevated temperature. Using these optimized conditions, a wide range of HMF-based α -aminophosphonates were prepared in modest to excellent yields. The hydroxymethyl group persisting in HMF-based α -aminophosphonates offers the possibilities of further modification and derivatization, illustrating the benefit of HMF as compared to furfural, for accessing a wider scope of chemical structures.

Key words: 5-hydroxymethylfurfural (HMF), multicomponent reaction (MCR), fine chemicals, biomass, Biginelli reaction, Kabachnik-Fields reaction

Résumé

L'utilisation de matières premières renouvelables pour la production de produits chimiques est un enjeu majeur de l'industrie chimique. Elle vise à répondre aux contraintes environnementales et économiques de disponibilité des ressources fossiles et de limitation de l'empreinte carbone des produits chimiques.

Il existe une famille de molécules fonctionnelles directement issues de la biomasse dénommées « molécules plateforme ». Parmi elles, le 5-hydroxyméthylfurfural (HMF), porteur d'une fonction aldéhyde, un motif furanique et un groupe CH_2OH , est particulièrement intéressante. Cependant, sa stabilité modérée, notamment en conditions acides, est une forte limitation de sa chimie et son utilisation vers des cibles en chimie fine reste un défi.

Les réactions multi-composantes conduisent à des architectures élaborées à partir de briques simples de manière économe en temps et nombre d'étapes. Beaucoup de ces réactions concernent la fonction aldéhyde, ce qui rend intéressant de les appliquer au 5-HMF. Ceci est l'objet de cette thèse, qui porte sur deux réactions en particulier, Biginelli et Kabachnik-Fields.

La réaction de Biginelli est la condensation d'un aldéhyde, un composé dicarboxylé et une urée conduisant à des dihydropyrimidinones (DHPMs). Etant acido-catalysée, il a été nécessaire d'optimiser les conditions pour l'appliquer au HMF. Les meilleures conditions (réaction sans solvant, ZnCl_2) ont permis d'atteindre une large variété de nouvelles DHPMs dans des rendements convenables à très bons.

La réaction de Kabachnik-Fields est la condensation d'un aldéhyde avec une amine et un dialkyl phosphate, conduisant à des α -aminophosphonates. Les conditions optimales trouvées pour son application au 5-HMF sont l'utilisation d'iode comme catalyseur dans le solvant biosourcé 2-MeTHF à température ambiante ou modérément élevée. Une série de nouveaux α -aminophosphonates comportant le motif HMF a été préparée. Le groupe hydroxyméthyle issu du HMF persiste dans le produit, offrant de nombreuses possibilités de dérivation et démontrant son utilité comparativement à la chimie du furfural.

Mots-clés: 5-hydroxyméthylfurfural (HMF), réactions multicomposantes, chimie fine, biomasse, Biginelli, Kabachnik-Fields

Contents

Acknowledgement	1
List of Abbreviations	3
Abstract	7
Résumé	9
General Introduction	13
Chapter I. Bibliography	15
1.1. General aspects of HMF	15
1.1.1. Introduction	15
1.1.2. Stability of HMF	17
1.1.3. Production of HMF	18
1.1.4. Main uses of HMF towards bulk chemicals	20
1.2. Applications of HMF towards fine chemicals	21
1.2.1. Reactions on the carbonyl group	21
1.2.1.1. C-C bond formation reactions	21
1.2.1.1.1. Reactions with α -position of carbonyl compounds	21
1.2.1.1.2. Reactions with enamines and other nucleophiles	28
1.2.1.1.3. Alkenylation and alkynylation	30
1.2.1.1.4. Friedel-Crafts reactions	31
1.2.1.1.5. Benzoin condensation	32
1.2.1.1.6. Oxidative transformations	33
1.2.1.2. C-N bond formation reactions	34
1.2.1.2.1. Synthesis of imines, hydrazones, oximes and nitrones	34
1.2.1.2.2. Preparation of amines	37
1.2.1.2.3. Synthesis of nitrogen-containing heterocycles	39
1.2.1.2.4. Oxidative transformations	41
1.2.1.3. Simultaneous formation of C-C and C-N bonds by multicomponent reactions	42
1.2.1.3.1. General introduction of MCR	42
1.2.1.3.2. The use of HMF in MCRs	44
1.2.1.4. C-O or C-S bond formation reactions	46
1.2.2. Reactions on the hydroxyl group	48
1.2.2.1. Esterification	48
1.2.2.2. Conversion to ethers and acetals	50

1.2.2.3.	Conversion to halides	52
1.2.2.4.	Amination reaction	54
1.2.2.5.	Friedel-Crafts alkylation	55
1.2.3.	Reactions on furan ring	55
1.2.3.1.	Ring opening/rearrangement	55
1.2.3.2.	Singlet oxygen oxidation	57
1.2.3.3.	Diels-Alder reaction	58
1.2.4.	Multi-step and multi-functionalization sequences	59
1.3.	Conclusion	63
Chapter II. The Biginelli Reaction of 5-Hydroxymethylfurfural		64
2.1.	Introduction	64
2.1.1.	The discovery of the Biginelli reaction	64
2.1.2.	The mechanism of the Biginelli reaction	65
2.1.3.	The pharmacological properties of DHPMs	68
2.2.	The utilization of HMF in the Biginelli reaction	71
2.2.1.	Optimization of the reaction conditions	71
2.2.2.	Substrate scope study	75
2.2.3.	Mechanistic study	80
2.3.	Conclusion	83
Chapter III. Synthesis of HMF-derived α-Aminophosphonates <i>via</i> One-pot Kabachnik-		
Fields Reaction		84
3.1.	Introduction	84
3.1.1.	Overview on α -aminophosphonates	84
3.1.2.	Overview on the Kabachnik-Fields reaction	85
3.2.	HMF in the Kabachnik-Fields reaction	91
3.2.1.	Screening of reaction conditions	92
3.2.2.	Substrate scope of the reaction	95
3.2.3.	Derivatization of HMF-derived α -aminophosphonate	101
3.2.4.	Mechanistic study	102
3.3.	Conclusion	105
Conclusion and Perspectives		106
Experimental Section		112
Reference		146

General Introduction

In recent years, the increasing demand for the chemicals and fuels due to the development of global economy, the massive emission of greenhouse gases, and the excessive use of fossil resources, have impelled governments and societies to encourage the use of renewable resources to replace fossil ones. Biomass, considered as the most abundant renewable organic carbon resource in nature, has thus attracted significant attention from both academia and industry.

In the context of biomass valorization, some platform molecules have been developed in the past decades. Their increasing availability has, in turn, stimulated chemists' interest for converting them towards various valuable down-stream chemicals. Among these platform molecules, 5-hydroxymethylfurfural (HMF) appears as one of the most promising: this apparently simple molecule, obtained by dehydration of hexoses and derivatives, consists of an aldehyde group on C2 position, a hydroxymethyl group on C5 position as well as a reactive furan ring, making its derivation possible through a wide range of chemical transformations. The production of HMF has been studied thoroughly and the industrial manufacture has been realized recently. From the viewpoint of a chemist, it is time to pay more attention to expand the space of HMF utilization.

The first realm of the application of HMF is to make polymer materials *via* a series of HMF-derived monomers. The second one is to convert HMF to less-oxygen-containing chemicals or oxygen-free hydrocarbons that can be used as biofuels. Last but not least, utilization of HMF as a starting material to prepare complex fine chemicals would be a promising direction as well, and this is the principle of this thesis.

Of course, the valorization process of HMF to fine chemicals should correspond to green chemistry principles as much as possible. With respect to "atom economy", multicomponent reaction represents an ideal tool to prepare complex chemicals directly from simple starting materials. In light of these benefits, multicomponent reactions are expected to be efficient and green strategies to integrate HMF into value-added fine chemicals.

In this thesis, we will mainly discuss the valorization of HMF to complex fine chemicals by multicomponent reactions. The first chapter gives an overview of the existing synthetic approaches involving HMF as a starting material reported in literature. Then we present our results on two multicomponent reactions, namely the Biginelli reaction and the Kabachnik-Fields reaction, which exemplify the incorporation of HMF into complex chemical architectures by multicomponent synthetic strategies.

Chapter I. Bibliography

This chapter aims at giving an overview on HMF and its use in organic synthesis to prepare complex fine chemicals. After a general introduction of HMF, applications of HMF towards fine chemicals are elaborated, and organized with respect to the chemical functions, namely transformations on the aldehyde group, on the hydroxymethyl group and on the furan ring.

1.1. General aspects of HMF

1.1.1. Introduction

Nowadays, fossil-based feedstocks are the primary resources for fuels and the basis for most of the carbon-based chemicals and polymer materials that humankind uses. However, the reserve of fossil resources under the ground is diminishing due to the large consumption while their formation takes over millions of years. Furthermore, the use of fossil resources leads to the generation of a large amount of carbon dioxide, which contributes to the global climate change (the greenhouse effect). All these facts have forced the humankind to seek renewable alternatives, such as biomass, to fossil feedstocks. The utilization of biomass can allow us to relieve our heavy dependence on fossil resources, and is also recognized as an effective way to reduce the net emission of carbon dioxide, taking into account that carbon dioxide is absorbed in the process of photosynthesis in plants. Conversion of biomass into value-added chemicals, fuel products and materials thus conforms to the principles of green chemistry within the context of renewable feedstocks utilization.^[1] This field has been well documented in a number of reviews.^[2-8]

A series of basic chemicals obtained from carbohydrates, the main components in biomass, have been regarded as the “primary platform chemicals”. These chemicals are the link between biomass and down-stream chemicals and materials. In 2010, Bozell reported an updated version of the “top 10” list of biomass-derived platform chemicals suggested originally by the US Department of Energy (DOE) (Table 1).^[9] In Bozell’s report, 5-hydroxymethylfurfural (HMF) was selected as a biomass-based platform molecule in the new top chemicals list (the so-called “top 10 + 4” list). This apparently approved the potent competence of HMF serving as a platform chemical or a building block for the preparation of diverse chemicals. Indeed, HMF, consisting of a furan ring, an aldehyde group and a hydroxyl group, makes itself a versatile starting material for preparing a wide range of down-stream chemicals and polymer materials.

Table 1. The new list of top bio-based chemicals suggested by Bozell, 2010 (Chemicals in the original DOE list 2004 are in bold).

Ethanol	Furfural
5-Hydroxymethylfurfural	2,5-Furan dicarboxylic acid
Glycerol and derivatives	Biohydrocarbons
Lactic acid	Succinic acid
Hydroxypropionic acid /aldehyde	Levulinic acid
Sorbitol	Xylitol

The research on the chemistry of HMF started at the end of the 19th century. Dull^[10] and Kiermayer^[11] first prepared HMF independently in 1895, at that moment they called HMF “oxymethylfurfurol”. In 1919, Middendorp published a detailed account in French concerning the synthesis, the physical characterization and the chemical behavior of HMF.^[12] Since then, HMF has been a continuing interest in chemical community. It is worthy to mention that many French chemists contribute to this field, like Gaset (Toulouse), Cottier and Descotes (Lyon), Gelas (Clermont-Ferrand), and so on. The history of the development of HMF chemistry was depicted in Lewkowski’s review in 2001.^[13]

Entering the 21st century, the antique HMF chemistry has never lost its charm to chemists. With the advancement of modern chemical techniques as well as the increasing interests on renewable feedstocks, more and more research groups have involved themselves in the study of HMF chemistry, including the development of HMF production and purification employing new processes and also its applications in many directions. Especially the past decade has seen an enormous increase in the number of publications about HMF chemistry, as described in Figure 1. Several exceptional comprehensive reviews on HMF chemistry were published by Afonso (2011),^[14] de Vries (2013),^[15] and Ananikov(2018).^[16]

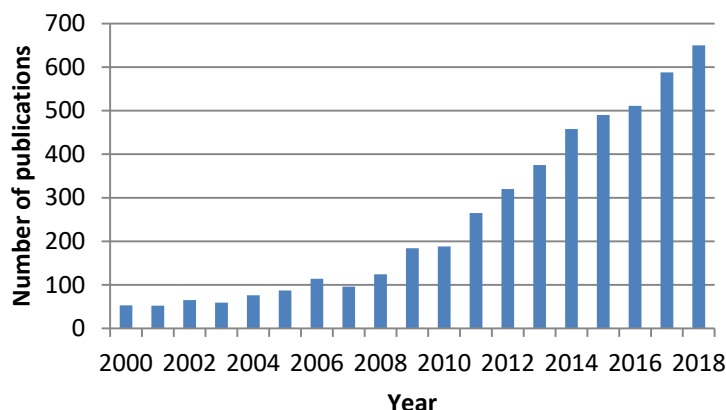


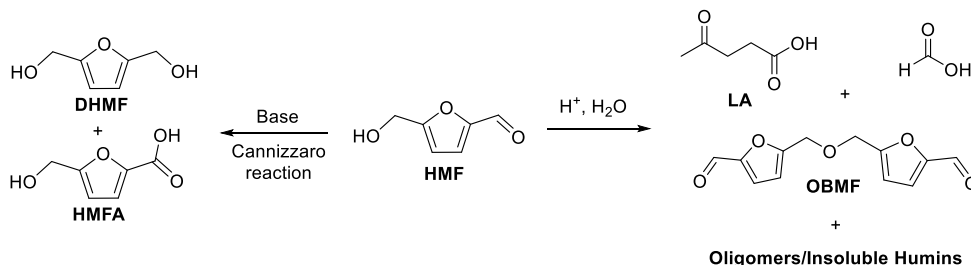
Figure 1. Number of publications on HMF per year (2000-2018), as registered by Web of Science® before Jan 15th 2019

HMF is not only existing in chemistry laboratories, but also existing in our daily life. The process of heating food, like baking bread, generates a small quantity of HMF, as HMF is formed during the thermal decomposition of carbohydrates *via* caramelization or the Maillard reaction. The estimated daily intake of HMF is 5-150 mg/per person depending on various diets taken. It is not very clear whether normal intake of HMF from heating food affects human's health potentially or not. However, animal experiments reveal that there is no obvious adverse effect with a daily intake in the range of 80-100 mg/kg body weight. Safety margins are generally sufficient.^[17]

1.1.2. Stability of HMF

It is reported that the exposure of HMF to acidic and elevated temperature conditions results into degradation.^[18] By heating in acidic aqueous solution, HMF is hydrolyzed to levulinic acid (LA) and formic acid, together with some insoluble dark brown substances, often mentioned as humins (Scheme 1). Oppositely, in a strong basic solution, HMF can undergo the Cannizzaro reaction to 2,5-dihydroxymethylfurfural (DHMF) and 5-hydroxymethyl furanoic acid (HMFA) (Scheme 1).^[19] Recently, Ananikov disclosed that the physical appearance of HMF has a huge effect on its stability during storage and utilization.^[20] Because of the low melting point (30-34 °C), HMF may be produced in the crystalline state or in the oil state. The stability of HMF in its crystalline state is superior to that in the oil form. In the case of oily HMF, the intermolecular self-etherification to the dimer 5,5'-[oxybis(methylene)]bis-2-furfural (OBMF) was reported to occur during the period of storage at room temperature. Besides the dimer OBMF, a number of complex oligomers

with three to ten furan cores were detected by mass spectroscopy. Ananikov presumed that the tiny quantity of acidic impurities in HMF, remaining from the acid-catalyzed production process, might be a reason facilitating the oligomerization. On the other hand, the aggregation behavior of HMF in solution (likely by formation of hydrogen-bonding network between hydroxyl and aldehyde groups) observed by the author can also contribute to the oligomerization.



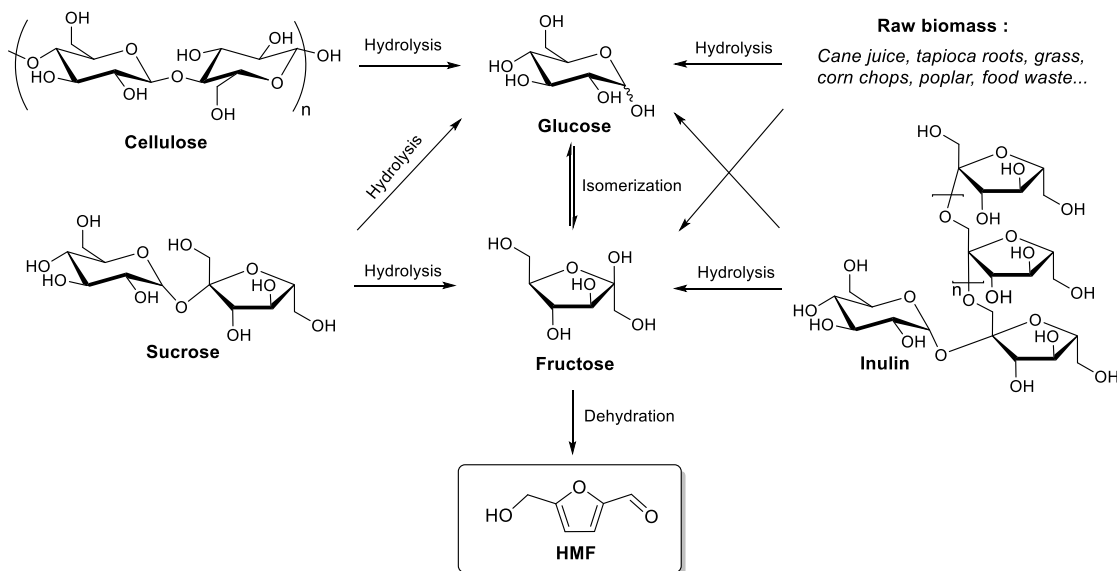
Scheme 1. Possible undesired side-reactions occurring in HMF storage or utilization

One solution to improve the stability of HMF is to add some antioxidant additives to the HMF solution. Sodium dithionite^[21] and butylated hydroxyanisole (BHA)^[22] were found to be effective additives to stabilize HMF during its utilization or production processes.

1.1.3. Production of HMF

The production of HMF mainly relies on the dehydration of six-carbon monosaccharides (Scheme 2). Disaccharides or polysaccharides, such as cellulose, sucrose and inulin, can be also used as starting materials, but hydrolysis is necessary for releasing monosaccharides. In addition, a more challenging method is employing raw biomasses to produce HMF, either by stepwise pretreatment-hydrolysis-dehydration processes or by direct one-pot strategies.^[23] At the moment, fructose is still the most easy-handling starting material for the preparation of HMF, while glucose is less reactive to produce HMF, as it has to undergo isomerization to yield fructose before the dehydration. The case of glucose often employs a bifunctional catalyst, because the glucose-fructose isomerization is a base-catalyzed process and the dehydration of fructose is an acid-catalyzed process, which makes the process more complex. Overall, the dehydration of carbohydrates to HMF is often complicated, because the low stability of HMF could result into a number of side reactions, such as rehydration of HMF to levulinic and formic acids, polymerization of HMF to insoluble humins, and so on. The key point to achieve a high yield of HMF is to strengthen the desirable reactions and suppress or avoid the side reactions by choosing

suitable conditions and proper catalytic systems. Due to its inherent instability and comparative complex production process, HMF was not produced on a large commercial scale until 2010s, when the first production plant was set up by AVA Biochem Company in Switzerland.^[24] While the other furan-based platform chemical furfural had been produced on a large scale over 90 years ago.^[25]



Scheme 2. The overview of HMF production from biomass feedstocks

Water is a common solvent in carbohydrate chemistry. The dehydration of sugars to HMF was also mainly performed in water with mineral acid as a catalyst in the early stage of studies. But the selectivity and the yield of HMF were often low under aqueous conditions, because of the inferior stability of HMF under aqueous acidic conditions. To overcome that, a huge amount of

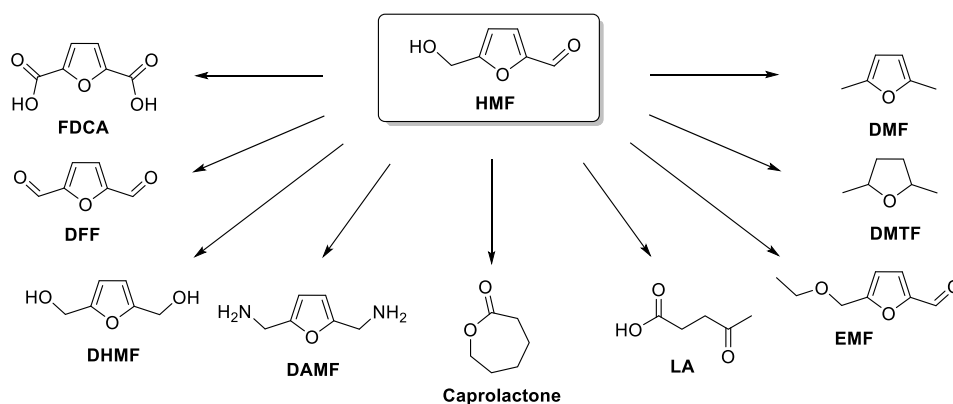
Table 2. Principle processes developed for HMF production

Production process	Strength and weakness
Simple aqueous phase system (acidic cat. + water)	High solubility for carbohydrates and low cost, low selectivity
Biphasic solvent system (acidic cat. + water + organic solvent)	Improved selectivity
Polar aprotic organic solvent system (acidic cat. + organic solvent, e.g., DMSO, DMF)	High selectivity, difficult extraction of HMF from high boiling point solvents
Ionic liquid system (acidic cat. + IL or sole acidic IL)	High selectivity, high cost and difficult isolation from ILs

processes have been developed for the production of HMF from biomass feedstocks, from initial simple aqueous phase systems, to biphasic systems,^[26] and ionic liquid systems,^[27-28] and others.^[29-30] The principle production processes and their features are summarized in Table 2. In addition, an impressive number of homogeneous/heterogeneous acidic catalysts were studied in combination with various reaction media.

1.1.4. Main uses of HMF towards bulk chemicals

As a multifunctional platform chemical, HMF can undergo various transformations offering access to chemicals of industrial importance (Scheme 3).^[31-33] Considerable efforts have been devoted to the catalytic conversion of HMF to 2,5-furandicarboxylic acid (FDCA),^[34-35] 2,5-diformylfuran (DFF), 5-hydroxymethyl-2-furanoic acid (HMFA), 2,5-dihydroxymethylfuran (DHMF),^[36] 2,5-diaminomethylfuran (DAMF), caprolactone, and so on, which can serve as monomers in polymer chemistry.^[37-38] Especially, FDCA has gathered much attention, because it is expected to replace terephthalic acid, a fossil-based chemical, to prepare polyesters, polyamides and polyurethanes. One example is polyethylene furandioate (PEF), a 100% bio-based polyester, which might replace polyethylene terephthalate (PET) in typical applications like films, fibers and plastic bottles (Figure 2).^[39] In addition to the transformations to monomers, HMF can also be converted to 2,5-dimethylfuran (DMF), 2,5-dimethyltetrahydrofuran (DMTF), 5-ethoxymethylfurfural (EMF), which are considered as potential biofuels. Furthermore, HMF can be transformed to another platform chemical LA as well.



Scheme 3. Presentative industrially valuable chemicals produced from HMF



PET

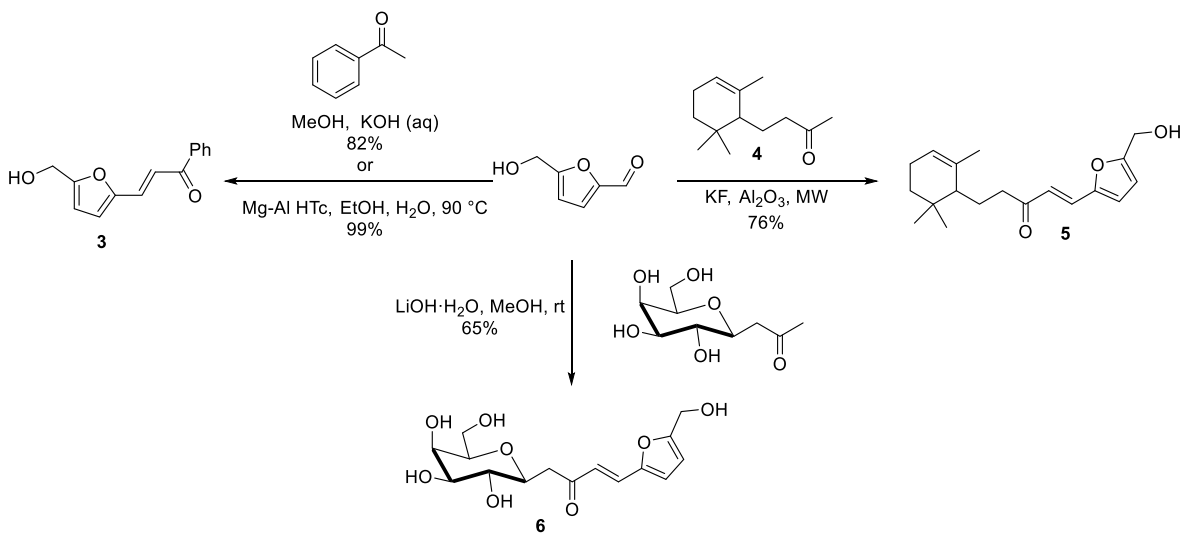
Different research groups have explored the reaction of acetone with HMF under basic conditions. This transformation provides a straightforward access to the natural products rhemanones A, B and C, owning interesting biological activities such as blood platelet aggregation inhibitors or immunostimulant. The challenge relies on the control of the mono- or bis-condensation between the ketone and HMF, as the monoadduct leads to rhemanone B and C, whereas bis-condensation gives an advanced intermediate for the preparation of rhemanone A (Table 3). The group of Tamariz used sodium hydroxide to promote the reaction, and a good control of the selectivity (ratio **1** vs **2**) was obtained by tuning the quantity of acetone used.^[40] The yield of mono adduct **1** reached 91% when acetone was used in excess, whereas the di-adduct **2** was obtained in 60% yield when HMF was used in excess. Palkovits described a selective condensation mediated by mesoporous magnesium aluminate (81% yield of **1** and 11% yield of **2**).^[41] Roman-Leshkov carried out the condensation using hafnium- β zeolite as a catalyst, providing the mono-adduct **1** with 73% conversion and >99% selectivity.^[42] Another selective mono-condensation, promoted by CO₂ under elevated pressure with an excellent yield, was reported by Jessop.^[43] A high conversion to the mono-adduct **1** was obtained under heterogeneous catalytic conditions using amine-grafted Faujasite (FAU) zeolite nanosheets.^[44] Zirconium carbonate was also used to promote the same condensation under mild conditions.^[45]

Table 3. Synthesis of the precursors of rhemanones

Rhemanone A
 Blood platelet aggregation inhibitor
 R = Me **Rhemanone B**
 R = H **Rhemanone C**
 Immunostimulant

Entry	Conditions	Product (yield)	Ref
1	Acetone (2 eq.), NaOH (aq), EtOH, rt	1 (91%)	[40]
2	Acetone (0.5 eq.), NaOH (aq), EtOH, rt	2 (60%)	[40]
3	Acetone (as solvent), MgAl ₂ O ₄ , 140 °C	1 (81%) + 2 (11%)	[41]
4	Acetone (3 eq.), Hf-Beta zeolite, toluene, 90 °C	1 (73% conv)	[42]
5	Acetone (solvent), H ₂ O, 2.5 MPa CO ₂ , 200 °C, 20 h	1 (95%)	[43]
6	Acetone (solvent), amine-grafted FAU nanosheets, 130 °C	1 (92% conv)	[44]
7	Acetone (20 eq.), zirconium carbonate, H ₂ O, 54 °C	1 (92%)	[45]

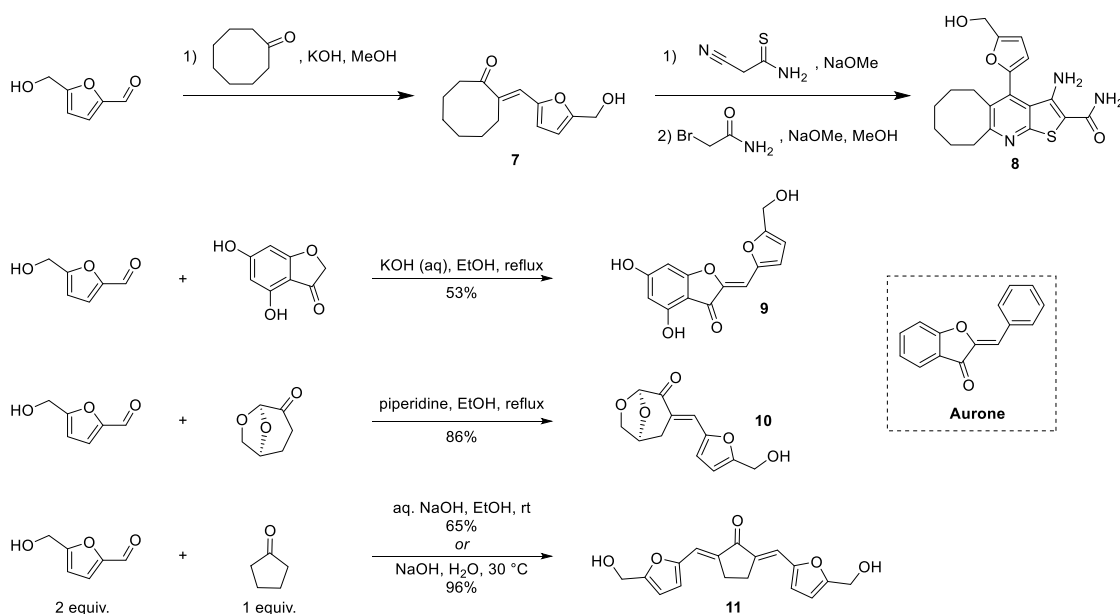
Skowronski^[46] and Corma^[47] independently reported the efficient condensation of acetophenone derivatives with HMF. The reaction, promoted by potassium hydroxide in methanol, produced 5-hydroxymethyl-furfurylidene-acetophenone **3**, later named furanochalcone, in 82 % yield (Scheme 4). The same transformation was also performed with almost quantitative yield in the presence of Mg-Al mixed oxide (HTc). Different 5-hydroxymethyl furanochalcones have then been prepared following similar strategies, and evaluated for diverse biological activities, such as phosphatase inhibitor^[48] or synergistic antifungal.^[49] The group of Surwayanshi described the preparation of the enone **5** by condensation of the dihydro- α -ionone **4** with HMF under microwave irradiation using KF and aluminate as heterogeneous bases.^[50] The product **5** was then evaluated for its antileishmanial properties. A condensation with 1-C-(β -D-galactopyranosyl)-propan-2-one in the presence of lithium hydroxide was performed to prepare the galactose-derived chalcone **6** in 65% yield, which proved to be an effective antimycobacterial agent (Scheme 4).^[51] A C-4 epimer of **6** from 1-C- β -glucosylacetone could also be prepared in dichloromethane in the presence of pyrrolidine in 87% yield.^[52]



Scheme 4. Condensation with ketones

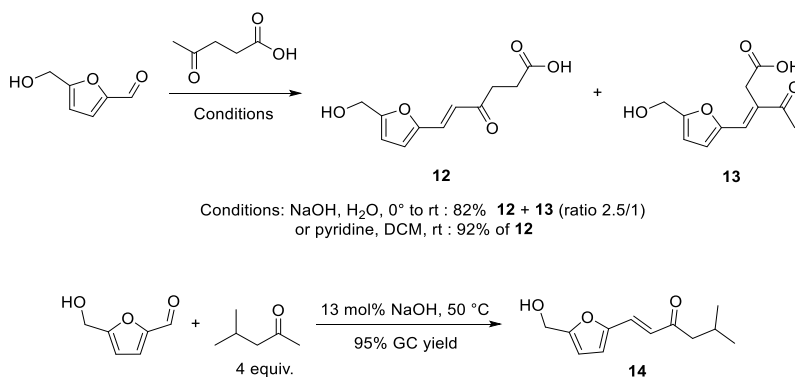
Some more elaborated ketones have been employed in aldol condensations with HMF to produce molecules with high added-value. One example relies on its condensation with cyclooctanone to generate the intermediate **7**, which can be further converted into the thieno[2-3-*b*]pyridine **8**, found to be active against the elongation factor-2 kinase (eEF2-K) (Scheme 5).^[53] Some benzofuran-3-ones were also employed to condense with HMF to prepare the furanic analogues of aurone. The KOH-mediated aldol condensation of dihydroxybenzofuranone with HMF provided **9** in 53% yield.^[54] The reaction between benzofuranone and HMF under microwave

irradiation in a deep eutectic solvent gave only 20% yield of the corresponding product.^[55] Finally, a base-catalyzed aldol condensation between dihydrolevoglucosenone and HMF was described by Witczak and Bielski.^[56] Piperidine gave superior efficiency when the reaction was conducted in refluxing ethanol, providing the chiral building block **10** in 86% yield. The base-mediated double condensation of cyclopentanone on HMF proved to be an efficient route towards molecule **11**. This compound has been studied as a synergistic antifungal agent,^[57] but also constituted a valuable intermediate in the preparation of long-chain cycloalkanes from bio-renewable resources.^[58]



Scheme 5. Condensation on more elaborated ketones as targets in medicinal chemistry

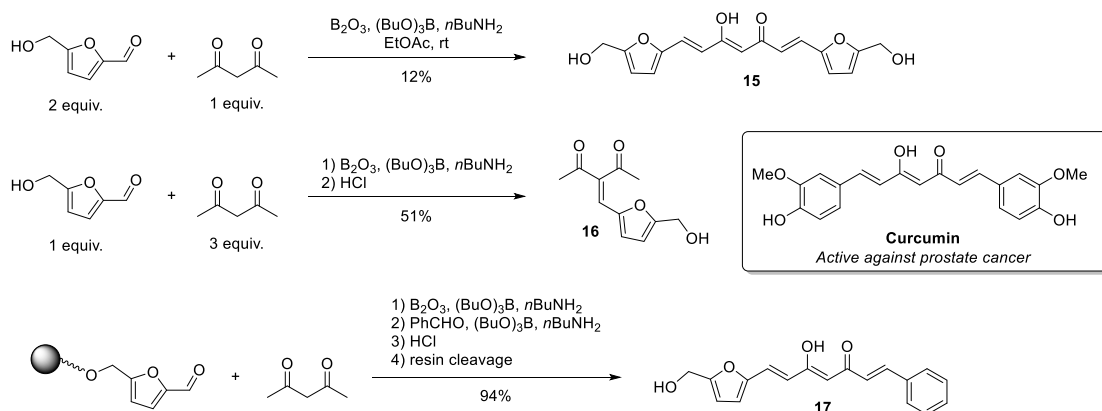
The condensation of unsymmetrically substituted ketones bearing two enolizable positions with HMF raises a problem of regioselectivity, as it can be seen in the following examples. Aqueous sodium hydroxide was employed by Amarasekara and coworkers to condense levulinic acid on HMF.^[59] The reaction produced a mixture of kinetic and thermodynamic products (respectively **12** and **13**) in a 2.5:1 ratio and 82% total yield (Scheme 6). This problem could be avoided by performing the reaction under pyridine/DCM conditions, which only provided the kinetic product **12** in 92% yield.^[52] The condensation of HMF with methyl isobutyl ketone (MIBK) in the presence of NaOH also led to the kinetic product **14** in 95% GC yield (Scheme 6).^[60]



Scheme 6. Regioselective condensation with levulinic acid or MIBK

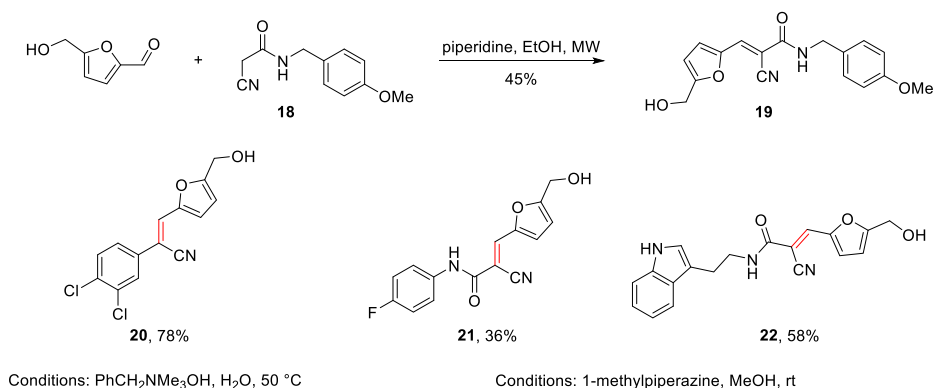
The regioselective condensation of acetylacetone with HMF was also studied (Scheme 7). Acetylacetone bearing highly acidic protons at *C3* position, the selective condensation at *C1* and/or *C5* without the formation of the Knoevenagel adduct (*C3* condensation) represented a synthetic challenge and could lead to curcumin analogs. A solution emerged from Lee's group^[61] who developed a double *C1* and *C5* enolization in the presence of boric anhydride, tributylborate, butylamine and an excess of HMF, giving the symmetrical double condensation product **15** but only in 12% yield. When the same reaction was carried out with an excess of acetylacetone, the Knoevenagel adduct **16**, arising from the functionalization at *C3*, was obtained in 51% yield.^[62]

The most efficient alternative reported to date for the synthesis of unsymmetrical HMF-derived curcumin analogues such as **17**, consisted in a solid-phase synthesis strategy. Supporting HMF on a 2-chlorotriethyl chloride resin led to a significant improvement of the yields.^[63] After completion of the reaction, the resin was cleaved by treatment with a mixture of DCM/TFA/MeOH, releasing the desired product **17** in excellent yield (Scheme 7).



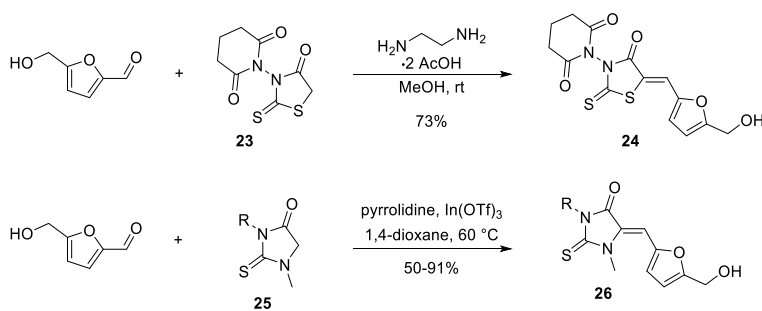
Scheme 7. Strategies for regioselective aldolisation of HMF with acetylacetone

The cyanoamide **18** was reacted with HMF to produce the cyano-acrylamide **19** under microwave irradiation in a modest yield (45%) (Scheme 8).^[64] McCluskey and coworkers carried out the reaction of dichlorophenylacetonitrile and HMF by phase transfer catalysis which provided the acrylonitrile **20** in 78% yield (Scheme 8).^[65] In parallel, two other derivatives **21** and **22** (supposed to exhibit anti-senile dementia activities) were prepared by condensation with corresponding activated methylene compounds.^[66]



Scheme 8. Condensation of nitrile derivatives with HMF

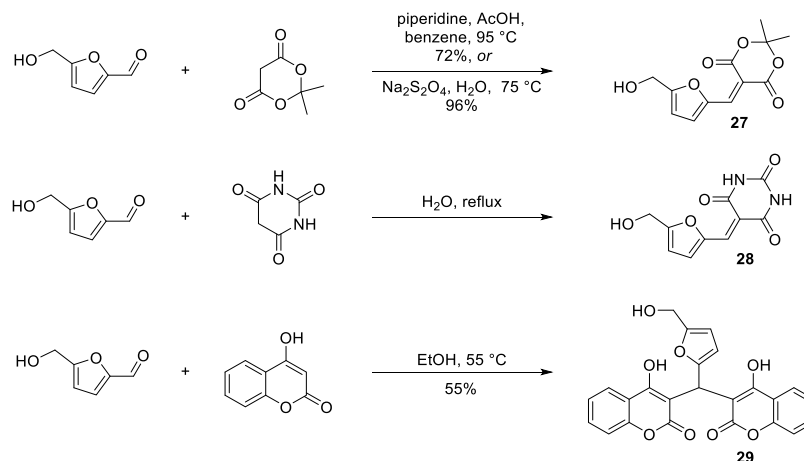
Cyclic amides such as rhodanine **23**^[67] and thiohydantoin **25**^[68] have been employed for the preparation of 5-hydroxymethylfurfurylidene-substituted heterocycles, designed for pharmacological tests (Scheme 9). The furfurylidene-rhodanine **24** was obtained in the presence of ethylenediammonium diacetate with 73% yield whereas thiohydantoin **26** were formed in the presence of pyrrolidine and Lewis acid indium triflate.



Scheme 9. Cyclic amides in the condensation with HMF

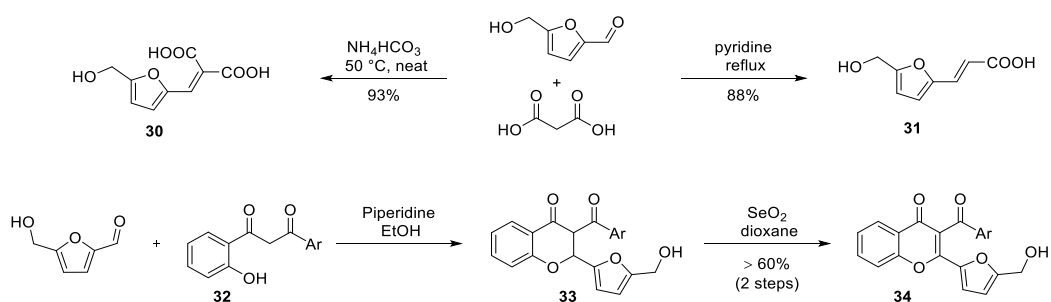
Several activated methylene compounds have been used in Knoevenagel-type condensations with HMF yielding push-pull olefins which could be further used as building blocks or directly studied for their biological properties. Highly acidic cyclic 1,3-dicarbonyl derivatives such as Meldrum's acid and barbituric acid proved their efficiency, reacting with HMF smoothly. The condensation

with Meldrum's acid using a mixture of piperidine and acetic acid in benzene afforded compound **27** in 72% yield, and its antitumor and psychotropic activities were evaluated (Scheme 10).^[69] Another experimental procedure reported by Afonso's group referred to the use of water as solvent with 1 wt% Na₂S₂O₄, leading to 96% yield of **27**.^[21] The same group also reported an interesting transformation of **27** to lactone-fused cyclopentenones by treatment with various amines.^[70] Nikolov et al. carried out the condensation between HMF and barbituric acid in refluxing water, and assessed the photochemical properties of the product **28**.^[71] Finally, 4-hydroxycoumarin reacted with HMF without a catalyst to produce dimeric compound **29** in 55% yield, where the mono-addition led to the Knoevenagel intermediate exhibiting structural analogy with the *ortho*-quinone methide skeleton, facilitating the addition of a second molecule of 4-hydroxycoumarin.^[72]



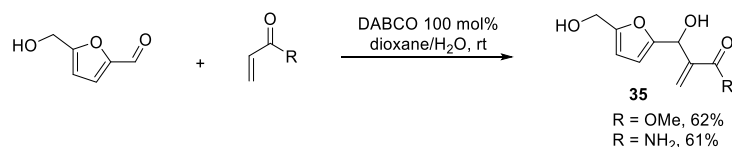
Scheme 10. Condensation of cyclic activated methylene derivatives with HMF

Acyclic activated methylene compounds are also good nucleophiles for condensation with HMF. For example, the reaction of HMF with malonic acid in the presence of ammonium bicarbonate without solvent at 50 °C afforded the product **30** in 93% yield.^[73] Decarboxylation took place at a higher temperature in pyridine, leading to the acrylic acid **31** with 88% yield.^[46, 52] Finally, the Knoevenagel condensation of the dione **32** promoted by piperidine allowed the preparation of the dihydrochromone **33** which could be rapidly converted into the chromone **34**, a photo-activable fluorophore (Scheme 11).^[74]



Scheme 11. Condensation of acyclic activated methylene compounds

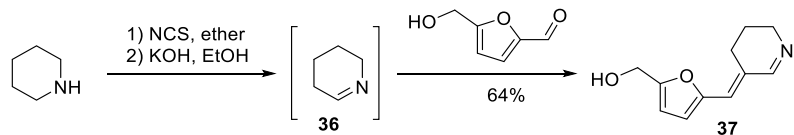
A last type of C-C bond forming reaction with carbonyl derivatives exploiting the Morita-Baylis-Hillman reaction has been reported. The use of electron-deficient alkenes such as methyl acrylate^[75] and acrylamide^[76] in combination with DABCO in a dioxane/water mixture at room temperature gave access to conjugated compounds **35** (Scheme 12). Our group more recently extended this reactivity to glycosylated derivatives of HMF.^[77-78]



Scheme 12. Morita-Baylis-Hillman reaction of HMF

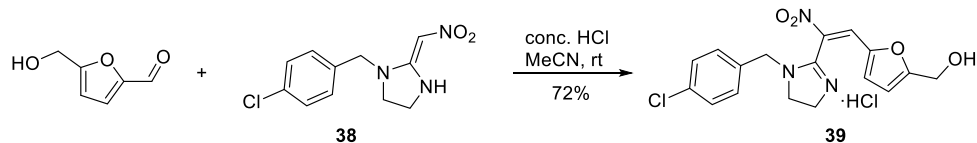
1.2.1.1.2. Reactions with enamines and other nucleophiles

Compound **37** was identified as a side product of the reaction between D-glucose and L-lysine under acidic conditions. In order to support the mechanism explaining its formation, compound **37** was prepared by reacting HMF with the cyclic imine **36** (obtained from piperidine by treatment with *N*-chlorosuccinimide and potassium hydroxide) in 64% yield (Scheme 13).^[79]



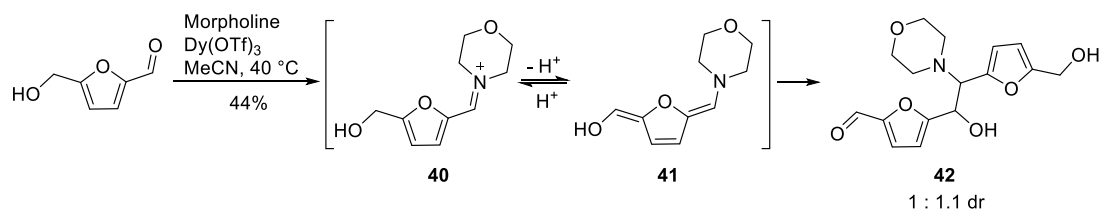
Scheme 13. Condensation of HMF with imine **36**

Condensation of the diaminonitroalkene **38** with HMF in the presence of concentrated hydrochloric acid in MeCN at room temperature provided the neonicotinoid **39** in 72% yield, which exhibited 18.8 fold insecticidal potency against *Nephotettix bipunctatus* compared with imidacloprid (Scheme 14).^[80]



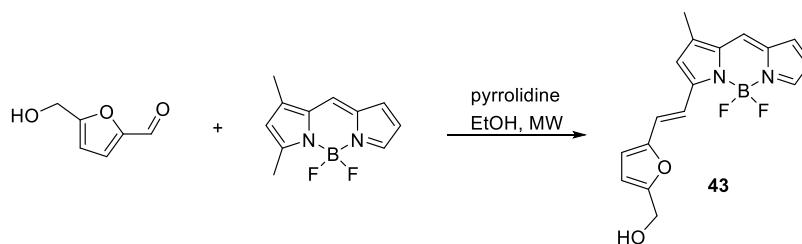
Scheme 14. Condensation of HMF with activated enamine **38**

Afonso and coworkers reported the preparation of a highly functionalized furan skeleton *via* a novel reaction pathway from HMF or *O*-protected HMF and a secondary amine.^[81] HMF could react with morpholine to provide the iminium intermediate **40**, which is in equilibrium with the trienamine **41** under acidic catalysis (Scheme 15). The two intermediates react together, releasing a molecule of amine to yield the coupling product **42**.



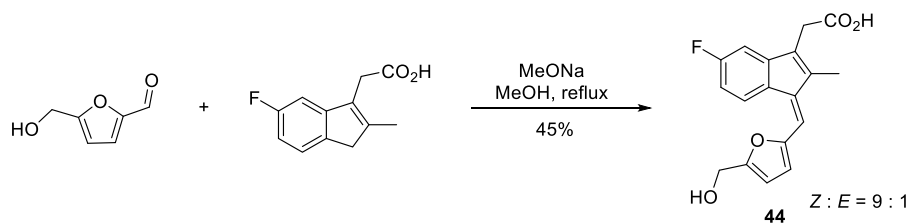
Scheme 15. Homo-bis-vinylogous Mannich-type reaction on HMF

The HMF-modified boron-dipyrromethene (BODIPY) **43** was prepared *via* a aldol-like condensation between HMF and 1,3-dimethyl-BODIPY in the presence of pyrrolidine under microwave irradiation (Scheme 16).^[82]



Scheme 16. Synthesis of a BODIPY molecule

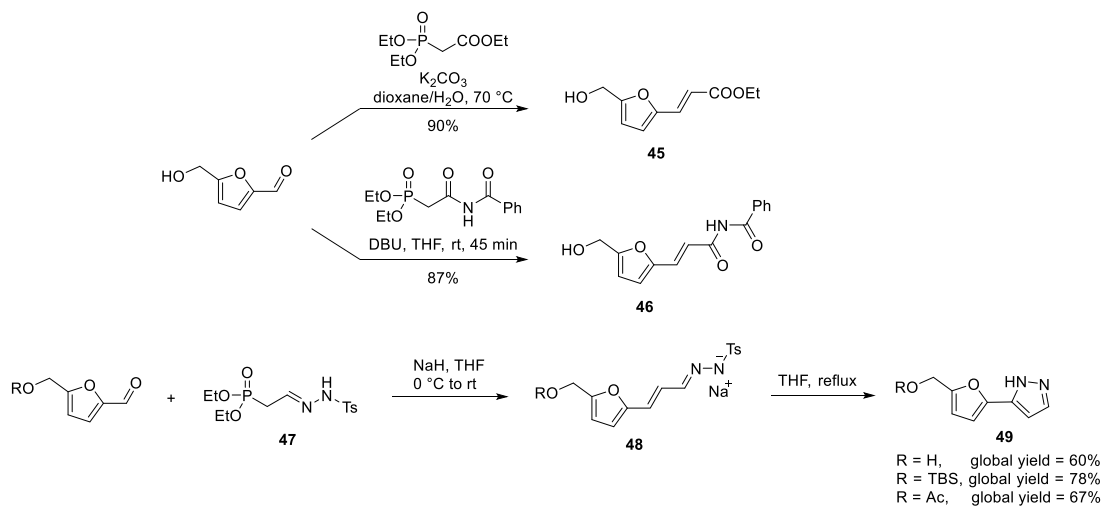
The indene derivative **44** was prepared as a mixture of isomers by condensation of 2-methylindene-3-acetic acid and HMF in the presence of sodium methoxide in refluxing methanol, and its sodium salt displayed anti-proliferative activity (Scheme 17).^[83]



Scheme 17. Condensation with 2-methylindene-3-acetic acid

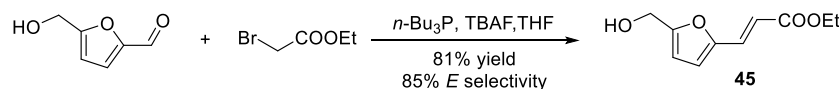
1.2.1.1.3. Alkenylation and alkylation

In 1984, the first Horner-Wadsworth-Emmons reaction of HMF was reported by Delmas. Reaction of HMF with triethylphosphonoacetate in the presence of potassium carbonate in a mixture of 1,4-dioxane and water afforded the α,β -unsaturated ester **45** as *E* isomer exclusively in 90% yield (Scheme 18).^[84] When the reaction was performed in alcoholic medium such as *n*-octanol, further transesterification occurred.^[85] A DBU-mediated Horner-Wadsworth-Emmons reaction on HMF was used to synthesize α,β -unsaturated imide **46**, which was obtained as a single distereoisomer in 87% yield.^[86] The Horner-Wadsworth-Emmons reaction of HMF was also used as the key step in a one-pot preparation of substituted pyrazoles.^[87] HMF or *O*-protected derivatives reacted with diethoxyphosphorylacetaldehyde tosylhydrazone **47** in the presence of NaH in THF, yielding α,β -unsaturated tosylhydrazones sodium salts **48**, which released sodium *p*-toluenesulphonate and underwent cyclization upon heating THF to reflux to provide the pyrazoles **49** in 60-78% yield for 2 steps (Scheme 18).



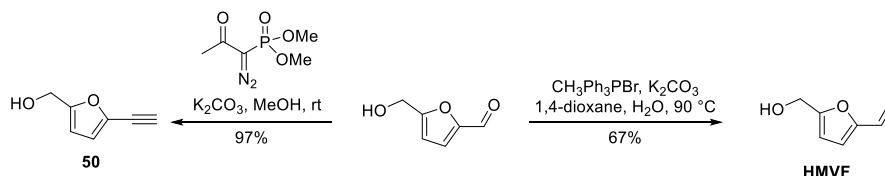
Scheme 18. Horner-Wadsworth-Emmons reactions on HMF

The α,β -unsaturated ester **45** could also be prepared by one-pot Wittig reaction. The *in situ* formed Wittig reagent from ethyl α -bromoacetate and tributylphosphane reacted with HMF in the presence of *tetra-n*-butylammonium fluoride (TBAF) providing **45** with 81% yield and 85% selectivity in favor of *E* isomer (Scheme 19).^[88]



Scheme 19. One-pot Wittig reaction on HMF

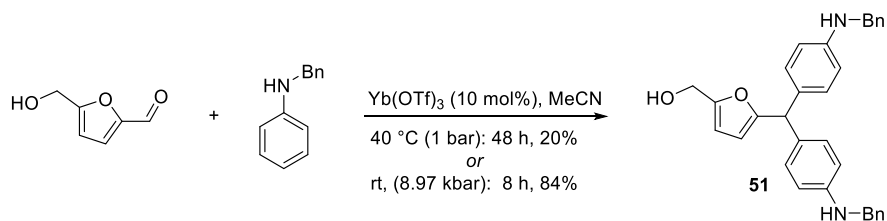
The synthesis of monomer 5-hydroxymethyl-2-vinylfuran (HMFV) was achieved using methyltriphenylphosphonium bromide and potassium carbonate in 67% yield, as an adaptation of a procedure reported on furfural (Scheme 20).^[89] The resulting HMFV could be efficiently polymerized by AIBN-initiated radical polymerization. Recently, Ji demonstrated that HMFV itself exhibits strong adhesion to metals *via in-situ* polymerization and crosslinking after either heating or acid treatment, concluding that HMFV could serve as a biomass-based adhesive.^[90] Direct alkenylation of HMF to **50** was performed with 97% yield using the Ohira–Bestmann reagent in MeOH in the presence of K_2CO_3 (Scheme 20). 2-Hydroxymethyl-5-ethynylfuran **50** was used as a platform to conduct various chemical transformations targeting furanic pharmaceuticals as well as conjugated polymers.^[91]



Scheme 20. Direct alkenylation and alkynylation of HMF

1.2.1.1.4. Friedel-Crafts reactions

The synthesis of the symmetric triarylmethane **51** was achieved by reaction of a secondary aniline on HMF in the presence of $Yb(OTf)_3$, following a double Friedel-Crafts reaction (Scheme 21).^[92] The scope of the reaction was successfully extended to *O*-substituted hydroxymethylfurfurals. The reaction was found to be significantly accelerated by high pressure, especially in the case of less reactive anilines. The authors suggested that the first Friedel-Crafts reaction proceeded *via* the addition of the aniline to a transient iminium ion formed by reaction of secondary aniline and aldehyde. Then a second Friedel-Crafts reaction took place in a non-concerted mechanism suggesting a secondary carbocation as the transient intermediate for this step.



Scheme 21. Synthesis of symmetric triarylmethanes *via* Friedel-Crafts mechanism

1.2.1.1.5. Benzoin condensation

The benzoin condensation is an efficient method to upgrade HMF to C₁₂ furoins, potential fuel intermediates. During the course of a study on the degradation of HMF in ionic liquids such as 1-ethyl-3-methylimidazolium acetate ([EMIM]OAc), Chen found that 1-ethyl-3-methylimidazolin-2-ylidene carbene could catalyze the self-condensation of HMF to form 5,5'-dihydroxymethylfuroin with high conversion and selectivity (Table 4).^[93] Since this pioneering

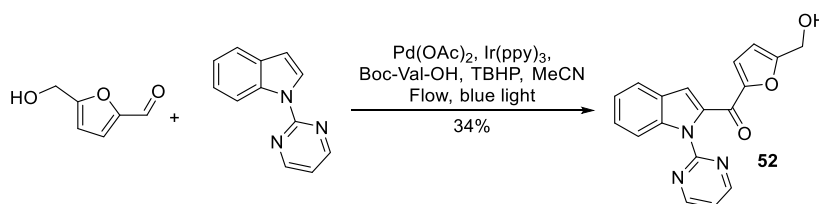
Table 4. Organocatalysis and biocatalysis for benzoin condensation

Entry	Catalyst	Conditions	Yield	Ref
1		[EMIM]OAc, 80 °C	50% (isolated)	[93]
		or 5 mol% [EMIM]Cl, DBU, THF, 80 °C	or 97% (HPLC)	
2	 TPT	0.1-5 mol% TPT, neat or in THF, 60 °C	87-95% (isolated)	[93-95]
3		10 mol% Silica-g-[BI]-C ₁₂ azolium salt, DBU, THF, 25 °C, 6 h	94% (NMR)	[96]
4		Thiazolium derived ILs, Et ₃ N, 120 °C	97-98% (NMR)	[97-98]
5	Benzaldehyde lyase	potassium phosphate buffer /DMSO, rt	70% conversion	[99]

work, several NHC catalysts derived from ILs and discrete catalysts proved their efficiency for the benzoin condensation of HMF.^[94-98] Benzaldehyde lyase could also be used as a biocatalyst for this umpolung condensation.^[99] However, under those conditions, a partial spontaneous oxidation to the corresponding diketone was observed.

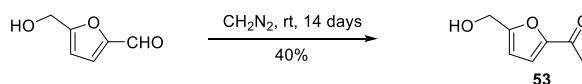
1.2.1.1.6. Oxidative transformations

Van der Eycken and Noël reported a C-2 acylation protocol for *N*-pyrimidylindole using a range of aldehydes as acylating reagents *via* dual photoredox/transition-metal catalysis in flow conditions (Scheme 22).^[100] In this work, HMF also showed certain reactivity leading to compound **52**, but with a low isolated yield (34%) in comparison with furfural (85%). This important difference of yields between similar substrates suggests detrimental effect of the hydroxymethyl group, moderately compatible with an oxidative single electron transfer pathway.



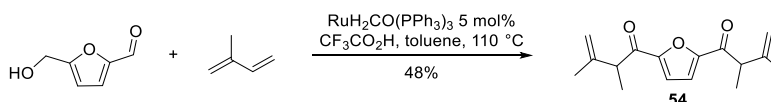
Scheme 22. Acylation of indole using HMF in a photoredox strategy

Following the Büchner-Curtius-Schlotterbeck reaction, HMF was reacted with diazomethane yielding 1-(5-(hydroxymethyl)furan-2-yl)ethan-1-one **53** in 40% yield after 14 days (Scheme 23).^[101]



Scheme 23. Reaction between HMF and diazomethane

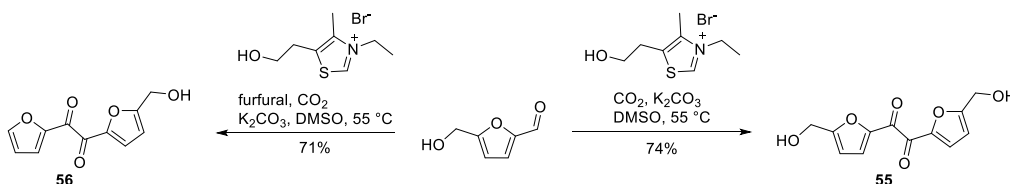
De Vries and coworkers reported a ruthenium dihydride complex-catalyzed double coupling reaction between HMF and isoprene, leading to compound **54** in 48% yield (Scheme 24).^[102]



Scheme 24. Coupling of HMF and isoprene

Das reported a novel route to prepare α -diketone by performing the NHC-catalyzed HMF self-

condensation in DMSO under CO₂ atmosphere (Scheme 25).^[103] DFT calculations lightened the role of CO₂ in the mechanism, by reacting with the hydroxyl group of the so formed furoin, producing a carboxylate, which is a good leaving group. DMSO was prone to act as an oxidant allowing the access to the diketone **55**. The non-symmetrical α -diketone **56** could also be prepared in good yield employing a 1:1.5 ratio of furfural and HMF, although the formation of the homo α -diketone could not be suppressed completely.



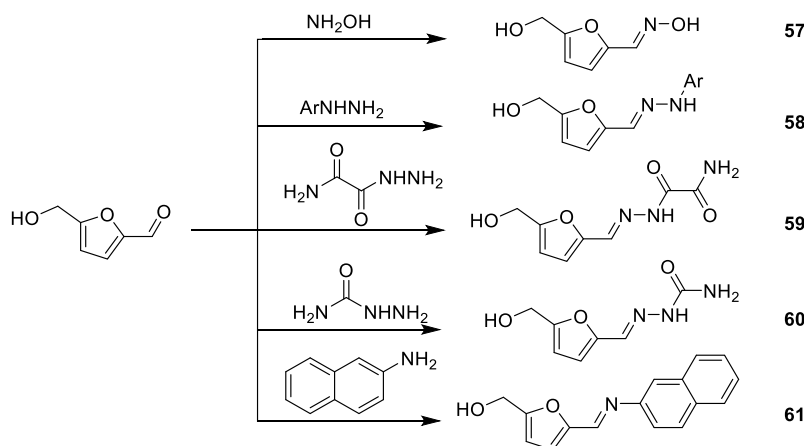
Scheme 25. NHC and CO₂-mediated homo and cross-coupling of HMF

1.2.1.2. C-N bond formation reactions

The condensation of nitrogen nucleophiles with the aldehyde moiety of HMF can provide a variety of new molecules with interesting properties. It can also be a step of more complex chemical sequences towards nitrogen-containing scaffolds that can be useful for agrochemical and pharmaceutical applications.

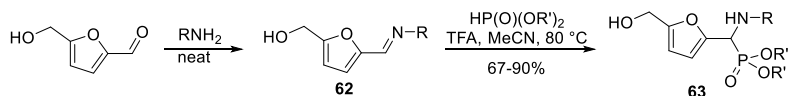
1.2.1.2.1. Synthesis of imines, hydrazones, oximes and nitrones

In the early stage study on HMF from the end of the 19th century to the beginning of the 20th century, researchers already showed that HMF could react with a range of nitrogen nucleophiles, such as hydroxylamine, arylhydrazine, semioxamazide, semicarbazide or amine to form respectively oxime **57**, hydrazone **58**, semioxamazone **59**, semicarbazone **60** and imine **61**^[104] (Scheme 26).^[12] These reactions with nitrogen nucleophiles were carried out mainly for purification and identification purposes because the products are often in crystalline form and easy to handle.



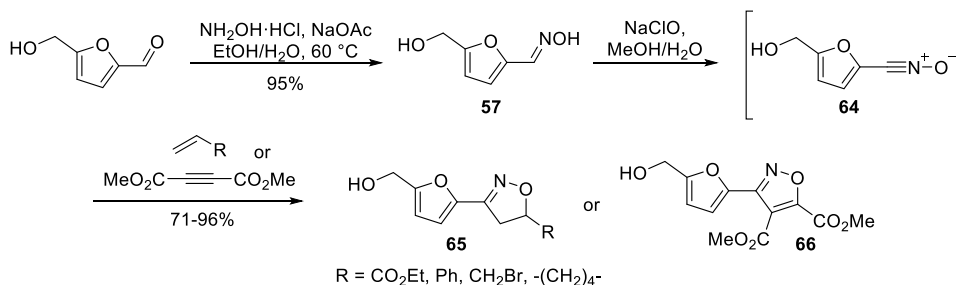
Scheme 26. Reactions between HMF and diverse nitrogen-nucleophiles in early studies

Skowroński et al. prepared a couple of imines **62** from HMF and subjected them to the Pudovik reaction in the presence of a catalytic amount of TFA at 80 °C to prepare the α -aminophosphonates **63** (Scheme 27).^[105] A 2 : 1 *dr* value was observed when a chiral imine derived from chiral 1-methylbenzylamine was employed.



Scheme 27. Synthesis of α -aminophosphonates *via* the Pudovik reaction

Amarasekara reported an interesting application of the HMF-derived oxime **57**.^[106] Oxidation of **57** in aqueous bleach solution provided the nitrile oxide **64**, which readily underwent 1,3-dipolar cycloaddition with alkenes or alkynes to give the corresponding dihydro-isoxazoles **65** or isoxazoles **66** depending on the nature of the dipolarophiles (Scheme 28).



Scheme 28. Application of HMF-derived oxime in 1,3-dipolar cycloaddition

The condensation of HMF with rhodamine B hydrazide delivered the hydrazone **67**, which could serve as a chemosensor for the detection of pH and Cu²⁺.^[107] A couple of HMF-derived *N*-acyl-

hydrazones **68** were prepared as nifuroxazide analogues for antimicrobial activity screening.^[108] Unfortunately, the prepared HMF-based hydrazones **68** displayed no biological properties. The hydrazone **69** was also prepared to study its activity as a kinase inhibitor,^[109] whereas compound **70** (from 1-aminoquinolin-2(1*H*)-one) was studied as a ligand for making metal complexes (Figure 3).^[110]

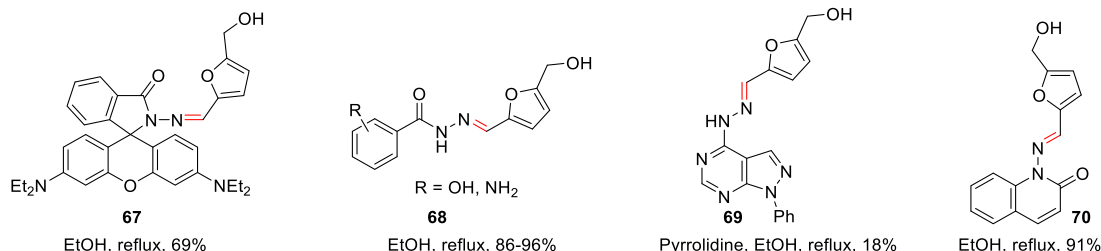
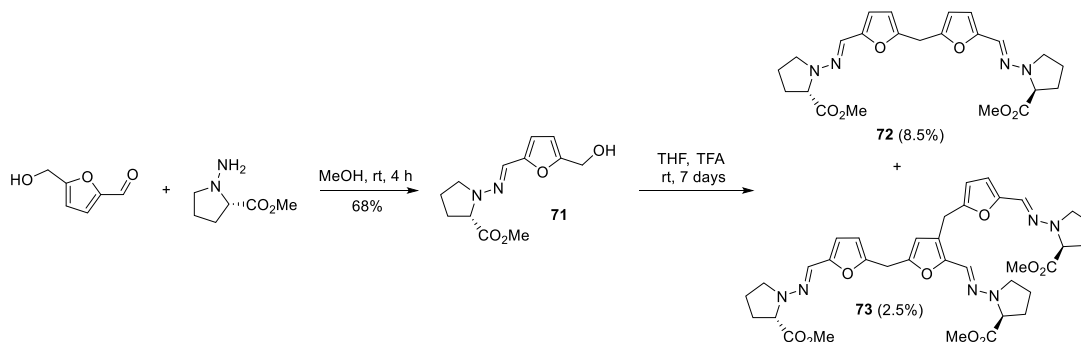


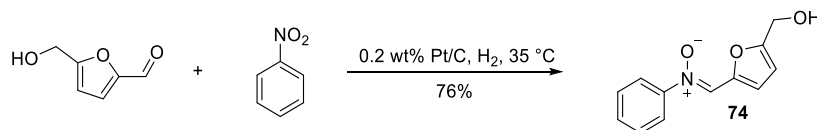
Figure 3. Examples of valuable HMF-based acylhydrazones and hydrazones

Capon and coworkers isolated several naturally occurring prolinimines from a fish gastrointestinal tract-derived fungus, *Trichoderma sp.* CMB-F563 (Scheme 29).^[111] To confirm their structures, the authors performed the biomimetic synthesis of the prolinimine **71** by reacting HMF with *N*-amino-L-Pro methyl ester. Treatment of the prolinimine **71** in acidic conditions led to oligomeric prolinimines **72** and **73**.



Scheme 29. Synthesis of natural prolinimines from HMF

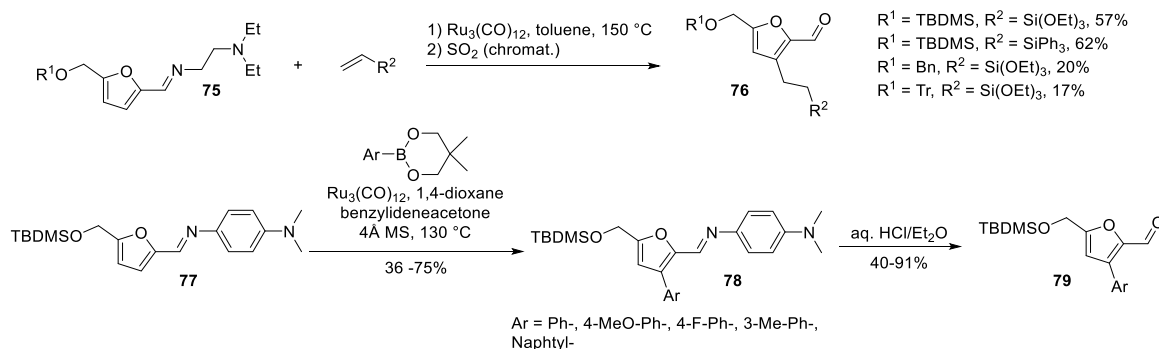
The preparation of nitrone **74** was investigated with heterogeneous reductive coupling of nitrobenzene and HMF under H₂ atmosphere in the presence of platinum nanoparticles (Scheme 30).^[112] Under these conditions, the nitrone **74** could be obtained with 76% isolated yield.



Scheme 30. Preparation of nitrone

The imine directing group assisted C-H activation on the furan ring of HMF *via* the Murai reaction was first reported by Poli, Oble and coworkers (Scheme 31).^[113] A diamine reacted with *O*-protected HMF derivatives to form products **75** in which the amino-imine moiety served as a *N,N'*-bidentate directing group. The reaction was performed using a typical ruthenium catalyst $\text{Ru}_3(\text{CO})_{12}$ and vinylsilanes as olefin partners in toluene at high temperature. The directing group was removed by hydrolysis during the silica gel column chromatography purification to release the C3-functionalized furfurals **76**.

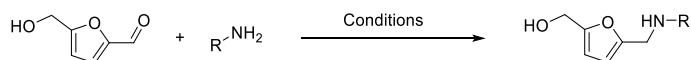
More recently, the same group reported a Ru-catalyzed imine-directed C3-arylation of compound **77** with aryl boronate esters.^[114] In this case, a *p*-dimethylaminophenyl-imine proved to be the best directing group. In contrast to their previous study, the arylated imines **78** could survive from silica gel chromatography purification. The arylated aldehydes with TBDMS retained **79** were obtained after mild hydrolysis with aqueous HCl in Et_2O , sometimes together with deprotected products (Scheme 31).



Scheme 31. Imine as a directing group for C-H activation

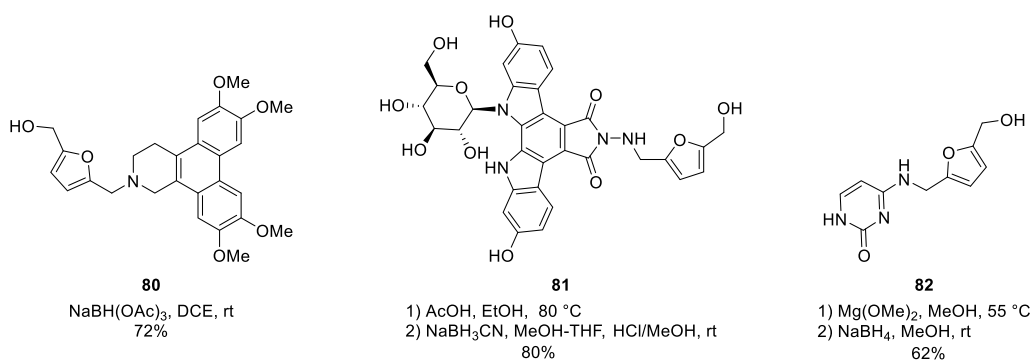
1.2.1.2.2. Preparation of amines

Many examples of reductive amination of HMF to target 5-aminomethyl-2-furfuryl alcohols have been reported (Table 5). The utilization of NaBH_4 as a reducing agent was proved to be efficient,^[115] but many studies described the use of H_2 together with a wide range of heterogeneous catalysts. Other reducing agents such as water and silanes have also been reported. Throughout these studies, aromatic and aliphatic amines, as well as ammonia, were introduced on the HMF scaffold.

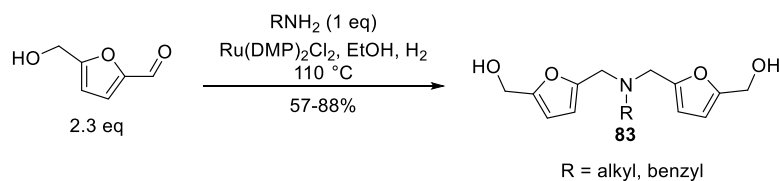
Table 5. Reductive amination with simple amines

Entry	Conditions	RNH ₂	Yield	Ref
1	NaBH ₄ , H ₂ O or EtOH	aromatic/aliphatic amines	77-99%	[115]
2	H ₂ , Raney Ni	NH ₃ (liq.)	72%	[116]
3	H ₂ (1.2 MPa), Ru(DMP) ₂ Cl ₂ , EtOH, 60 °C	aromatic/aliphatic amines	66-95%	[117]
4	H ₂ (2 MPa), Rh/Al ₂ O ₃ , 80 °C	NH ₃ (aq.)	86%	[118]
5	H ₂ (4 MPa), Ru/Nb ₂ O ₅ , MeOH, 90 °C	NH ₃ (in MeOH solution)	96%	[119]
6	H ₂ (2 MPa), RuNPs, MeOH, 90 °C	NH ₃ (in MeOH solution)	95%	[120]
7	H ₂ (4 MPa), CoNPs, <i>t</i> -BuOH, 120 °C	NH ₃ (gas)	89%	[121]
8	H ₂ O/CO (2 MPa)/MeOH, Au/TiO ₂ -R, 60°C	aromatic/aliphatic amines	60-99%	[122]
9	PhMe ₂ SiH, Au@APTES@SBA, IPA, 60 °C	aniline	65%	[123]

The reductive amination was applied to a phenanthropiperidine derivative using NaBH(OAc)₃ as a reducing agent, to deliver the *N*-substituted phenanthropiperidine derivative **80** in 72% yield (Figure 4).^[124] The indolopyrrolocarbazole derivative **81**^[125] and the cytosine derivative **82**^[126] were also synthesized by reductive amination, and their antitumor effect and DNA methylation inhibition activity were respectively studied (Figure 4).

**Figure 4.** Reductive amination with complex amines and derivatives

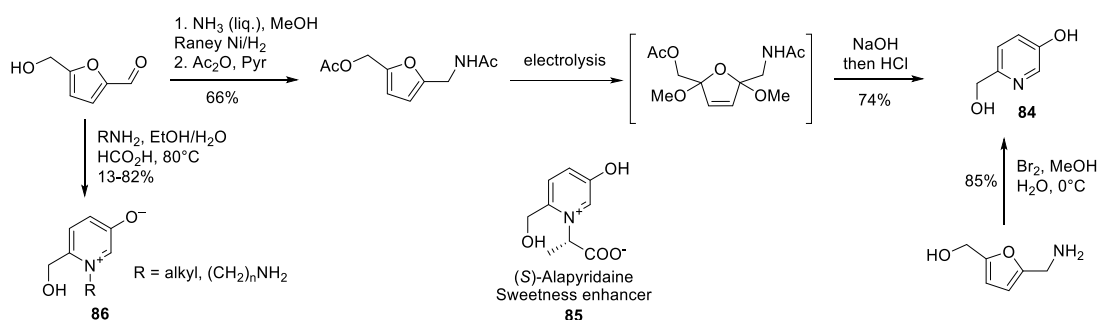
By switching the ratio of HMF and amine, Zhang's group was able to convert HMF to bis(hydroxymethylfurfuryl)amines **83** using Ru(DMP)₂Cl₂ as a catalyst (Scheme 32).^[127] The *in situ* generated secondary amine further reacts with excess HMF to form an iminium ion intermediate, followed by hydrogenation to produce bis(hydroxymethylfurfuryl)amines **83**.



Scheme 32. Double reductive amination

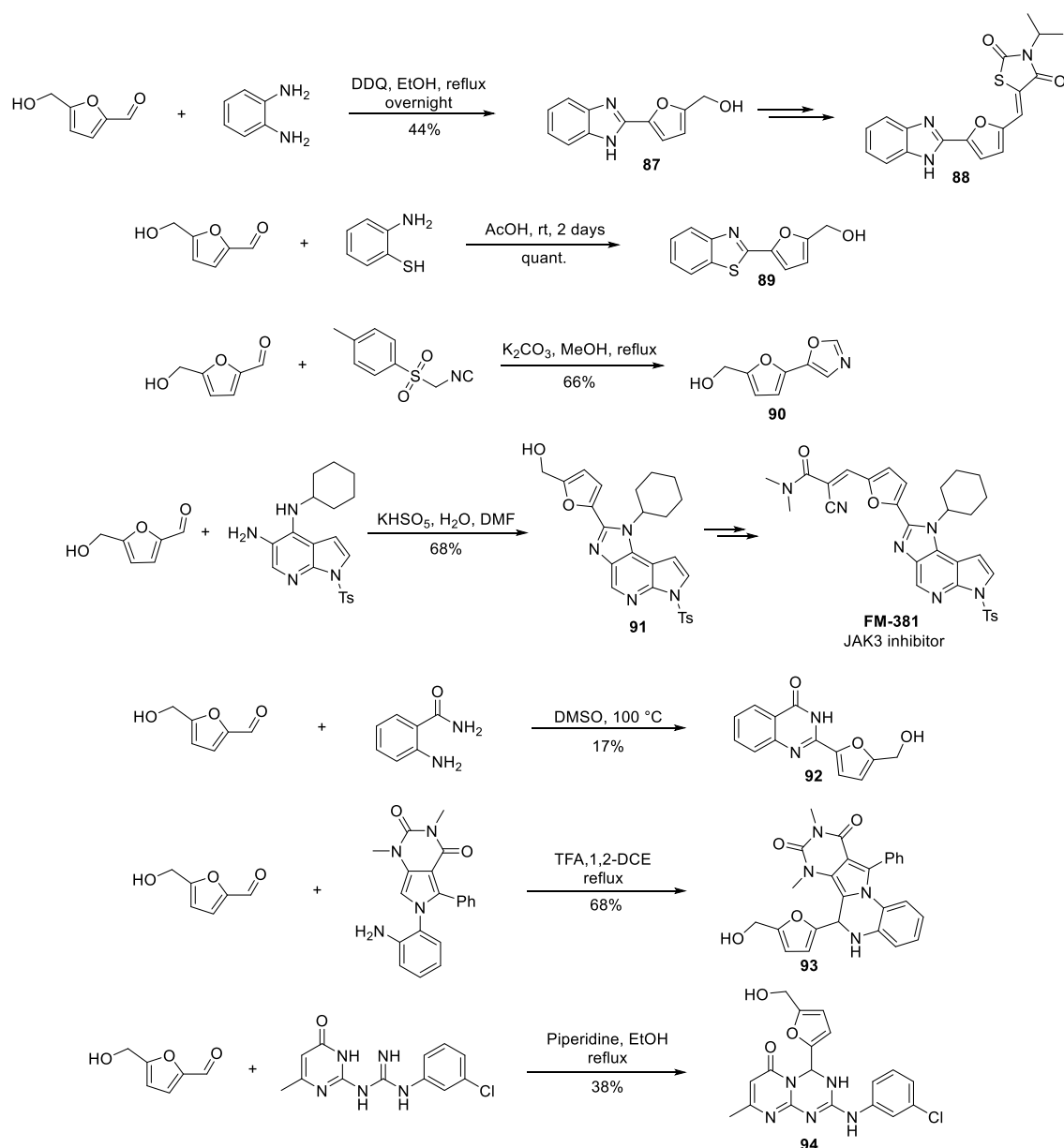
1.2.1.2.3. Synthesis of nitrogen-containing heterocycles

In 1956, Elming reported the synthesis of 6-hydroxymethyl-3-pyridinol **84** starting with reductive amination of HMF, followed by acetylation, electrolysis and rearrangement (Scheme 33).^[116] This compound could also be prepared by exposing 5-hydroxymethylfurfurylamine to bromine in water/methanol at 0 °C.^[128] Enantiopure synthesis of pyridinium salt (*S*)-alapyridaine **85** (a sweetness enhancer) was achieved under Br₂/MeOH/H₂O conditions from the amine formed from the reductive amination of HMF with L-alanine.^[129] Direct treatment of HMF with alkylamines in refluxing EtOH/H₂O under basic conditions (pH ~ 9.4, adjusted with NaOH) has been a frequently-used method to prepared pyridinium inner salts in the past.^[130-132] Several pyridinium betaines derived from glycine, β-alanine and γ-aminobutyric acid proved to be potential bitter-suppressing candidates. More recently, an alternative method employing formic acid as a catalyst in EtOH/H₂O to synthesize pyridinium inner salts **86** from HMF was reported by Afonso and coworkers.^[133]



Scheme 33. Conversion of HMF to pyridinol and pyridinium salt

HMF has been often used for the synthesis of complex heterocyclic compounds included in libraries designed for possible bioactivity evaluations (Scheme 34). For example, the condensation of HMF with *o*-phenyldiamine in the presence of DDQ in refluxing EtOH yielded the benzo[*d*]imidazole derivative **87**, which served as an intermediate for the preparation of molecule **88**, a potential Myc modulator.^[134] Similarly, the benzothiazole **89** was prepared by



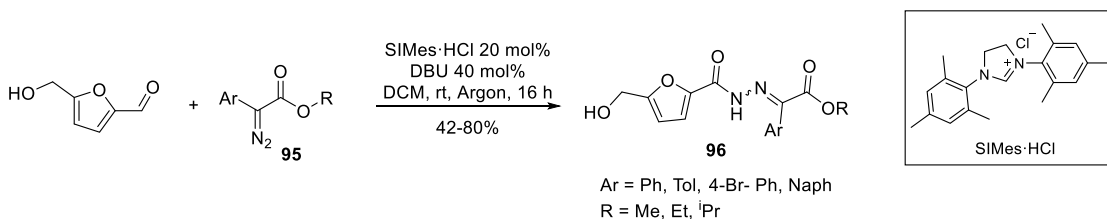
Scheme 34. Synthesis of nitrogen-containing heterocycles

reaction of HMF with 2-aminothiophenol after spontaneous oxidation.^[135] Treatment of HMF with *p*-toluenesulfonylmethyl isocyanide and potassium carbonate in refluxing methanol produced 5-(5-hydroxymethyl-2-furyl)oxazole **90** in 66% yield.^[136] FM-381, an outstanding JAK3 inhibitor, has been synthesized by Laufer and coworkers.^[137-138] HMF was condensed on 4,5-diamino-7-azaindole to provide the tricyclic skeleton **91** as a precursor of FM-381. The furan moiety in FM-381 played a crucial role with respect to the inhibitory activity, as the replacement of the furan link by a phenyl generally led to lower activities. The group of Soava prepared a range

of quinazolinone derivatives such as **92** to study their antimicrobial activities, among which the HMF-derived product did not show significant activities.^[139] A fused tetracyclic heterocycle **93** was prepared in 68% yield by the TFA-catalyzed condensation of HMF and 2-(1*H*-pyrrol-1-yl)aniline derivative.^[140] The condensation of HMF with pyrimidinylguanidine furnished the pyrimido[1,2-*a*][1,3,5]triazin-6-one **94** in 38% yield.^[141]

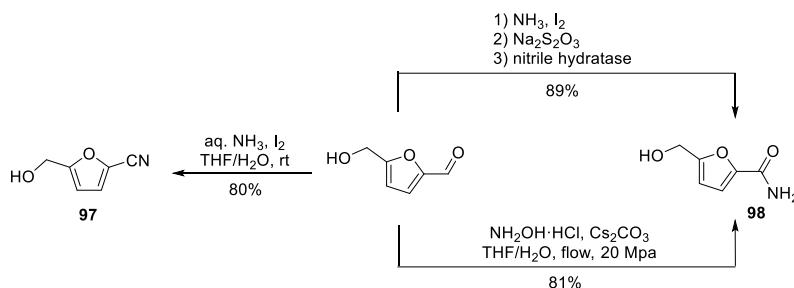
1.2.1.2.4. Oxidative transformations

The reaction of diazo derivatives **95** on HMF catalyzed by *N*-heterocyclic carbene (NHC) allowed the preparation of acylhydrazones **96**, displaying some antitumor activity (Scheme 35).^[142] An *in situ*-generated NHC catalyst (by reacting imidazolidinium SiMes HCl with DBU) was used to reverse the reactivity of the aldehyde group of HMF. The authors observed neither the Cannizzaro reaction nor NHC-catalyzed benzoin condensation. In some cases, the expected acylhydrazone was obtained as a mixture of *E/Z* geometric isomers. The extension of the scope to hydroxymethyl protected substrates pointed out significant differences in terms of reactivity. For example, the HMF protected with a benzoyl group gave only 3% yield of acylhydrazone, while HMF with a benzyl and TBDMS protection afforded 89% and 99% yields respectively.



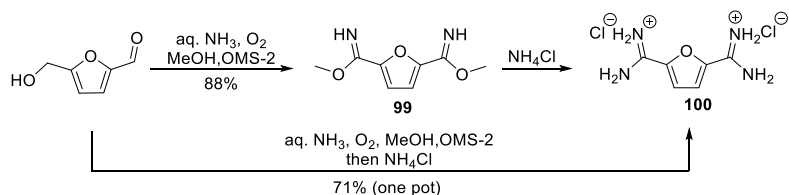
Scheme 35. Reaction between HMF and diazo derivatives

HMF has been converted to the nitrile **97** by treatment with an ammonia solution in the presence of molecular iodine in a mixture of water and THF (Scheme 36).^[143] A similar oxidative cyanation was implemented in a one pot procedure for converting HMF into amide **98**,^[144] where the *in situ*-generated nitrile was hydrolyzed to the corresponding carboxamide under the action of a nitrile hydratase from *R. rhodochrous* IFO 15564. The same transformation could be performed under modified conditions by flow process with hydroxylamine hydrochloride as nitrogen source.^[145] The reaction was completed in 5 minutes taking advantage of the flow chemistry technique.



Scheme 36. Conversion HMF to nitrile **97** and amide **98**

Catalytic oxidation of HMF in the presence of aqueous ammonia and manganese oxide octahedral molecular sieves (OMS-2) as catalysts afforded the bis-imidate **99** in good yield (Scheme 37). Subsequent treatment with ammonium chloride provided the bis-amidine **100**.^[146]



Scheme 37. Transformation of HMF to dicarboximidate and diamidine salt

1.2.1.3. Simultaneous formation of C-C and C-N bonds by multicomponent reactions

Compared to furfural which has been often used as a substrate in multicomponent reactions (MCRs), HMF was barely involved in MCRs. All the reported MCRs involving HMF as a building block occurred on the aldehyde group. In view of its importance, the use of HMF in MCRs is described in a separated section. A short introduction of the multicomponent reaction is provided before discussing the detailed examples.

1.2.1.3.1. General introduction of MCR

A multicomponent reaction (MCR) is generally defined as a reaction in which three or more reactants react to form a single product, incorporating most of the atoms of the reactants into the final product.^[147-148] The concept of MCR is not quite precise. Undoubtedly, MCRs are under the category of one-pot reactions, but the frontier between MCRs and one-pot reactions remains controversial, as it is still discussed whether sequential one-pot reactions where reactants or reagents are added at different stages should be recognized as MCRs or not.^[149-150] Due to the

importance of MCRs in synthetic chemistry, a nomenclature has been established to design a MCR involving n different components, thus called n -CR. Depending on the reactivity of engaged chemical entities and the reaction conditions, the chemical entities in MCRs might assemble in linear form (like the Mannich reaction) or undergo further cyclization (like the Biginelli reaction) to provide complex molecules.

MCRs have been known for more than 160 years. The reaction of an aldehyde, ammonia and hydrogen cyanide discovered by Adolph Strecker in 1850 was generally recognized as the first MCR.^[151] Since then, numerous nowadays popular MCRs have been reported, such as the Hantzsch dihydropyridine synthesis (1881),^[152] the Biginelli reaction (1891),^[153] the Mannich reaction (1912),^[154] the Passerini reaction (1921),^[155] and the Ugi reaction (1959)^[156] (Table 6). The fact that all these MCRs are name reactions undoubtedly indicates the tremendous interest of MCRs in organic synthesis.

Table 6. Examples of some well-known MCRs

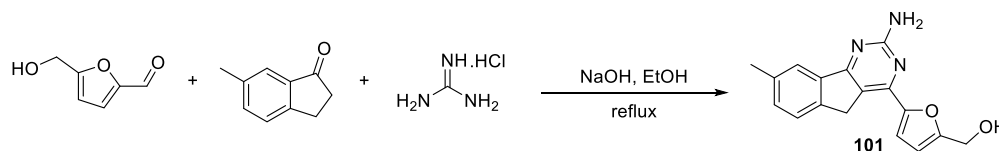
Strecker reaction	$\text{R}-\text{CHO} + \text{HCN} + \text{NH}_3 \longrightarrow \text{R}-\text{CH}(\text{NH}_2)\text{CN} \xrightarrow{\text{H}^+} \text{R}-\text{CH}(\text{NH}_2)\text{COOH}$
Hantzsch dihydropyridine synthesis	$\text{R}^1-\text{CHO} + \text{R}^2-\text{CO}-\text{CH}_2-\text{CO}-\text{OR}^3 + \text{NH}_3 \longrightarrow \text{R}^3\text{O}-\text{C}(=\text{O})-\text{C}(\text{R}^1)=\text{C}(\text{R}^2)-\text{N}(\text{H})-\text{C}(\text{R}^2)=\text{C}(=\text{O})-\text{OR}^3$
Biginelli reaction	$\text{R}^1-\text{CHO} + \text{R}^2-\text{CO}-\text{CH}_2-\text{CO}-\text{OR}^3 + \text{H}_2\text{N}-\text{C}(=\text{O})-\text{NH}_2 \longrightarrow \text{R}^3\text{O}-\text{C}(=\text{O})-\text{C}(\text{R}^1)=\text{C}(\text{R}^2)-\text{N}(\text{H})-\text{C}(=\text{O})-\text{NH}_2$
Mannich reaction	$\text{R}^1-\text{CHO} + \text{R}^2-\text{NH}-\text{R}^3 + \text{R}^4-\text{CO}-\text{CH}_2-\text{R}^5 \longrightarrow \text{R}^1-\text{CH}(\text{R}^5)-\text{N}(\text{R}^2)(\text{R}^3)-\text{CH}_2-\text{C}(=\text{O})-\text{R}^4$
Passerini reaction	$\text{R}^1-\text{CHO} + \text{R}^2-\text{COOH} + \text{R}^3\text{NC} \longrightarrow \text{R}^2-\text{O}-\text{C}(=\text{O})-\text{CH}(\text{R}^1)-\text{C}(=\text{O})-\text{NHR}^3$
Ugi Reaction	$\text{R}^1-\text{CHO} + \text{R}^2-\text{COOH} + \text{R}^3\text{NC} + \text{R}^4\text{NH}_2 \longrightarrow \text{R}^2-\text{O}-\text{C}(=\text{O})-\text{N}(\text{R}^4)-\text{CH}(\text{R}^1)-\text{C}(=\text{O})-\text{NHR}^3$

MCRs possess many apparent advantages over multistep processes, like high efficiency, atom economy, reduced waste generation, time and energy economy and so on. These features comply with the majority of Anastas and Warner's principles of green chemistry,^[1] and make MCR an ideal synthetic strategy. Indeed, MCRs have been widely used in combinatorial chemistry,

sometimes in combination with solid-phase synthesis and the split-pool technique, to produce large libraries of molecules for the discovery of lead chemicals in the fields of pharmaceutical and agrochemical chemistry.^[157-158] Recently, the utilization of MCRs in polymer chemistry has also been revealed as a promising strategy to make highly functionalized polymers.^[159]

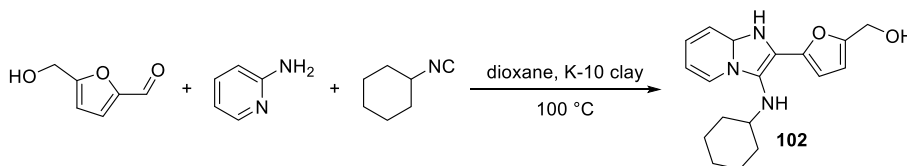
1.2.1.3.2. The use of HMF in MCRs

Tulshian and coworkers carried out a variant of the Biginelli reaction of HMF to prepare adenosine receptor (A_{2A}) antagonists (Scheme 38).^[160] The condensation of HMF, indanone and guanidine in refluxing EtOH provided the compound **101**, with very few information about the detailed conditions and the yield. Satisfyingly, the HMF-adorned analog **101** appeared as a promising active compound, among the different fused pyrimidines tested, as A_{2A} adenosine receptor antagonist with approximately 100-fold selectivity over the A_1 receptor.



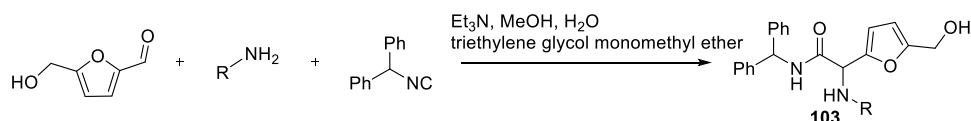
Scheme 38. Synthesis of a bioactive pyrimidine through Biginelli-like reaction of HMF

The Groebke-Blackburn-Bienaymé reaction of HMF, 2-aminopyridine and cyclohexyl isocyanide was reported in a patent expected to find novel compounds with activity against HIV-1 reverse transcriptase (Scheme 39).^[161] The reaction was performed in dioxane in the presence of montmorillonite K10 clay at 95-100 °C. The yield was not given either.



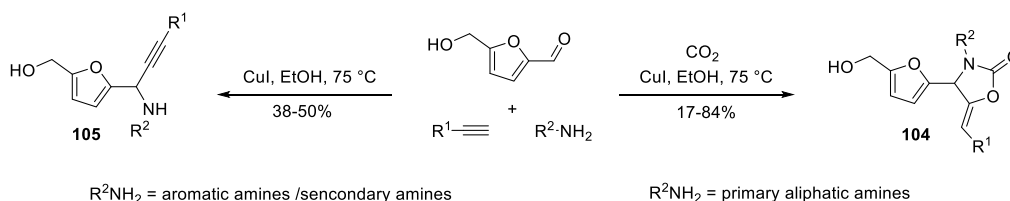
Scheme 39. The Groebke-Blackburn-Bienaymé reaction of HMF

Griffiths and Huck reported an Ugi-like 3-CR of HMF, amines and diphenylmethyl isocyanides using microfluidic technology, to produce a small library of Ugi 3-CR adducts **103** (Scheme 40).^[162] However, the products were only detected by mass spectrometry and the yields were assumed to be modest.



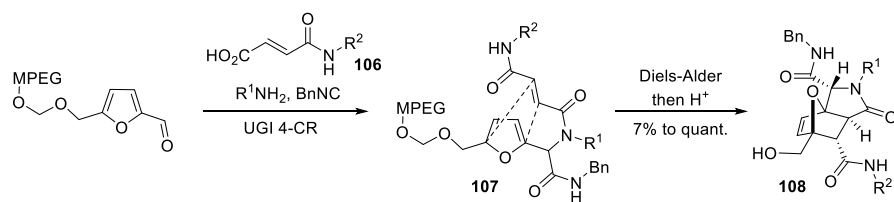
Scheme 40. Ugi-type 3-CR of HMF

In 2018, Xu's group described a modified A^3 coupling of HMF, incorporating carbon dioxide into the MCR, namely a 4-CR of HMF, terminal aromatic alkynes, primary aliphatic amines and carbon dioxide, to produce 1,3-oxazolidin-2-ones **104** (Scheme 41).^[163] The reaction was performed in the presence of copper(I) iodide with 0.5 Mpa pressure of CO_2 in EtOH at 75 °C. Various aromatic alkynes and primary aliphatic amines were employed under the optimized conditions, leading to the corresponding oxazolidinones **104** in 17-84% yields. It was found that aniline was not able to yield the oxazolidinone, where the reaction halted at the propargylamines **105**, perhaps due to the low nucleophilicity on nitrogen atom of aniline. In the case of secondary aliphatic amines, such as diethylamine and pyrrolidine, the corresponding propargylamines **105** were also obtained without incorporation of CO_2 .



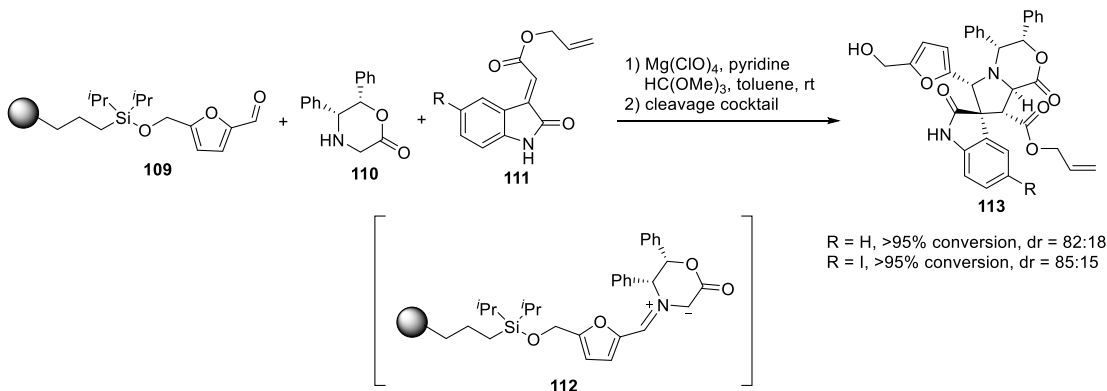
Scheme 41. CO_2 -participated A^3 coupling of HMF

In addition to the direct use of HMF in MCRs, Oikawa and coworkers employed a polymer-supported HMF as a platform substrate to prepare a series of tricyclic molecules **108** taking advantage of the tandem Ugi/Diels-Alder reaction (Scheme 42).^[164] The authors implemented a 4-CR Ugi reaction of MPEG-grafted HMF, benzyl isocyanide and various primary amines and the fumaric acid mono-amides **106** to generate the intermediates **107**, that can undergo a tandem intramolecular Diels-Alder reaction on the furan ring followed by acidic workup to release final products **108**. The split-pool technique was employed in this parallel synthesis. Twenty amines and five fumaric acid mono-amide building blocks **106** were tested. Finally, it was found that insoluble polymer beads TentaGel® S OH resin-supported HMF was also an efficient platform for solid phase synthesis of **108** via Ugi/Diels-Alder reaction.



Scheme 42. Ugi/Diels-Alder tandem reaction

Schreiber prepared a couple of HMF-based spirooxindole derivatives **113** via the 3-CR between macrobead-supported HMF **109**, 5,6-diphenylmorpholin-2-one **110** and oxindolydeneacetate **111** (Scheme 43).^[165] The reaction proceeds through a 1,3-dipolar cycloaddition between *in situ* formed chiral azomethine ylide **112** and the isatin-derived dipolarophiles **111**. Magnesium perchlorate was employed as a mild Lewis acid to promote this reaction. Pyridine and methylorthoformate were added to serve as a buffer to minimize the cleavage of the loaded aldehyde from the silicon linker and as a dehydrating agent respectively. After the completion of this 3-CR, the macrobeads were treated with the cleavage cocktail to release the products **113**.

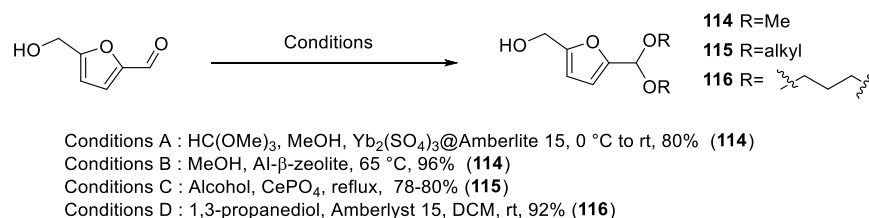


Scheme 43. Construction of spirooxindoles from HMF

1.2.1.4. C-O or C-S bond formation reactions

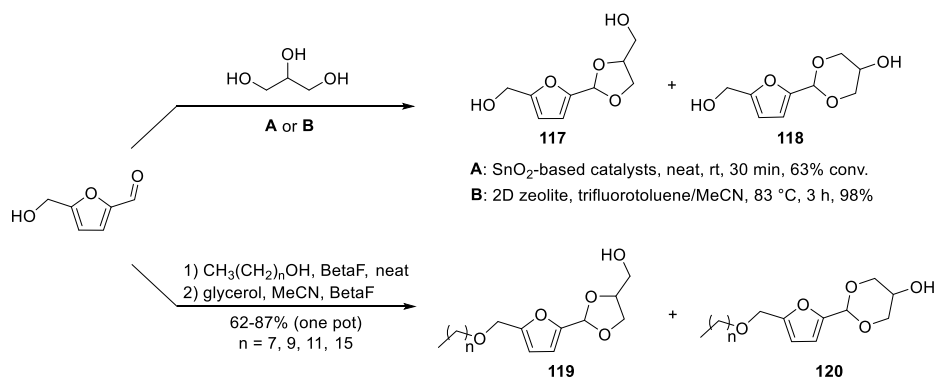
The nucleophilic attack of alcohols on aldehyde groups forms acetals, which is often applied as a strategy for the protection of carbonyl groups due to the reversibility of the acetal formation. Treatment of HMF with trimethyl orthoformate in the presence of ytterbium sulfate supported on Amberlite 15 gave access to the acetal **114** in 80% yield (Scheme 44).^[166] The same protected HMF can also be obtained in high yield by Al-beta-Zeolite-catalyzed acetalization in methanol.^[167] Using cerium phosphate as a catalyst in alcohols, both cyclic and acyclic acetals have been obtained in good yields.^[168] Amberlyst 15 was also found to be an efficient catalyst for

the preparation of HMF cyclic acetals.^[169]



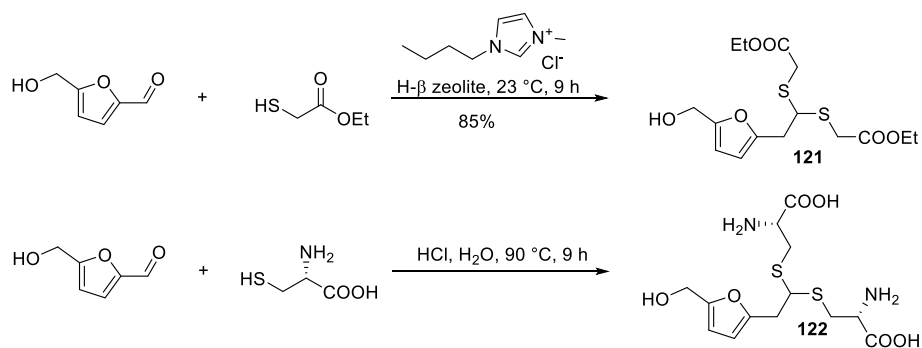
Scheme 44. Acetalization of HMF with simple alcohols

The acetalization of HMF with glycerol was performed by means of solid acid catalysis, yielding a mixture of 1,3-dioxolane **117** and 1,3-dioxane **118** (Scheme 45).^[170-171] The acetalization with glycerol was extended to several *in situ* formed 5-(alkyloxymethyl)furfurals for the preparation of potential surfactant molecules **119** and **120** in a one-pot process.^[172] The resulting compounds exhibited HLB values ranging from 4.9 to 6.6 and good thermal and water stability, consistent with industrial applications as W/O emulsifiers.



Scheme 45. The acetalization of HMF and its derivative with glycerol

Likewise, thioacetalization of HMF under various catalytic conditions has also been reported. The reaction with ethyl-2-mercaptoacetate in the presence of acidic H-β zeolite and 1-butyl-3-methylimidazolium chloride provided the corresponding dithioacetal **121** in 85% yield (Scheme 46).^[173] Ou and coworkers prepared the dithioacetal **122** by reacting HMF with cysteine in order to evaluate its cytotoxicity, as this dithioacetal was found to be formed during food processing and digestion.^[174]



Scheme 46. Thioacetalization of HMF

1.2.2. Reactions on the hydroxyl group

Apart from several reactions where the hydroxyl group is used for grafting HMF onto solid supports for solid-phase synthesis, other transformations, namely the formation of esters, ethers, halides and amines, as well as the reactivity of HMF as a alkylating reagent in the Friedel-Crafts alkylation reaction taking advantage of the hydroxymethyl group, have been reported.

1.2.2.1. Esterification

Classical esterification conditions were applied to the functionalization of the hydroxyl group of HMF. The reaction with acetic anhydride in the presence of a base such as pyridine or sodium acetate, furnished 5-acetoxymethylfurfural in up to 93% yield.^[81, 175] Benzoate esters can be prepared by reaction with benzoyl halides under similar conditions.^[176-177]

The esterification of 4-*O*-acetylferulic acid with HMF was performed with DCC as a coupling reagent and *p*-toluenesulfonic acid in pyridine, providing the corresponding ester **123** in 40% yield (Figure 5).^[178] The ester **124** was also prepared *via* DCC-promoted coupling between HMF and coumarin-derived acid, and its inhibitory activity against protein tyrosine phosphatase 1B was studied.^[179]

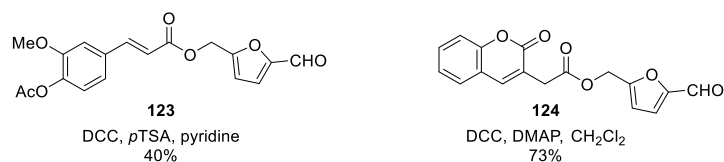
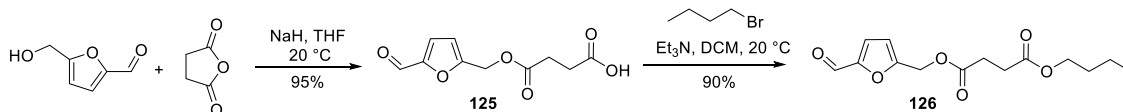


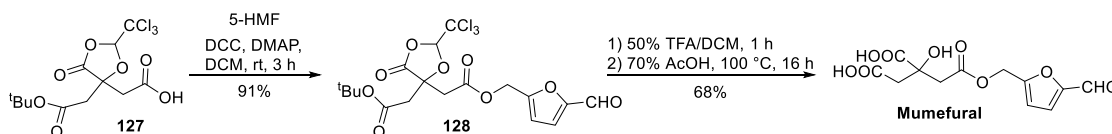
Figure 5. DCC-promoted esterification between HMF and carboxylic acids

Tamariz's group prepared the natural product **126**, isolated from the Noni fruit, by two successive ester formations: first, the esterification of HMF on hydroxyl group with succinic anhydride leading to acid **125**, then the acid **125** reacted with *n*-butyl bromide to provide the natural diester **126** (Scheme 47). The stepwise and one-pot processes gave same overall yield of **126** (85%).^[180]



Scheme 47. Synthesis of natural succinate derivative

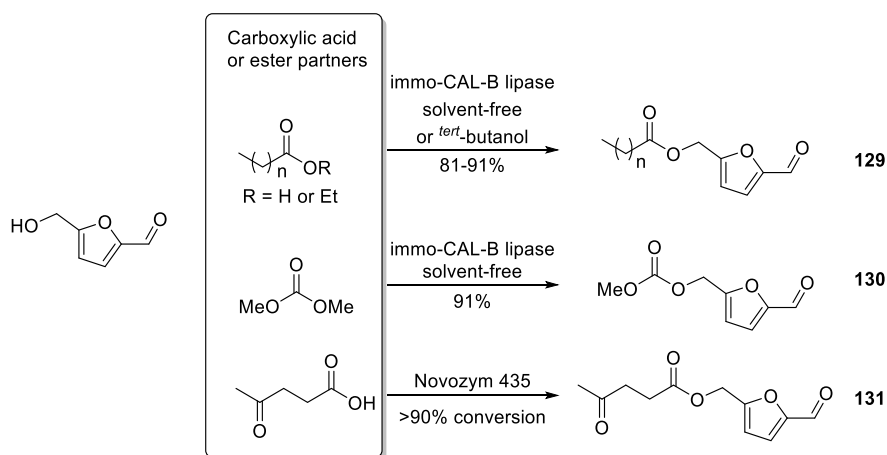
Mumefural, a citrate ester of HMF known to improve human blood fluidity, can be prepared from malic acid and HMF.^[181] The intermediate **127** (prepared from malic acid) reacted with HMF in the presence of DCC and a catalytic amount of DMAP in dichloromethane to deliver the ester **128** in 91% yield (Scheme 48). Subsequent deprotection gave access to mumefural in 68% yield.



Scheme 48. Synthesis of mumefural from HMF

Biocatalytic esterification of HMF with different acyl donors such as carboxylic acids and methyl or ethyl esters has been reported (Scheme 49). Good to excellent yields of esters **129** were obtained using the lipase CAL-B as a catalyst in solvent-free conditions.^[182] In the case of short-chain acids, a mixture of carboxylic acid and *tert*-butanol (1:1 v/v) was used instead of solvent-free conditions to avoid the deactivation of the lipase because of the high acidity of the medium. Interestingly the same enzyme proved also efficient to prepare the methyl carbonate **130** from dimethyl carbonate as well as HMF-esters directly from soybean oil.

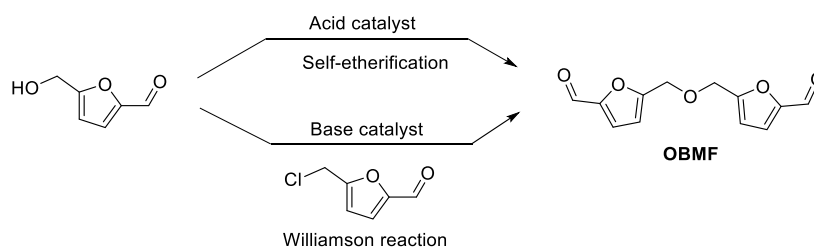
The enzymatic esterification between HMF and levulinic acid to the levulinate **131** was reported by Li et al.^[183] Novozym 435 was selected as the best catalyst and the reaction could proceed in alcoholic solvents such as *tert*-butanol or 2-methyl-2-butanol, as well as in ethereal solvents (CPME, or 2-MeTHF), with more than 90% conversion.



Scheme 49. Biocatalytic esterification

1.2.2.2. Conversion to ethers and acetals

HMF can undergo self-etherification to yield 5,5'-[oxybis(methylene)]bis-2-furfural (OBMF) under acidic medium (Scheme 50). It is one of the processes resulting into degradation of HMF during storage.^[20] The dehydration of HMF in the presence of *p*-TSA and phosphorus pentoxide in toluene with a Dean-Stark trap gave access to OBMF in 76% yield.^[184] The thermal dehydration in DMSO without any acidic catalyst also delivered OBMF in 55% yield.^[185] Additionally, several heterogeneous solid acids were reported to catalyze this reaction (e.g. Amberlyst-15, Amberlite IR 120, Preyssler heteropolyacids, graphene oxide).^[20, 175, 186-189] Finally, the OBMF could also be obtained by Williamson reaction of HMF and 5-chloromethylfurfural.^[190]



Self-etherification

Conditions A: *p*-TSA, P₂O₅, toluene, reflux, 76%
 Conditions B: DMSO, 155 °C, 55%
 Conditions C: Amberlyst-15, benzene, reflux, 79%
 Conditions D: Amberlite IR 120 (H), benzene, reflux, 38%
 Conditions E: Preyssler HPA, 70 °C, 84%
 Conditions F: graphene oxide, DCM, 100 °C, 86%
 Conditions G: Al-MCM-41, trifluorotoluene, 100 °C, 99%
 Conditions H: Sn-Mont catalyst, DCM, 100 °C, 96%

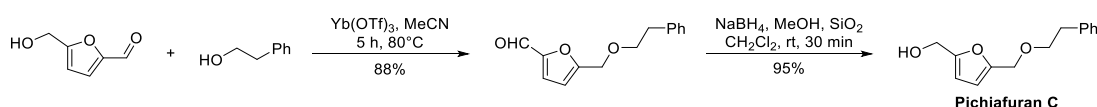
Williamson reaction

Conditions: K₂CO₃, KI, acetone, reflux, 43%

Scheme 50. Conversion of HMF to OBMF

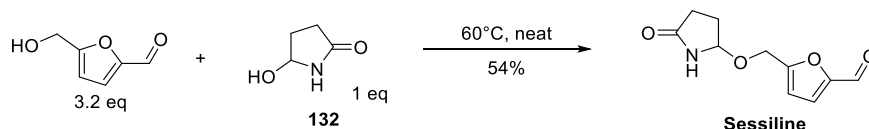
Simple alkyl ethers (e.g. 5-ethoxymethylfurfural) can be prepared by catalytic etherification of HMF and alcohols at high temperature.^[191-192] A milder alternative is the Williamson reaction between HMF and an alkyl halide. It was reported that treatment of HMF with sodium hydride/iodomethane could give the methyl ether in 94% yield.^[40] HMF reacted with benzyl bromide in the presence of Ag₂O in DMF to afford 5-benzyloxymethylfurfural in 72% yield.^[175]

Pichiafuran C, a monofuran metabolite isolated from *Pichia membranifaciens* yeast, was synthesized *via* Yb(OTf)₃-catalyzed etherification between HMF with 2-phenylethanol and subsequent reduction of the aldehyde with NaBH₄ (Scheme 51).^[193]



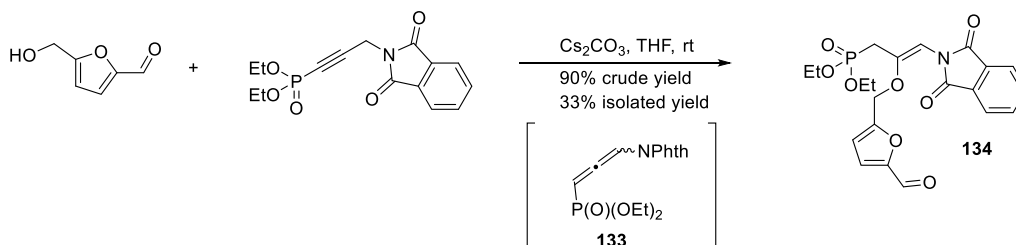
Scheme 51. Synthesis of Pichiafuran C

Sessiline, an alkaloid isolated from the fruits of *Acanthopanax sessiliflorus*, was prepared in 54% yield in neat conditions by reaction of HMF with the amidocarbinol **132** (obtained in 3 steps and 28% yield from succinimide).^[194] The proposed mechanism is the nucleophilic addition of HMF onto the iminium intermediate, which is in equilibrium with the amidocarbinol (Scheme 52).



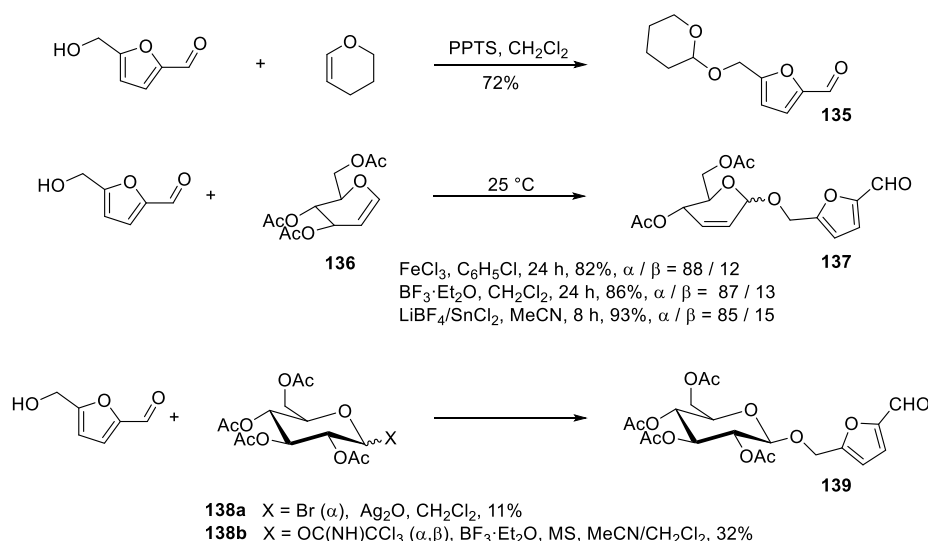
Scheme 52. Synthesis of Sessiline

Stevens and coworkers performed the β -alkoxylation of the *in situ* formed 3-imidoallenylphosphonate **133** with a range of alcohols (Scheme 53).^[195] Despite a crude yield estimated to 90%, the product **134** was isolated only in 33% yield. The authors assumed that the low isolated yield of **134** was attributed to partial degradation during reverse phase flash chromatography purification.



Scheme 53. Alkoxylation of 3-imidoallenylphosphonate with HMF

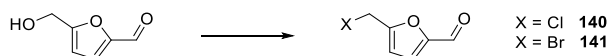
Descotes prepared a tetrahydropyranyl ether **135** in 72% yield by reaction of HMF and dihydropyran with pyridinium *p*-toluenesulfonate as a catalyst (Scheme 54).^[196] The Ferrier rearrangement reaction of HMF and the peracetylated glycal **136** under Lewis acid catalysis was reported by the same group in 2001 (Scheme 54).^[197] The best yield was obtained when the combination of LiBF₄/SnCl₂ was employed as Lewis acid catalysts. More recently, Zhang described the transformations of various glycals including **136** with HMF in the presence of FeCl₃·6H₂O/C as a recyclable catalyst in DCE, leading to a range of 2,3-unsaturated glycosides in 67-92% yields.^[198] Cottier et al. investigated several possible pathways to prepare the β -glucosylmethylfurfural **139** starting from HMF and glycosyl partners such as **138**.^[166] The Ag₂O-catalyzed coupling of HMF and the glycosyl bromide **138a** gave only 11% yield of the β -glucosylmethylfurfural **139**. The yield was improved to 32% using the imidate **138b** as a glycosyl partner with boron trifluoride diethyl etherate (Scheme 54).



Scheme 54. Acetal formation

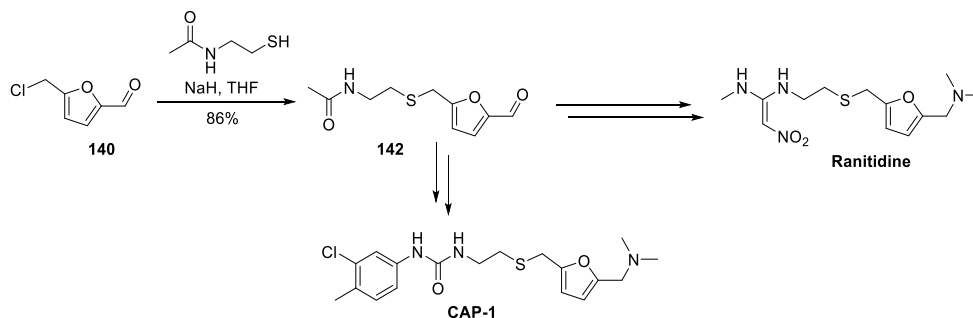
1.2.2.3. Conversion to halides

HMF can be easily converted to 5-chloromethylfurfural **140** or 5-bromomethylfurfural **141** via halogen substitution on hydroxyl group. A range of classical halogenating conditions could be successfully applied to HMF (Table 7). The resulting halogenated HMF derivatives proved to be useful intermediates for the synthesis of several valuable furan-based complex compounds. Moreover, 5-chloromethylfurfural **140** was also claimed as a platform chemical as it could be prepared directly from sugars.^[199]

Table 7. Halogenation experimental conditions

Entry	Product	Conditions	Yield	Ref.
1	140	HCl (gas), Et ₂ O, 9 h	87%	[200]
2		HCl (aq), DCM or DCE, rt, 24 h	86-92%	[20, 201-202]
3		SOCl ₂ , pyridine, DCE, 5 h	71%	[200]
4		Me ₃ SiCl, CDCl ₃ , 6 h	92%	[200]
5		POCl ₃ , DMF, 5 h	77%	[203]
6	141	HBr (gas), Et ₂ O, 5 h	64%	[200, 204]
7		HBr (aq), DCE, 65 °C, 1 h	94%	[201]
8		SOBr ₂ , pyridine, DCE, 5 h	75%	[200]
9		PBr ₃ , CaCO ₃ , DCE, 5 h	62%	[200]
10		Me ₃ SiBr, CHCl ₃ or CHCl ₂ CH ₂ Cl, 3 h	>98%	[200, 205]
11		NBS, PPh ₃ , DCM, -5 °C, 0.5 h	87%	[206]

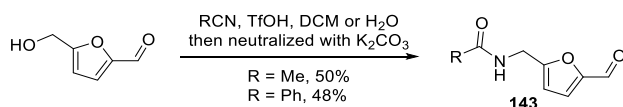
Taking advantage of chlorination of HMF as a key step, Ananikov and coworkers reported an efficient synthetic route to ranitidine, a medication which decreases stomach acid production, (Scheme 55).^[20] The synthetic route consists of the nucleophilic substitution of 5-chloromethylfurfural **140** by *N*-acetylcysteamine. Subsequent transformations of the thioether **142** proceeded smoothly affording ranitidine in 65% overall yield from HMF. Changing the reagent to an arylisocyanate in last step provided CAP-1, a novel compound with inhibition of HIV-1 capsid protein assembly activity.^[202]

**Scheme 55.** Synthesis of ranitidine and CAP-1 from HMF

1.2.2.4. Amination reaction

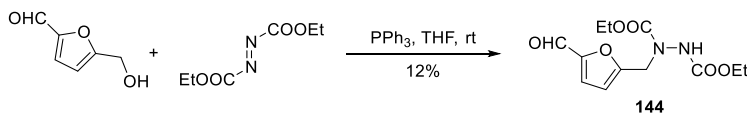
Strictly speaking, there are no examples of real amination on the OH group of HMF to make amines. However, a few studies about the preparation of amides, hydrazines and urea derivatives have been reported.

Treatment of HMF with trifluoromethanesulfonic acid in acetonitrile or benzonitrile at room temperature gave access to corresponding amides **143** in around 50% yield *via* Ritter reaction (Scheme 56).^[175]



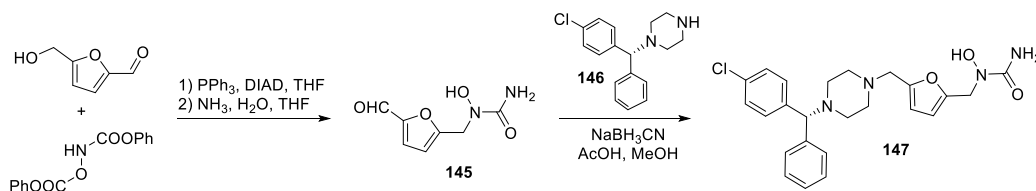
Scheme 56. Ritter reaction between HMF and nitriles

The group of Wierenga reported a transformation of HMF in Mitsunobu conditions but in the absence of other nucleophile.^[207] Treatment of HMF with diethyl azodicarboxylate in the presence of triphenylphosphine resulted into hydrazine interchange affording the product **144** in 12% yield (Scheme 57). Comparatively, furfuryl alcohol and acetal-protected HMF provided much higher yields (60% and 86% respectively).



Scheme 57. Reaction between HMF and diethyl azodicarboxylate

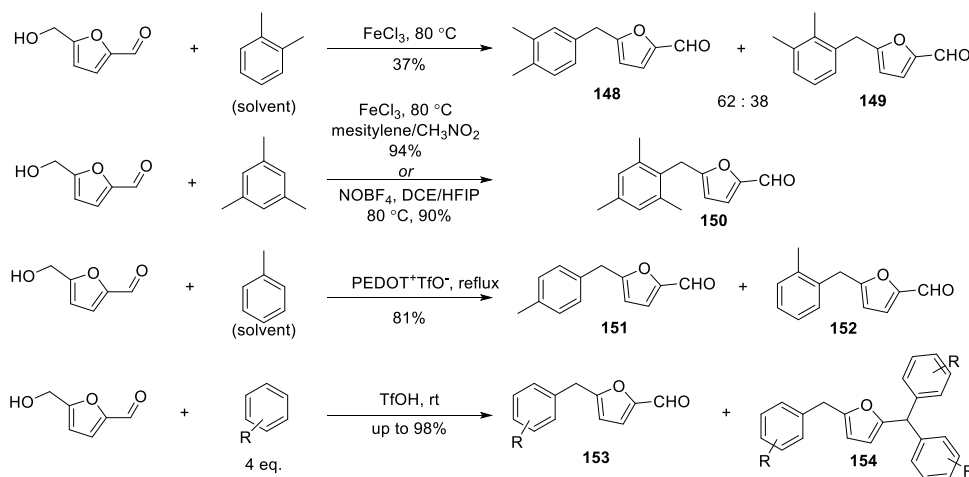
Lewis and coworkers prepared a *N*-hydroxyurea derivative **145** by reacting HMF with *N,O*-(bisphenoxycarbonyl)hydroxylamine under Mitsunobu conditions, followed by treatment with ammonia. Subsequent reductive amination with the piperazine derivative **146** released the final product **147** (yield not given), which exhibited antihistaminergic activity (Scheme 58).^[208]



Scheme 58. Reaction between HMF and *N,O*-(bisphenoxycarbonyl) hydroxylamine

1.2.2.5. Friedel-Crafts alkylation

The Friedel-Crafts alkylation of arenes using HMF as an alkylating agent has been reported by different research groups. Beller et al. implemented the alkylation of *o*-xylene using FeCl₃ (10 mol%) as a catalyst providing a mixture of regioisomers in 37% yield (ratio of **148/149**: 62/38) (Scheme 59).^[209] The reaction with mesitylene promoted by FeCl₃ or nitrosonium tetrafluoroborate provided the product **150** in excellent yield.^[210-211] Heating HMF in refluxing toluene in the presence of poly(3,4-ethylenedioxythiophene) salt gave rise to a mixture of two isomers **151** and **152** in a global 81% yield.^[212] Employing Glu-Fe₃O₄-SO₃H as a magnetic carbonaceous solid acid catalyst in toluene led to a mixture of **151** and **152** as well, together with some traces of the *meta* isomer.^[213] Recently, Vasilyev and coworkers reported the arylation of HMF with arenes in trifluoromethanesulfonic acid medium at room temperature.^[214] 5-Arylmethylfurfurals **153** were prepared in 17–91% yields, along with by-products 2-arylmethyl-5-(diarylmethyl)furans **154** (5-37% yields) when highly nucleophilic arenes were used. Increasing the reaction time significantly affected the yield of the by-product. The same reactions using acidic zeolites CBV-720 as catalysts at 130 °C resulted in the selective formation of 5-arylmethylfurfurals **153** (11-79% yield).



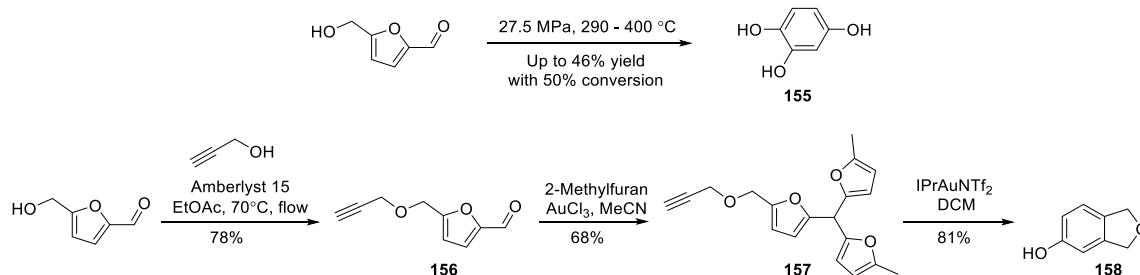
Scheme 59. Friedel-Crafts alkylation of arenes

1.2.3. Reactions on furan ring

1.2.3.1. Ring opening/rearrangement

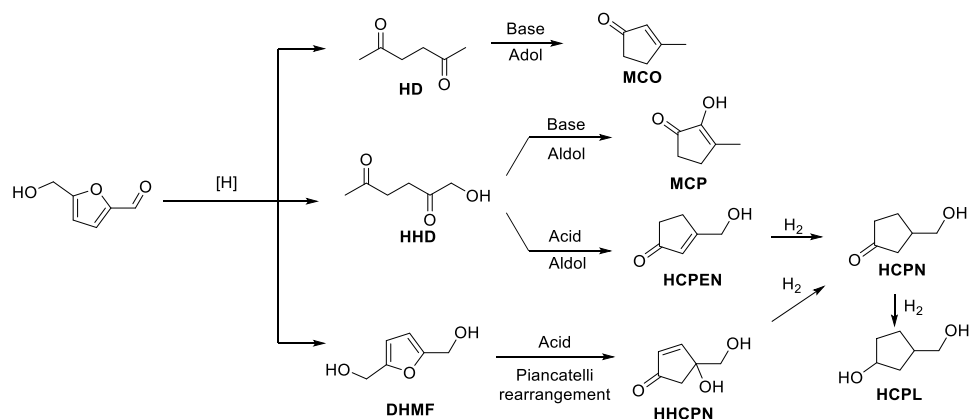
It is well known that HMF decomposes under acidic conditions at elevated temperature leading to

the ring-opening product levulinic acid.^[18, 215] However, subjecting HMF to hydrothermolysis at high temperature and pressure led to 1,2,4-benzenetriol **155** as the major product in yields up to 46% with 50% HMF conversion (Scheme 60).^[216] The other example converting HMF to phenols was reported by Hashmi's group.^[217] HMF first underwent *O*-propargylation and the resulting aldehyde **156** was converted into the trifurylmethane **157** by gold(III) catalysis. Finally, a gold (I) catalyst was employed for the direct conversion of **157** into fused phenol **158** through ring rearrangement.



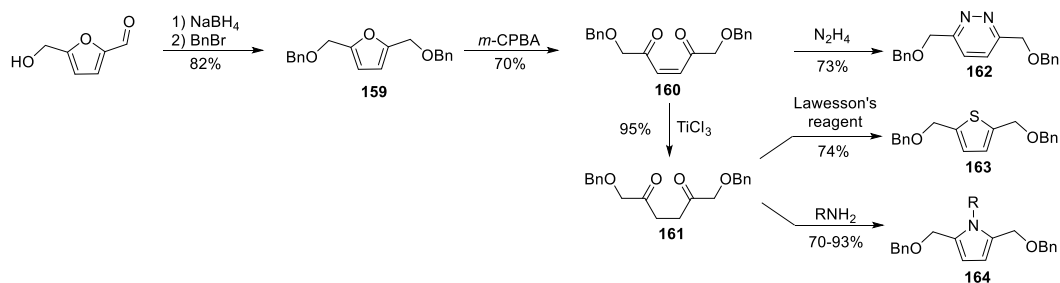
Scheme 60. Transformation of HMF and its derivatives to phenols

The hydrogenative/hydrolytic ring-opening of HMF in water led to 2,5-hexanedione (HD)^[218-219] or 1-hydroxy-2,5-hexanedione (HHD)^[220-221] depending on the catalytic conditions employed (Scheme 61). The latter was reported to be used as a 1,4-diketone partner in the Paal-Knorr pyrrole synthesis.^[222] HD and HHD can be converted into cyclopentanic derivatives, respectively 3-methyl-2-cyclopenten-1-one (MCO)^[223] and 2-hydroxy-3-methylcyclopent-2-enone (MCP)^[224-225] *via* base-catalyzed intramolecular aldol reactions. Following acid-catalyzed aldol reaction and subsequent hydrogenation, HHD can be transformed into 3-hydroxymethyl cyclopentanone (HCPN)^[226-227]. An alternative route toward cyclopentanic derivatives like HCPN from HMF relies on a first catalytic reduction of the aldehyde generating 2,5-dihydroxymethylfuran (DHMF) followed by Piancatelli rearrangement to 4-hydroxy-4-(hydroxymethyl)cyclopent-2-en-1-one (HHCPN) and subsequent reduction (Scheme 61).^[228]



Scheme 61. Ring-opening/rearrangement of HMF derivatives

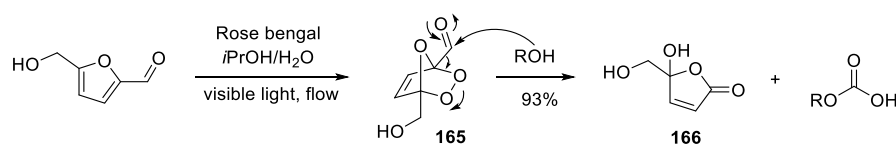
Oxidative conditions have also been employed to achieve ring opening of HMF. Lichtenthaler and coworkers reported the preparation of diverse heterocycles such as pyridazine **162**, thiophene **163** or pyrrole **164** from HMF (Scheme 62).^[229] The strategy relies on a first reduction of the aldehyde and benzylation of the diol intermediate to produce **159**. This symmetrical disubstituted furan can undergo oxidative ring opening upon treatment with *m*-CPBA to yield the diketone **160**. Chemoselective hydrogenation of **160** provided the diketone **161**. These 1,4-diketones were rapidly converted in heterocyclic scaffolds **162-164** *via* diverse transformations.



Scheme 62. Application of oxidative ring-opening of furan for the synthesis of heterocycles

1.2.3.2. Singlet oxygen oxidation

HMF can react with singlet oxygen *via* [4 + 2] cycloaddition in alcohol to give rise to 5-hydroxy-5-(hydroxymethyl)-furan-2(5*H*)-one **166**.^[175] The adduct **165** rearranged *via* a solvent-assisted decarbonylation reaction to produce efficiently the butenolide **166**. The same reaction was recently reinvestigated by Kappe under continuous flow conditions (Scheme 63).^[230] The best yield obtained was 93% using 1 mM Rose Bengal as a photosensitizer in a mixture of *i*-PrOH/H₂O as solvent with 0.5 mL/min flow rate.

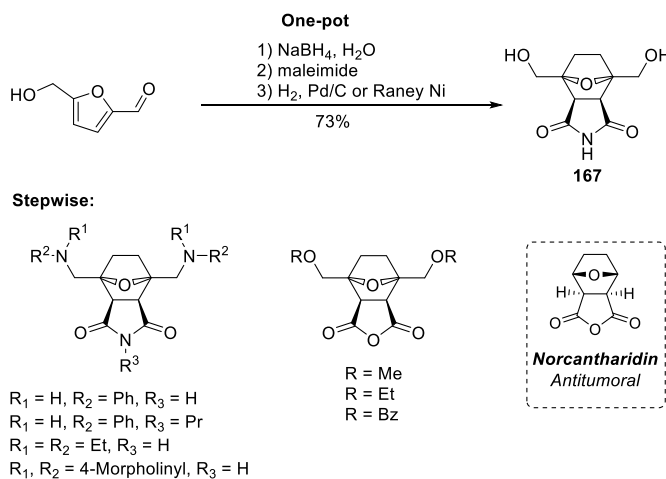


Scheme 63. Reaction of HMF with singlet oxygen

1.2.3.3. Diels-Alder reaction

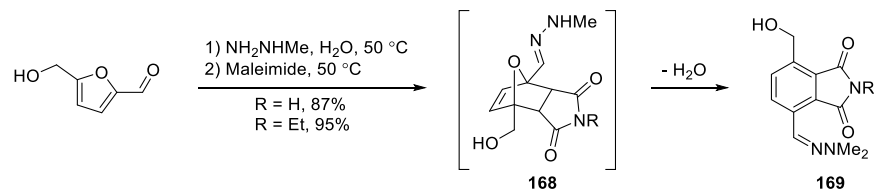
Electron-rich furans have been widely employed as dienes in Diels-Alder reactions reacting with electron-deficient dienophiles. In contrast to other furanic compounds, the presence of the strongly electron withdrawing aldehyde group on the furan ring of HMF tends to deactivate the aromatic ring towards Diels-Alder reactions. In order to use HMF in this cycloaddition process, it usually requires chemical modifications on HMF skeleton first, such as conversions to 2,5-dihydroxymethylfuran (DHMF) or 2,5-dimethylfuran (DMF).

Ananikov and coworkers reported the synthesis of a series of oxabicyclic compounds starting from HMF and maleimide *via* a one-pot reduction/cycloaddition/hydrogenation sequence or stepwise processes involving the Diels-Alder reaction as a key step (Scheme 64).^[231] Reduction of HMF to DHMF followed by *endo*-selective Diels-Alder cycloaddition with maleimide and hydrogenation in a single pot provided the product **167** in 73% yield (that could also be prepared in a sequential-step procedure). The authors also applied the Diels-Alder reaction on HMF-derived bis(aminomethyl)furans and bis(alkoxymethyl)furans. Reactions with maleic anhydride were also performed to prepare analogues of the anticancer drug norcantharidin.^[232]



Scheme 64. Diels-Alder reaction of DHMF, bis(aminomethyl)furans and bis(alkoxymethyl)furans

Sheppard's group reported a strategy to efficiently react HMF with dienophiles, without changing the oxidation state of the aldehyde (Scheme 65).^[233] HMF was first reacted with *N*-methylhydrazine to produce the corresponding hydrazone before reacting with maleimide to provide cycloadduct intermediate **168**. The latter underwent deoxyaromatisation to produce phthalimides **169**. The reaction was carried out in water and the products were isolated with high yields by simple filtration.



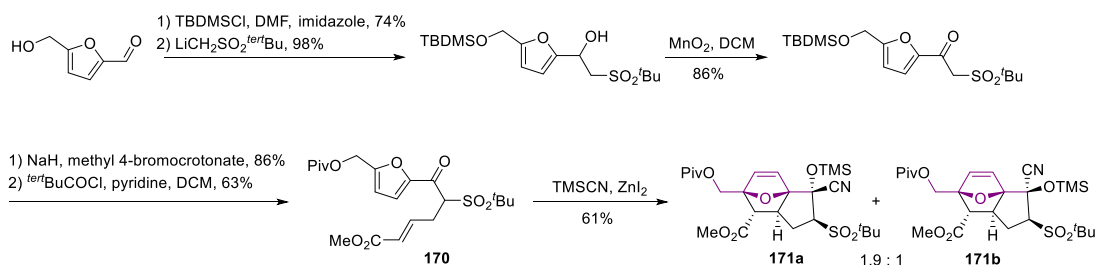
Scheme 65. Diels-Alder reaction of HMF-derived hydrazone

In addition, a range of HMF-derived furans such as 2,5-dimethylfuran (DMF) and dimethyl furan-2,5-dicarboxylate have been utilized as dienes reacting with various dienophiles (e.g., ethylene, acrolein and benzyne) to accomplish the Diels-Alder reaction. Subsequent deoxyaromatisation of the Diels-Alder adducts leads to *p*-xylene or other substituted aromatic compounds.^[234-242]

1.2.4. Multi-step and multi-functionalization sequences

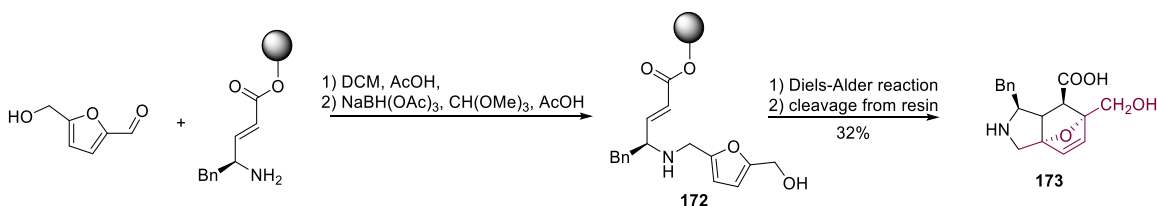
As it has been shown throughout this bibliographic section, a number of methodological studies on the chemical modifications of HMF have been conducted, showing the high versatility of this C-6 synthon. In a synthetic perspective, HMF has been used in more complex multistep sequences, targeting complex and/or natural scaffolds.

In order to study the intramolecular Diels-Alder reaction (IMDA) of furan derivatives, Sternbach used HMF as a platform for the preparation of highly substituted keto-sulfone **170** by nucleophilic addition of organolithium reagent to TBDMS-protected HMF and subsequent oxidation and alkylation (Scheme 66).^[243] The intermediate **170** is poorly reactive in IMDA cycloaddition, however, conversion of **170** to cyanohydrin using TMSCN/ZnI₂ activates the furan ring that can undergo IMDA with a good yield and moderate diastereoselectivity, producing tricyclic derivative **171a** and isomer **171b**.



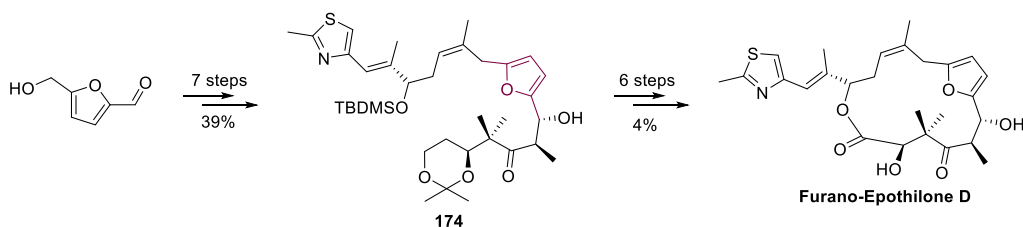
Scheme 66. Intramolecular Diels-Alder reaction of HMF-derived **170**

The reductive amination of HMF with resin-bound amine was implemented to prepare the Diels-Alder reaction precursor **172** (Scheme 67).^[244] The resulting **172** underwent intramolecular Diels-Alder reaction followed by cleavage from resin to yield the polycyclic compound **173** in 32% yield.



Scheme 67. Solid-phase Diels-Alder reaction of HMF-derived **172**

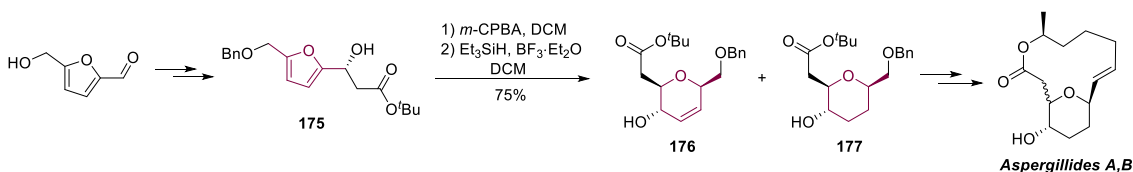
Schinz et al. completed the stereoselective synthesis of furano-epothilone D, analog of natural epothilone, a powerful antitumor molecule, using HMF as a building block (Scheme 68).^[245] Bromination of the hydroxymethyl group in HMF-derived (5-(((tert-butyldimethylsilyl)oxy)methyl)furan-2-yl)methanol allowed the introduction of an olefinic partner *via* the Negishi-type coupling, and a subsequent diastereoselective aldol reaction with a chiral ketone yielded the intermediate **174**. This advanced intermediate was then converted to the furanic analogs of epothilone D and its diastereoisomer. Both furano-epothilone D and its diastereoisomer displayed only moderate effect on tubulin assembly.



Scheme 68. Synthesis of furano-epothilone D and its diastereoisomer from HMF

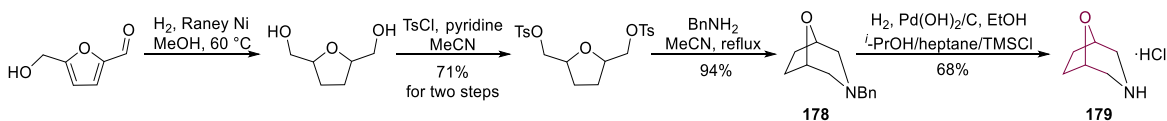
Loh's group reported a synthetic route to natural products aspergillides A and B, which exhibit

potent cytotoxic activities towards mouse lymphocytic leukemia cell (Scheme 69).^[246] In this route, all the carbon atoms in target molecules come from biomass-derived platform chemicals such as levulinic acid and HMF. The key steps in this synthesis consisted of the Noyori's asymmetric transfer hydrogenation to produce enantiopure alcohol **175**, which was subjected to the Achmatowicz rearrangement and subsequent reduction to yield pyranes **176** and **177**. Both were advanced intermediates in the preparation of aspergillides A and B.



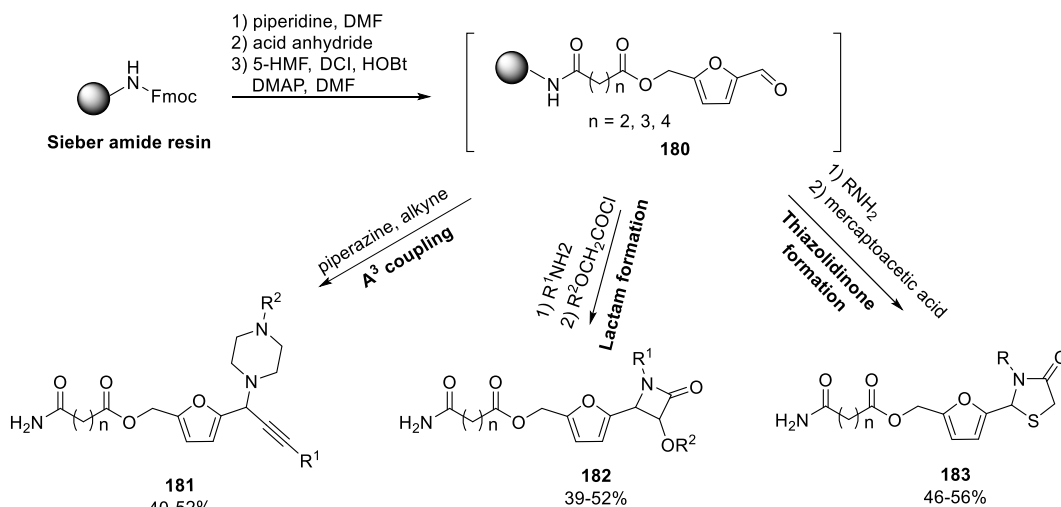
Scheme 69. Synthetic route to aspergillides A and B

A four-step process to prepare 8-oxa-3-aza-bicyclo[3.2.1]octane hydrochloride **179** starting from HMF was described by Connolly et al.^[247] Reduction of HMF to the corresponding saturated diol followed by double tosylation and cyclization with benzylamine generated the bicyclic intermediate **178**. The latter was hydrogenated using Pearlman's catalyst to provide the final bridged bicyclic adduct **179** in good yield (Scheme 70).



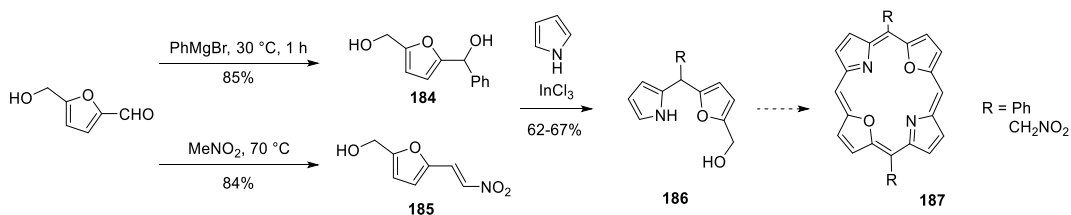
Scheme 70. Synthesis of 8-oxa-3-aza-bicyclo[3.2.1]octane hydrochloride **179**

The hydroxymethyl group presenting in HMF makes it convenient to link onto a solid support. The solid-supported HMF with a free carbonyl group could serve as a good scaffold in combinatorial synthesis of furan-based libraries. Kundu and coworkers loaded HMF onto Sieber amide resin *via* the formation of amide and ester bonds using aliphatic dicarboxylic acid anhydride (Scheme 71).^[248] The resin-supported HMFs **180** could be engaged in multicomponent A³ couplings to provide propargylamines **181** after separation from the solid support. Other multi-step transformations giving access to diverse nitrogen-containing heterocycles such as **182** and **183** were also successfully implemented using this solid-supported synthesis strategy.



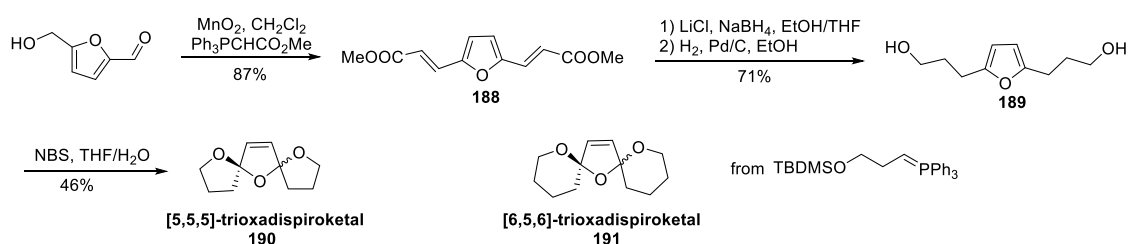
Scheme 71. Solid-phase combinatorial synthesis of HMF-based scaffolds

The preparation of key intermediates involved in the synthesis of 21,23-dioxaporphyrins **187** was reported as an alternative to known but complex synthetic procedures, addressing drawbacks such as low yields and purification issues (Scheme 72).^[249] The addition of a phenyl-Grignard reagent on HMF as well as the Henry reaction with nitromethane gave access respectively to the furylcarbinol **184** and the nitroalkene **185** in good yields. Those intermediates were then reacted with pyrrole under indium chloride catalysis to generate diversely substituted bis-heteroarylmethanes **186**, highly valuable building-blocks for the preparation of 21,23-dioxaporphyrins **187**.



Scheme 72. Preparation of key intermediates from HMF for 21,23-dioxaporphyrin synthesis

An example of the olefination of HMF was reported for the synthesis of trioxadispiroketal by Stockman.^[250] In that strategy, HMF was subjected to tandem oxidation/Wittig reaction providing the diester **188** as a 6.6:1 mixture of (*E,E*)- and (*E,Z*)-isomers (Scheme 73). Reduction of esters followed by hydrogenation of alkene afforded the corresponding diol **189**. Further treatment with *N*-bromosuccinimide furnished [5,5,5]-trioxadispiroketal **190**. [6,5,6]-Trioxadispiroketal **191** was also prepared *via* a similar strategy using a homologated phosphonium ylide.



Scheme 73. Application of the olefination of HMF for the synthesis of trioxadispiroketal

1.3. Conclusion

As shown in this bibliographic introduction, HMF has been the object of numerous studies on its use in fine chemical synthesis. Its relatively modest stability has been shown to be overcome by choosing adequately mild reaction conditions, notably with respect to acid-catalyzed reactions. Addition of some antioxidants is another way to improve the stability of HMF in reaction mixture. Thanks to the presence of different functional groups on this platform molecule, it proved to be a powerful substrate for the preparation of analogs of drugs, adhesives or complex heterocyclic scaffolds. The utilization of this C-6 synthon in novel synthetic routes is appealing, as it allows the incorporation of renewable carbon-sources into the final targets, thereby expands the biomass derived chemical space. Especially, applying MCRs on HMF offers an opportunity to make complex fine chemicals from HMF with high efficiency.

Chapter II. The Biginelli Reaction of 5-Hydroxymethylfurfural

2.1. Introduction

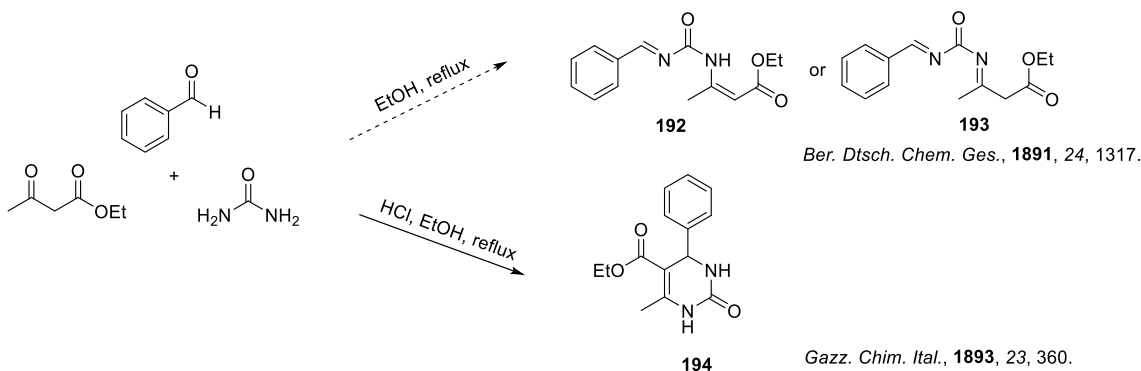
The Biginelli reaction, named after its discoverer Dr. Pietro Biginelli, refers to a one-pot 3-component condensation of aldehydes, 1,3-dicarbonyl compounds and (thio)urea, giving access to functionalized 3,4-dihydropyrimidin-2(*1H*)-ones/thiones (DHPMs). The Biginelli reaction is one of the most important and oldest multicomponent reactions. It has been a long-standing interest of synthetic chemists and medicinal chemists over the past decades, mainly thanks to the wide-ranging pharmacological properties of the Biginelli products. Apart from the application of Biginelli reaction in the preparation of diverse bioactive molecules from easily-accessible starting materials, taking advantage of the Biginelli reaction to prepare functionalized polymers has also been realized recently.^[251] Several exceptional comprehensive reviews and monographs about the Biginelli reaction have been published by Kappe,^[252-255] Singh,^[256] Sandhu^[257] and Moorthy.^[258]

In this chapter, we present and discuss our experimental results about the Biginelli reaction involving HMF. This includes the screening of reaction conditions to adapt to the stability of HMF, the study of the substrate scope and the mechanistic investigation. Before describing the experimental results, a general introduction about the Biginelli reaction is given.

2.1.1. The discovery of the Biginelli reaction

The history of the discovery of the Biginelli reaction was documented by Tron et al.^[259] In 1891, Italian chemist Pietro Biginelli (University of Florence) carried out a condensation reaction employing benzaldehyde, ethyl acetoacetate and urea in refluxing absolute ethanol.^[153] After cooling the reaction mixture, he obtained a precipitate from the solution, which was then filtrated and recrystallized to provide a pure compound. Analysis of this compound pointed to the formula $C_{14}H_{16}N_2O_3$, indicating it incorporated all the atoms from the three reactants except the tiny portion contributing to the formation of water. But at that moment, Biginelli assigned this ternary adduct as an open-chain uramidocrotonate structure (**192** or **193**, in scheme 74) rather than a heterocyclic structure which it was supposed to be. As mentioned in Neto's review,^[260] two years later, the structure was revised by Biginelli himself in a full account concerning this reaction, in which he disclosed the product of the Biginelli reaction was in a pyrimidine form (**194**) rather than a linear structure (Scheme 74). And during the study he also found addition of drops of

concentrated hydrogen chloride had a beneficial effect on this 3-component reaction. As a result, the birthdate of the Biginelli reaction was recognized as either 1891 or 1893 in chemistry community.



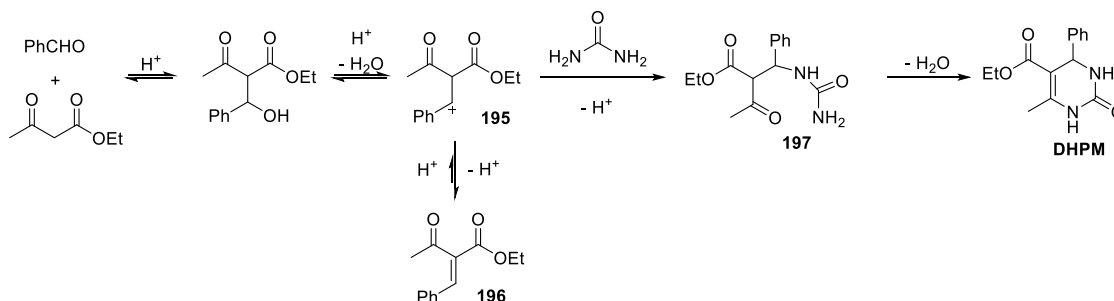
Scheme 74. The seminal report on the Biginelli reaction in 1891 and 1893

2.1.2. The mechanism of the Biginelli reaction

Almost all the conditions reported for the Biginelli reaction involve an acidic catalyst, so we only discuss acid-catalyzed reaction mechanism here. The mechanism of the Biginelli reaction has been studied by many research groups, but also been controversial for a long time. It seems that the Biginelli reaction does not likely undergo a concerted process (three components react simultaneously to give the product). Instead, the reaction might proceed through different pathways depending on the initial bimolecular reactions, that is, two of the components react first yielding an intermediate, which then incorporates the third component giving access to the final product. Basically, there are three major possible acid-catalyzed mechanisms proposed in literature.

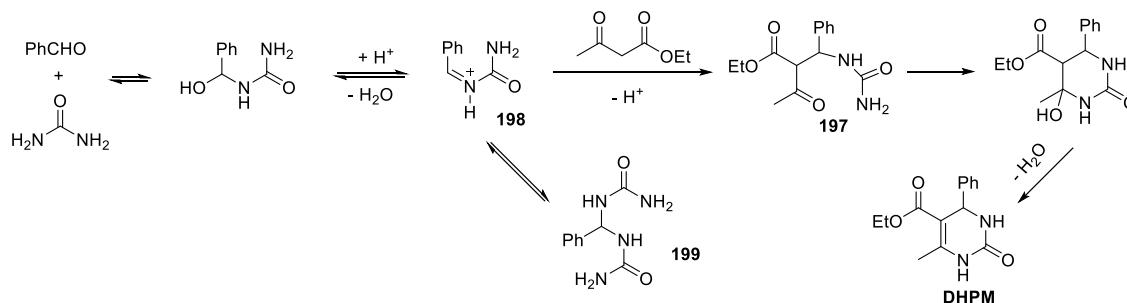
The first pathway reported by Sweet and coworkers in 1973 is the so-called Knoevenagel route (Scheme 75).^[261] The aldol condensation of an aldehyde and a 1,3-dicarbonyl compound yields the carbenium ion **195** as a key reaction intermediate, which reacts with the third component urea followed by cyclization to provide the final product DHPM. The authors claimed that the Knoevenagel mechanism was supported by the fact that DHPM could be prepared by reaction of preformed Knoevenagel adduct **196** (as a cis/trans mixture from the condensation between benzaldehyde and ethyl acetoacetate) with urea or *N*-methylurea in refluxing MeOH solution containing a catalytic amount of HCl, albeit at a very slow reaction rate. Sweet suggested that the slow conversion of the Knoevenagel adduct **196** to DHPM was because the protonation of **196** to

the real reactive intermediate carbenium ion **195** was rather slow. The other argument supporting this mechanism was that only *N1*-substituted DHPM rather than *N3*-substituted isomer was formed when *N*-methylurea was used.

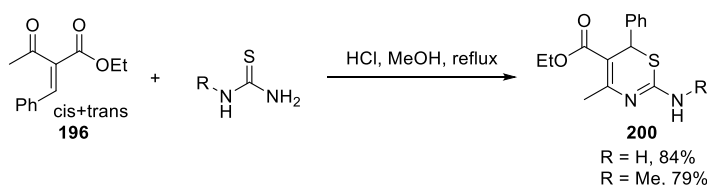


Scheme 75. The Knoevenagel mechanism of the Biginelli reaction

The second mechanism involving an iminium intermediate was proposed by Kappe in 1997 (Scheme 76).^[262] Kappe performed several control experiments in CD₃OH with a catalytic amount of HCl and monitored them by means of NMR spectroscopy. They observed the formation of bisureide **199** in the absence of ethyl acetoacetate, which had been regarded as a possible intermediate by Folkers.^[263] In the presence of ethyl acetoacetate, final product DHPM rather than the bisureide **199** was observed. Neither Knoevenagel condensation nor other reactions were observed when benzaldehyde and ethyl acetoacetate were mixed in the absence of urea in HCl/CD₃OH at room temperature. In addition, replacing urea with thiourea or *N*-methylthiourea in the reaction with preformed Knoevenagel adduct **196** generated 2-amino-1,3-thiazines **200** instead of DHPM (Scheme 77). On the other hand, the preformed enamine intermediates (prepared from ethyl acetoacetate and urea or *N*-methyl urea) was hydrolyzed rapidly when exposed to catalytic amounts of conc. HCl. Based on the experimental results, they detailed the mechanism based on Folkers's proposal. The condensation of aldehyde and urea occurs first to give the *N*-acyliminium ion intermediate **198**, which reacts with ethyl acetoacetate to form the intermediate **197**, the latter undergoes cyclization providing DHPM (Scheme 76).

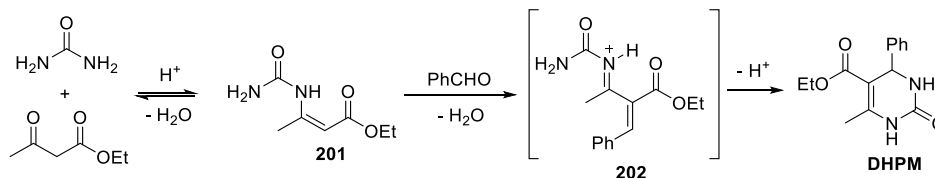


Scheme 76. The iminium mechanism of the Biginelli reaction



Scheme 77. The reactions between enone **196** and thioureas performed by Kappe

The last mechanism is enamine route (Scheme 78). It was first proposed by Folkers and coworkers in 1933, who suggested enamine **201** might be an intermediate involved in the Biginelli reaction.^[263] Recently, Capanec et al.^[264] mixed any two among the three components (benzaldehyde, ethyl acetoacetate and urea) with antimony(III) chloride as a Lewis acid catalyst in anhydrous acetonitrile, they isolated the enamine **201** as the sole product (9% yield), which reacted with benzaldehyde smoothly providing DHPM in almost quantitative yield. Neither the bisureide **199** nor the Knoevenagel adduct **196** was observed. Based on the observation of experiments, Capanec proposed a brief mechanism: the enamine intermediate **201** generated from biomolecular reaction of urea and 1,3-dicarbonyl compound under Lewis acid catalytic conditions reacts with a third partner aldehyde providing DHPM. The authors pointed out this enamine pathway should be the dominant one in the case of Lewis acid-catalyzed version in aprotic solvents. However, the iminium pathway was often presented in some publications concerning Lewis acid-catalyzed Biginelli reaction without any proof given.



Scheme 78. The enamine mechanism of the Biginelli reaction (the intermediate **202** in bracket was suggested by Morokuma)

More recently, Morokuma's group reinvestigated the entire mechanism of the Biginelli reaction with benzaldehyde, urea, and ethyl acetoacetate as reactants by using artificial force induced reaction (AFIR) method, combined with density functional theory calculations (DFT).^[265] They found all the three routes above-mentioned were suitable to lead to the Biginelli product. Among them, the iminium route is the most favorable one, thanks to a low overall barrier of the rate-determining step. With respect to iminium and enamine routes, the rate-determining step is the cyclization step (21.5 kcal mol⁻¹ and 31.2 kcal mol⁻¹ respectively). But in the Knoevenagel pathway, the rate-determining step refers to the formation of carbenium ion intermediate **195**

(28.0 kcal mol⁻¹). According to Morokuma's calculation, the intermediates before cyclization are supposed to be different in the three mechanisms. In the Knoevenagel and iminium routes, the cyclization takes place on the intermediate **197** (Scheme 75 and 76), while in the enamine mechanism, the intermediate **202** is involved in the cyclization (Scheme 78). In addition, the excess of urea was found to play a catalytic role in nearly all steps of all the routes. For instance, urea can reserve/release a proton during the reaction and lower the reaction barriers.

2.1.3. The pharmacological properties of DHPMs

The Biginelli reaction was overlooked for a long period since its discovery, as at the initial time, the chemical community probably considered the product DHPM was nothing but an esoteric heterocycle.^[259] But that all changed when DHPMs were found to exhibit a wide range of biological activities in past decades. Extensive attention has been paid to this reaction, both in synthetic strategies and in medicinal aspects. The main pharmacological activities associated with this scaffold are antitumor, anti-inflammatory, antibacterial, antiviral, and antihypertensive activities, etc. Considering the importance, these biological properties were specially reviewed by Kappe,^[266] Fima,^[267] Rawal,^[268] and Homem-de-Mello,^[269] as well as covered in the aforementioned comprehensive reviews. Some DHPMs with pharmacological properties are shown in Figure 6.

2.1.4. The synthetic methodology

As we mentioned, the discovery of the potent pharmaceutical application of the Biginelli adducts has led to a boom of the study of the Biginelli reaction over past decades. A tremendous number of catalysts were reported to promote this reaction, mainly including Bronsted acids and Lewis acids. The Biginelli reaction generally proceeds rather slowly at room temperature. As a result, the reaction is usually performed at elevated temperature in common organic solvent, such as ethanol or MeCN. Green alternatives using water, ionic liquids or solvent-free conditions emerged as well.^[270] And sometimes the combination with modern synthetic technique, such as sonication or microwave irradiation would accelerate the Biginelli reaction. Allowing for the real large quantity of the catalysts and conditions developed for Biginelli reactions, a cursory summary of the developed catalysts rather than details is given below, which are already covered in Singh's^[256] and Sandhu's^[257] reviews.

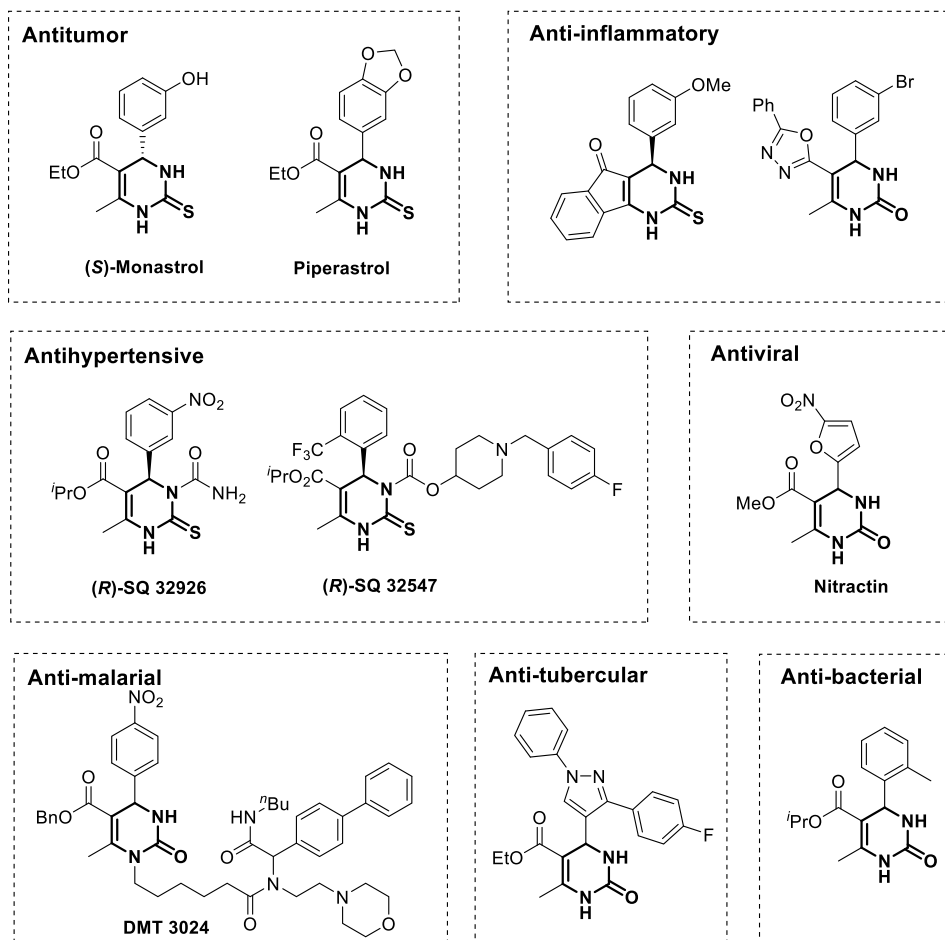


Figure 6. Selected examples of DHPMs exhibiting pharmacological activities

1) Brønsted acid catalysts^[256-257]

Concentrated HCl was the first Brønsted acid catalyst employed in the original reports by Biginelli. Besides HCl, many protonic acids have been proved to be efficient catalysts, including mineral and organic acids, such as H₂SO₄, HClO₄, HBF₄, H₃PO₄, H₃PW₁₂O₄₀, formic acid, acetic acid, trifluoroacetic acid, trifluoromethane sulfonic acid, *p*-toluenesulfonic acid (*p*-TSA), dodecylphosphonic acid, sulfamic acid and so on. Supported Brønsted acids (like PEG-SO₃H, Dowex-50W, Amberlyst-70, Nafion-H resin) were also employed in previous reports.

2) Lewis acid catalysts^[256-257]

The most frequently-used catalysts in the Biginelli reaction are Lewis acids, especially metallic Lewis acids. A large amount of halides, triflates or other salts of Li, Mg, Al, Ca, Sc, Ti, V, Fe, Co, Ni, Cu, Zn, Ga, Sr, Y, Zr, Nb, Mo, Ru, Ag, Cd, In, Sn, Sb, La, Ce, Pr, Sm, Yb, Se, W, Bi, etc.

have been utilized to promote this reaction. In addition to metallic Lewis acids, non-metal Lewis acids, such as molecular iodine, proved to be efficient catalysts as well.

3) Others^[256-257]

The majority of Biginelli reactions were catalyzed by acidic catalysts. An exception reported in literature was that some bases, such as *t*-BuOK, *n*-BuLi, triethylamine, could also promote the reaction. Regarding the green chemistry principles, carrying out the Biginelli reaction in ionic liquids (ILs) or without solvent also attracted much attention in the past. Likewise, several research groups carried out the bio-catalytic Biginelli reaction successfully using bakers' yeast^[271] or α -chymotrypsin enzyme^[272] as catalyst. Catalyst-free protocols were also claimed but were then proved to be unreliable.^[273] Modern synthetic techniques such as microwave irradiation^[274] and sonication^[275] were also employed to facilitate the Biginelli reaction.

The DHPM moiety has an inherent stereogenic center at *C4* position. However, in most reports, the conventional Biginelli reaction provided racemic DHPMs. Optically pure DHPMs could be obtained relying on the chiral resolution or asymmetric Biginelli reactions catalyzed by chiral organocatalysts or chiral complexes (Figure 7).^[276-277]

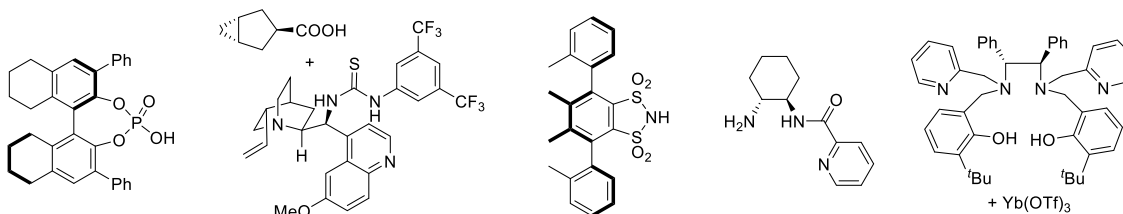
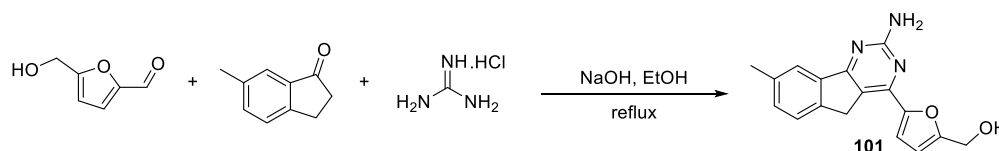


Figure 7. Chiral catalysts employed in the asymmetric Biginelli reaction

As we can see, the Biginelli reaction is a very mature reaction after the extensive investigation over the past decades. Most of the reported work focused on developing new catalytic conditions, keeping little space for further innovation in the catalytic conditions. However, extending the Biginelli reaction to special substrates to furnish more structural diversity of DHPMs might still be a promising research approach, as well as incorporating renewable biomass-derived molecules into DHPMs.

2.2. The utilization of HMF in the Biginelli reaction

As part of our ongoing research on the conversion of biomass-derived platform chemicals to complex fine molecules *via* efficient routes, we selected the Biginelli reaction to start the investigation of multicomponent reactions involving HMF as an aldehyde component. Furfural, another furan-based platform chemical, has been utilized in the Biginelli reaction many times. The reactivity of HMF has never been systemically studied in the Biginelli reaction. The sole related example is a variant of the Biginelli reaction performed by Tulshian and coworkers for the purpose of preparing an adenosine receptor (A_{2A}) antagonist (Scheme 79).^[160] The reaction was conducted with HMF, ketone and guanidine hydrochloride salt in the presence of sodium hydroxide in refluxing EtOH. Regretfully, the yield and detailed reaction conditions were not mentioned in this publication.



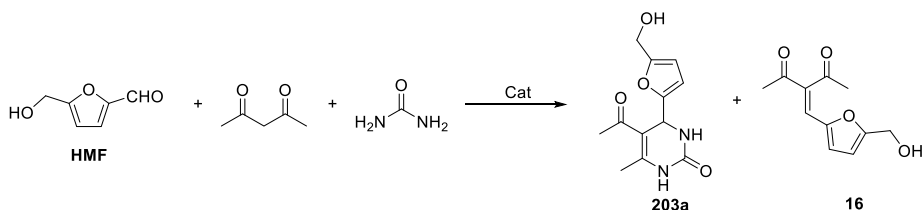
Scheme 79. The sole Biginelli-type reaction involving HMF in literature

2.2.1. Optimization of the reaction conditions

We initiated our investigation of the Biginelli reaction with HMF (1 mmol), acetylacetone (1 mmol) and urea (1.5 mmol) as model substrates. Following the seminal work of Pietro Biginelli who used mineral acid HCl as a catalyst, we ran our first experiment by reacting HMF in refluxing ethanol (2.5 mL, 0.4 M) in the presence of concentrated HCl as a catalyst (2 drops). Unexpectedly, a complex mixture was obtained with no trace of expected product although HMF was consumed completely after 24 hours (Table 8, entry 1). Same results were observed when the reaction was performed in the presence of trifluoroacetic acid (Table 8, entry 2). These results could be attributed to the degradation or oligomerization of HMF under heating acidic conditions. In refluxing acetic acid and in the presence of an equimolar amount of acetylacetone and urea, a messy mixture was obtained from HMF (in which no trace of the Biginelli product was observed), whereas under same conditions, furfural led to 40% isolated yield of the corresponding Biginelli product (not shown in Table 8). This fact confirmed that the relatively poor stability of HMF under acidic conditions as already discussed in bibliography part and the behaviour of HMF in acid-catalyzed Biginelli reaction is much more complicated compared with furfural.

When a heterogeneous resin Amberlyst® 15 (50 mg) was used instead of homogeneous protonic acids, ¹H NMR of the crude reaction mixture showed the formation of the Biginelli product **203a** (59% NMR ratio), together with residual HMF (14% NMR ratio) and the Knoevenagel adduct **16** (27% ratio), arising from the condensation between acetylacetone and HMF (Table 8, entry 3).

Table 8. Optimization of the Biginelli reaction of HMF^a



Entry	Catalyst	Solvent	Temperature	Time	¹ H NMR Ratio ^b HMF/203a/16
1	Conc. HCl (2 drops)	EtOH	reflux	24 h	messy
2	CF ₃ COOH (50 uL)	MeCN	reflux	24 h	messy
3	Amberlyst-15 (50 mg)	EtOH	reflux	24 h	14 / 59 / 27
4	Amberlyst-15 (100 mg)	EtOH	reflux	24 h	10 / 63 / 27
5	ZnCl ₂ (20 mol %)	EtOH	reflux	24 h	6 / 65 / 29
6	ZnCl ₂ (20 mol %)	MeCN	reflux	24 h	2 / 77 / 21
7	ZnCl ₂ (20 mol %)	neat	60 °C	4 h	0 / 82 / 18
8	ZnCl₂ (20 mol %)	neat	80 °C	4 h	0 / 94 / 6
9 ^c	ZnCl ₂ (20 mol %)	neat	80 °C	4 h	0 / 88 / 12
10	ZnCl ₂ (10 mol %)	neat	80 °C	4 h	0 / 87 / 13
11	ZnCl ₂ (5 mol %)	neat	80 °C	4 h	0 / 84 / 16
12	ZnBr ₂ (20 mol %)	neat	80 °C	4 h	0 / 93 / 7
13	Zn(ClO ₄) ₂ 6H ₂ O (20 mol %)	neat	80 °C	4 h	0 / 78 / 22
14	-	neat	80 °C	4 h	3 / 55 / 42

^a Reaction conditions: The reaction was carried out in the presence of HMF (1 mmol), acetylacetone (1 mmol) and urea (1.5 mmol) in solvent (2.5 mL) or solvent-free conditions, stirred at corresponding temperature for indicated time. ^b Ratio of products were calculated on the base of ¹H NMR analysis. ^c 1 mmol urea was used.

The ratio shown in Table 8 was estimated on the base of ¹H NMR spectra of the crude reaction mixture, in which integration of specific peaks belonging to the furan rings in starting material HMF, in the Biginelli product **203a** and in the Knoevenagel adduct **16**, allowed to determine the proportions of these three compounds (Figure 8).

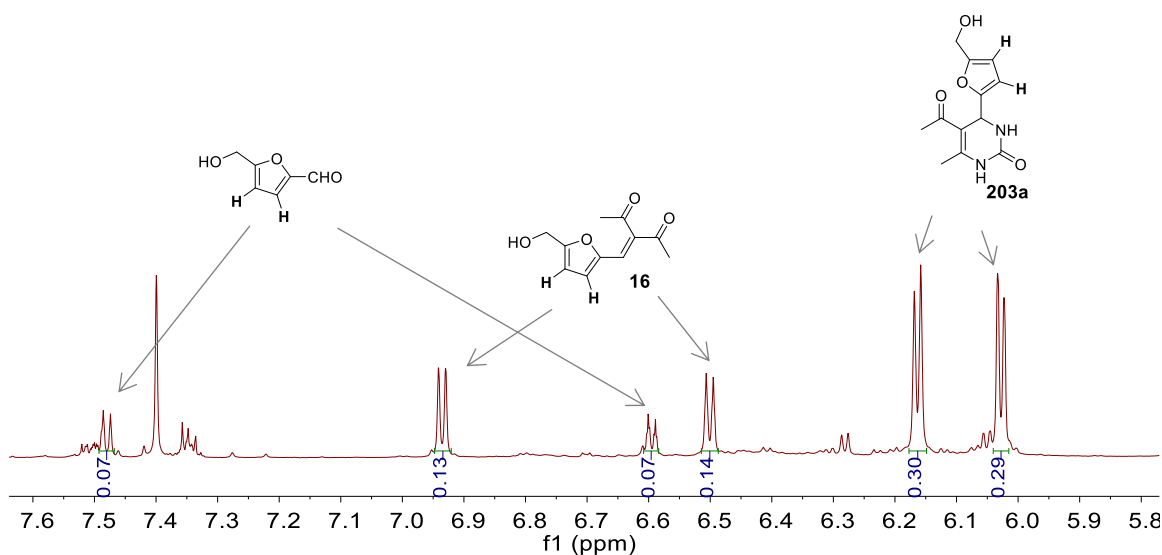


Figure 8. The selected proton signals used for estimating the ratio between HMF, **203a** and **16** (Taking NMR spectrum from conditions in Table 8 entry 3 for example)

The structure of the Biginelli adduct **203a** was confirmed by NMR spectra (^1H , ^{13}C , DEPT 135, ^1H - ^1H COSY, HSQC and HMBC). The correlations of *H4-H3* and *H4-C5*, *H1-C5*, *H1-(CH₃-C6)* were observed in ^1H - ^1H COSY spectrum and HMBC spectrum respectively, which clearly ascertained the formation of a pyrimidine ring by incorporating the three reactants (Figure 9).

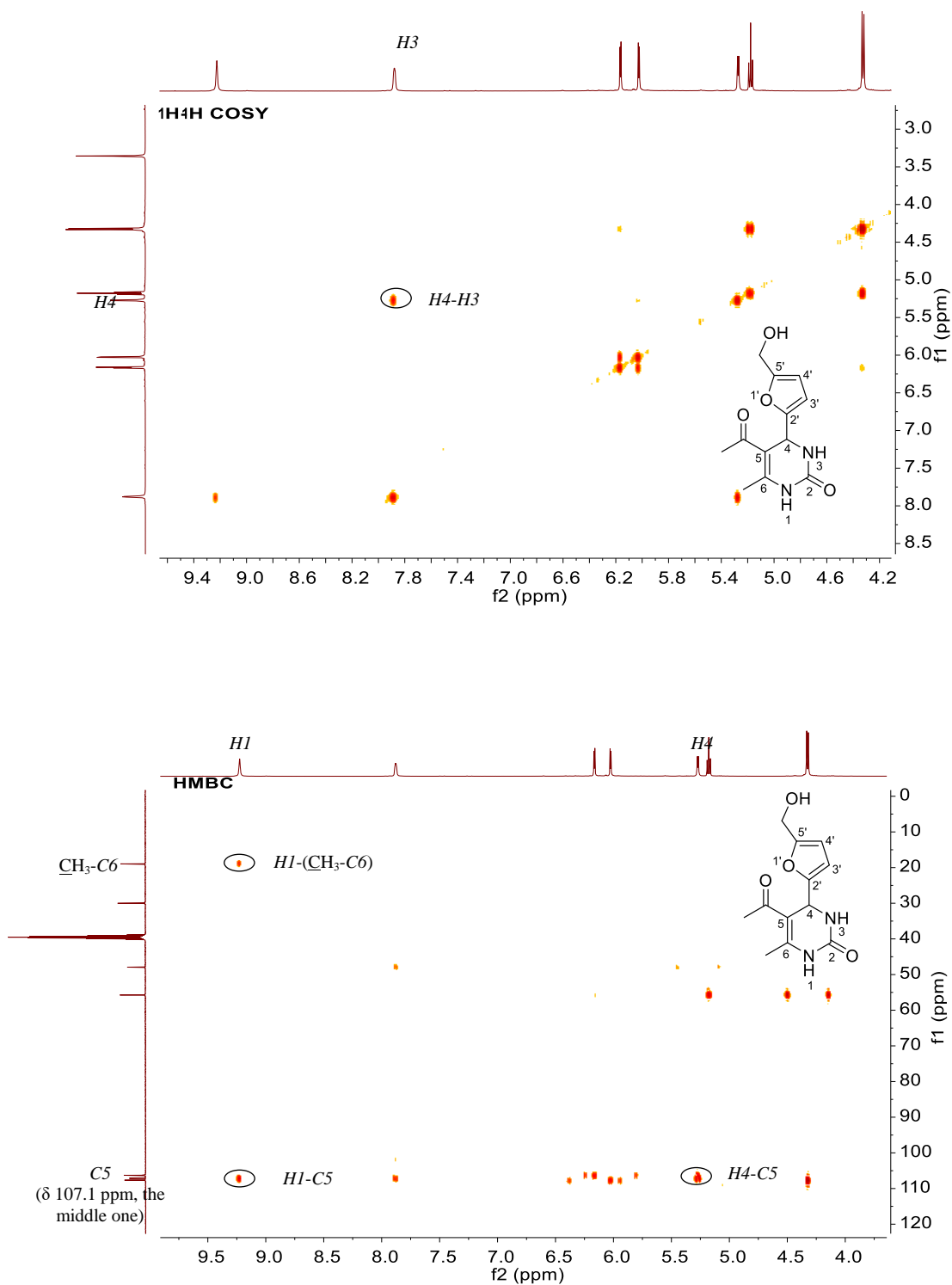


Figure 9. 1H - 1H COSY and HMBC NMR spectra of DHPM 203a

Attempt to increase the loading of Amberlyst® 15 only resulted into a slightly better result (Table 8, entry 4). Given that HMF could not survive through the strong homogeneous Brønsted acid catalytic conditions and the heterogeneous resin exhibited only moderate efficiency, the range of catalyst species was then restricted to Lewis acids. The reaction performed in the presence of 20 mol% of zinc chloride in refluxing EtOH [0.4 M for HMF] led to a 94% conversion of HMF, 65% in favor of the desired Biginelli product **203a** along with the Knoevenagel adduct **16** (29% ratio) (Table 8, entry 5). Using acetonitrile instead of ethanol slightly improved the conversion of HMF as well as the selectivity in favor of the Biginelli product (Table 8, entry 6). When the reaction was conducted in solvent-free conditions at 60 °C, a complete conversion was observed after 4 hours with 82% ratio of DHPM **203a** (Table 8, entry 7). By increasing the reaction temperature to 80 °C, the ratio of **203a** was raised to 94% after 4 hours (Table 8, entry 8). The neat conditions with ZnCl₂ as a catalyst provided a rather clean reaction, no other significant side-product except the Knoevenagel adduct **16** and DHPM **203a** was observed in the crude proton NMR. An equimolar ratio between the three partners (instead of 1.5 equiv. of urea) led to a modest decrease of the selectivity towards product **203a** (Table 8, entry 9). Decreasing the loading of catalyst (Table 8, entries 10 and 11) has a moderate but perceptible impact on the yield, which encouraged us to go on, for further experiments, with a 20 mol% loading of the catalyst. Freshly opened anhydrous ZnCl₂ gave same results as a long-term stored one. Other zinc salts such as ZnBr₂ or Zn(ClO₄)₂·6H₂O provided similar or inferior efficiency compared to zinc chloride (Table 8, entries 12 and 13). It was notable that in the absence of any catalysts, conversion of HMF was almost quantitative (97%), but with a poor selectivity for DHPM **203a** (only 55% ratio), which was not sufficiently satisfactory for selecting catalyst-free conditions (Table 8, entry 14).

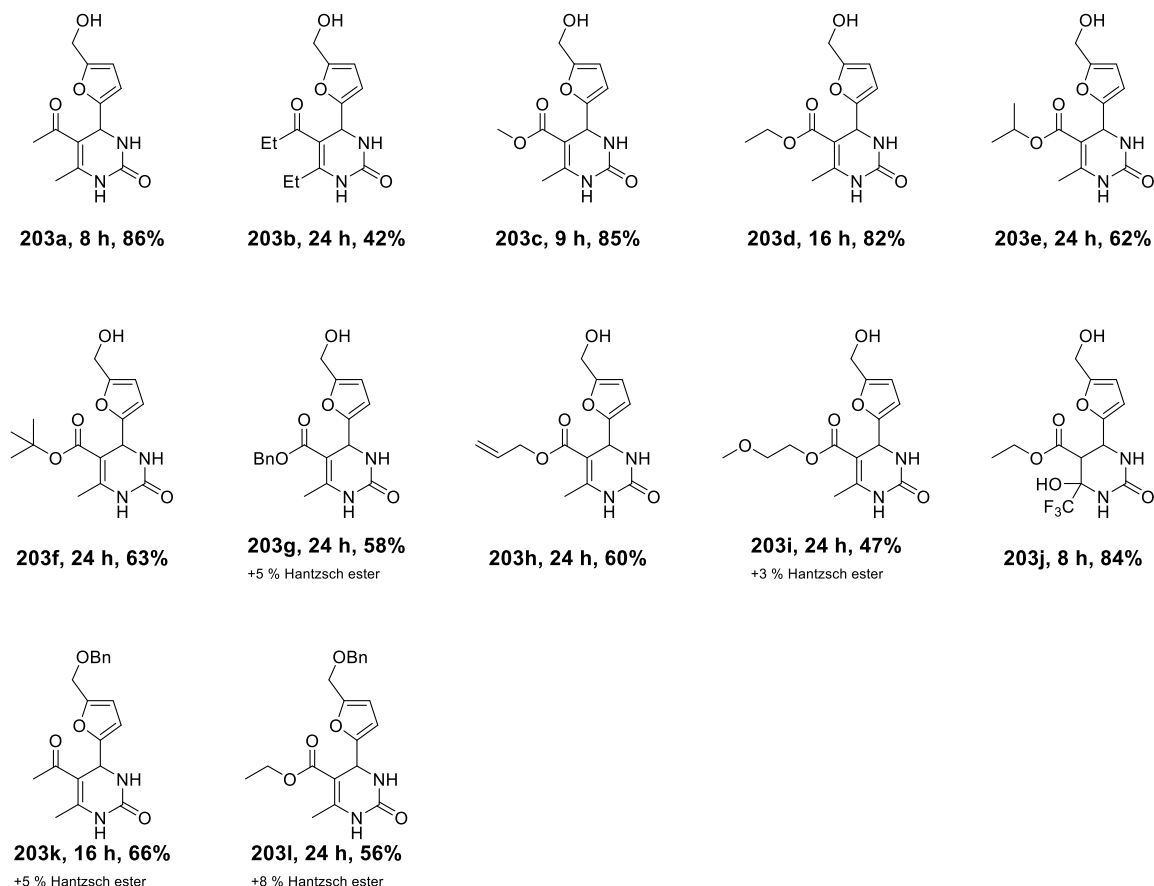
2.2.2. Substrate scope study

The substrate scope was next examined under the optimized conditions, [i.e, 1 equiv. of HMF, 1 equiv. of dicarbonyl compound, 1.5 equiv. of urea, ZnCl₂ (20 mol%), 80 °C, neat]. Depending on the substrates, the reaction time was extended to 24 hours to allow a complete conversion. A range of 1,3-diketones and β-keto esters were tolerated (Figure 10).

Acetylacetone afforded the Biginelli product **203a** in 78% yield by simple filtration and washing with cold water to remove remaining urea and the catalyst. However, it was found that DHPM **203a** exhibited some solubility in water, and additional 8% yield of **203a** was recovered from the aqueous filtrate after column chromatography purification, increasing the isolated yield of **203a**

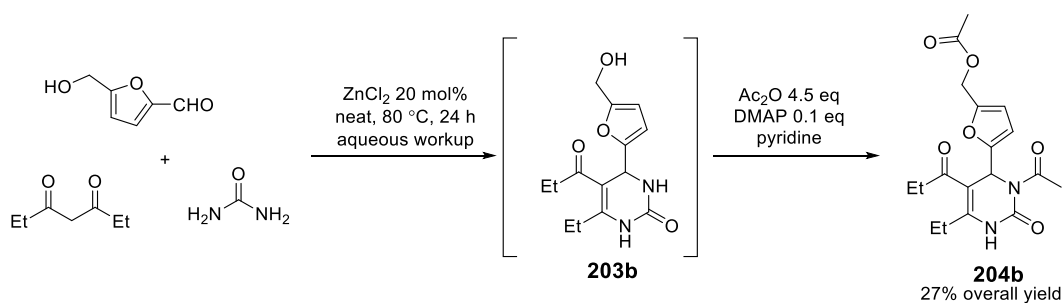
to 86%. In addition, two other products were identified in negligible quantity from the filtrate: the Knoevenagel product (2%) and the Hantzsch dihydropyridine (2%), which were not easily visible in the crude NMR due to their very low amount.

Running the reaction with heptane-3,5-dione gave **203b** in only 42% yield (with 1% of Hantzsch ester) after purification by column chromatography. Purification through preparative TLC gave a comparable 36% yield. The drop of yield could be probably explained by a less efficient reaction (both TLC and crude NMR were less clean). In order to figure out whether the purification resulted into the decrease of the isolated yield, we subjected the crude Biginelli reaction mixture obtained from heptane-3,5-dione to acetic anhydride in pyridine in the presence of a catalytic amount of DMAP (Scheme 80). Only 27% overall yield of di-acetylated compound **204b** (at OH and C3 positions) was obtained from HMF, confirming the low yield was due to the Biginelli reaction step.



^a Reaction conditions: The reactions were carried out with HMF or its derivatives (2 mmol), 1,3-dicarbonyl compounds (2 mmol), urea (3 mmol) and ZnCl₂ (20 mol%) under solvent-free conditions, stirred at 80 °C for indicated time. ^b Isolated yield.

Figure 10. The Biginelli reaction of HMF with various 1,3-dicarbonyl compounds^{a,b}

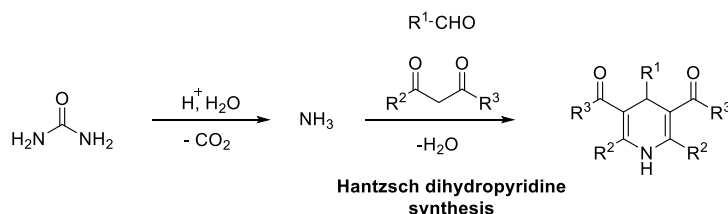


Scheme 80. The acetylation of **203b**

A range of acetoacetates (methyl-, ethyl-, *isopropyl*-, *tertbutyl*-, benzyl-, allyl- and 2-methoxyethyl acetoacetate) reacted smoothly, giving corresponding DHPMs **203c-i** in 85%, 82%, 62%, 63%, 58%, 60% and 47% yield respectively. For some reactions giving high yields (**203a**, **203c**, **203d**, **203j** and **203p**), simple filtration and water rinsing led to satisfactory purity of the products. Other compounds required the purification by column chromatography.

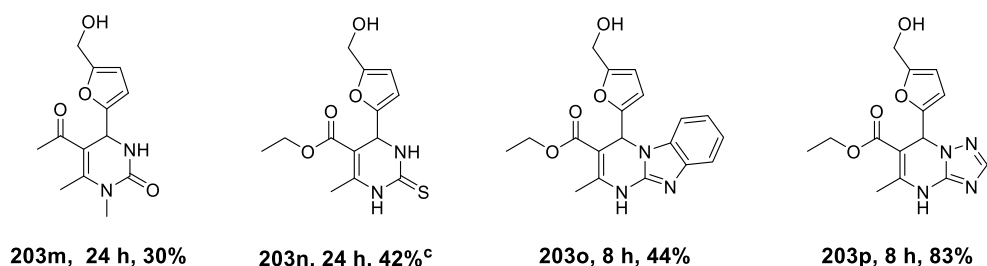
In the case of ethyl trifluoroacetoacetate, the intermediate hexahydropyrimidine derivative **203j** was obtained with 84% yield, which was in accordance with previous reports.^[278-280] Probably, the strongly electron-withdrawing group CF_3 - inhibits the elimination of H_2O . When HMF was protected with a benzyl group, moderate yields were obtained in the case of acetylacetone (66% for **203k**) and ethyl acetoacetate (56% for **203l**). The hexafluoroacetylacetone containing two CF_3 groups led to a complicated mixture, but not the desired DHPM neither the hexahydropyrimidine. Similar results were faced when ethyl 4-chloroacetoacetate was used (Figure 12).

Notably, in the case of some 1,3-dicarbonyl compounds, small amounts of Hantzsch dihydropyridines were isolated as side-products (around 5%), explaining the decrease in the yields. The formation of the Hantzsch dihydropyridine can be rationalized in terms of the dissociation of urea to ammonia at high temperature, which then reacts with 1,3-dicarbonyl partner and aldehyde in a classical Hantzsch-type fashion to produce the side-product (Scheme 81).^[281-283]



Scheme 81. The Hantzsch reaction observed as a side-reaction

The scope of urea-type building blocks were investigated next (Figure 11). *N*-Methylurea yielded the *N1*-substituted DHPM **203m** as the major product albeit in poor yield (30%), along with trace amount of *N3*-substituted regioisomer (< 1%). Similar yield was obtained with thiourea (42% for **203n**) but the reaction required a higher temperature (100 °C instead of 80 °C), probably due to competitive nucleophilic sites. 2-Aminobenzimidazole was tested as an alternative partner, giving a fused pyrimidine derivative **203o** in 44% yield. Furthermore, 3-amino-1,2,4-triazole afforded the corresponding product in 83% yield (**203p**). Despite the use of optimized conditions, the reactions with other ureas led to unsatisfactory results with a serious decrease of the yields of DHPMs, except for compound **203p**. In addition, the reactions with *N*-benzylurea and *N*-phenyl urea only led to Knoevenagel adducts under the identical conditions. In the case of 5-aminotetrazole and guanidine (freshly prepared from guanidine hydrochloride salt), no desired products were obtained either (Figure 12).



^a Reaction conditions: The reactions were carried out with HMF (2 mmol), 1,3-dicarbonyl compounds (2 mmol), urea-like building blocks (3 mmol) and ZnCl₂ (20 mol%) under solvent-free conditions, stirred at 80 °C for indicated time. ^b Isolated yield. ^c at 100 °C

Figure 11. The Biginelli reaction of HMF with various urea-type building blocks^{a,b}

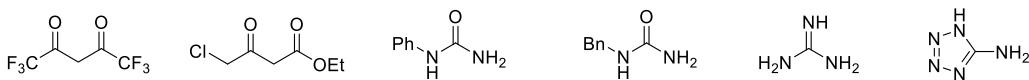
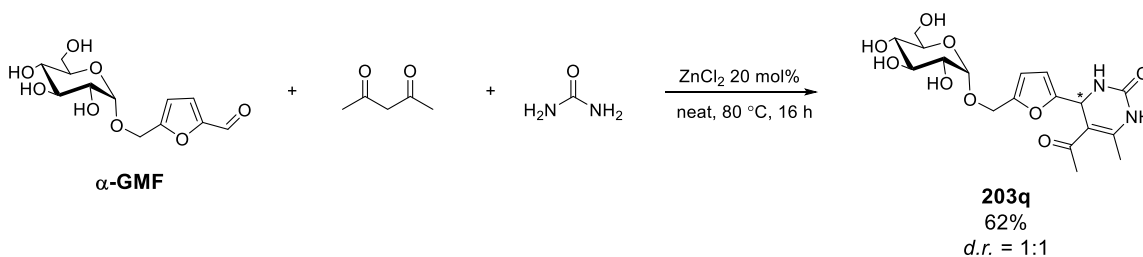


Figure 12. Unsuccessful substrates

α -Glucosyloxymethylfurfural (α -GMF), as a glucosylated derivative of HMF, can be generated from an acidic resin-catalyzed dehydration of isomaltulose. It has been used as a promising molecule in various aspects of carbohydrate-based chemistry.^[284-285] In order to further extend the scope of *O*-substituted HMF, the Biginelli reaction was next applied to α -GMF, giving access to the corresponding DHPM **203q** in 62% yield under identical conditions (Scheme 82). Because the sugar part is a chiral moiety, two diastereoisomers were formed at *C4* position (as a 1:1 mixture),

which was observed by ^{13}C NMR spectrum where some peaks (C4 , furan ring, and sugar part) were split (Figure 13).



Scheme 82. The Biginelli reaction of α -GMF

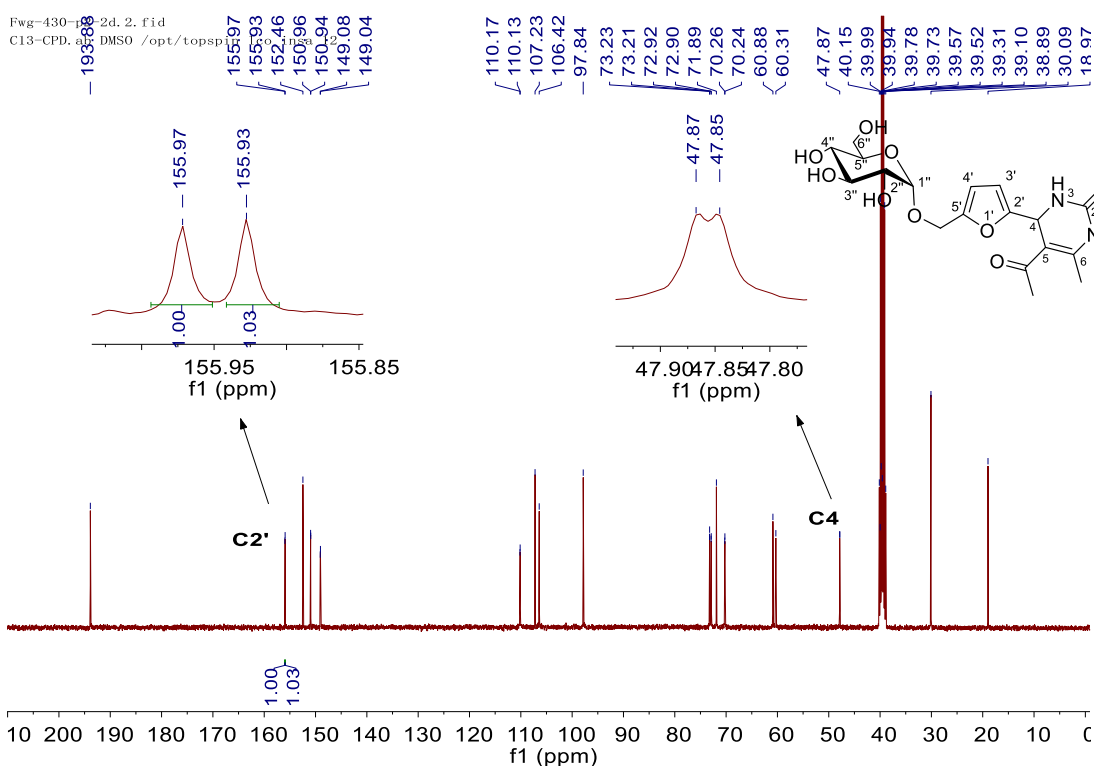
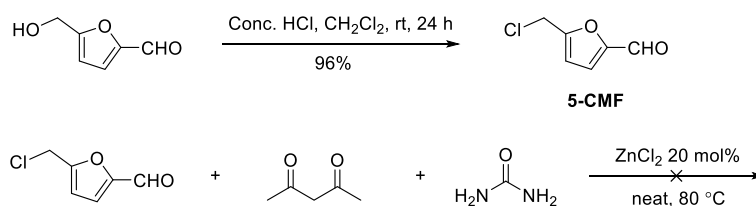


Figure 13. ^{13}C NMR spectrum of DHPM 203q

Another HMF analogue, 5-chloromethylfurfural (5-CMF), is also claimed as a platform molecule due to its availability from cellulosic biomass, as well as its rich derivative chemistry.^[199] We prepared 5-CMF from HMF in the presence of conc. HCl in dichloromethane with an excellent yield and then subjected it to the Biginelli reaction under the identical conditions (Scheme 83). Unfortunately, the reaction mixture decomposed or polymerized rapidly, resulting into black asphalt-like material in several minutes, and then turned into black insoluble solid in hours.



Scheme 83. The preparation of 5-CMF and attempted use in the Biginelli reaction

2.2.3. Mechanistic study

As mentioned, the Biginelli reaction might proceed through different reaction pathways depending on the conditions and the substrates engaged in the reaction. In order to understand which mechanism is the most dominant route in our case, we used NMR spectroscopy to monitor the reaction (Figure 14), by selecting the protons of the furan ring. The protons of the starting material HMF appeared at 7.49 and 6.60 ppm, the signals of the Knoevenagel compound **16** were at 6.94 and 6.51 ppm, and the peaks of the Biginelli product **203a** were at 6.17 and 6.03 ppm. It was noticeable that the reaction took place rapidly during the first 30 min, and then slowed down. The Knoevenagel compound **16** was the sole by-product or intermediate detected by ¹H NMR, and was always in a small quantity throughout the reaction. Compound **16** was generated from the beginning, and then was transformed to the Biginelli product **203a** quite slowly. No other intermediate was found in ¹H NMR through the reaction.

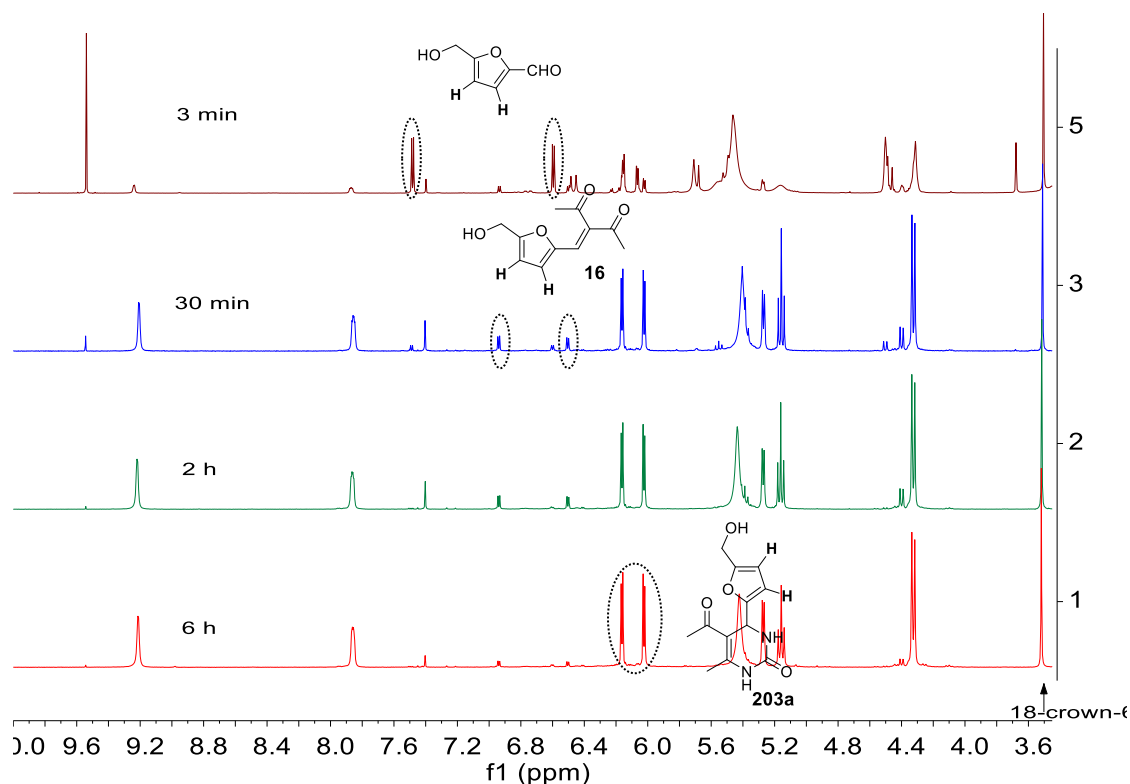
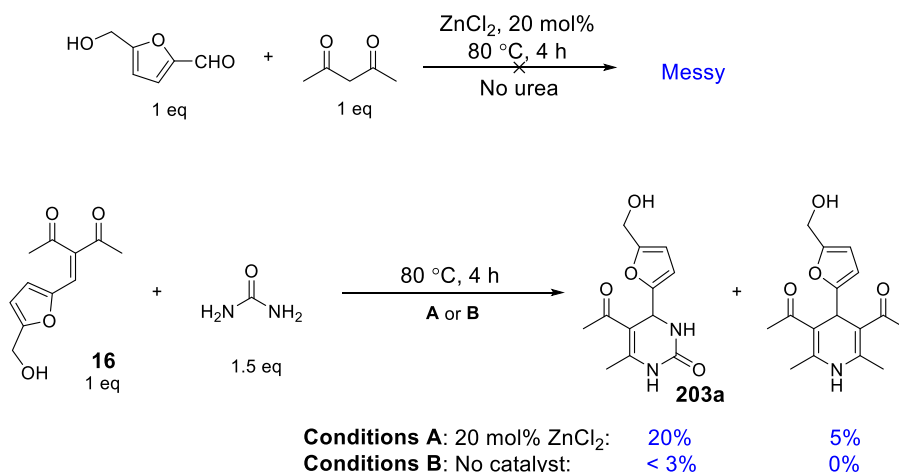


Figure 14. NMR monitoring of the Biginelli reaction of HMF, acetylacetone and urea

In order to figure out whether the Knoevenagel adduct is a key intermediate or just a side-product, we carried out a couple of control experiments, shown in Scheme 84. When the mixture of HMF and acetylacetone in the absence of urea, was subjected to the identical conditions used in the Biginelli reaction, an unexpected messy result was obtained. In the second control experiment, we treated the preformed Knoevenagel compound **16** (prepared by L-proline-catalyzed condensation of HMF and acetylacetone) with urea under identical conditions. Consistently with the observation in kinetic study just shown above, only 25% conversion of **16** was achieved after 4 hours based on the crude NMR, to provide the Biginelli product **203a** (20%) along with the Hantzsch dihydropyridine (5%). In contrast, the transformation of compound **16** to the Biginelli product **203a** hardly occurred without ZnCl₂ catalyst (Scheme 84). These results show that the Knoevenagel product cannot be considered as a simple intermediate towards the Biginelli product.



Scheme 84. Control experiments

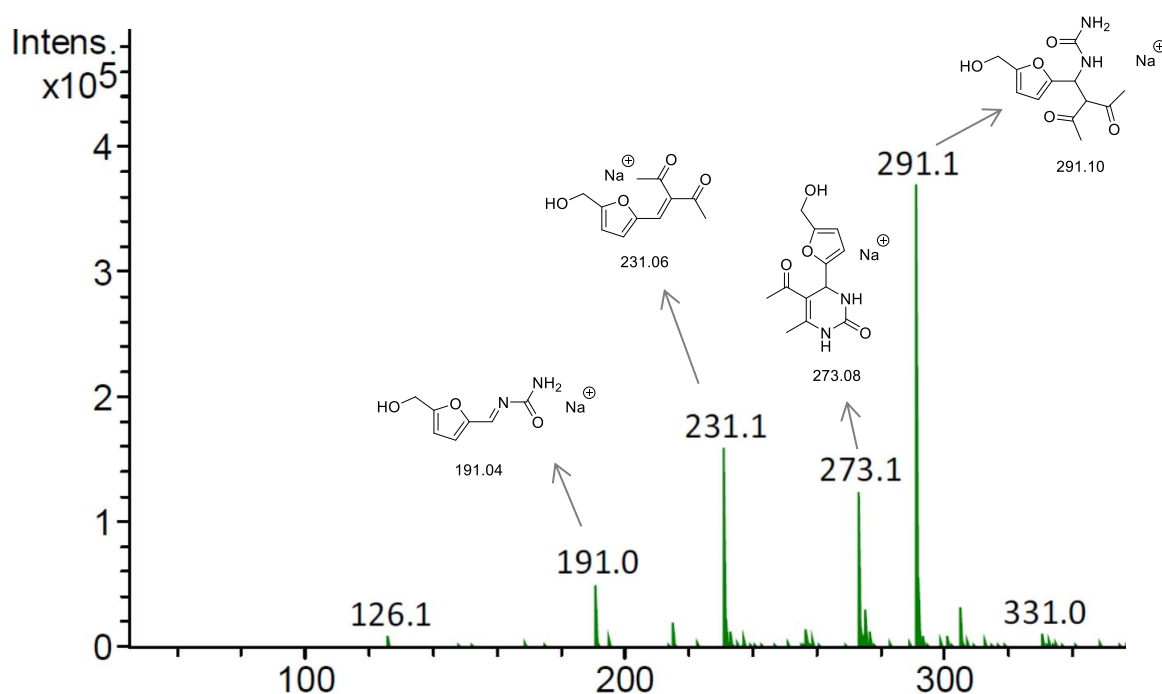


Figure 15. Mass spectrum of crude reaction mixture

We also used mass spectroscopy (with ESI ion source) to detect possible intermediates (Figure 15). In the 3-component reaction mixture, apart from the Knoevenagel adduct (231.1, [M + Na⁺]), the imine from the condensation between HMF and urea (191.0, [M + Na⁺]) and the intermediate just before cyclization in the iminium and Knoevenagel routes (291.1, [M + Na⁺]) were detected. According to the experimental results and literature, we thus suggest that the Knoevenagel route might not be the dominant mechanism, even though the Knoevenagel adduct was the sole intermediate observed by ¹H NMR during the reaction. The enamine pathway can be excluded

because neither the enamine nor other related intermediates belonging to the enamine mechanism were observed either by NMR or mass spectroscopies. The other strong evidence to rule out the enamine pathway was the selective formation of *NI*-substituted DHPM when *N*-methylurea was used. Overall, our experimental results are in favor of a mixed mechanism that includes the iminium route and the Knoevenagel route.

2.3. Conclusion

In summary, we have explored the use of biomass-derived HMF in the multicomponent Biginelli reaction. After screening several sets of conditions, solvent-free reaction conditions have been selected as a simple, economical, and environmentally benign protocol. The substrate scope study shows the versatility of this reaction which can even involve functionalized HMF derivatives as complex as α -GMF. All the DHPM products obtained here are new compounds, which undoubtedly extended the DHPM libraries. The hydroxymethyl moiety in target DHPMs, provides a much wider scope of possible derivatization compared to simpler systems such as those obtained from furfural.

Chapter III. Synthesis of HMF-derived α -Aminophosphonates *via* One-pot Kabachnik-Fields Reaction

3.1. Introduction

α -Aminophosphonates are the esters of α -aminophosphonic acids which are the structural analogs to α -amino acids. They have been considered as a class of compounds of significant importance thanks to their wide spectrum of biological properties. As a consequence, intense efforts have been made on developing effective synthetic routes to prepare α -aminophosphonates and their derivatives. Among them, the Kabachnik-Fields reaction involving a one-pot condensation of a carbonyl compound (usually an aldehyde), an amine and a dialkyl phosphite is the most efficient and convenient strategy.^[286-289]

In this chapter, we will describe and discuss our results of the study on the Kabachnik-Fields reaction using HMF as a starting material. Like in chapter II, we will first give an overview on α -aminophosphonates and the Kabachnik-Fields reaction before detailing our experimental results.

3.1.1. Overview on α -aminophosphonates

It is well known that organophosphorus compounds play a pivotal role in agricultural chemistry. Some agrochemicals contain an α -aminophosphonic acid or an α -aminophosphonate moiety. One of the most famous and widely used α -aminophosphonic acid-based organophosphorus agrochemicals is Glyphosate (Roundup[®]), which is a broad-spectrum systemic herbicide and crop desiccant.^[290] Another example is Dufulin, an α -aminophosphonate, widely used in China to prevent plant viral diseases.^[291]

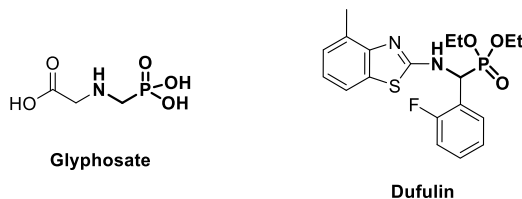
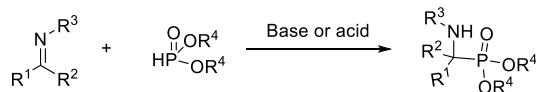


Figure 16. α -Aminophosphonic acid or ester based agrochemicals

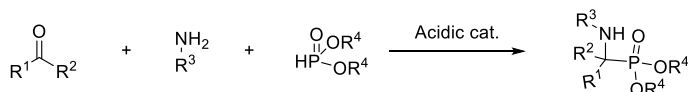
Apart from applications in agrochemistry, α -aminophosphonates have diverse potential applications in pharmaceutical chemistry as well, as some of them exhibit antitumor,^[292-293] antibacterial,^[294] and antitubercular^[295] activities.

Generally, the preparation of α -aminophosphonates relies on two principal methods (Scheme 85):^[296] (i) the Pudovik reaction,^[297] where a dialkyl phosphite is added to an imine; (ii) the Kabachnik-Fields reaction,^[288] in which a 3-component condensation of a carbonyl compound, an amine and a dialkyl phosphite takes place in a single pot. Other novel methods like C-H amination of alkylphosphonates^[298] or Cu(I)-catalyzed carbene insertion^[299] have been developed more recently (Scheme 85). However, of the reported methods, the Kabachnik-Fields reaction is obviously the most straightforward and efficient one to prepare α -aminophosphonates, thanks to the easy availability of starting materials and also its simple operation.

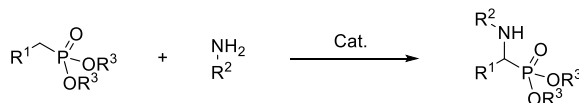
Pudovik reaction



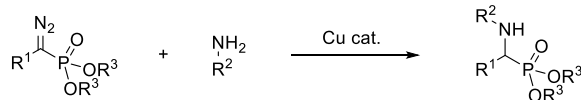
Kabachnik-Fields reaction



C-H amination of alkylphosphonates



Carbene Insertion



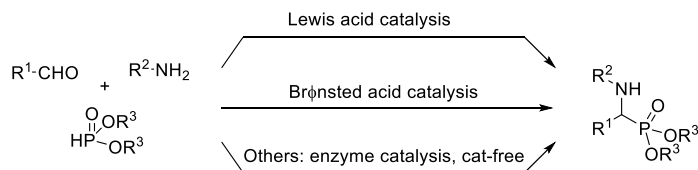
Scheme 85. Different approaches to α -aminophosphonates

3.1.2. Overview on the Kabachnik-Fields reaction

The Kabachnik-Fields reaction was first reported independently in 1952 by the Soviet chemist Martin Izrailevich Kabachnik^[300] and the American chemist Ellis K. Fields.^[301] It can be regarded as a variant of the Pudovik reaction, which was discovered in 1950.^[297] The Kabachnik-Fields reaction can also be considered as a specific case of the Mannich reaction, in which the nucleophilic phosphorus atom takes the place of the enolate to implement the nucleophilic addition onto the C=N double bond. Therefore, sometimes, it may be referred to as the phospha-

Mannich reaction. Currently, the Kabachnik-Fields reaction appears to be the most efficient and frequently-used method to prepare α -aminophosphonates.

In a popular procedure, the 3-component Kabachnik-Fields reaction is carried out with a catalyst, often a Lewis acid catalyst, in organic solvent, at room or moderate temperature. In the case of water-sensitive Lewis acid catalysts, a dehydrating agent (e.g. MgSO_4 or molecular sieves) is added to the reaction to avoid the possible deactivation by the water formed during the condensation of the aldehyde and the amine. Besides Lewis acid catalysts, some Brønsted acids, especially heterogeneous Brønsted acid catalysts such as supported sulfonic acids, are also employed to promote this reaction. Enzyme catalysis and even catalyst-free protocols have also emerged. The reaction can be performed in ionic liquids (ILs) and even in water (when water-compatible catalysts are used) instead of conventional organic solvents, as well as under solvent-free conditions. Also, microwave irradiation and ultrasonication have been applied to the Kabachnik-Fields reaction.



Scheme 86. Typical methods developed for the Kabachnik-Fields reaction

A wide range of conditions for the Kabachnik-Fields reaction have been developed and some typical conditions are listed in Table 9.

Table 9. Some catalytic conditions presented for the visualization

Lewis acid catalysis system		
$\text{FeCl}_3/\text{EtOH}/\text{rt}$	$\text{FeCl}_3/\text{THF}/60\text{ }^\circ\text{C}$	$\text{CuI}/\text{neat}/50\text{ }^\circ\text{C}$
$\text{Cu}(\text{OTf})_2/\text{MeCN}/\text{rt}$	$\text{ZnBr}_2/\text{SiO}_2/\text{neat}/100\text{ }^\circ\text{C}$	$\text{LiOTf}/\text{neat}/80\text{ }^\circ\text{C}$
$\text{Mg}(\text{OTf})_2/\text{neat}/80\text{ }^\circ\text{C}$	$\text{Al}(\text{OTf})_3/\text{neat}/80\text{ }^\circ\text{C}$	$\text{Cu}(\text{OTf})_2/\text{neat}/80\text{ }^\circ\text{C}$
$\text{SnCl}_2/\text{neat}/\text{rt}$	$\text{Sn}(\text{OTf})_2/\text{CH}_2\text{Cl}_2/\text{rt}$	$\text{InCl}_3/\text{THF}/66\text{ }^\circ\text{C}$
$\text{YbCl}_3/\text{MeCN}/\text{rt}$	$\text{Yb}(\text{OTf})_3/\text{H}_2\text{O}/\text{PTS}/\text{rt}$	$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}/\text{neat}/\text{rt}$
$\text{SmI}_2/\text{MS}/\text{MeCN}/80\text{ }^\circ\text{C}$	$\text{SbCl}_3/\text{Al}_2\text{O}_3/\text{MeCN}/\text{rt}$	$\text{TaCl}_5/\text{SiO}_2/\text{MeCN}/\text{rt}$
$\text{Mg}(\text{ClO}_4)_2/\text{EtOH}/50\text{ }^\circ\text{C}$	$\text{InCl}_3/\text{DMF}/\text{MW}$	$\text{Ce}(\text{OTf})_4/\text{neat}/80\text{ }^\circ\text{C}$
$\text{Cd}(\text{ClO}_4)_2 \cdot x\text{H}_2\text{O}/\text{neat}/40\text{ }^\circ\text{C}$	$\text{Al}(\text{OTf})_3/\text{neat}/100\text{ }^\circ\text{C}$	$\text{Sc}(\text{OTf})_3/[\text{bmim}][\text{PF}_6]/\text{rt}$
$\text{Zn}(\text{OTf})_2/\text{neat}/\text{rt}$	$\text{TiO}_2/\text{neat}/50\text{ }^\circ\text{C}$	$\text{HfCl}_4/\text{EtOH}/60\text{ }^\circ\text{C}$

AgOAc/DME/MS/90 °C	I ₂ /EtOH/rt	BF ₃ · Et ₂ O/benzene/reflux
BiCl ₃ /MeCN/reflux	AlCl ₃ /MeCN/rt	Titanocene dichloride/neat/rt
Zirconocene dichloride/neat/rt	NbCl ₅ /neat/60 °C	SiO ₂ -supported AlCl ₃ /neat/rt
Brønsted acid catalysis system		
Fe ₃ O ₄ @SiO ₂ -SO ₃ H/CH ₂ Cl ₂ /rt	TFA/neat/rt	Amberlyst-15/MeCN/rt
Amberlite-IR 120/neat/MW	Amberlyst-IRC748/tol/reflux	KSF clay/neat/MW
Sulfamic acid/neat/rt	Sulfated polyborate/neat/90 °C	Oxalic acid/neat/50 °C
H ₃ PMO ₁₂ O ₄₀ /CH ₂ Cl ₂ /rt	H-beta zeolite/MeCN/reflux	PPA/neat/50 °C
Other conditions		
MCM-41@PEI/neat/50-80 °C	GO nano sheet/neat/rt	Candida antarctica lipase B/neat/rt
Cat-free/neat/75-80 °C	Cat-free/H ₂ O/ultrasonication/rt	Cat-free/toluene/110 °C

Note: MW = Microwave; MS = Molecular sieve; PPA = Phenylphosphonic acid; PTS = Polyoxyethanyl α -tocopheryl sebacate; GO = Graphene oxide.

With respect to the asymmetric version, only a few examples of Kabachnik-Fields reactions have been reported for the enantioselective synthesis of optically active α -aminophosphonates.^[302-303] These stereoselective approaches consisted of either chiral-catalyst catalysis or chiral substrate induction. Several chiral phosphoric acid-based catalysts,^[304] thiourea-based catalysts^[305] and metal complex catalysts (or metal Lewis acid catalyst + chiral ligand)^[306-307] have been employed, providing modest to good diastereo- or enantioselectivity (Figure 17). When starting from optically active substrates, especially chiral amines, only modest *dr* values were observed.

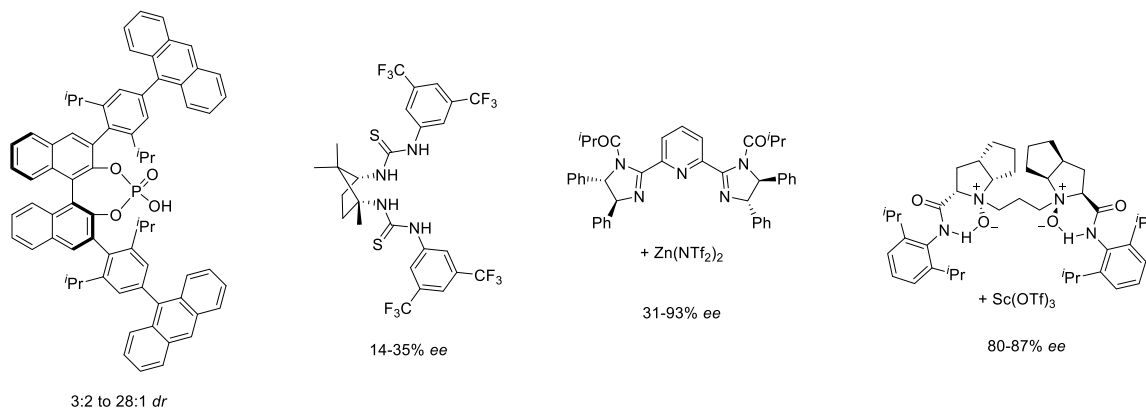
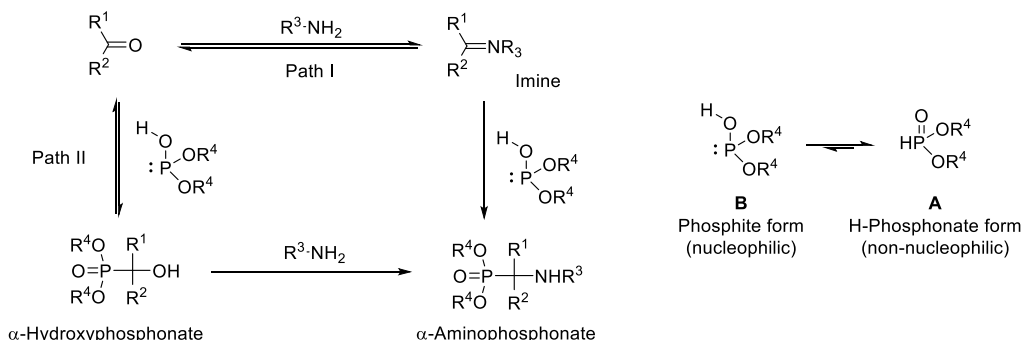


Figure 17. The chiral catalysts employed in the asymmetric Kabachnik-Fields reaction

Like the Biginelli reaction, the mechanism of the Kabachnik-Fields reaction was also a subject of debate. Before going to the mechanistic discussion, we should clarify the concepts of “dialkyl

phosphite” and “*H*-phosphonate”, both of which have been used to refer to the “P”-component in Kabachnik-Fields reactions. Generally, “dialkyl phosphite” is a more frequently-used name of this species. But in fact, there are two tautomeric forms in dialkyl phosphites: the *H*-phosphonate form (**A**) and the phosphite form (**B**) (Scheme 87, right).^[308-309] There is an equilibrium between *H*-phosphonate **A** and phosphite **B**, and the *H*-phosphonate tautomer **A** is the major form. However, only the phosphite tautomer **B** can serve as a nucleophile in addition reactions thanks to the lone electron pair on the phosphorus atom.

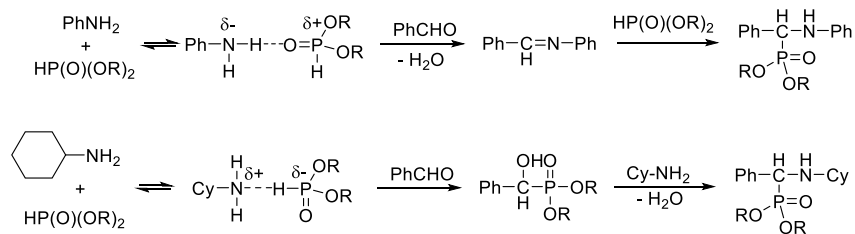
Because both amines and dialkyl phosphites can act as nucleophiles and undergo competitive additions to carbonyl compounds, the 3-component Kabachnik-Fields reaction might proceed through two pathways (Scheme 87): The first possible route is the imine pathway, where an imine is formed by the condensation of a carbonyl compound and an amine, followed by the addition of the phosphite to the C=N bond (like in the Pudovik reaction) to provide the α -aminophosphonate (Path I). The other possibility would involve a α -hydroxyphosphonate intermediate. A dialkyl phosphite would react with the carbonyl compound to yield a α -hydroxyphosphonate (the Abramov reaction), followed by substitution of the hydroxyl group of α -hydroxyphosphonate by an amine to furnish the α -aminophosphonate (Path II).



Scheme 87. The possible pathways in the Kabachnik-Fields reaction

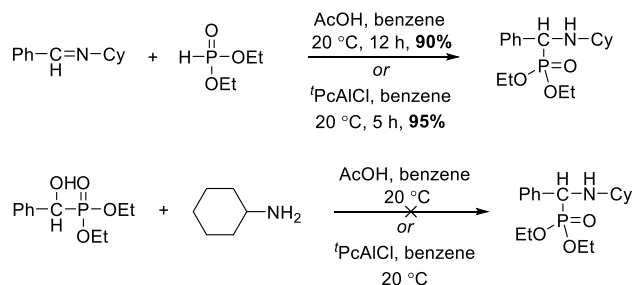
Cherkasov postulated that the reaction can follow both of the pathways discussed above depending on the nature of the reactants, especially the basicity of the amine employed (Scheme 88).^[286] For example, the reaction between benzaldehyde, aniline and dialkyl phosphite was assumed to undergo through the imine pathway, as the reaction between benzaldehyde and aniline to form imine is fast. In addition, an interaction between aniline and dialkyl phosphite *via* hydrogen bond before the formation of imine was claimed (Scheme 88). In the case of more basic cyclohexylamine, they suggested that the α -hydroxyphosphonate route was more favorable. The main argument supporting the hydroxyphosphonate route claimed by Cherkasov was that the

preformed *N*-cyclohexylbenzylideneamine failed to react with dialkyl phosphite, whereas the intermediate α -hydroxyphosphonate was detected by ^{31}P NMR in the 3-component reaction.



Scheme 88. The mechanism proposed by Cherkasov

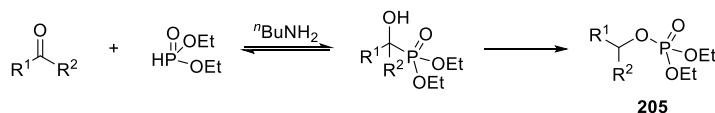
Later, the α -hydroxyphosphonate route was refuted by Zefirov et al. (Scheme 89).^[310] Zefirov carried out the reaction between preformed *N*-cyclohexylbenzylideneamine and diethyl phosphite in the presence of a catalytic amount of formic acid or ${}^t\text{PcAlCl}$ (a *tetra*-*tert*-butylphthalocyanine complex), leading to the α -aminophosphonate in high yield. Oppositely, the α -hydroxyphosphonate did not react with cyclohexylamine under these conditions. Zefirov suspected that the so-called “*N*-cyclohexylbenzylideneamine” observed by Cherkasov was not the imine, but cyclohexylamine benzoate from benzoic acid.



Scheme 89. Reinvestigation of the reaction between *N*-cyclohexylbenzylideneamine and phosphite

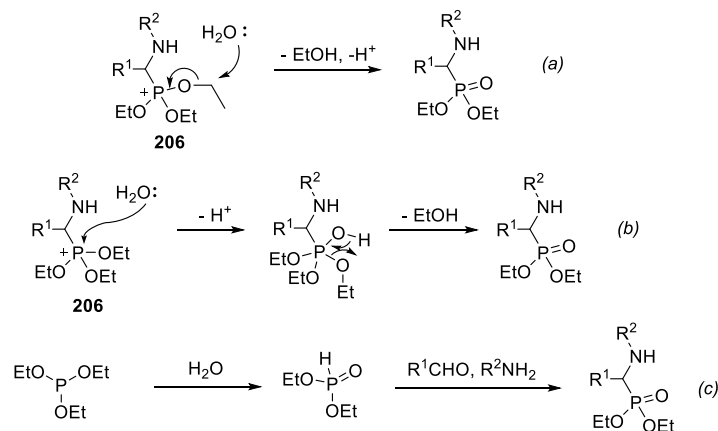
Another proof supporting imine pathway came from Keglevich.^[288, 311] In the 3-component reaction of benzaldehyde, cyclohexylamine and dimethyl phosphite, the characteristic $\nu_{\text{C=N}}$ stretching vibration at 1644 cm^{-1} was detected by *in situ* FT IR spectroscopy, which evidenced the existence of imine as an intermediate. Additionally, a 13% yield of α -hydroxyphosphonate was isolated in this case, but which did not undergo amination with cyclohexylamine under these conditions.

Gancarz et al. substantiated the formation of α -hydroxyphosphonate to be reversible (Scheme 90).^[312-313] It was found that α -hydroxyphosphonates obtained from aliphatic/aromatic aldehydes and ketones could go back to the original carbonyl compounds and dialkyl phosphites under certain conditions in the presence of a primary amine such as butylamine. Either, it rearranged to the corresponding phosphate **205** when an aromatic ketone was employed, resulting into a “dead-end” route from the viewpoint of formation of α -aminophosphonates (Scheme 90). However, there are few examples claiming the synthesis of α -aminophosphonates by nucleophilic amination of α -hydroxyphosphonates using an excess of amines under MW irradiation.^[314-315] Anyway, it can be concluded that the imine pathway is likely to be more general than α -hydroxyphosphonate one for the Kabachnik-Fields reaction.



Scheme 90. The possible transformations of α -hydroxyphosphonate claimed by Gancarz

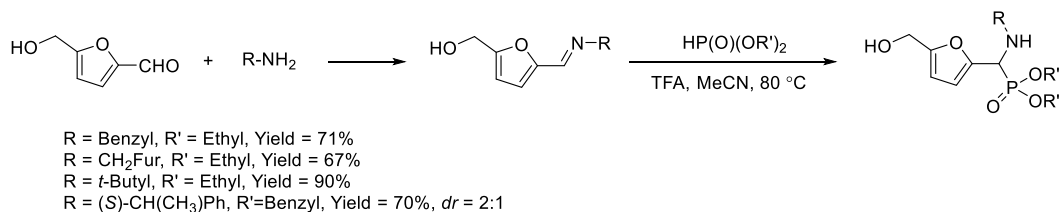
With respect to the substrates scope, most reported Kabachnik-Fields reactions employ aldehydes as carbonyl compound components, which usually exhibit satisfactory efficiency. Benzaldehyde is often used as a model substrate for this reaction. In contrast, only a few examples involve ketones as substrates.^[316] The amine component can be aromatic, aliphatic primary or secondary amine, or even ammonia. For the phospho-containing component, besides the commonly used dialkyl phosphites, trialkyl phosphites were also reported as phospho-nucleophiles in Kabachnik-Fields reactions. For trialkyl phosphites, water either generated from the condensation of aldehyde and amine or from solvent plays a crucial role in the formation of α -aminophosphonates. The alkyl-oxygen or phosphorus-oxygen fission assisted by water on the intermediate **206** after the Kabachnik-Fields reaction might be pathways to yield the α -aminophosphonate (Scheme 91, path *a* and *b*).^[317-318] The other possibility is the direct hydrolysis of trialkyl phosphite leads to dialkyl phosphite, which participates in the further reaction (Scheme 91, path *c*).^[319]



Scheme 91. Possible pathways in the Kabachnik-Fields-type reaction involving trialkyl phosphites

3.2. HMF in the Kabachnik-Fields reaction

As mentioned in Chapter I, several HMF-derived α -aminophosphonates had been prepared by Cottier and Skowroński by means of the Pudovik reaction (Scheme 92).^[105] The synthesis was achieved by a two-step strategy and required the preparation and the isolation of the imine. The subsequent Pudovik reaction was performed at 80 °C with trifluoroacetic acid as a catalyst, providing α -aminophosphonates in good yields.

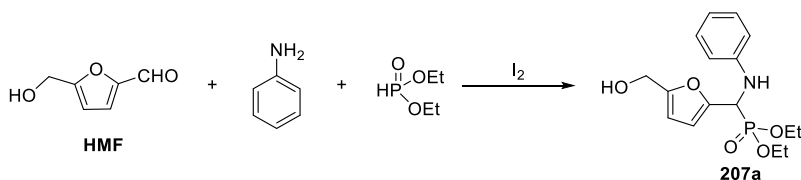


Scheme 92. Two-step approach to α -aminophosphonates from HMF *via* the Pudovik reaction

To the best of our knowledge, the direct synthesis of HMF-based α -aminophosphonates *via* 3-component Kabachnik-Fields reaction has never been investigated, despite the operational simplicity and high efficiency of this approach. As part of our on-going interest on the application of HMF towards fine chemicals and on green and sustainable chemistry, we explored the possibility to synthesize furan-based α -aminophosphonates *via* the one-pot Kabachnik-Fields condensation, directly from HMF.

3.2.1. Screening of reaction conditions

For this study, we selected molecular iodine as a mild Lewis acid catalyst, which has been often used in multicomponent reactions or heterocycle synthesis because of its operational simplicity, low cost, low toxicity and likely to be compatible with HMF sensitivity to acidic conditions.^[320-321] Wu and co-workers have confirmed the catalytic capability of molecular iodine in the Kabachnik–Fields reaction.^[322] They carried out the transformations employing several simple aldehydes such as benzaldehyde and furfural with I₂ as a catalyst in ethanol, obtaining corresponding α -aminophosphonates in good to excellent yields. The primary set of experimental conditions has been fixed as 5 mol% iodine in ethanol [0.5 M] with equimolar stoichiometric ratio of HMF, aniline and diethyl phosphite. The Kabachnik-Fields product **207a** was obtained in 71% isolated yield after 24 h, together with around 11% of starting material HMF and 6% of the intermediate imine (Table 10, entry 1).

Table 10. Optimization of the Kabachnik-Fields reaction of HMF^a

Entry	Cat. loading	Solvent [0.5 M]	Temp.	Ratio HMF/aniline/phosphite	Time	Isolated yield
1	5 mol%	EtOH	25 °C	1:1:1	24 h	71%
2	5 mol%	MeCN	25 °C	1:1:1	24 h	60%
3	5 mol%	DCM	25 °C	1:1:1	24 h	31%
4	5 mol%	THF	25 °C	1:1:1	24 h	84%
5	5 mol%	2-MeTHF	25 °C	1:1:1	24 h	74%
6	5 mol%	THF	25 °C	1:1:1.5	24 h	90%
7	5 mol%	2-MeTHF	25 °C	1:1:1.5	8 h	91%
8	5 mol%	-	25 °C	1:1:1.5	6 h	86%
9	2.5 mol%	2-MeTHF	25 °C	1:1:1.5	8 h	77%
10	1 mol%	2-MeTHF	25 °C	1:1:1.5	8 h	61%
11	-	2-MeTHF	25 °C	1:1:1.5	8 h	54% (80%) ^b
12	5 mol%	2-MeTHF	50 °C	1:1:1.5	4 h	83%
13	5 mol%	2-MeTHF	78 °C	1:1:1	3 h	71%

^a The reaction was carried out in a sealed tube with HMF(1 mmol), aniline, diethyl phosphite, solvent (2 mL) and iodine, stirred at corresponding temperature for indicated time. ^b 24 h.

The structure of obtained product **207a** was confirmed by ¹H NMR, ¹³C NMR, ³¹P NMR, ¹H-¹H COSY, HSQC and HMBC spectra (Figure 18). The signal of phosphorus shifted to 20.3 ppm ("P" in α-aminophosphonate) from 7.3 ppm ("P" in diethyl phosphite) in ³¹P NMR. The newly formed C-N and C-P bonds could be verified by the interactions between *H1* (4.86 ppm) and *C3'* (109.6 ppm), *C1''* (146.0 ppm), *C2'* (148.6 ppm) on HMBC spectrum. In addition, the existence of ¹H-³¹P coupling resulted into a doublet peak of *H1* with a large coupling constant (*J* = 23.5 Hz). The ¹³C-³¹P couplings were also observed on ¹³C NMR spectrum.

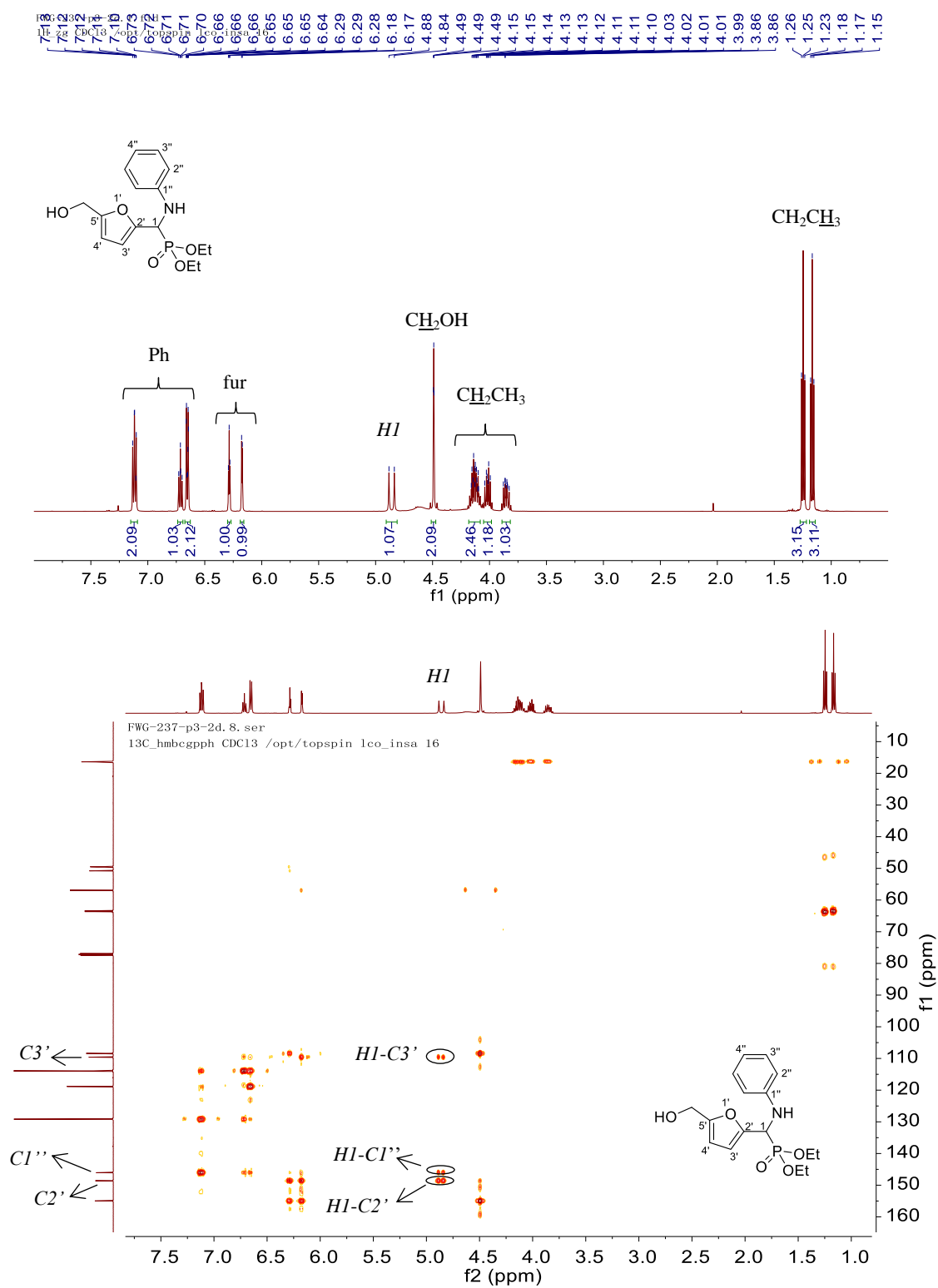


Figure 18. ¹H NMR and HMBC spectrum of compound **207a**

Based on this preliminary result, the reaction conditions were optimized, first by studying the influence of solvents. THF was found to provide a better result than EtOH, MeCN and DCM, affording product **207a** in 84% yield (Table 10, entries 1 - 4). The biomass-derived 2-methyltetrahydrofuran (2-MeTHF) which has been considered as a greener alternative to THF proved to be also efficient (Table 10, entry 5). Increasing the dosage of diethyl phosphite to 1.5 equivalents led to improved yields both in THF and in 2-MeTHF (Table 10, entries 6 and 7). The reaction took place smoothly under solvent-free conditions, giving access to **207a** in slightly decreased yield (86%) after 6 h (Table 10, entry 8). Considering the high reaction efficiency and the inherent merits of 2-MeTHF (production from renewable resources, low miscibility with water and enhanced stability),^[323] we decided to continue the investigation with 2-MeTHF as the solvent.

Decreasing the catalyst loading to 2.5 mol% and 1 mol% led to slower reactions (77% and 61% respectively after 8 h) (Table 10, entries 9 and 10). It is important to note that the reaction could proceed even without any catalysts, giving the expected product in a moderate yield (54%) after 8 h, but in a satisfactory yield (80%) after 24 h (Table 10, entry 11). Even though the catalyst-free conditions afforded a good yield in long enough reaction time, the 5 mol% of I₂ conditions gave the best balance between reaction efficiency and reaction duration. As a result, the I₂ catalyst was preserved in the rest of the study. With respect to temperature, performing the reaction at 50 °C led to total conversion of HMF within 4 h but with a slight decrease of the yield (Table 10, entry 12). Prolongation of the reaction time at 50 °C led to lower yields, which indicated the HMF-based α -aminophosphonates might decompose at high temperature under reaction conditions. The same result was observed when the reaction of equimolar quantities of all reactants was refluxed in 2-MeTHF (Table 10, entry 13).

3.2.2. Substrate scope of the reaction

With the optimized conditions in hand (Table 10, entry 7), the scope of the reaction was investigated with respect to the nature of amines and dialkyl phosphites, allowing the access to a library of novel HMF-derived α -aminophosphonates. The scope of amines was shown in Scheme 93.

Whatever the electron-donating or electron-withdrawing nature of the para substituents (methoxy-, chloro-, bromo-, iodo- and nitro-) on the aniline, the corresponding α -aminophosphonates **207b** -

207f were obtained in good to excellent yields (71-90%). An exception was observed in the case of *p*-iodo-aniline where a moderately elevated temperature (50 °C) was required for producing **207e** in 77% yield in acceptable reaction time. The comparable yields were obtained for meta-substituted anilines (yield of 93% for **207g** and 87% for **207h**), and 2-chloroaniline (82% for **207i**). These results revealed that the substituted group on phenyl ring of aniline has globally a low effect on the reaction efficiency. Compared to anilines, aliphatic amines were found consistently less reactive. In the case of aliphatic amines, elevated temperature (50 °C) was required to promote the reaction. Benzylamine and furfurylamine provided the corresponding α -aminophosphonates **207j** and **207k** in moderate yields, respectively 71% and 70%. Similar results were obtained for *n*-butylamine, cyclohexylamine and allylamine (**207l** - **207n**). Non-protected tryptamine afforded compound **207o** in 57% yield. The product possibly arising from the reaction of the pyrrolic amine of tryptamine was not observed. *tert*-Butyl glycinate (freshly prepared from hydrochloride salt) also worked under the same conditions but gave a poor yield of **207p** (31%). *N*-Methyl aniline, as an example of secondary amine, was also less reactive than aniline, giving **207q** in yield of 58% at 50 °C. When the chiral (*R*)- α -methylbenzylamine was used, a mixture of products **207r** was obtained in 72% yield, from which the two isomers could not be separated entirely by silica gel column chromatography. A modest diastereoselectivity with a 3.3 : 1 ratio of two diastereoisomers was observed on the basis of ^{31}P NMR spectrum (Figure 19). Similarly, (*S*)- α -methylbenzylamine gave the products **207s** as a 3.5 : 1 mixture of two diastereoisomers in 70% yield.

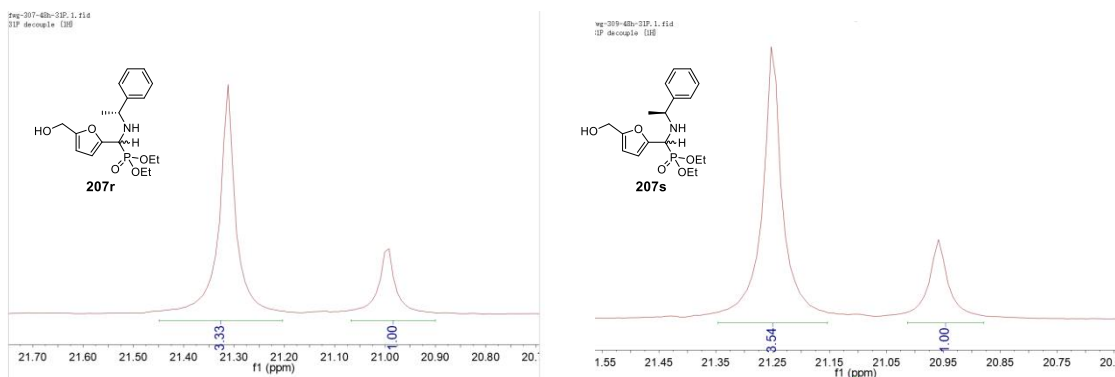
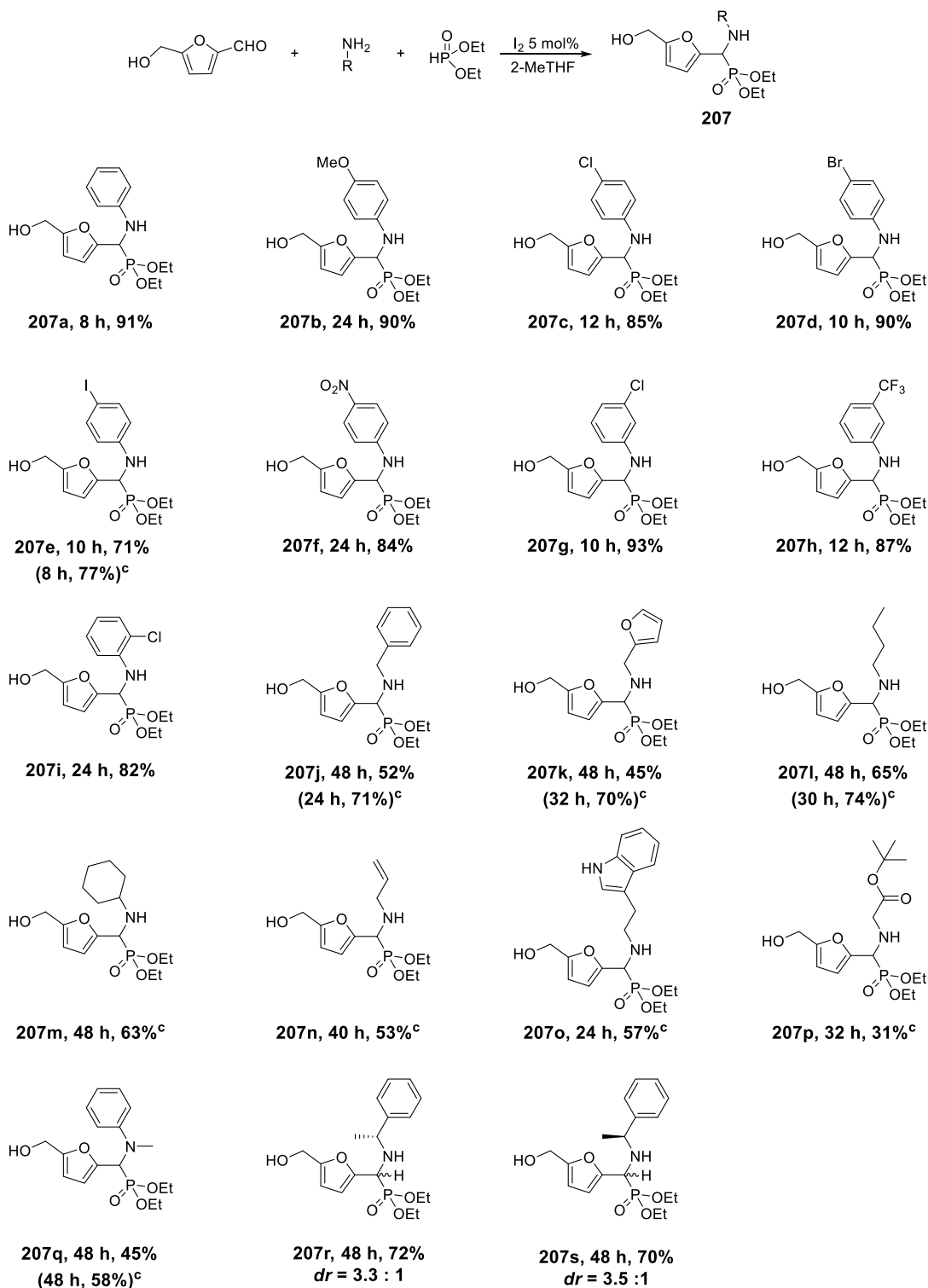


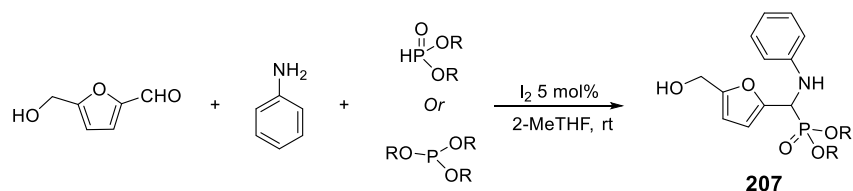
Figure 19. ^{31}P NMR spectra of **207r** and **207s**

Scheme 93. The Kabachnik-Fields reaction of HMF and different amines^{a,b}



^a The reaction was carried out with HMF (1 mmol), amine (1 mmol), diethyl phosphite (1.5 mmol) with I₂ (5 mol%) in 2-MeTHF (2 mL), stirred at 25 °C for indicated time. ^b Isolated yield. ^c at 50 °C.

Table 11. The scope of phospho-nucleophiles in the Kabachnik-Fields reaction



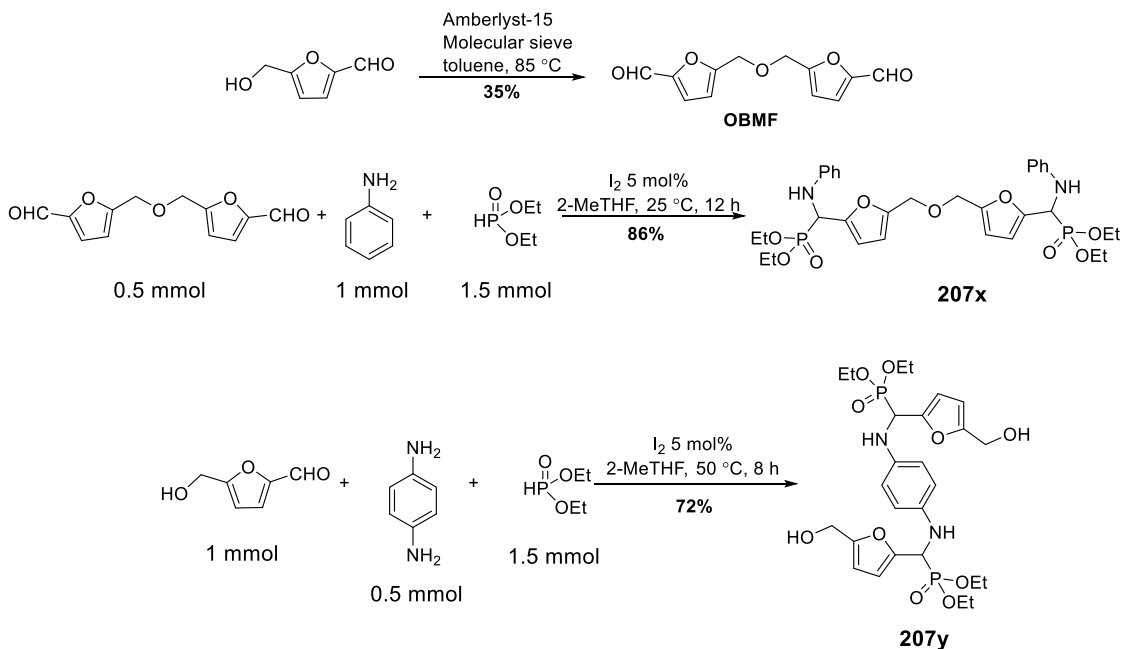
Entry	Phospho-nucleophile	Product	Reaction time	Isolated yield
1		 207t	10 h	89%
2		 207u	32 h	87%
3		 207v	8 h	86%
4		 207w	10 h	54%
5		 207a	24 h	74%

The nature of the dialkyl phosphite was also examined but to a minor extent due to the low diversity of commercially available dialkyl phosphite reagents (Table 11). Dimethyl-, diisopropyl- and dibenzyl- phosphites afforded the corresponding products (**207t** – **207v**) in a range of yields of 86-89%. Among them, the reaction of diisopropyl phosphite was relatively slow compared to dimethyl- and dibenzyl- phosphites, perhaps due to the steric hindrance of the

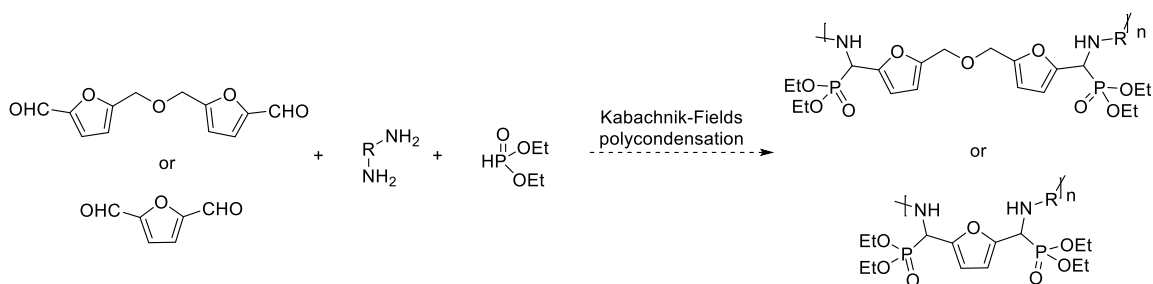
isopropyl group. Interestingly, bis(2,2,2-trifluoroethyl)phosphite which has two strongly electron-withdrawing groups also led to the target product **207w**, albeit with a modest yield (54%).

Apart from dialkyl phosphites, triethyl phosphite was also successfully transformed to α -aminophosphonate under the identical conditions, giving **207a** in 74% yield after 24 h. In this case, the formation of α -aminophosphonate was assumed to go through either the alkyl-oxygen (or phosphorus-oxygen) fission assisted by water after the Kabachnik-Fields reaction or the hydrolysis of trialkyl phosphite to dialkyl phosphite in the beginning.^[319]

Inspired by Theato's work in which several polymers were synthesized from dialdehydes, diamines, and phosphites by the Kabachnik-Field reaction,^[324] we prepared HMF dimer 5,5'-[oxybis(methylene)]bis-2-furfural (OBMF) *via* acid-catalyzed self-etherification of HMF and subjected it to the Kabachnik-Fields conditions replacing HMF, the expected di-Kabachnik-Fields product **207x** was obtained in 86% yield (Scheme 94). Alternatively, using *p*-phenylenediamine instead of aniline led to the other type of di-Kabachnik-Fields product **207y**. These results indicate the possibility of the preparation of highly functional polymers *via* Kabachnik-Fields polycondensation from 5,5'-[oxybis(methylene)]bis-2-furfural, diformylfuran and suitable diamines (Scheme 95).

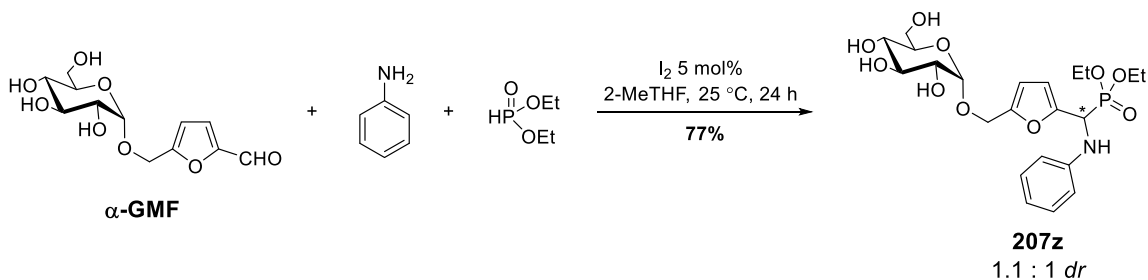


Scheme 94. The double Kabachnik-Fields reaction



Scheme 95. The possible approach to polymers

The Kabachnik-Fields reaction was successfully extended to α -glucosyloxymethylfurfural (α -GMF) as well, leading to **207z** in 77% yield under the optimized conditions (Scheme 96). The asymmetric induction from sugar part was presumed to be quite weak considering the long distance between the chiral sugar part and the newly formed tertiary carbon. Indeed, only 1.1 : 1 *dr* value was observed on ^{31}P NMR spectrum of product **207z** (Figure 20). The performance of 5-chloromethylfurfural (5-CMF) in the Kabachnik-Fields reaction was same as that in the Biginelli reaction, resulting into a quite complex mixture.



Scheme 96. The Kabachnik-Fields reaction on α -GMF

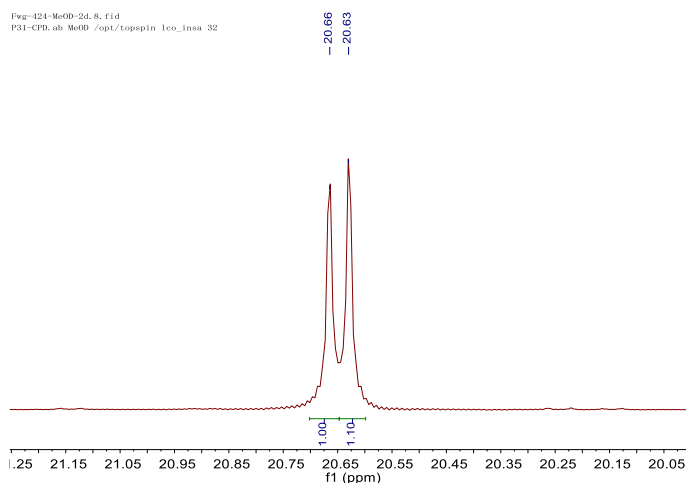
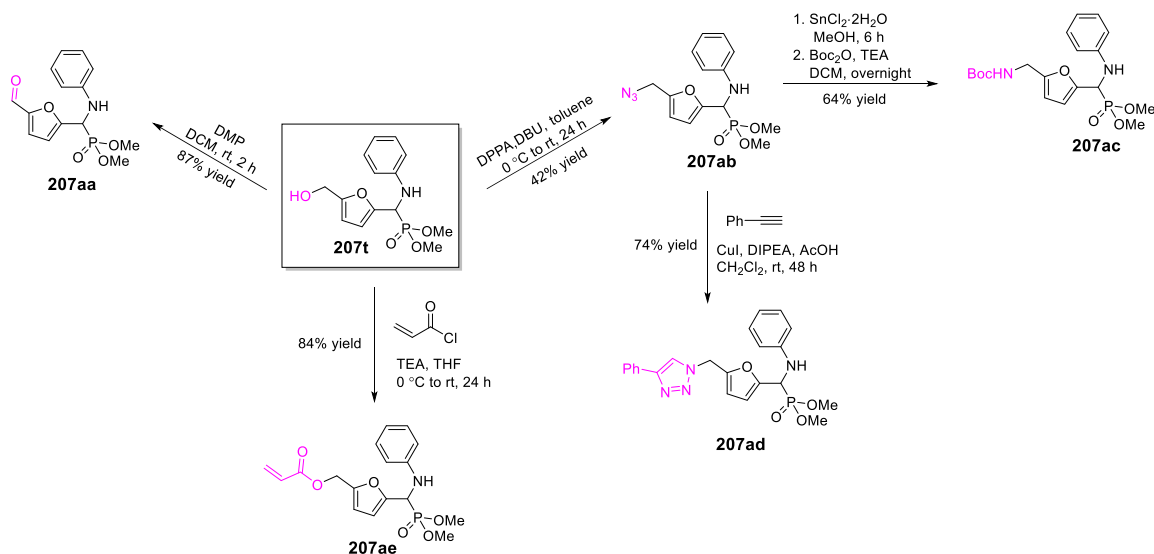


Figure 20. ^{31}P NMR spectrum of product **207z** (in CD_3OD)

3.2.3. Derivatization of HMF-derived α -aminophosphonate

Compared with furfural-derived α -aminophosphonates, the products from HMF provide a range of possibilities of derivatizations and modifications. The derivatizations on hydroxyl group of the Kabachnik-Fields product were investigated using **207t** as a model substrate (Scheme 97). The aldehyde **207aa** could be prepared in 87% yield by oxidation of **207t** using Dess-Martin periodinane (DMP). The hydroxyl group of **207t** could be also converted into an azido group after treatment with diphenylphosphoryl azide in the presence of DBU (**207ab**). The obtained **207ab** could be further transformed to Boc-protected amine **207ac** (64% yield) by reduction with tin(II) chloride and to triazole **207ad** (74% yield) by copper-catalyzed alkyne-azide cycloaddition (CuAAC) “click” reaction. It was found that the unprotected primary amine from **207ab** could only exist in solution. It decomposed quickly in pure form at room temperature. Thus once remove the tin species and solvent (The course of rotary evaporation must be kept in short time and at low temperature), the amino group was protected with Boc immediately. The decomposition of this unprotected amine was also observed during the attempt of reductive amination of **207aa**. The acrylate **207ae** was also easily obtained in a good yield by treatment of **207t** with acryloyl chloride, without affection on the free amino group in **207t**.



Scheme 97. The derivatization of Kabachnik-Fields product **207t**

There were also some unsuccessful attempts on the transformations on hydroxymethyl group of **207t**. In contrast to the easy halogenation on HMF, the halogen substitution of hydroxyl group of

the Kabachnik-Fields product **207t** proved to be quite difficult. Neither direct halogenation nor the Appel reaction gave desired product. Failure was also faced when we tried to transform the OH group to better leaving groups, such as -OSO₂CF₃ or -OSO₂Me. In most cases, the α -aminophosphonate **207t** decomposed under the employed conditions leading to a very complex TLC and crude proton NMR spectrum. The unsuccessful attempts are listed in Table 12.

Table 12. Unsuccessful attempts on the hydroxymethyl group conversion

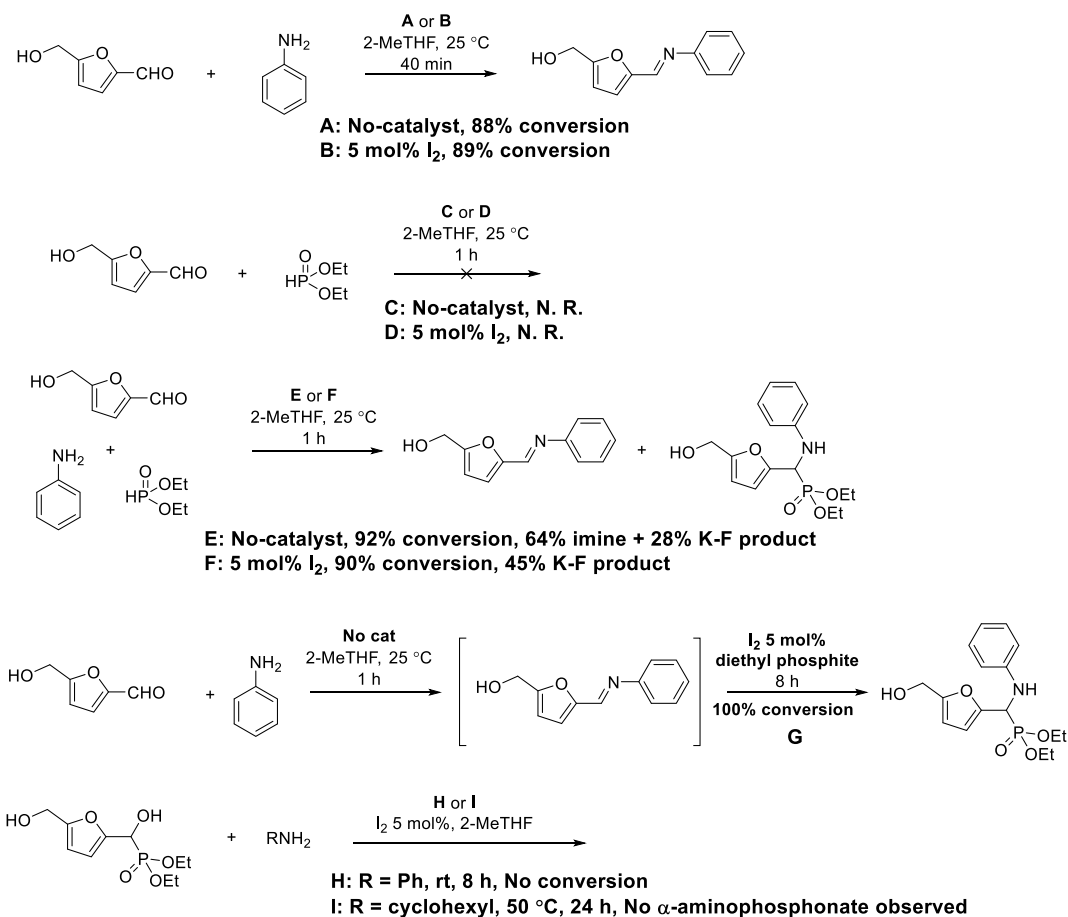
Entry	Purpose	Conditions
1	OH to I	BF ₃ Et ₂ O, KI, dioxane, rt
2	OH to Br	PBr ₃ , DCM, 0 °C to rt
3	OH to Br	Ph ₃ P, CBr ₄ , DCM, 0 °C to rt
4	OH to Br	Ph ₃ P, NBS, DCM, 0 °C to rt
5	OH to Cl	SOCl ₂ , DMF, DCM, 0 °C to rt
6	OH to F	Ishikawa reagent, DCM, 0 °C to rt
7	OH to F	DAST, DCM, -78 °C
8	OH to OSO ₂ CH ₃	MeSO ₂ Cl, TEA, DCM, 0 °C to rt
9	OH to OSO ₂ CF ₃	Tf ₂ O, TEA, DMAP, DCM, 0 °C
10	OH to SCF ₃	TBAI, AgSCF ₃ , toluene, 80 °C
11	CH ₂ OH to COOH	CuCl, <i>t</i> BuOOH, MeCN
12	CH ₂ OH to CN	TEMPO, PhI(OAc) ₂ , NH ₄ OAc, MeCN-H ₂ O

3.2.4. Mechanistic study

Like in other multicomponent reactions, the reaction may undergo different pathways depending on which reactants react at first. In order to gain insight into the mechanism of the Kabachnik-Fields reaction in our case, a series of control “stepwise” experiments were carried out and monitored by means of NMR (Scheme 98 and Figure 21). Mixing HMF and aniline in 2-MeTHF yielded the imine rapidly with and without iodine, with around 90% conversion observed in the crude NMR after 40 min in both cases (Exp. A and B). Subsequent addition of diethyl phosphite and I₂ (5 mol%) to the solution of the *in-situ* formed imine (HMF, aniline, 1 h) afforded cleanly the Kabachnik-Fields product **207a** after 8 h as seen by NMR (Exp. G). On the other hand, no reaction occurred when HMF and diethyl phosphite were mixed, either in the presence or in the absence of iodine (Exp. C and D). These results indicate that the reaction likely undergoes the

imine pathway, followed by nucleophilic attack by the dialkyl phosphite to afford the α -aminophosphonate.^[310, 325-326] Furthermore, the capacity of molecular iodine to activate imines in nucleophilic addition reactions has been confirmed in literature.^[326-328] This imine pathway was also corroborated by the observation of the imine in the crude NMR of the three-component reaction mixture in the absence of iodine (Exp. E). In the presence of iodine, the proton of CH=N appeared to shift from 8.17 ppm to 8.42 ppm which made it difficult to identify, but the imine component was detected in the crude reaction mixture by MS (imine plus H⁺: 202.0), thus also supporting the imine mechanism (Exp. F).

In order to confirm that the α -hydroxyphosphonate involved mechanism is impossible, reactions between preformed α -hydroxyphosphonate and amines were checked (NMR spectra not shown). No reaction took place when aniline was used as an amine component at room temperature in the presence of iodine (Exp. H). Even for the reaction with more nucleophilic cyclohexylamine at 50 °C, we did not observe the formation of α -aminophosphonate either (Exp. I).



Scheme 98. Control experiments

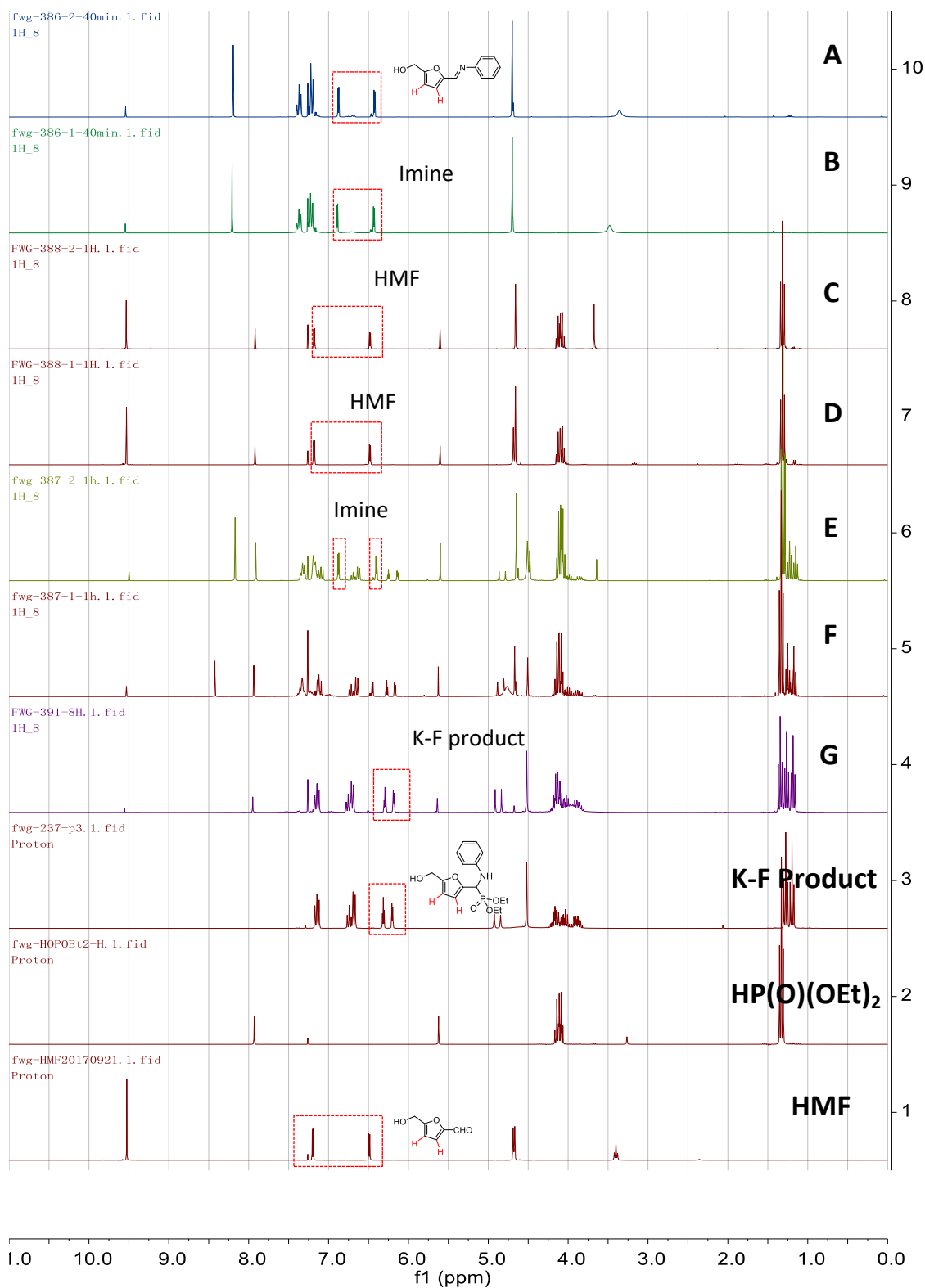
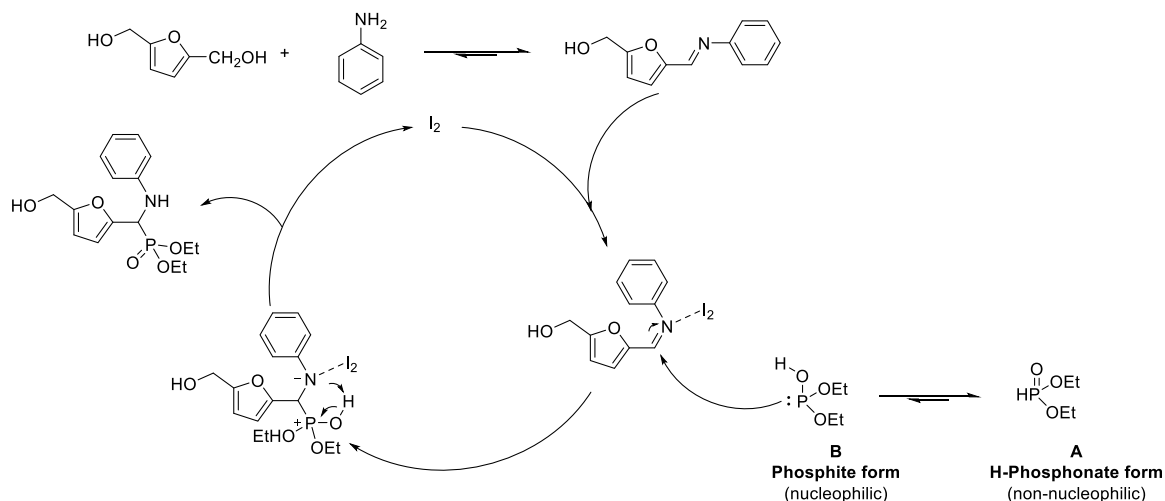


Figure 21. NMR spectra of control experiments

Based on the literature and our experimental results, a plausible mechanism can be suggested as what is drawn in Scheme 99. The catalytic cycles starts with the condensation of HMF and the amine to form the imine. The nucleophilic dialkyl phosphite (phosphite tautomeric form) adds to the iodine-activated imine, then proton transfer occurs to provide the α -aminophosphonate and regenerate iodine.



Scheme 99. The plausible mechanism

3.3. Conclusion

To summarize, we have investigated the application of biomass-derived HMF in the one-pot Kabachnik-Fields reaction, leading to hydroxymethylated heterocyclic α -aminophosphonates. The conditions are simple to settle, effective and environmentally benign. The hydroxymethylfuran moiety in the targeted Kabachnik-Fields products provides additional opportunities for further modification widening the scope of possibly reachable α -amino phosphonates by this route. Moreover, a new possibility for the synthesis of functional polymers *via* the Kabachnik-Fields polycondensation from the 5,5'-[oxybis(methylene)]bis-2-furfural is proposed.

Conclusion and Perspectives

General conclusion

In this thesis, we have investigated the application of two 3-component reactions, namely the Biginelli reaction and the Kabachnik-Fields reaction, to the renewable platform chemical HMF. By employing mild catalytic conditions, it was possible to avoid undesired acid-catalyzed decomposition and oligomerization reactions normally observed in HMF chemistry. The reactions gave access to novel biomass-derived valuable chemicals.

The conditions for the Biginelli reaction of HMF were screened, allowing the use of ZnCl_2 as a catalyst at 80 °C under solvent-free conditions. A range of 1,3-dicarbonyl compounds and urea-like building blocks were tolerant in this protocol, leading to a library of new HMF-derived DHPMs and analogues mostly in fair to good yields. Consistently with previous reports, Hantzsch dihydropyridines present in small amounts were identified as by-products. The mechanism of the reaction was studied by means of NMR and mass spectroscopy, suggesting that the imine-pathway is the most likely one, and that the Knoevenagel adduct cannot be considered as a main intermediate towards the Biginelli product, but the Knoevenagel pathway cannot be excluded.

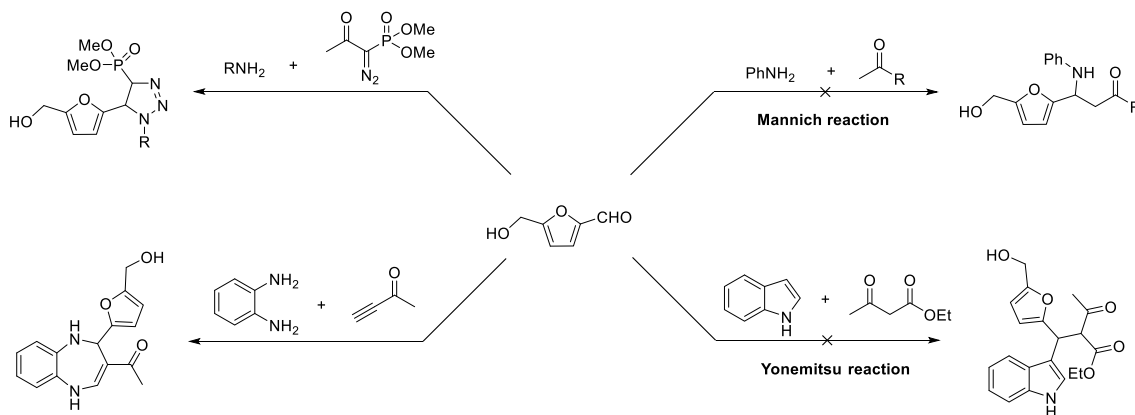
The Kabachnik-Fields reaction of HMF was found to proceed well using molecular iodine as a catalyst in the bio-based solvent 2-MeTHF, at room or moderately elevated temperature. HMF-derived α -aminophosphonates were prepared in fair to excellent yields from various amines and dialkyl phosphites. Mechanistic study suggested that the reaction proceeds *via* the imine route. Generally, anilines showed higher reactivity than aliphatic amines. Triethyl phosphite was also found to be a possible phospho-nucleophile substrate. Double Kabachnik-Fields reactions performed with HMF dimer as dialdehyde and a monoamine, or with HMF and *p*-phenylenediamine as diamine, were found to work smoothly, suggesting that the strategy might be further applied to Kabachnik-Fields polymerization. Several modifications were implemented on HMF-derived α -aminophosphonate, highlighting the benefit of the presence of the hydroxymethyl appendage of HMF for extending the diversity of the products obtained by this route compared with furfural chemistry.

Two analogues of HMF, namely α -GMF and 5-CMF, were also investigated in these two reactions: α -GMF reacted smoothly leading to corresponding products in fair yields, while 5-CMF decomposed to a complex mixture quickly in both reactions.

Overall, this thesis contributed to developing efficient routes to synthesize novel fine chemicals using HMF as a starting material. As illustrated by this work, it is clear that MCRs are indeed a powerful strategy to incorporate bio-sourced aldehydes into complex architectures with high atom- and step- economy.

Perspectives

Extending the idea to develop the use of HMF in other multicomponent strategies for accessing novel furan-based new architectures in straightforward manner is however still a challenge. In this section, we present our preliminary results, positive or negative, on several other reactions which were considered in the frame of this project, namely the Mannich reaction, the Yonemitsu-type reaction, the 3-component synthesis of 1,5-benzodiazepines and the one-pot synthesis of 1,2,3-triazolines (Scheme 100).



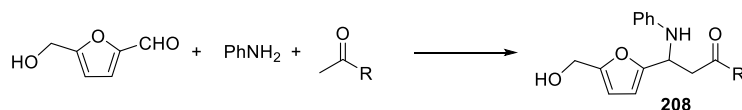
Scheme 100. Preliminarily examined MCRs involving HMF

The Mannich reaction is a very useful synthetic tool for the synthesis of β -amino carbonyl compounds. It can be performed directly on an aldehyde, an amine and a ketone, which is referred to as direct Mannich reaction. It is quite odd that there are more than 100 publications describing the direct Mannich reaction of benzaldehyde, aniline and acetophenone, but only very few papers concerning furfural-involved direct Mannich reaction.

We first checked the direct Mannich reaction with HMF, aniline and acetone. Molecular iodine was chosen as a catalyst, because it had been used in a direct Mannich reaction involving furfural.^[329] The desired β -amino carbonyl product **208** from HMF was not observed, only trace

of di-Mannich adduct was obtained (Table 13, entry 1). Decreasing the loading of iodine gave no better results (Table 13, entry 2). In order to avoid the double Mannich reaction, acetophenone was used instead of acetone. The reaction of acetophenone in EtOH at 60 °C gave the aldol adduct in around 50% isolated yield (NMR not perfect). The preliminary study using I₂ as a catalyst did not yield any trace of desired Mannich adduct from HMF. Appropriate conditions for efficient Mannich reaction of HMF are still to be found.

Table 13. The direct Mannich reaction of HMF



Entry	Ketone	Conditions	Result
1	Acetone (as solvent)	I ₂ (5 mol%), rt	1% Yield of double-Mannich adduct was isolated
2	Acetone (as solvent)	I ₂ (2.5 mol%), rt	Same result as above
3	Acetophenone	I ₂ (5 mol%), EtOH, 60 °C	The aldol adduct was isolated (ca. 50% yield)

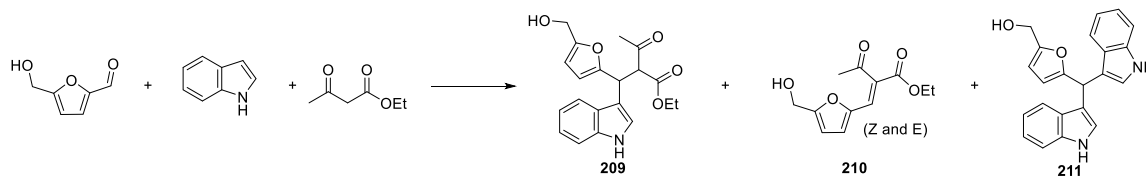
Reaction conditions: HMF (1 mmol), aniline (1 mmol), ketone (1 mmol), catalyst, solvent (2 mL), stirred at indicated temperature for 24 h.

The second MCR is the Yonemitsu-type reaction, a 3-component condensation of an aldehyde, indole and an active 1,3-dicarbonyl compound. Notably, cyclic 1,3-dicarbonyl compounds, such as Meldrum's acid and dimedone, usually gave satisfactory efficiency in this 3-CR, while acyclic 1,3-dicarbonyl compounds gave only modest yields in several previous reports. Thus extending the scope to more general 1,3-dicarbonyl compounds is needed and still challenging for the Yonemitsu-type reaction.

We sought to perform the Yonemitsu condensation on HMF, indole and simpler 1,3-dicarbonyl compounds, such as ethyl acetoacetate. No reaction took place without catalyst (Table 14, entry 1). Addition of several Lewis acids (InCl₃, FeCl₃ and Yb(OTf)₃) as catalysts, resulted into the complete consumption of indole, but most of HMF remained unchanged (Table 14, entry 2-4). The Knoevenagel adduct **210** was observed when Yb(OTf)₃ was employed (Table 14, entry 4). Proline, which had been used as a catalyst in the original Yonemitsu's protocol, led to only the Knoevenagel adduct **210** also. Bis-indole **211** was isolated in 25% yield when the reaction was

performed in water without any catalyst at 80 °C. No desired product **209** was observed under these employed conditions.

Table 14. The Yonemitsu-type reaction of HMF



Entry	Catalyst	Solvent	Temp.	Time	Results	Ref
1	Non	MeCN	rt	6 h	NR	
2	InCl ₃	MeCN	rt	6 h	A lot of HMF remained, while indole was consumed.	
3	FeCl ₃	CH ₃ NO ₂	rt	24 h	A lot of HMF remained, while indole was consumed.	
4	Yb(OTf) ₃	MeCN	rt	6 h	Knoevenagel product 210 (<i>E</i> and <i>Z</i>) was observed, Some HMF remained and indole was consumed.	[330]
5	L-proline	MeCN	60 °C	24 h	Knoevenagel product 210 (<i>E</i> and <i>Z</i>) was observed. Some HMF and a lot of indole remained.	[331]
6	Non	H ₂ O	80 °C	8 h	25% Yield of 211 was isolated (based on HMF)	[332]

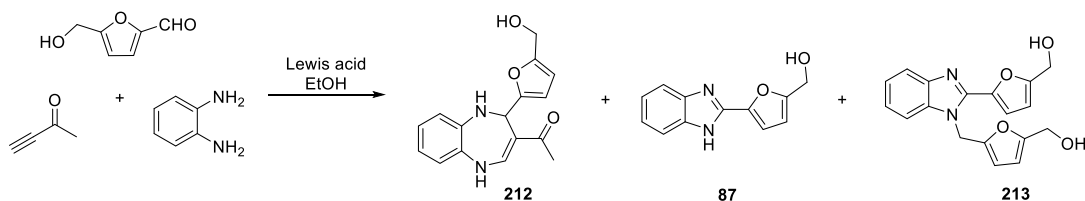
Reaction conditions: HMF (1 mmol), indole (1 mmol), ethyl acetoacetate (1 mmol), catalyst (5 mol%), solvent (2 mL), stirred at indicated temperature.

Another MCR we examined is for the synthesis of benzodiazepines, as benzodiazepines are important seven-membered heterocycles thanks to their significant pharmacological activities, such as antipsychotic properties.

For the purpose of synthesizing novel 1,5-benzodiazepine derivatives by incorporating HMF, we sought to perform the one-pot condensation with equimolar quantities of HMF, *o*-phenylenediamine and 3-butyne-2-one in EtOH [0.5 M] by choosing different Lewis acid catalysts. The reaction employing ZnCl₂ as a catalyst at room temperature afforded the desired benzodiazepine **212** in 37% yield after 48 h (Table 15, entry 1). Increasing temperature to 50 °C provided **212** in 42%, together with a by-product benzimidazole **87** (7% yield) (Table 15, entry 2).

The yield of **212** could be improved to 60% when cesium bromide was used at room temperature (Table 15, entry 3). Another by-product containing two furyl moieties (likely structure **213** from NMR and MS and present in ca. 10% yield) was identified. When indium(III) chloride was employed, the purity of isolated benzodiazepine **212** was not satisfactory.

Table 15. The condensation of HMF, *o*-phenylenediamine and 3-butyn-2-one



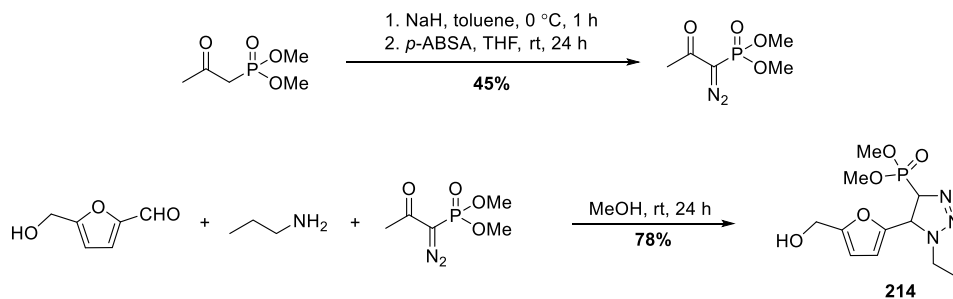
Entry	Catalyst	Temp.	Time	Yield of 212
1	ZnCl ₂	rt	48 h	37%
2	ZnCl ₂	50 °C	24 h	42%
3	CsBr	rt	48 h	60%
4	InCl ₃	rt	6 h	ca. 50%

Reaction conditions: HMF (1 mmol), *o*-phenylenediamine (1 mmol), 3-butyn-2-one (1 mmol), catalyst (20 mol%), EtOH (2 mL), stirred at indicated temperature. For entry 4, purity of cpd **212** was not perfect so the yield was approximate.

For this MCR route towards novel benzodiazepines, the progress is satisfactory. However, several undesired side reactions always occurred indicated by TLC, which made the chromatography purification quite difficult. The reaction conditions must be further optimized to suppress the side reactions and to promote the desired reaction.

The last MCR strategy was examined for the preparation of substituted triazoles. It was reported that diazo compounds such as the Bestmann-Ohira reagent could undergo 1,3-dipolar cycloaddition with Schiff bases (imines), providing 1,2,3-triazoles.^[333] However, the Bestmann-Ohira reagent is often used to convert aldehydes to alkynes in the Seyferth-Gilbert homologation. Therefore, the key to the successful one-pot reaction of HMF, amine and the Bestmann-Ohira reagent is that the formation of the imine should be much faster than undesired aldehyde homologation. During the study of the Kabachnik-Fields reaction, we found the reaction between HMF and an amine was quite fast. We therefore speculated that HMF should work well in this 3-component reaction to yield 1,2,3-triazolines.

In order to study this 1,3-dipolar cycloaddition, we prepared the Bestmann-Ohira reagent from dimethyl 2-oxopropylphosphonate by diazo transfer with 4-acetamidobenzenesulfonyl azide (*p*-ABSA). As expected, the 3-component reaction of HMF (0.5 mmol), *n*-propylamine (0.75 mmol) and the Bestmann-Ohira reagent (0.75 mmol) in methanol (3 mL) proceeded smoothly at room temperature, giving phosphonyltriazoine **214** as a single isomer in 78% yield (Scheme 101).



Scheme 101. The 3-component reaction of HMF, *n*-propylamine and the Bestmann-Ohira reagent

A large range of aliphatic and aromatic amines are expected to be tolerant in this reaction. However, the diversity of the 1,3-dipoles is limited. Analogues of the Bestmann-Ohira reagent in below figure might be feasible 1,3-dipoles.



Figure 22. Possibly feasible 1,3-dipoles.

Overall, several MCRs have been preliminarily examined. The direct Mannich reaction and the Yonemitsu-type condensation did not afford satisfactory results. But the 3-component one-pot approaches for the synthesis of 1,5-benzodiazepine and 1,2,3-triazoline provided promising results, which were expected as efficient routes for the preparation of novel fine chemicals by incorporating HMF.

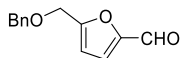
Experimental Section

1. General information

All reagents and solvents were purchased from Sigma-Aldrich, TCI, Alfa Aesar, Fluka, and 5-HMF was purchased from Carbosynth. Unless specified noted, the chemicals were used without further purification. Thin layer chromatography (TLC) was carried out on 0.20 mm silica gel (ALUGRAM TLC sheet, Macherey-Nagel) and visualized using UV light or phosphomolybdic acid stain. Column chromatography was generally performed on silica gel (0.04-0.063 mm, Macherey-Nagel). The NMR spectra were recorded in DMSO-*d*₆, CDCl₃, or MeOD, on Bruker spectrometers (300 MHz, 400 MHz or 500 MHz). Chemical shifts were reported in parts per million (δ) relative to TMS or residual solvent peak. The chemical shifts (δ ppm) and coupling constants (Hz) were reported in the standard fashion. The following abbreviations are used to explain the multiplicities: The abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, m = multiplet, br = broad signal. The NMR spectra of new compounds were assigned taking advantage of 2D NMR (¹H-¹H COSY, HSQC and HMBC). High-resolution mass spectra (HRMS) were recorded on Bruker MicrOTOF-Q II XL spectrometer using ESI as ionization source.

2. Preparation of starting materials or intermediates

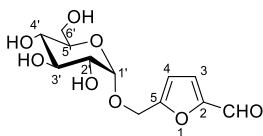
5-((Benzyloxy)methyl)furan-2-carbaldehyde



Under N₂ atmosphere, benzyl bromide (15 mmol) and silver oxide (10 mmol) were added to the solution of HMF (10 mmol, 1.26g) in anhydrous DMF (8 mL). The flask was covered with aluminium foil to avoid light and the suspension was allowed to stir at room temperature for 4 h. The suspension was diluted with ethyl acetate (10 mL) and filtered through a pad of celite, washed with ethyl acetate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (pentane/ethyl acetate = 10:1 to 7:1) to afford the product as a yellowish oil (1.523 g, 71%).^[246]

¹H NMR (300 MHz, DMSO-*d*₆) δ 9.60 (s, 1H), 7.53 (d, *J* = 3.5 Hz, 1H), 7.42 – 7.27 (m, 5H), 6.77 (d, *J* = 3.5 Hz, 1H), 4.60 (s, 2H), 4.56 (s, 2H).

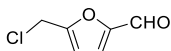
α -Glucosyloxymethylfurfural



The α -GMF was prepared by L. Wang following Lichtenthaler's procedure.^[285] A solution of isomaltulose (30 mmol, 10 g) in anhydrous DMSO (70 mL) was heated to 120 °C. Acidic resin Dowex 50 WX4 (1.2 g) and freshly desiccated 4 Å molecular sieve (6 g) were added. The mixture was stirred at 120 °C overnight. The mixture was filtered. The filtrate was collected and concentrated under reduced pressure. The residue was purified by column chromatography with acetone as eluent to yield α -GMF as a yellowish solid (30% yield). The proton NMR is consistent with literature.^[285]

¹H NMR (300 MHz, DMSO-*d*₆) δ 9.57 (s, 1H, CHO), 7.52 (d, *J* = 3.5 Hz, 1H, H_{fur}), 6.76 (d, *J* = 3.5 Hz, 1H, H_{fur}), 4.89 (d, *J* = 5.6 Hz, 1H, OH), 4.82 (d, *J* = 6.3 Hz, 1H, OH), 4.79 – 4.74 (m, 2H, H_{1'} + OH), 4.68 and 4.55 (AB, *J* = 13.6 Hz, 2H, C₅-CH₂O), 4.48 (t, *J* = 5.8 Hz, 1H, C_{6'}-OH), 3.65 – 3.35 (m, 4H, H_{3'}, H_{5'}, H_{6'}), 3.30 – 3.15 (m, 1H, H_{2'}), 3.14 – 3.04 (m, 1H, H_{4'}).

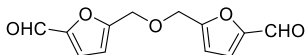
5-(Chloromethyl)furfural (140)



20 mmol of HMF (2.52 g) was dissolved in DCM (100 mL) and concentrated HCl (50 mL) was added. The mixture was stirred at room temperature for 24 h. During the reaction, the reaction mixture turned into dark and a few insoluble materials appeared. After the reaction completion, the organic phase was separated from HCl. The aqueous layer was extracted with DCM (3 × 70 mL). The combined organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified through a short silica gel column with DCM as eluent to provide 5-(chloromethyl)furfural as yellowish liquid (2.78 g, 96% yield). The product should be stored below +5 °C to prevent decomposition. The proton NMR is consistent with previous report.^[20]

¹H NMR (300 MHz, CDCl₃) δ 9.61 (s, 1H, CHO), 7.19 (d, *J* = 3.6 Hz, 1H, H_{fur}), 6.57 (d, *J* = 3.6 Hz, 1H, H_{fur}), 4.60 (s, 2H, CH₂OH).

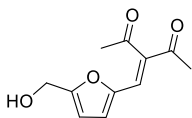
5-HMF dimer (5,5'-[oxybis(methylene)]bis-2-furfural)



The suspension of HMF (16.6 mmol, 2.1 g), Amberlyst-15 (0.6 g) and molecular sieve (2 g) in toluene was stirred at 85 °C. The reaction was stopped after 23 h with some HMF remaining. The hot solution was filtered. The filtrate was concentrated under reduced pressure to semisolid. The semisolid was dissolved in a minimal amount of DCM (approx. 4 mL). Then 40 mL of Et₂O was added slowly and precipitate appeared. The precipitate was filtered and rinsed with Et₂O, and dried in vacuum to provide HMF dimer as brownish powder (682 mg, 35% yield). The NMR is consistent with previous report.^[20]

¹H NMR (300 MHz, CDCl₃) δ 9.62 (s, 2H, CHO), 7.21 (d, *J* = 3.6 Hz, 2H, H_{fur}), 6.56 (d, *J* = 3.6 Hz, 2H, H_{fur}), 4.63 (s, 4H, CH₂OCH₂). ¹³C NMR (75 MHz, CDCl₃) δ 177.7, 157.2, 152.8, 122.1, 111.9, 64.6.

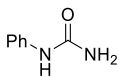
3-((5-(Hydroxymethyl)furan-2-yl)methylene)pentane-2,4-dione (16)



A mixture of HMF (3 mmol, 378.3 mg), acetylacetone (3.3 mmol, 337 uL) and L-proline (0.3 mmol, 34.5 mg) was stirred without solvent at room temperature for 4 h. After the reaction completion, ethyl acetate (20 mL) and water (20 mL) were added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine, dried over Na₂SO₄, concentrated under reduced pressure. The residue was purified by column chromatography to provide the product as a yellowish solid (525.1 mg, 84% yield). The NMR is consistent with literature.^[62]

¹H NMR (300 MHz, CDCl₃) δ 7.11 (s, 1H, C=CH), 6.71 (d, *J* = 3.4 Hz, 1H, H_{fur}), 6.39 (d, *J* = 3.5 Hz, 1H, H_{fur}), 4.57 (s, 2H, CH₂OH), 2.41 (s, 3H, CH₃), 2.34 (s, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 205.3, 196.1, 159.1, 148.4, 138.1, 125.2, 119.5, 110.7, 57.4, 31.5, 26.2.

N-phenylurea

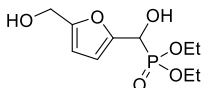


Aniline (20 mmol, 1.82 mL) was dissolved in 2 M hydrochloric acid (10 mL) and cooled with ice bath. Potassium cyanate (24 mmol, 1.95 g) was added. The resulting mixture was not able to be stirred, so 20 mL water was added and stirred at room temperature for 4 h. Then the reaction mixture was cooled down in ice bath again. The solid was separated by filtration, washed well

with cold water and dried under vacuum to provide *N*-phenylurea as a white solid (2.30 g, 85%).^[334]

¹H NMR (300 MHz, DMSO-*d*₆) δ 8.47 (s, 1H), 7.41 -7.35 (m, 2H), 7.25 – 7.16 (m, 2H), 6.93 – 6.84 (m, 1H), 5.80 (s, 2H).

Diethyl (hydroxy(5-(hydroxymethyl)furan-2-yl)methyl)phosphonate



To a mixture of HMF (2 mmol) and diethyl phosphite (2.2 mmol) was added triethyl amine (4.4 mmol). The mixture was stirred at rt overnight. After the reaction was complete indicated by TLC, the mixture was diluted with DCM and evaporated to remove triethyl amine. The crude product was purified through column chromatography (pure EA to EA:MeOH = 30:1), providing the product as yellowish syrup (356.7 mg, 68%).

¹H NMR (300 MHz, CDCl₃) δ 6.31 (t, *J* = 3.0 Hz, 1H), 6.13 (d, *J* = 3.2 Hz, 1H), 5.44 – 5.30 (m, 1H), 4.86 (dd, *J* = 14.2, 4.5 Hz, 1H), 4.56 (br, 1H), 4.41 (s, 2H), 4.14 – 3.82 (m, 4H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 154.92 (d, *J* = 3 Hz), 149.6, 110.0 (d, *J* = 7 Hz), 108.3 (d, *J* = 2 Hz), 64.3 (d, *J* = 169 Hz), 63.5 and 63.4 (2d, *J* = 7.0, 2CH₂CH₃), 56.7, 16.3 (2d, *J* = 6 Hz, 2CH₂CH₃). ³¹P NMR (122 MHz, CDCl₃) δ 19.6.

HRMS (ESI) *m/z*: Calcd for [M+Na]⁺ C₁₀H₁₇NaO₆P 287.0655; Found 287.0658.

3. Experimental data in Chapter II

3.1. General procedure for the Biginelli reaction

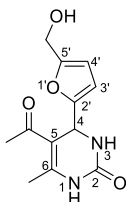
A mixture of HMF (2 mmol), 1,3-dicarbonyl compound (2 mmol), urea-type compound (3 mmol) and ZnCl₂ (20 mol%) was stirred at 80 °C in a sealed tube during 8 h to 24 h.

Depending on the substrates, two work-ups were performed after completion of the reaction. For the preparation of products **203a**, **203c**, **203d**, **203j** and **203p**, after addition of water (3 mL) to the reaction vessel, the mixture was stirred and cooled down to 0 °C. The expected product precipitated and was then filtered. The cake was rinsed with cold water (3 mL) and dried overnight giving the Biginelli product. After concentration, the filtrate was purified by column chromatography on silica gel with DCM/MeOH (50:1 – 15:1) as eluent. For the preparation of products **203b**, **203e** - **203i** and **203k** - **203o**, the reaction mixture was transferred into a

separating funnel with MeOH (3 mL). After addition of water (50 mL), the mixture was extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with DCM/MeOH (50 : 1 - 15 : 1).

3.2.Characterization data of products

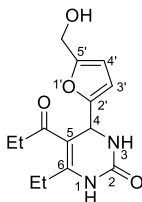
5-Acetyl-4-[5'-(hydroxymethyl)furan-2'-yl]-6-methyl-3,4-dihydropyrimidin-2(1H)-one (203a):



Reaction time: 8 h; Global yield: 86%; (78% yield after simple filtration + additional 8% yield after purification of the filtrate by column chromatography).

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.22 (d, 1H, *J* = 1.2 Hz, H₁), 7.88 (dd, 1H, *J* = 3.4, 1.2 Hz, H₃), 6.16 (d, 1H, *J* = 3.1 Hz, H_{4'}), 6.03 (d, 1H, *J* = 3.1 Hz, H_{3'}), 5.27 (d, 1H, *J* = 3.4 Hz, H₄), 5.18 (t, 1H, *J* = 5.6 Hz, OH), 4.33 (d, 2H, *J* = 5.6 Hz, CH₂), 2.25 (s, 3H, CH₃-C₆), 2.17 (s, 3H, CH₃CO).
¹³C NMR (100 MHz, DMSO-*d*₆) δ 193.9 (C=OCH₃), 155.1, 154.9 (C₂, C_{5'}), 152.4 (C₂), 149.0 (C₆), 107.7 (C_{4'}), 107.1 (C₅), 106.3 (C_{3'}), 55.7 (CH₂OH), 47.9 (C₄), 30.0 (CH₃CO), 19.0 (CH₃-C₆).
 HRMS (ESI) *m/z*: Calcd for [M+Na]⁺ C₁₂H₁₄N₂NaO₄ 273.0846; Found 273.0850.

6-Ethyl-4-[5'-(hydroxymethyl)furan-2'-yl]-5-propionyl-3,4-dihydropyrimidin-2(1H)-one (203b):

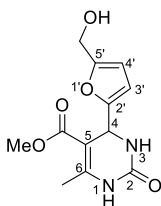


Reaction time: 24 h; Global yield: 42% after purification by column chromatography.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.17 (d, 1H, *J* = 1.8 Hz, H₁), 7.84 (dd, 1H, *J* = 3.6, 1.8 Hz, H₃), 6.17 (d, 1H, *J* = 3.1 Hz, H_{4'}), 6.02 (d, 1H, *J* = 3.1 Hz, H_{3'}), 5.31 (d, 1H, *J* = 3.6 Hz, H₄), 5.19 (t, 1H, *J* = 5.6 Hz, OH), 4.34 (d, 2H, *J* = 5.5 Hz, CH₂OH), 2.79-2.50 (m, 3H, CH₂, CHCO), 2.31-2.25 (m, 1H, CHCO), 1.10 (t, 3H, *J* = 7.4 Hz, C₆-CH₂CH₃), 0.88 (t, 3H, *J* = 7.2 Hz, COCH₂CH₃).

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 196.8 (COCH_2CH_3), 155.2, 155.1 (C_2 , C_5), 153.9 (C_6), 152.8 (C_2), 107.8 (C_4), 106.6 (C_3), 105.4 (C_5), 55.9 (CH_2OH), 48.0 (C_4), 33.1 (COCH_2), 24.6 ($\text{C}_6\text{-CH}_2$), 13.0 ($\text{C}_6\text{-CH}_2\text{CH}_3$), 8.4 (COCH_2CH_3). HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+$ $\text{C}_{14}\text{H}_{18}\text{N}_2\text{NaO}_4$ 301.1159; Found 301.1164.

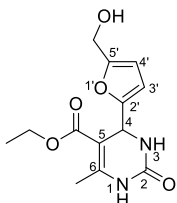
Methyl 4-[5'-(hydroxymethyl)furan-2'-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (203c):



Reaction time: 9 h; Global yield: 85% yield after filtration.

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.23 (d, 1H, $J = 1.3$ Hz, H_1), 7.78 (dd, 1H, $J = 3.6, 1.3$ Hz, H_3), 6.16 (d, 1H, $J = 3.1$ Hz, H_4), 6.00 (d, 1H, $J = 3.1$ Hz, H_3), 5.18-5.13 (m, 2H, H_4 and OH), 4.32 (d, 2H, $J = 5.6$ Hz, CH_2), 3.57 (s, 3H, OCH_3), 2.24 (s, 3H, $\text{C}_6\text{-CH}_3$). ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 165.5 (CO_2), 155.0, 154.8 (C_2 , C_5), 152.3 (C_2), 149.8 (C_6), 107.7 (C_4), 106.0 (C_3), 96.4 (C_5), 55.7 (CH_2OH), 50.9 (CO_2CH_3), 47.7 (C_4), 17.8 ($\text{C}_6\text{-CH}_3$). HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+$ $\text{C}_{12}\text{H}_{14}\text{N}_2\text{NaO}_5$ 289.0795; Found 289.0791.

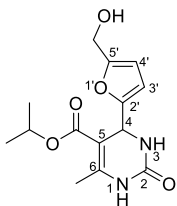
Ethyl 4-[5'-(hydroxymethyl)furan-2'-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (203d):



Reaction time: 16 h; Global yield: 82% yield after filtration.

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.20 (s, 1H, H_1), 7.76 (d, 1H, $J = 1.2$ Hz, H_3), 6.16 (d, 1H, $J = 3.1$ Hz, H_4), 6.00 (d, 1H, $J = 3.1$ Hz, H_3), 5.20-5.12 (m, 2H, H_4 and OH), 4.32 (d, 2H, $J = 5.6$ Hz, CH_2OH), 4.04 (q, 2H, $J = 7.1$ Hz, CH_2CH_3), 2.23 (s, 3H, $\text{C}_6\text{-CH}_3$), 1.14 (t, 3H, $J = 7.1$ Hz, CH_2CH_3). ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 165.1 (CO_2), 155.2, 154.7 (C_2 , C_5), 152.4 (C_2), 149.4 (C_6), 107.7 (C_4), 105.9 (C_3), 96.7 (C_5), 59.3 (OCH_2CH_3), 55.7 (CH_2OH), 47.8 (C_4), 17.8 ($\text{C}_6\text{-CH}_3$), 14.2 (CH_2CH_3). HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+$ $\text{C}_{13}\text{H}_{16}\text{N}_2\text{NaO}_5$ 303.0951; Found 303.0951.

Isopropyl 4-[5'-(hydroxymethyl)furan-2'-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (203e):

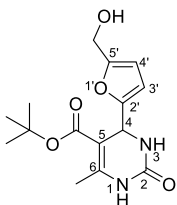


Reaction time: 24 h; Global yield: 62% after purification by column chromatography.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.19 (d, 1H, $J = 2.0$ Hz, H_1), 7.75 (dd, $J = 3.4, 1.8$ Hz, 1H, H_3), 6.16 (d, 1H, $J = 3.1$ Hz, H_4), 5.99 (d, 1H, $J = 3.1$ Hz, H_3), 5.18-5.15 (m, 2H, H_4 and OH), 4.93 - 4.80 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 4.31 (d, 2H, $J = 5.6$ Hz, CH_2OH), 2.22 (s, 3H, $\text{C}_6\text{-CH}_3$), 1.18 (d, 3H, $J = 6.3$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.09 (d, 3H, $J = 6.3$ Hz, $\text{CH}(\text{CH}_3)_2$). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 164.6 (CO_2), 155.3 (C_2), 154.6 (C_5), 152.4 (C_2), 149.1 (C_6), 107.6 (C_4), 105.9 (C_3), 97.0 (C_5), 66.4 ($\text{CH}(\text{CH}_3)_2$), 55.7 (CH_2OH), 47.9 (C_4), 21.8 ($\text{CH}(\text{CH}_3)_2$), 21.6 ($\text{CH}(\text{CH}_3)_2$), 17.8 ($\text{C}_6\text{-CH}_3$).

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+ \text{C}_{14}\text{H}_{18}\text{N}_2\text{NaO}_5$ 317.1108; Found 317.1105.

***tert*-Butyl 4-[5'-(hydroxymethyl)furan-2'-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (203f):**

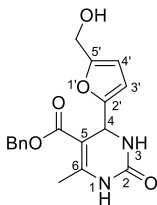


Reaction time: 24 h; Global yield: 63% after purification by column chromatography.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.10 (d, 1H, $J = 1.6$ Hz, H_1), 7.70 (dd, 1H, $J = 3.3$ Hz, 1.6 Hz, H_3), 6.17 (d, 1H, $J = 3.1$ Hz, H_4), 5.98 (d, 1H, $J = 3.1$ Hz, H_3), 5.17 (t, 1H, $J = 5.4$ Hz, OH), 5.12 (d, 1H, $J = 3.3$ Hz, H_4), 4.32 (d, 2H, $J = 5.4$ Hz, CH_2OH), 2.19 (s, 3H, $\text{C}_6\text{-CH}_3$), 1.36 (s, 9H, $\text{C}(\text{CH}_3)_3$). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 164.5 (CO_2), 155.5 (C_2), 154.6 (C_5), 152.4 (C_2), 148.3 (C_6), 107.6 (C_4), 105.7 (C_3), 98.1 (C_5), 79.2 ($\text{C}(\text{CH}_3)_3$), 55.8 (CH_2OH), 48.2 (C_4), 27.9 ($\text{C}(\text{CH}_3)_3$), 17.7 ($\text{C}_6\text{-CH}_3$).

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+ \text{C}_{15}\text{H}_{20}\text{N}_2\text{NaO}_5$ 331.1264; Found 331.1274.

Benzyl 4-[5'-(hydroxymethyl)furan-2'-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (203g):

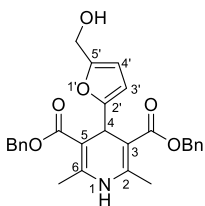


Reaction time: 24 h; Global yield: 58% after purification by column chromatography.

^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 9.30 (d, 1H, $J = 1.2$ Hz, H_1), 7.81 (dd, 1H, $J = 3.4, 1.2$ Hz, H_3), 7.40-7.20 (m, 5H, H_{Ar}), 6.17 (d, 1H, $J = 3.1$ Hz, H_4), 5.98 (d, 1H, $J = 3.1$ Hz, $\text{H}_{3'}$), 5.23 (d, 1H, $J = 3.4$ Hz, H_4), 5.18 (t, 1H, $J = 5.6$ Hz, OH), 5.15-5.02 (AB, 2H, PhCH_2), 4.33 (d, 2H, $J = 5.6$ Hz, CH_2OH), 2.27 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ 164.8 (CO_2), 155.1, 154.8 (C_2 , C_5), 152.3 (C_2), 150.3 (C_6), 136.7 (C_{qAr}), 128.4 (2 CH_{Ar}), 127.7 (CH_{Ar}), 127.5 (2 CH_{Ar}), 107.7 (C_4), 106.1 (C_3), 96.3 (C_5), 64.9 (CH_2Ph), 55.8 (CH_2OH), 47.8 (C_4), 17.9 (CH_3).

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+$ $\text{C}_{18}\text{H}_{18}\text{N}_2\text{NaO}_5$ 365.1108; Found 365.1115.

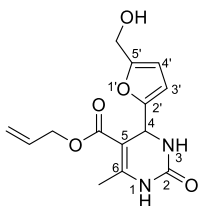
Dibenzyl 4-[5'-(hydroxymethyl)furan-2'-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (203g')



5% yield of Hantzsch product **203g'** was obtained along with Biginelli Product **203g**.

^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 9.07 (s, 1H, H_1), 7.36-7.26 (m, 10H, H_{Ar}), 6.06 (d, 1H, $J = 3.1$ Hz, H_4), 5.72 (dd, 1H, $J = 3.1, 0.7$ Hz, H_3), 5.21-5.00 (m, 6H, H_4 , 2 CH_2Ph and OH), 4.26 (d, 2H, $J = 5.5$ Hz, CH_2OH), 2.27 (s, 6H, 2 CH_3). ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ 166.4 (2 CO_2), 158.0 (C_2), 153.7 (C_5), 147.1 (C_2 , C_6), 136.9 (2 C_{qAr}), 128.3 (4 CH_{Ar}), 127.6 (2 CH_{Ar}), 127.4 (4 CH_{Ar}), 107.5 (C_4), 104.9 (C_3), 98.4 (C_3 , C_5), 64.7 (2 CH_2Ph), 55.8 (CH_2OH), 32.7 (C_4), 18.3 (2 CH_3).
HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+$ $\text{C}_{28}\text{H}_{27}\text{NNaO}_6$ 496.1731; Found 496.1709.

Allyl 4-[5'-(hydroxymethyl)furan-2'-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (203h):

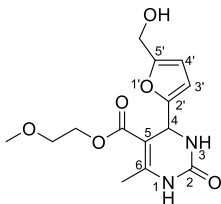


Reaction time: 24 h; Global yield: 60% after purification by column chromatography.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.29 (d, 1H, $J = 2.0$ Hz, H_1), 7.82 (dd, 1H, $J = 3.8, 2.0$ Hz, H_3), 6.16 (d, 1H, $J = 3.1$ Hz, H_4), 6.01 (d, 1H, $J = 3.1$ Hz, H_3), 5.94-5.82 (m, 1H, CHCH_2), 5.26-5.08 (m, 4H, OH, CHCH_2 and H_4), 4.60-4.46 (m, 2H, $\text{OCH}_2\text{CH}=\text{CH}_2$), 4.32 (d, 2H, $J = 5.7$ Hz, CH_2OH), 2.26 (s, 3H, $\text{C}_6\text{-CH}_3$). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 164.7 (CO_2), 155.1 (C_2), 154.8 (C_5), 152.3 (C_2), 150.2 (C_6), 133.1 ($\text{CH}=\text{CH}_2$), 117.0 ($\text{CH}=\text{CH}_2$), 107.7 (C_4), 106.1 (C_3), 96.4 (C_5), 63.8 ($\text{OCH}_2\text{CH}=\text{CH}_2$), 55.8 (CH_2OH), 47.7 (C_4), 17.9 ($\text{C}_6\text{-CH}_3$).

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+$ $\text{C}_{14}\text{H}_{16}\text{N}_2\text{NaO}_5$ 315.0951; Found 315.0945.

2-Methoxyethyl -4-[5'-(hydroxymethyl)furan-2'-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (203i):

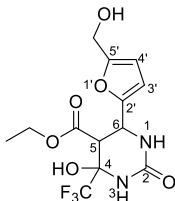


Reaction time: 24 h; Global yield: 47% after purification by column chromatography.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.26 (d, 1H, $J = 2.0$ Hz, H_1), 7.79 (dd, 1H, $J = 3.6, 2.0$ Hz, H_3), 6.17 (d, 1H, $J = 3.1$ Hz, H_4), 6.03 (dd, 1H, $J = 3.1, 0.6$ Hz, H_3), 5.21 (d, 1H, $J = 3.6$ Hz, H_4), 4.34 (s, 2H, CH_2OH), 4.14-4.10 (m, 2H, CH_2OCO), 3.72-3.39 (m, 2H, CH_3OCH_2), 3.22 (s, 3H, OCH_3), 2.25 (s, 3H, $\text{C}_6\text{-CH}_3$). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 165.2 (CO_2), 155.2, 154.9 (C_2 and C_5), 152.6 (C_2), 149.9 (C_6), 107.8 (C_4), 106.2 (C_3), 96.8 (C_5), 70.1 (CH_3OCH_2), 62.6 (CH_2OCO), 58.2 (OCH_3), 55.9 (CH_2OH), 48.0 (C_4), 18.0 ($\text{C}_6\text{-CH}_3$).

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+$ $\text{C}_{14}\text{H}_{18}\text{N}_2\text{NaO}_6$ 333.1057; Found 333.1051.

Ethyl 4-hydroxy-6-[5'-(hydroxymethyl)furan-2'-yl]-2-oxo-4-(trifluoromethyl)hexahydro pyrimidine-5-carboxylate (203j):

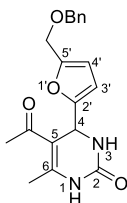


Reaction time: 8 h; Global yield: 84%; (66% yield after simple filtration + additional 18% yield after purification of the filtrate by column chromatography).

^1H NMR (400 MHz, DMSO- d_6) δ 7.74 (s, 1H, H₃), 7.47 (s, 1H, C₄-OH), 7.32 (d, 1H, J = 1.2 Hz, H₁), 6.30 (d, J = 3.2 Hz, 1H, H_{3'}), 6.19 (d, J = 3.2 Hz, 1H, H_{4'}), 5.24 (t, 1H, J = 5.8 Hz, CH₂OH), 4.86 (d, 1H, J = 11.7 Hz, H₆), 4.33 (d, 2H, J = 5.8 Hz, CH₂OH), 3.96-3.88 (m, 2H, CH₂CH₃), 3.08 (d, 1H, J = 11.7 Hz, H₅), 0.98 (t, 3H, J = 7.1 Hz, CH₃). ^{13}C NMR (100 MHz, DMSO- d_6) δ 166.8 (CO₂), 155.6 (C_{5'}), 153.3 (C₂), 149.8 (C_{2'}), 133.1-116.2 (q, J = 286 Hz, CF₃), 109.3 (C_{3'}), 107.4 (C_{4'}), 80.3 (q, J = 31 Hz, C₄), 60.5 (CH₂CH₃), 55.6 (CH₂OH), 48.1 (C₅), 47.1 (C₆), 13.7 (CH₃). ^{19}F NMR (282 MHz, DMSO- d_6) δ -80.70.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+$ C₁₃H₁₅F₃N₂NaO₆ 375.0774; Found 375.0771.

5-Acetyl-4-[5'-((benzyloxy)methyl)furan-2'-yl]-6-methyl-3,4-dihydropyrimidin-2(1H)-one (203k):

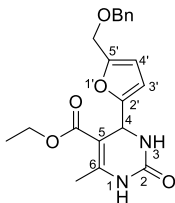


Reaction time: 16 h; Global yield: 66% after purification by column chromatography.

^1H NMR (400 MHz, DMSO- d_6) δ 9.27 (d, 1H, J = 1.8 Hz, H₁), 7.93 (dd, 1H, J = 3.5, 1.8 Hz, H₃), 7.40-7.25 (m, 5H, H_{Ar}), 6.34 (d, 1H, J = 3.1 Hz, H_{4'}), 6.08 (d, 1H, J = 3.1 Hz, H_{3'}), 5.31 (d, 1H, J = 3.6 Hz, H₄), 4.48 (s, 2H, PhCH₂), 4.39 (s, 2H, CH₂OCH₂Ph), 2.26 (s, 3H, C₆-CH₃), 2.18 (s, 3H, COCH₃). ^{13}C NMR (100 MHz, DMSO- d_6) δ 193.8 (COCH₃), 156.1 (C_{2'}), 152.4 (C₂), 151.1 (C_{5'}), 149.0 (C₆), 138.1 (C_{q,Ar}), 128.3 (2 CH_{Ar}), 127.7 (2 CH_{Ar}), 127.5 (C_{Ar}), 110.3 (C_{4'}), 107.1 (C₅), 106.3 (C_{3'}), 71.0 (PhCH₂), 63.4 (CH₂OCH₂Ph), 47.9 (C₄), 30.0 (COCH₃), 19.0 (C₆-CH₃).

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+$ C₁₉H₂₀N₂NaO₄ 363.1315; Found 363.1305.

Ethyl 4-[5'-((benzyloxy)methyl)furan-2'-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (203l):



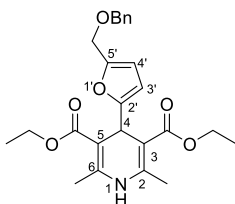
Reaction time: 24 h; Global yield: 56% after purification by column chromatography.

^1H NMR (400 MHz, DMSO- d_6) δ 9.30 (d, 1H, J = 1.6 Hz, H₁), 7.83 (dd, 1H, J = 3.1 Hz, 1.6 Hz, H₃), 7.40-7.20 (m, 5H, H_{Ar}), 6.34 (d, 1H, J = 3.1 Hz, H_{4'}), 6.07 (d, 1H, J = 3.1 Hz, H_{3'}), 5.23 (d,

1H, $J = 3.1$ Hz, H_4), 4.47 (s, 2H, $\underline{\text{CH}_2\text{Ph}}$), 4.40 (s, 2H, $\text{C}_5\text{'-}\underline{\text{CH}_2}$), 4.11-3.95 (m, 2H, $\underline{\text{CH}_2\text{CH}_3}$), 2.26 (s, 3H, $\text{C}_6\text{-}\underline{\text{CH}_3}$), 1.13 (t, 3H, $J = 7.1$ Hz, $\underline{\text{CH}_2\text{CH}_3}$). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 165.1 (CO_2), 156.3 ($\text{C}_{2\text{'}}$), 152.4 (C_2), 150.9 ($\text{C}_{5\text{'}}$), 149.5 (C_6), 138.1 ($\text{C}_{\text{q, Ar}}$), 128.3 (2 CH_{Ar}), 127.7 (2 CH_{Ar}), 127.5 (CH_{Ar}), 110.3 ($\text{C}_{4\text{'}}$), 106.0 ($\text{C}_{3\text{'}}$), 96.7 (C_5), 71.0 ($\underline{\text{CH}_2\text{Ph}}$), 63.4 ($\text{C}_{5\text{'-}}\underline{\text{CH}_2}$), 59.3 ($\underline{\text{CH}_2\text{CH}_3}$), 47.9 (C_4), 17.8 ($\text{C}_6\text{-}\underline{\text{CH}_3}$), 14.2 ($\underline{\text{CH}_2\text{CH}_3}$).

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+ \text{C}_{20}\text{H}_{22}\text{N}_2\text{NaO}_5$ 393.1421; Found 393.1435.

Diethyl 4-[5'-((benzyloxy)methyl)furan-2'-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (203l'):

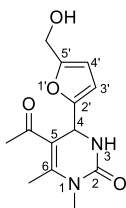


8% yield of Hantzsch product **203l'** was obtained along with Biginelli Product **203l**.

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.93 (s, 1H, H_1), 7.38-7.24 (m, 5H, H_{Ar}), 6.23 (d, 1H, $J = 3.1$ Hz, $H_{4\text{'}}$), 5.81 (d, 1H, $J = 3.1, 1.0$ Hz, $H_{3\text{'}}$), 5.06 (s, 1H, H_4), 4.43 (s, 2H, $\text{Ph}\underline{\text{CH}_2}$), 4.32 (s, 2H, $\underline{\text{CH}_2\text{OBn}}$), 4.15-3.95 (m, 4H, OCH_2CH_3), 2.26 (s, 6H, $\text{C}_6\text{-CH}_3$, $\text{C}_2\text{-CH}_3$), 1.16 (t, 6H, $J = 7.1$ Hz, OCH_2CH_3). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 166.7 (CO_2), 159.3 ($\text{C}_{2\text{'}}$), 149.8 ($\text{C}_{5\text{'}}$), 146.44 (C_2 , C_6), 138.2 ($\text{C}_{\text{q, Ar}}$), 128.2 (2 CH_{Ar}), 127.6 (2 CH_{Ar}), 127.5 (CH_{Ar}), 110.2 ($\text{C}_{4\text{'}}$), 104.7 ($\text{C}_{3\text{'}}$), 98.5 (C_3 , C_5), 70.8 ($\text{Ph}\underline{\text{CH}_2}$), 63.4 ($\underline{\text{CH}_2\text{OBn}}$), 59.1 (2 $\underline{\text{CH}_2\text{CH}_3}$), 33.0 (C_4), 18.2 ($\text{C}_2\text{-CH}_3$, $\text{C}_6\text{-CH}_3$), 14.3 (2 OCH_2CH_3).

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+ \text{C}_{25}\text{H}_{29}\text{NNaO}_6$ 462.1887; Found 462.1876.

5-Acetyl-4-[5'-(hydroxymethyl)furan-2'-yl]-1,6-dimethyl-3,4-dihydropyrimidin-2(1H)-one (203m):



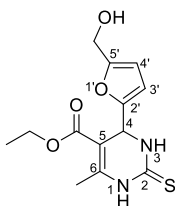
Reaction time: 24 h; Global yield: 30% after purification by column chromatography.

^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 8.08 (d, 1H, $J = 4.2$ Hz, H_3), 6.17 (d, 1H, $J = 3.1$ Hz, $H_{4\text{'}}$), 6.05 (dd, 1H, $J = 3.1, 0.5$ Hz, $H_{3\text{'}}$), 5.22 (d, 1H, $J = 4.1$ Hz, H_4), 5.16 (t, 1H, $J = 5.7$ Hz, OH), 4.33 (d, 2H, $J = 5.6$ Hz, $\underline{\text{CH}_2\text{OH}}$), 3.07 (s, 3H, NCH_3), 2.42 (s, 3H, $\text{C}_6\text{-CH}_3$), 2.19 (s, 3H, COCH_3). ^{13}C

NMR (75 MHz, DMSO-*d*₆) δ 195.0 (COCH₃), 155.2, 154.5 (C_{2'} and C_{5'}), 153.3 (C₂), 150.5 (C₆), 110.1 (C₅), 107.6 (C_{4'}), 106.4 (C_{3'}), 55.7 (CH₂OH), 47.0 (C₄), 30.0 (COCH₃), 29.8 (NCH₃), 16.6 (C₆-CH₃).

HRMS (ESI) *m/z*: Calcd for [M+Na]⁺ C₁₃H₁₆N₂NaO₄ 287.1002; Found 287.0999.

Ethyl 4-[5'-(hydroxymethyl)furan-2'-yl]-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (203n):

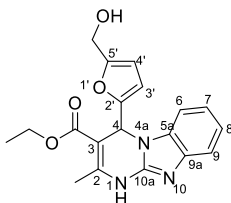


Reaction time: 24 h; Global yield: 42% after purification by column chromatography.

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.37 (s, 1H, H₁), 9.65 (s, 1H, H₃), 6.18 (d, 1H, *J* = 3.0 Hz, H_{4'}), 6.05 (d, 1H, *J* = 3.1 Hz, H_{3'}), 5.24-5.17 (m, 2H, H₄ and OH), 4.33 (d, 2H, *J* = 5.5 Hz, CH₂OH), 4.10-3.98 (m, 2H, CH₂CH₃), 2.29 (s, 3H, C₆-CH₃), 1.13 (t, 3H, *J* = 7.1 Hz, CH₂CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 174.9 (C₂), 164.9 (CO₂), 155.3 (C_{5'}), 153.9 (C_{2'}), 146.2 (C₆), 107.9 (C_{4'}), 107.1 (C_{3'}), 98.3 (C₅), 59.8 (CH₂CH₃), 55.8 (CH₂OH), 47.9 (C₄), 17.3 (C₆-CH₃), 14.2 (CH₂CH₃).

HRMS (ESI) *m/z*: Calcd for [M+Na]⁺ C₁₃H₁₆N₂NaO₄S 319.0723; Found 319.0729.

Ethyl 4-[5'-(hydroxymethyl)furan-2'-yl]-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylate (203o):

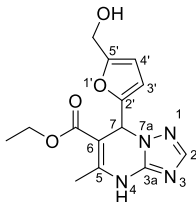


Reaction time: 8 h; Global yield: 44% after purification by column chromatography.

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.81 (s, 1H, H₁), 7.46 – 7.42 (m, 1H, H₉), 7.39 – 7.34 (m, 1H, H₆), 7.11 – 7.00 (m, 2H, H₇, H₈), 6.53 (d, 1H, *J* = 0.8 Hz, H₄), 6.38 (d, 1H, *J* = 3.2 Hz, H_{3'}), 6.14 (d, 1H, *J* = 3.1 Hz, H_{4'}), 5.11 (t, 1H, *J* = 5.7 Hz, CH₂OH), 4.20 (d, 2H, *J* = 5.7 Hz, CH₂OH), 4.14-3.98 (m, 2H, CH₂CH₃), 2.46 (s, 3H, C₂-CH₃), 1.17 (t, 3H, *J* = 7.1 Hz, CH₂CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 165.1 (CO₂), 155.1 (C_{5'}), 151.9 (C_{2'}), 147.7 (C₂), 145.5 (C_{10a}), 142.2 (C_{9a}), 131.6 (C_{5a}), 121.9 (C₈), 120.2 (C₇), 116.8 (C₆), 109.8 (C₉), 108.4 (C_{3'}), 107.6 (C_{4'}), 94.3 (C₃), 59.4 (CH₂CH₃), 55.6 (CH₂OH), 49.4 (C₄), 18.8 (C₂-CH₃), 14.1 (CH₂CH₃).

HRMS (ESI) m/z : Calcd for $[M+H]^+$ $C_{19}H_{20}N_3O_4$ 354.1448; Found 354.1445.

Ethyl 7-[5'-(hydroxymethyl)furan-2'-yl]-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (203p)

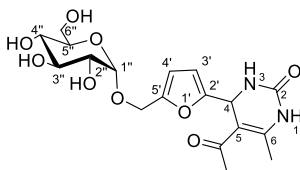


Reaction time: 8 h; Global yield: 83% after filtration.

1H NMR (300 MHz, $DMSO-d_6$) δ 10.84 (s, 1H, H_4), 7.70 (s, 1H, H_2), 6.34 (s, 1H, H_7), 6.22 (d, 1H, $J = 3.2$ Hz, $H_{3'}$ or $H_{4'}$), 6.17 (d, 1H, $J = 3.2$ Hz, $H_{3'}$ or $H_{4'}$), 5.16 (t, 1H, $J = 5.8$ Hz, OH), 4.26 (d, 2H, $J = 5.8$ Hz, CH_2OH), 4.10-3.92 (m, 2H, CH_2CH_3), 2.40 (s, 3H, C_5-CH_3), 1.11 (t, 3H, $J = 7.1$ Hz, CH_2CH_3). ^{13}C NMR (75 MHz, $DMSO-d_6$) δ 165.0 (CO_2), 155.2 ($C_{5'}$), 152.6 ($C_{2'}$), 150.1 (C_2), 147.4 (C_5), 147.1 (C_{3a}), 108.1 ($C_{3'}$ or $C_{4'}$), 107.8 ($C_{3'}$ or $C_{4'}$), 94.6 (C_6), 59.5 (CH_2CH_3), 55.6 (CH_2OH), 53.1 (C_7), 18.5 (C_5-CH_3), 14.0 (CH_2CH_3).

HRMS (ESI) m/z : Calcd for $[M+H]^+$ $C_{14}H_{17}N_4O_4$ 305.1244; Found 305.1244.

5-Acetyl-4-[5'-(α -D-glucosyloxymethyl)furan-2'-yl]-6-methyl-3,4-dihydropyrimidin-2(1H)-one (203q)



Because the product has good solubility in water, the aqueous workup was avoided here. After the reaction completion, the reaction mixture was purified directly through column chromatography (DCM : MeOH = 7 : 1 – 6: 1) afford product **203q** (1:1 mixture of diastereomers) as white solid in 62% yield.

1H NMR (400 MHz, $DMSO-d_6$) δ 9.22 (2d, $J = 2.0$ Hz, 1H, H_1), 7.91 (2dd, $J = 3.7, 2.0$ Hz, 1H, H_3), 6.32 (d, $J = 3.2$ Hz, 1H, $H_{4'}$), 6.06 (2dd, $J = 3.2, 0.9$ Hz, 1H, $H_{3'}$), 5.29 (d, $J = 3.7$ Hz, 1H, H_4), 4.88 (dd, $J = 9.9, 5.5$ Hz, 1H, $C_{4''}-OH$), 4.78 – 4.70 (m, 3H, $H_{1''}$ + $C_{3''}-OH$ + $C_{2''}-OH$), 4.52 and 4.36 (AB, $J = 12.9$ Hz, 2H, $C_{5''}-CH_2O$), 4.48 (dd, $J = 5.9, 6.0$ Hz, 1H, $C_{6''}-OH$), 3.66 – 3.57 (m, 1H, $H_{6''}$), 3.50 – 3.43 (m, 1H, $H_{6''}$), 3.42 -3.37 (m, 2H, $H_{3''}$ + $H_{5''}$), 3.25 – 3.18 (m, 1H, $H_{2''}$), 3.12 – 3.04 (m, 1H, $H_{4''}$), 2.26 (s, 3H, CH_3-C_6), 2.18 (2s, 3H, $COCH_3$).

^{13}C NMR (100 MHz, DMSO- d_6) δ 193.9 (COCH_3), 156.0 (2s, $\text{C}_{2'}$), 152.5 (C_2), 151.0 (2s, C_5), 149.1 (2s, C_6), 110.2 (2s, $\text{C}_{4'}$), 107.2 (C_5), 106.4 ($\text{C}_{3'}$), 97.8 ($\text{C}_{1''}$), 73.2 (2s, $\text{C}_{5''}$ / $\text{C}_{3''}$), 72.9 (2s, $\text{C}_{5''}$ / $\text{C}_{3''}$), 71.9 ($\text{C}_{2''}$), 70.3 (2s, $\text{C}_{4''}$), 60.9 ($\text{C}_{6''}$), 60.3 ($\text{C}_{5''}\text{-CH}_2$), 47.9 (2s, C_4), 30.1 (COCH_3), 19.0 ($\text{C}_6\text{-CH}_3$).

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+ \text{C}_{18}\text{H}_{24}\text{N}_2\text{NaO}_9$ 435.1374; Found 435.1370.

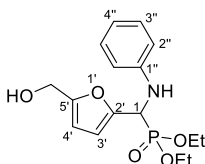
4. Experimental data in Chapter III

4.1. General procedure for the Kabachnik-Fields reaction

A solution of HMF (1 mmol) in 2-MeTHF (2 mL), amine (1 mmol), dialkyl phosphite (1.5 mmol) and iodine (5 mol%) was stirred at room temperature (25 °C) or 50 °C for indicated time. Then the mixture was concentrated under reduced pressure and purified by column chromatography on silica gel to provide pure α -amino phosphonate **207**.

4.2. Characterization data of products

Diethyl ((5-(hydroxymethyl)furan-2-yl)(phenylamino)methyl)phosphonate (**207a**)

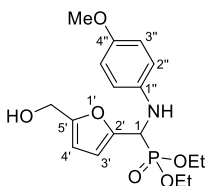


The title compound was obtained in 91% yield as a pale yellow sticky syrup after column chromatography (pentane: ethyl acetate = 1: 5 – 1: 10).

^1H NMR (500 MHz, CDCl_3) δ 7.15 – 7.09 (m, 2H, $\text{H}_{3''}$), 6.74 – 6.69 (m, 1H, $\text{H}_{4''}$), 6.68 – 6.63 (m, 2H, $\text{H}_{2''}$), 6.29 (dd, $J = 3.2$ Hz, 1H, $\text{H}_{3'}$), 6.17 (d, $J = 3.2$ Hz, 1H, $\text{H}_{4'}$), 4.86 (d, $J = 23.5$ Hz, 1H, H_1), 4.53 – 4.45 (AB, 2H, CH_2OH), 4.19 – 4.08 (m, 2H, CH_2CH_3), 4.06 – 3.97 (m, 1H, CH_2CH_3), 3.89 – 3.82 (m, 1H, CH_2CH_3), 1.25 (t, $J = 7.0$ Hz, 3H, CH_2CH_3), 1.17 (t, $J = 7.0$ Hz, 3H, CH_2CH_3). ^{13}C NMR (125 MHz, CDCl_3) δ 155.0 (d, $^4J = 3$ Hz, C_5), 148.6 (d, $^2J = 2$ Hz, $\text{C}_{2'}$), 146.0 (d, $^3J = 13$ Hz, $\text{C}_{1''}$), 129.2 ($2\text{C}_{3''}$), 118.8 ($\text{C}_{4''}$), 113.9 ($2\text{C}_{2''}$), 109.6 (d, $^3J = 8$ Hz, $\text{C}_{3'}$), 108.4 (d, $^4J = 2$ Hz, $\text{C}_{4'}$), 63.7 (d, $^2J = 7$ Hz, CH_2CH_3), 63.5 (d, $^2J = 7$ Hz, CH_2CH_3), 56.9 (CH_2OH), 50.2 (d, $^1J = 160$ Hz, C_1), 16.4 (d, $^3J = 6$ Hz, CH_2CH_3), 16.3 (d, $^3J = 6$ Hz, CH_2CH_3). ^{31}P NMR (202 MHz, CDCl_3) δ 20.3.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+ \text{C}_{16}\text{H}_{22}\text{NNaO}_5\text{P}$ 362.1128; Found 362.1118.

Diethyl ((5-(hydroxymethyl)furan-2-yl)((4-methoxyphenyl)amino)methyl)phosphonate (207b)

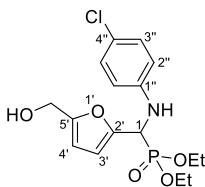


The title compound was obtained in 90% yield as a brown sticky syrup after column chromatography (pentane: ethyl acetate = 1: 5 – 1: 10).

^1H NMR (400 MHz, CDCl_3) δ 6.71 – 6.66 (m, 2H, H_{Ph}), 6.63 – 6.58 (m, 2H, H_{Ph}), 6.24 (dd, J = 3.2 Hz, 1H, $\text{H}_{3'}$), 6.15 (d, J = 3.2, 1H, $\text{H}_{4'}$), 4.74 (d, J = 23.6 Hz, 1H, H_1), 4.52 – 4.43 (AB, 2H, CH_2OH), 4.19 – 4.07 (m, 2H, CH_2CH_3), 4.06 – 3.94 (m, 1H, CH_2CH_3), 3.90 – 3.78 (m, 1H, CH_2CH_3), 3.66 (s, 3H, OCH_3), 1.25 (t, J = 7.1, 3H, CH_2CH_3), 1.16 (t, J = 7.1, 3H, CH_2CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 154.9 (d, 4J = 3 Hz, $\text{C}_{5'}$), 153.1 ($\text{C}_{4''}$), 148.8 (d, 2J = 2 Hz, $\text{C}_{2'}$), 140.0 (d, 3J = 14 Hz, $\text{C}_{1''}$), 115.7 (2CH_{Ph}), 114.7 (2CH_{Ph}), 109.6 (d, 3J = 8 Hz, $\text{C}_{3'}$), 108.4 (d, 4J = 3 Hz, $\text{C}_{4'}$), 63.7 (d, 2J = 7 Hz, CH_2CH_3), 63.4 (d, 2J = 7 Hz, CH_2CH_3), 56.9 (CH_2OH), 55.6 (OCH_3), 51.4 (d, 1J = 160 Hz, C_1), 16.4 (d, 3J = 6 Hz, CH_2CH_3), 16.3 (d, 3J = 6 Hz, CH_2CH_3). ^{31}P NMR (162 MHz, CDCl_3) δ 20.5.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{17}\text{H}_{25}\text{NO}_6\text{P}$ 370.1414; Found 370.1409.

Diethyl (((4-chlorophenyl)amino)(5-(hydroxymethyl)furan-2-yl)methyl)phosphonate (207c)



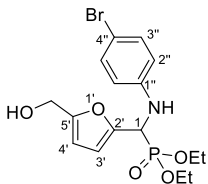
The title compound was obtained in 85% yield as a yellow sticky syrup after column chromatography (pentane: ethyl acetate = 1: 5 – 1: 10).

^1H NMR (300 MHz, CDCl_3) δ 7.14 – 7.06 (m, 2H, H_{Ph}), 6.64 – 6.55 (m, 2H, H_{Ph}), 6.31 (dd, J = 3.3 Hz, 1H, $\text{H}_{3'}$), 6.22 (d, J = 3.2 Hz, 1H, $\text{H}_{4'}$), 4.79 (d, J = 23.6 Hz, 1H, H_1), 4.55 (s, 2H, CH_2OH), 4.25 – 3.80 (m, 4H, CH_2CH_3), 1.29 (td, J = 7.1, 0.5 Hz, 3H, CH_2CH_3), 1.20 (td, J = 7.1, 0.6 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, CDCl_3) δ 155.1 (d, 4J = 3 Hz, $\text{C}_{5'}$), 148.1 (d, 2J = 3 Hz, $\text{C}_{2'}$), 144.7 (d, 3J = 13 Hz, $\text{C}_{1''}$), 128.9 (2CH_{Ph}), 123.3 ($\text{C}_{4''}$), 115.0 (2CH_{Ph}), 109.7 (d, 3J = 8 Hz, $\text{C}_{3'}$), 108.3 (d, 4J = 2 Hz, $\text{C}_{4'}$), 63.7 (d, 2J = 7 Hz, CH_2CH_3), 63.5 (d, 2J = 7 Hz, CH_2CH_3), 56.7

($\underline{\text{CH}_2\text{OH}}$), 50.2 (d, $^1J = 160$ Hz, C_1), 16.3 (d, $^3J = 6$ Hz, $\text{CH}_2\underline{\text{CH}_3}$), 16.2 (d, $^3J = 6$ Hz, $\text{CH}_2\underline{\text{CH}_3}$).
 ^{31}P NMR (122 MHz, CDCl_3) δ 20.0.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+ \text{C}_{16}\text{H}_{21}\text{ClNNaO}_5\text{P}$ 396.0738; Found 396.0719.

Diethyl (((4-bromophenyl)amino)(5-(hydroxymethyl)furan-2-yl)methyl)phosphonate (207d)

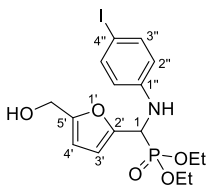


The title compound was obtained in 90% yield as a pale yellow sticky syrup after column chromatography (pentane: ethyl acetate = 1: 5 – 1: 10).

^1H NMR (300 MHz, CDCl_3) δ 7.18 – 7.12 (m, 2H, H_{Ph}), 6.54 – 6.47 (m, 2H, H_{Ph}), 6.26 (dd, $J = 3.2$ Hz, 1H, $\text{H}_{3'}$), 6.15 (d, $J = 3.1$ Hz, 1H, $\text{H}_{4'}$), 4.84 – 4.70 (m, 2H, H_1 and NH), 4.45 (s, 2H, $\underline{\text{CH}_2\text{OH}}$), 4.20 – 3.75 (m, 4H, $\underline{\text{CH}_2\text{CH}_3}$), 1.21 (td, $J = 7.0, 0.6$ Hz, 3H, $\text{CH}_2\underline{\text{CH}_3}$), 1.13 (td, $J = 7.0, 0.6$ Hz, 3H, $\text{CH}_2\underline{\text{CH}_3}$). ^{13}C NMR (75 MHz, CDCl_3) δ 155.0 (d, $^4J = 3$ Hz, $\text{C}_{5'}$), 148.1 (d, $^2J = 2$ Hz, $\text{C}_{2'}$), 145.1 (d, $^3J = 12$ Hz, $\text{C}_{1'}$), 131.8 (2CH_{Ph}), 115.5 (2CH_{Ph}), 110.5 ($\text{C}_{4'}$), 109.7 (d, $^3J = 7$ Hz, $\text{C}_{3'}$), 108.4 (d, $^4J = 2$ Hz, $\text{C}_{4'}$), 63.7 (d, $^2J = 7$ Hz, $\underline{\text{CH}_2\text{CH}_3}$), 63.5 (d, $^2J = 7$ Hz, $\underline{\text{CH}_2\text{CH}_3}$), 56.8 ($\underline{\text{CH}_2\text{OH}}$), 50.1 (d, $^1J = 160$ Hz, C_1), 16.4 (d, $^3J = 6$ Hz, $\text{CH}_2\underline{\text{CH}_3}$), 16.2 (d, $^3J = 6$ Hz, $\text{CH}_2\underline{\text{CH}_3}$).
 ^{31}P NMR (122 MHz, CDCl_3) δ 19.9.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+ \text{C}_{16}\text{H}_{21}\text{BrNNaO}_5\text{P}$ 440.0233; Found 440.0217.

Diethyl ((5-(hydroxymethyl)furan-2-yl)((4-iodophenyl)amino)methyl)phosphonate (207e)



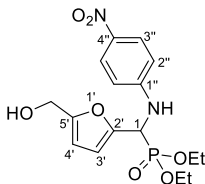
The title compound was obtained in 77% yield as a yellow sticky syrup after column chromatography (pentane: ethyl acetate = 1: 5 – 1: 10).

^1H NMR (300 MHz, CDCl_3) δ 7.39 – 7.29 (m, 2H, H_{Ph}), 6.46 – 6.38 (m, 2H, H_{Ph}), 6.26 (dd, $J = 3.2$ Hz, 1H, $\text{H}_{3'}$), 6.15 (d, $J = 3.2$ Hz, 1H, $\text{H}_{4'}$), 4.84 – 4.70 (m, 2H, H_1 and NH), 4.46 (s, 2H, $\underline{\text{CH}_2\text{OH}}$), 4.22 – 3.73 (m, 4H, $\underline{\text{CH}_2\text{CH}_3}$), 1.22 (t, $J = 7.1$ Hz, 3H, $\text{CH}_2\underline{\text{CH}_3}$), 1.14 (t, $J = 7.1$ Hz, 3H, $\text{CH}_2\underline{\text{CH}_3}$). ^{13}C NMR (75 MHz, CDCl_3) δ 155.0 (d, $^4J = 3$ Hz, $\text{C}_{5'}$), 148.1 (d, $^2J = 3$ Hz, $\text{C}_{2'}$), 145.7 (d, $^3J = 12$ Hz, $\text{C}_{1'}$), 137.7 (2CH_{Ph}), 116.1 (2CH_{Ph}), 109.7 (d, $^3J = 7$ Hz, $\text{C}_{3'}$), 108.4 (d, $^4J = 2$ Hz, $\text{C}_{4'}$), 79.9 ($\text{C}_{4'}$), 63.7 (d, $^2J = 7$ Hz, $\underline{\text{CH}_2\text{CH}_3}$), 63.5 (d, $^2J = 7$ Hz, $\underline{\text{CH}_2\text{CH}_3}$), 56.8 ($\underline{\text{CH}_2\text{OH}}$), 49.9

(d, $^1J = 160$ Hz, C₁), 16.4 (d, $^3J = 6$ Hz, CH₂C $\underline{\text{H}}$ CH₃), 16.3 (d, $^3J = 6$ Hz, CH₂C $\underline{\text{H}}$ CH₃). ^{31}P NMR (122 MHz, CDCl₃) δ 19.9.

HRMS (ESI) m/z : Calcd for [M+Na]⁺ C₁₆H₂₁INNaO₅P 488.0094; Found 488.0076.

Diethyl ((5-(hydroxymethyl)furan-2-yl)((4-nitrophenyl)amino)methyl)phosphonate (207f)

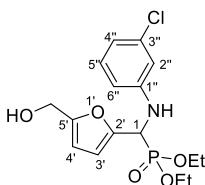


The title compound was obtained in 84% yield as a pale yellow sticky syrup after column chromatography (pentane: ethyl acetate = 1: 5 – 1: 10).

^1H NMR (300 MHz, CDCl₃) δ 8.04 – 7.97 (m, 2H, H_{Ph}), 6.72 – 6.65 (m, 2H, H_{Ph}), 6.40 (dd, $J = 3.2$ Hz, 1H, H_{3'}), 6.24 (d, $J = 3.2$ Hz, 1H, H_{4'}), 6.10 (dd, $J = 9.0, 5.7$ Hz, 1H, NH), 4.99 (dd, $J = 22.8, 9.0$ Hz, 1H, H₁), 4.53 (s, 2H, CH₂OH), 4.25 – 3.84 (m, 4H, CH₂CH₃), 1.27 (t, $J = 7.1$ Hz, 3H, CH₂CH₃), 1.21 (t, $J = 7.1$ Hz, 3H, CH₂CH₃). ^{13}C NMR (75 MHz, CDCl₃) δ 155.2 (d, $^4J = 3$ Hz, C_{5'}), 151.8 (d, $^3J = 10$ Hz, C_{1''}), 147.3 (d, $^2J = 2$ Hz, C_{2'}), 138.8 (C_{4''}), 126.0 (2CH_{Ph}), 112.2 (2CH_{Ph}), 110.1 (d, $^3J = 7$ Hz, C_{3'}), 108.6 (d, $^4J = 2$ Hz, C_{4'}), 63.9 (d, $^2J = 7$ Hz, CH₂CH₃), 63.7 (d, $^2J = 7$ Hz, CH₂CH₃), 56.8 (CH₂OH), 49.3 (d, $^1J = 160$ Hz, C₁), 16.4 (d, $^3J = 6$ Hz, CH₂C $\underline{\text{H}}$ CH₃), 16.2 (d, $^3J = 6$ Hz, CH₂C $\underline{\text{H}}$ CH₃). ^{31}P NMR (122 MHz, CDCl₃) δ 18.7.

HRMS (ESI) m/z : Calcd for [M+Na]⁺ C₁₆H₂₁N₂NaO₇P 407.0979; Found 407.0967.

Diethyl (((3-chlorophenyl)amino)(5-(hydroxymethyl)furan-2-yl)methyl)phosphonate (207g)



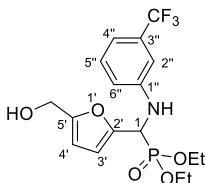
The title compound was obtained in 93% yield as a pale yellow sticky syrup after column chromatography (pentane: ethyl acetate = 1: 4 – 1: 8).

^1H NMR (400 MHz, CDCl₃) δ 7.01 (t, $J = 8.0$ Hz, 1H, H_{5''}), 6.71 – 6.64 (m, 2H, H_{2''} and H_{4''}), 6.56 – 6.51 (m, 1H, H_{6''}), 6.32 (dd, $J = 3.2$ Hz, 1H, H_{3'}), 6.19 (d, $J = 3.2$ Hz, 1H, H_{4'}), 4.95 (dd, $J = 9.5, 5.6$ Hz, 1H, NH), 4.83 (dd, $J = 23.0, 9.5$ Hz, 1H, H₁), 4.50 (s, 2H, CH₂OH), 4.33 (br, 1H, OH), 4.23 – 3.79 (m, 4H, CH₂CH₃), 1.26 (t, $J = 7.1$ Hz, 3H, CH₂CH₃), 1.18 (t, $J = 7.0$ Hz, 3H, CH₂CH₃). ^{13}C NMR (100 MHz, CDCl₃) δ 155.1 (d, $^4J = 3$ Hz, C_{5'}), 148.1 (d, $^2J = 2$ Hz, C_{2'}), 147.3 (d, $^3J = 12$ Hz, C_{1''}), 134.8 (C_{3''}), 130.1 (C_{5''}), 118.5 (C_{2''} or C_{4''}), 113.7 (C_{2''} or C_{4''}), 112.0

(C_{6''}), 109.8 (d, ³J = 8 Hz, C_{3'}), 108.4 (d, ⁴J = 2 Hz, C_{4'}), 63.7 (d, ²J = 7 Hz, CH₂CH₃), 63.5 (d, ²J = 7 Hz, CH₂CH₃), 56.8 (CH₂OH), 49.9 (d, ¹J = 161 Hz, C₁), 16.4 (d, ³J = 6 Hz, CH₂CH₃), 16.2 (d, ³J = 6 Hz, CH₂CH₃). ³¹P NMR (162 MHz, CDCl₃) δ 19.8.

HRMS (ESI) m/z: Calcd for [M+Na]⁺ C₁₆H₂₁ClNNaO₅P 396.0738; Found 396.0723.

Diethyl ((5-(hydroxymethyl)furan-2-yl)((3-(trifluoromethyl)phenyl)amino)methyl)phosphonate (207h)

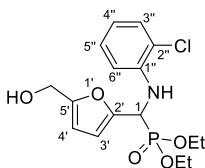


The title compound was obtained in 87% yield as a pale yellow sticky syrup after column chromatography (pentane: ethyl acetate = 1: 4 – 1: 8).

¹H NMR (400 MHz, CDCl₃) δ 7.23 – 7.17 (m, 1H, H_{5''}), 6.97 – 6.91 (m, 2H, H_{2''} and H_{4''}), 6.83 – 6.77 (m, 1H, H_{6''}), 6.35 (dd, *J* = 3.2 Hz, 1H, H_{3'}), 6.20 (d, *J* = 3.2 Hz, 1H, H_{4'}), 5.14 (br, NH), 4.89 (d, *J* = 23.0 Hz, 1H, H₁), 4.51 (AB, 2H, CH₂OH), 4.23 – 3.82 (m, 4H, CH₂CH₃), 1.26 (t, *J* = 7.1 Hz, 3H, CH₂CH₃), 1.18 (t, *J* = 7.0 Hz, 3H, CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 155.2 (d, ⁴J = 3 Hz, C_{5'}), 148.0 (d, ²J = 2 Hz, C_{2'}), 146.5 (d, ³J = 12 Hz, C_{1''}), 131.4 (q, ²J = 32 Hz, C_{3''}), 129.7 (C_{5''}), 124.2 (q, ¹J = 272 Hz, CF₃), 116.7 (C_{6''}), 115.1 (q, ³J = 4 Hz, C_{2''} or C_{4''}), 110.4 (q, ³J = 4 Hz, C_{2''} or C_{4''}), 110.0 (d, ³J = 8 Hz, C_{3'}), 108.5 (d, ⁴J = 2 Hz, C_{4'}), 63.7 (d, ²J = 7 Hz, CH₂CH₃), 63.7 (d, ²J = 7 Hz, CH₂CH₃), 56.9 (CH₂OH), 49.9 (d, ¹J = 161 Hz, C₁), 16.4 (d, ³J = 6 Hz, CH₂CH₃), 16.3 (d, ³J = 6 Hz, CH₂CH₃). ³¹P NMR (162 MHz, CDCl₃) δ 19.8.

HRMS (ESI) m/z: Calcd for [M+Na]⁺ C₁₇H₂₁F₃NNaO₅P 430.1002; Found 430.0998.

Diethyl (((2-chlorophenyl)amino)(5-(hydroxymethyl)furan-2-yl)methyl)phosphonate (207i)



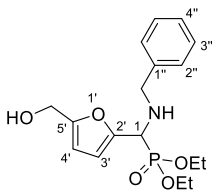
The title compound was obtained in 82% yield as a pale yellow sticky syrup after column chromatography (pentane: ethyl acetate = 1: 4 – 1: 8).

¹H NMR (300 MHz, CDCl₃) δ 7.24 (dd, *J* = 8.2, 1.5 Hz, 1H, H_{Ph}), 7.06 (td, *J* = 7.8, 1.5 Hz, 1H, H_{Ph}), 6.70 – 6.63 (m, 2H, H_{Ph}), 6.31 (dd, *J* = 3.3 Hz, 1H, H_{3'}), 6.20 (d, *J* = 3.2 Hz, 1H, H_{4'}), 5.11 (dd, *J* = 9.0, 7.1 Hz, 1H, NH), 4.89 (dd, *J* = 23.4, 9.0 Hz, 1H, H₁), 4.52 (s, 2H, CH₂OH), 4.23 –

3.87 (m, 4H, CH_2CH_3), 1.28 (td, $J = 7.1, 0.6$ Hz, 3H, CH_2CH_3), 1.22 (td, $J = 7.0, 0.6$ Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, CDCl_3) δ 155.2 (d, $^4J = 3$ Hz, C_5'), 148.2 (d, $^2J = 3$ Hz, C_2'), 142.1 (d, $^3J = 12$ Hz, C_1''), 129.3 (CH_{Ph}), 127.7 (CH_{Ph}), 120.3 (C_2''), 119.0 (CH_{Ph}), 112.6 (CH_{Ph}), 109.6 (d, $^3J = 7$ Hz, C_3'), 108.5 (d, $^4J = 3$ Hz, C_4'), 63.9 (d, $^2J = 7$ Hz, CH_2CH_3), 63.6 (d, $^2J = 7$ Hz, CH_2CH_3), 57.0 (CH_2OH), 50.1 (d, $^1J = 159$ Hz, C_1), 16.4 (d, $^3J = 6$ Hz, CH_2CH_3), 16.3 (d, $^3J = 6$ Hz, CH_2CH_3). ^{31}P NMR (122 MHz, CDCl_3) δ 19.4.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+$ $\text{C}_{16}\text{H}_{21}\text{ClNNaO}_5\text{P}$ 396.0738; Found 396.0729.

Diethyl ((benzylamino)(5-(hydroxymethyl)furan-2-yl)methyl)phosphonate (207j)

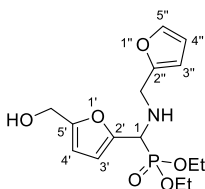


The title compound was obtained in 71% yield as a yellow sticky syrup after column chromatography (pure ethyl acetate).

^1H NMR (300 MHz, CDCl_3) δ 7.37 – 7.19 (m, 5H, H_{Ph}), 6.30 – 6.22 (m, 2H, H_3' and H_4'), 4.63 – 4.47 (AB, 2H, CH_2OH), 4.27 – 4.10 (m, 2H, CH_2CH_3), 4.08 – 3.95 (m, $J = 22.4$ Hz, 2H, CH_2CH_3 and H_1), 3.93 – 3.81 (m, 2H, CH_2CH_3 and CH_2Ph), 3.60 (d, $J = 13.3$ Hz, 1H, CH_2Ph), 1.32 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 1.17 (t, $J = 7.1$ Hz, 3H, CH_2CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 155.2 (d, $^4J = 3$ Hz, C_5'), 148.9 (d, $^2J = 4$ Hz, C_2'), 139.0 (C_1''), 128.44 (2CH_{Ph}), 128.39 (2CH_{Ph}), 127.2 (C_4''), 110.3 (d, $^3J = 8$ Hz, C_3'), 108.2 (d, $^4J = 2$ Hz, C_4'), 63.5 (d, $^2J = 7$ Hz, CH_2CH_3), 63.0 (d, $^2J = 7$ Hz, CH_2CH_3), 57.0 (CH_2OH), 53.0 (d, $^1J = 162$ Hz, C_1), 51.3 (d, $^3J = 16$ Hz, CH_2Ph), 16.5 (d, $^3J = 6$ Hz, CH_2CH_3), 16.3 (d, $^3J = 6$ Hz, CH_2CH_3). ^{31}P NMR (162 MHz, CDCl_3) δ 21.2.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{17}\text{H}_{25}\text{NO}_5\text{P}$ 354.1465; Found 354.1455.

Diethyl (((furan-2-ylmethyl)amino)(5-(hydroxymethyl)furan-2-yl)methyl)phosphonate (207k)

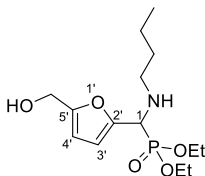


The title compound was obtained in 70% yield as a brown syrup after column chromatography (pentane: ethyl acetate = 1: 10 to pure ethyl acetate).

^1H NMR (400 MHz, CDCl_3) δ 7.34 (dd, $J = 1.9, 0.9$ Hz, 1H, $\text{H}_{5''}$), 6.34 – 6.26 (m, 2H, $\text{H}_{3'}$ and $\text{H}_{4'}$), 6.25 (d, $J = 3.1$ Hz, 1H, $\text{H}_{4'}$), 6.16 (dd, $J = 3.2, 0.9$ Hz, 1H, $\text{H}_{3''}$), 4.60 – 4.50 (AB, 2H, CH_2OH), 4.24 – 3.86 (m, 5H, H_1 and $2\text{CH}_2\text{CH}_3$), 3.74 (dd, $J = 84.0, 14.5$ Hz, 2H, CH_2Fur), 1.30 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 1.20 (t, $J = 7.1$ Hz, 3H, CH_2CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 155.1 (d, $^4J = 3$ Hz, $\text{C}_{5'}$), 152.6 ($\text{C}_{2''}$), 148.5 (d, $^2J = 4$ Hz, $\text{C}_{2'}$), 142.1 ($\text{C}_{5''}$), 110.4 (d, $^3J = 8$ Hz, $\text{C}_{3'}$), 110.2 ($\text{C}_{4''}$), 108.3 (d, $^4J = 2$ Hz, $\text{C}_{4'}$), 107.9 ($\text{C}_{3''}$), 63.5 (d, $^2J = 7$ Hz, CH_2CH_3), 63.1 (d, $^2J = 7$ Hz, CH_2CH_3), 57.1 (CH_2OH), 53.1 (d, $^1J = 162$ Hz, C_1), 44.0 (d, $^3J = 16$ Hz, CH_2Fur), 16.5 (d, $^3J = 6$ Hz, CH_2CH_3), 16.3 (d, $^3J = 6$ Hz, CH_2CH_3). ^{31}P NMR (162 MHz, CDCl_3) δ 20.8.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+$ $\text{C}_{15}\text{H}_{22}\text{NNaO}_6\text{P}$ 366.1077; Found 366.1064.

Diethyl ((butylamino)(5-(hydroxymethyl)furan-2-yl)methyl)phosphonate (207l)

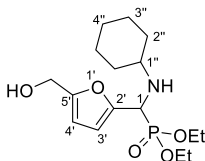


The title compound was obtained in 74% yield as a yellow sticky syrup after column chromatography (pure ethyl acetate).

^1H NMR (400 MHz, CDCl_3) δ 6.28 (dd, $J = 3.2$ Hz, 1H, $\text{H}_{3'}$), 6.24 (d, $J = 3.2$ Hz, 1H, $\text{H}_{4'}$), 4.59 – 4.48 (AB, 2H, CH_2OH), 4.25 – 3.86 (m, 5H, $2\text{CH}_2\text{CH}_3$ and H_1), 2.67 – 2.45 (m, 2H, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.49 – 1.26 (m, 7H, CH_2CH_3 and $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.21 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 0.87 (t, $J = 7.2$ Hz, 3H, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$). ^{13}C NMR (100 MHz, CDCl_3) δ 154.9 (d, $^4J = 3$ Hz, $\text{C}_{5'}$), 149.4 (d, $^2J = 3$ Hz, $\text{C}_{2'}$), 109.7 (d, $^3J = 8$ Hz, $\text{C}_{3'}$), 108.2 (d, $^4J = 2$ Hz, $\text{C}_{4'}$), 63.4 (d, $^2J = 7$ Hz, CH_2CH_3), 63.0 (d, $^2J = 7$ Hz, CH_2CH_3), 57.0 (CH_2OH), 54.7 (d, $^1J = 161$ Hz, C_1), 47.9 (d, $^3J = 15$ Hz, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 31.8 ($\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 20.2 ($\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 16.5 (d, $^3J = 6$ Hz, CH_2CH_3), 16.3 (d, $^3J = 6$ Hz, CH_2CH_3), 13.9 ($\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$). ^{31}P NMR (162 MHz, CDCl_3) δ 21.3.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+$ $\text{C}_{14}\text{H}_{26}\text{NNaO}_5\text{P}$ 342.1441; Found 342.1442.

Diethyl ((cyclohexylamino)(5-(hydroxymethyl)furan-2-yl)methyl)phosphonate (207m)

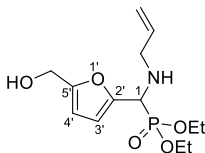


The title compound was obtained in 63% yield as a pale yellow sticky syrup after column chromatography (pure ethyl acetate).

^1H NMR (400 MHz, CDCl_3) δ 6.27 – 6.22 (m, 2H, $\text{H}_{3'}$ and $\text{H}_{4'}$), 4.59 – 4.49 (AB, 2H, CH_2OH), 4.28 – 4.12 (m, $J = 23.3$ Hz, 3H, CH_2CH_3 and H_1), 4.08 – 3.97 (m, 1H, CH_2CH_3), 3.95 – 3.83 (m, 1H, CH_2CH_3), 2.48 – 2.38 (m, 1H, $\text{H}_{1''}$), 1.92 – 1.50 (m, 5H, H_{Cy}), 1.33 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 1.23 – 0.99 (m, 8H, CH_2CH_3 and H_{Cy}). ^{13}C NMR (100 MHz, CDCl_3) δ 154.8 (d, $^4J = 3$ Hz, $\text{C}_{5'}$), 150.0 (d, $^2J = 3$ Hz, $\text{C}_{2'}$), 109.3 (d, $^3J = 8$ Hz, $\text{C}_{3'}$), 108.2 (d, $^4J = 2$ Hz, $\text{C}_{4'}$), 63.6 (d, $^2J = 7$ Hz, CH_2CH_3), 62.9 (d, $^2J = 7$ Hz, CH_2CH_3), 57.1 (CH_2OH), 54.2 (d, $^3J = 15$ Hz, $\text{C}_{1''}$), 51.6 (d, $^1J = 162$ Hz, C_1), 34.0 (C_{Cy}), 32.2 (C_{Cy}), 26.0 (C_{Cy}), 24.8 (C_{Cy}), 24.4 (C_{Cy}), 16.5 (d, $^3J = 6$ Hz, CH_2CH_3), 16.3 (d, $^3J = 6$ Hz, CH_2CH_3). ^{31}P NMR (162 MHz, CDCl_3) δ 21.6.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{16}\text{H}_{29}\text{NO}_5\text{P}$ 346.1778; Found 346.1767.

Diethyl ((allylamino)(5-(hydroxymethyl)furan-2-yl)methyl)phosphonate (207n)

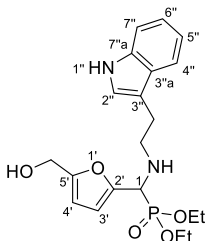


The title compound was obtained in 53% yield as a yellow sticky syrup after column chromatography (pure ethyl acetate).

^1H NMR (400 MHz, CDCl_3) δ 6.28 (dd, $J = 3.1$ Hz, 1H, $\text{H}_{3'}$), 6.24 (d, $J = 3.3$ Hz, 1H, $\text{H}_{4'}$), 5.86 – 5.75 (m, 1H, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 5.19 – 5.08 (m, 2H, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 4.60 – 4.50 (AB, 2H, CH_2OH), 4.26 – 3.87 (m, 5H, CH_2CH_3 and H_1), 3.35 – 3.05 (m, 2H, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 1.33 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 1.21 (t, $J = 7.1$ Hz, 3H, CH_2CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 155.0 (d, $^4J = 3$ Hz, $\text{C}_{5'}$), 149.0 (d, $^2J = 3$ Hz, $\text{C}_{2'}$), 135.7 ($\text{NHCH}_2\text{CH}=\text{CH}_2$), 117.2 ($\text{NHCH}_2\text{CH}=\text{CH}_2$), 110.1 (d, $^3J = 8$ Hz, $\text{C}_{3'}$), 108.2 (d, $^4J = 2$ Hz, $\text{C}_{4'}$), 63.4 (d, $^2J = 7$ Hz, CH_2CH_3), 63.1 (d, $^2J = 7$ Hz, CH_2CH_3), 57.1 (CH_2OH), 53.2 (d, $^1J = 162$ Hz, C_1), 50.1 (d, $^3J = 16$ Hz, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 16.5 (d, $^3J = 6$ Hz, CH_2CH_3), 16.4 (d, $^3J = 6$ Hz, CH_2CH_3). ^{31}P NMR (162 MHz, CDCl_3) δ 21.3.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+$ $\text{C}_{13}\text{H}_{22}\text{NNaO}_5\text{P}$ 326.1128; Found 326.1126.

Diethyl (((2-(1H-indol-3-yl)ethyl)amino)(5-(hydroxymethyl)furan-2-yl)methyl)phosphonate (207o)

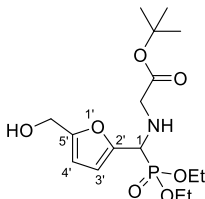


The title compound was obtained in 57% yield as a yellow sticky syrup after column chromatography (ethyl acetate: methanol = 100: 1 to 50: 1).

^1H NMR (400 MHz, CDCl_3) δ 9.14 (d, $J = 2.4$ Hz, 1H, $\text{H}_{1''}$), 7.47 (dd, $J = 7.9, 1.0$ Hz, 1H, $\text{H}_{4''}$), 7.31 – 7.27 (m, 1H, $\text{H}_{7''}$), 7.11 (ddd, $J = 8.1, 7.0, 1.2$ Hz, 1H, $\text{H}_{6''}$), 7.02 (ddd, $J = 8.0, 7.0, 1.1$ Hz, 1H, $\text{H}_{5''}$), 6.85 (d, $J = 2.4$ Hz, 1H, $\text{H}_{2''}$), 6.18 (dd, $J = 3.1$ Hz, 1H, $\text{H}_{3''}$), 6.14 (d, $J = 3.2$ Hz, 1H, $\text{H}_{4'}$), 4.33 (s, 2H, CH_2OH), 4.12 – 4.04 (m, 3H, CH_2CH_3 and H_1), 3.99 – 3.91 (m, 1H, CH_2CH_3), 3.85 – 3.74 (m, 1H, CH_2CH_3), 2.98 – 2.81 (m, 4H, CH_2CH_2), 1.22 (t, $J = 7.0$ Hz, 3H, CH_2CH_3), 1.11 (t, $J = 7.1$ Hz, 3H, CH_2CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 155.0 (d, $^4J = 3$ Hz, $\text{C}_{5'}$), 148.6 (d, $^2J = 4$ Hz, $\text{C}_{2'}$), 136.5 ($\text{C}_{7''\text{a}}$), 127.3 ($\text{C}_{3''\text{a}}$), 122.6 ($\text{C}_{2''}$), 121.5 ($\text{C}_{6''}$), 118.7 ($\text{C}_{5''}$), 118.5 ($\text{C}_{4''}$), 112.4 ($\text{C}_{3''}$), 111.4 ($\text{C}_{7''}$), 110.2 (d, $^3J = 8$ Hz, $\text{C}_{3'}$), 108.1 (d, $^4J = 2$ Hz, $\text{C}_{4'}$), 63.5 (d, $^2J = 7$ Hz, CH_2CH_3), 63.2 (d, $^2J = 7$ Hz, CH_2CH_3), 56.6 (CH_2OH), 54.5 (d, $^1J = 161$ Hz, C_1), 47.9 (d, $^3J = 15$ Hz, NHCH_2CH_2), 25.3 (NHCH_2CH_2), 16.3 (d, $^3J = 6$ Hz, CH_2CH_3), 16.2 (d, $^3J = 6$ Hz, CH_2CH_3). ^{31}P NMR (162 MHz, CDCl_3) δ 21.3.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_5\text{P}$ 407.1730; Found 407.1716.

***tert*-Butyl ((diethoxyphosphoryl)(5-(hydroxymethyl)furan-2-yl)methyl)glycinate (207p)**

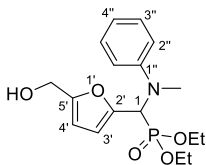


The title compound was obtained in 31% yield as a yellow syrup after column chromatography (pure ethyl acetate).

^1H NMR (400 MHz, CDCl_3) δ 6.33 (dd, $J = 3.2$ Hz, 1H, $\text{H}_{3'}$), 6.25 (d, $J = 3.2$ Hz, 1H, $\text{H}_{4'}$), 4.55 (AB, 2H, CH_2OH), 4.24 (d, $J = 20.3$ Hz, 1H, H_1), 4.22 – 3.96 (m, 4H, CH_2CH_3), 3.39 – 3.18 (m, 2H, CH_2COO), 1.43 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.33 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 1.26 (t, $J = 7.1$ Hz, 3H, CH_2CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 170.8 (COO), 155.2 (d, $^4J = 3$ Hz, $\text{C}_{5'}$), 148.3 (d, $^2J = 5$ Hz, $\text{C}_{2'}$), 110.7 (d, $^3J = 8$ Hz, $\text{C}_{3'}$), 108.5 (d, $^4J = 3$ Hz, $\text{C}_{4'}$), 81.5 ($\text{C}(\text{CH}_3)_3$), 63.4 (d, $^2J = 7$ Hz, CH_2CH_3), 63.2 (d, $^2J = 7$ Hz, CH_2CH_3), 57.2 (CH_2OH), 53.9 (d, $^1J = 161$ Hz, C_1), 49.4 (d, $^3J = 15$ Hz, CH_2COO), 28.2 ($\text{C}(\text{CH}_3)_3$), 16.5 (d, $^3J = 6$ Hz, CH_2CH_3), 16.4 (d, $^3J = 6$ Hz, CH_2CH_3). ^{31}P NMR (162 MHz, CDCl_3) δ 20.6.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{16}\text{H}_{29}\text{NO}_7\text{P}$ 378.1676; Found 378.1660.

Diethyl ((5-(hydroxymethyl)furan-2-yl)(methyl(phenyl)amino)methyl)phosphonate (207q)

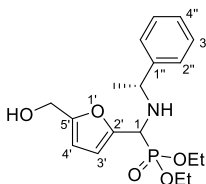


The title compound was obtained in 58% yield as a yellow sticky syrup after column chromatography (pentane: ethyl acetate = 1: 4 to 1: 6).

^1H NMR (400 MHz, CDCl_3) δ 7.27 – 7.21 (m, 2H, $\text{H}_{3''}$), 6.92 – 6.87 (m, 2H, $\text{H}_{2''}$), 6.82 – 6.77 (m, 1H, $\text{H}_{4''}$), 6.48 (dd, $J = 3.4, 1.4$ Hz, 1H, $\text{H}_{3'}$), 6.21 (d, $J = 3.2$ Hz, 1H, $\text{H}_{4'}$), 5.27 (d, $J = 24.5$ Hz, 1H, H_1), 4.49 (s, 2H, CH_2OH), 4.21 – 3.95 (m, 4H, CH_2CH_3), 2.92 (d, $J = 1.3$ Hz, 3H, NCH_3), 1.20 (2t, $J = 7.1$ Hz, 6H, $2\text{CH}_2\text{CH}_3$). ^{13}C NMR (100 MHz, CDCl_3) δ 155.1 (d, $^4J = 1$ Hz, $\text{C}_{5'}$), 145.0 (d, $^3J = 6$ Hz, $\text{C}_{1''}$), 147.4 (d, $^2J = 13$ Hz, $\text{C}_{2'}$), 129.2 ($2\text{C}_{3''}$), 118.5 ($\text{C}_{4''}$), 114.3 ($2\text{C}_{2''}$), 111.6 (d, $^3J = 4$ Hz, $\text{C}_{3'}$), 108.2 ($\text{C}_{4'}$), 63.4 (d, $^2J = 7$ Hz, CH_2CH_3), 62.8 (d, $^2J = 7$ Hz, CH_2CH_3), 57.1 (CH_2OH), 56.3 (d, $^1J = 165$ Hz, C_1), 34.5 (NCH_3), 16.5 (d, $^3J = 6$ Hz, CH_2CH_3), 16.4 (d, $^3J = 6$ Hz, CH_2CH_3). ^{31}P NMR (162 MHz, CDCl_3) δ 19.8.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{17}\text{H}_{25}\text{NO}_5\text{P}$ 354.1465; Found 354.1453.

Diethyl ((5-(hydroxymethyl)furan-2-yl)((*R*)-1-phenylethyl)amino)methylphosphonate (207r)



The title compound was obtained in 72% yield in total after column chromatography (pentane: ethyl acetate = 1: 10 to pure ethyl acetate).

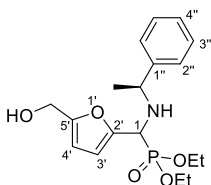
Diastereoisomer A: Major product, pale yellow sticky syrup. ^1H NMR (400 MHz, CDCl_3) δ 7.29 – 7.18 (m, 5H, H_{Ph}), 6.18 – 6.14 (m, 2H, $\text{H}_{3'}$ and $\text{H}_{4'}$), 4.54 – 4.43 (AB, 2H, CH_2OH), 4.31 – 4.15 (m, 2H, CH_2CH_3), 4.12 (d, $J = 21.6$ Hz, 1H, H_1), 4.08 – 3.97 (m, 1H, CH_2CH_3), 3.94 – 3.81 (m, 2H, CH_2CH_3 and PhCHCH_3), 1.35 (t, $J = 7.0$ Hz, 3H, CH_2CH_3), 1.33 (t, $J = 6.7$ Hz, 3H, PhCHCH_3), 1.19 (t, $J = 7.0$ Hz, 3H, CH_2CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 154.7 (d, $^4J = 3$ Hz, $\text{C}_{5'}$), 149.6 (d, $^2J = 2$ Hz, $\text{C}_{2'}$), 145.0 ($\text{C}_{1''}$), 128.4 (2CH_{Ph}), 127.2 ($\text{C}_{4''}$), 126.8 (2CH_{Ph}), 109.4 (d, $^3J = 8$ Hz, $\text{C}_{3'}$), 108.2 (d, $^4J = 2$ Hz, $\text{C}_{4'}$), 63.4 (d, $^2J = 7$ Hz, CH_2CH_3), 63.0 (d, $^2J = 7$ Hz, CH_2CH_3), 57.0 (CH_2OH), 56.0 (d, $^3J = 12$ Hz, PhCHCH_3), 52.2 (d, $^1J = 159$ Hz, C_1), 22.8 (PhCHCH_3), 16.6 (d, $^3J = 6$ Hz, CH_2CH_3), 16.4 (d, $^3J = 6$ Hz, CH_2CH_3). ^{31}P NMR (162 MHz, CDCl_3) δ 21.8.

HRMS (ESI) m/z : Calcd for $[M+H]^+$ $C_{18}H_{27}NO_5P$ 368.1621; Found 368.1604.

Diastereoisomer B: Minor product, pale yellow sticky syrup. 1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 5H, H_{Ph}), 6.25 (d, $J = 2.9$ Hz, 1H, H_4), 6.16 (dd, $J = 3.2$ Hz, 1H, H_3), 4.63 – 4.52 (AB, 2H, $\underline{CH_2OH}$), 4.29 – 4.11 (m, 2H, $\underline{CH_2CH_3}$), 4.03 – 3.92 (m, 1H, $\underline{CH_2CH_3}$), 3.86 – 3.75 (m, $J = 24.1$ Hz, 2H, $\underline{CH_2CH_3}$ and H_1), 3.72 – 3.65 (m, 1H, $Ph\dot{C}HCH_3$), 1.35 (td, $J = 7.0, 0.6$ Hz, 3H, $CH_2\dot{C}H_3$), 1.33 (t, $J = 6.5$ Hz, 3H, $PhCH\dot{C}H_3$) 1.14 (td, $J = 7.1, 0.6$ Hz, 3H, $CH_2\dot{C}H_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9 (d, $^4J = 3$ Hz, C_5), 149.6 (d, $^2J = 3$ Hz, C_2), 144.1 ($C_{1'}$), 128.6 ($2CH_{Ph}$), 127.4 ($C_{4'}$), 127.3 ($2CH_{Ph}$), 110.3 (d, $^3J = 9$ Hz, C_3), 108.4 (d, $^4J = 2$ Hz, C_4), 63.5 (d, $^2J = 7$ Hz, $\underline{CH_2CH_3}$), 62.9 (d, $^2J = 7$ Hz, $\underline{CH_2CH_3}$), 57.4 ($\underline{CH_2OH}$), 55.7 (d, $^3J = 17$ Hz, $Ph\dot{C}HCH_3$), 51.9 (d, $^1J = 163$ Hz, C_1), 25.1 ($PhCH\dot{C}H_3$), 16.6 (d, $^3J = 6$ Hz, $CH_2\dot{C}H_3$), 16.4 (d, $^3J = 6$ Hz, $CH_2\dot{C}H_3$). ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.3.

HRMS (ESI) m/z : Calcd for $[M+H]^+$ $C_{18}H_{27}NO_5P$ 368.1621; Found 368.1610.

Diethyl ((5-(hydroxymethyl)furan-2-yl)((*S*)-1-phenylethyl)amino)methylphosphonate (207s)



The title compound was obtained in 70% yield in total after column chromatography (pentane: ethyl acetate = 1: 10 to pure ethyl acetate).

Diastereoisomer A: Major product, pale yellow sticky syrup. 1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.18 (m, 5H, H_{Ph}), 6.19 – 6.15 (m, 2H, H_3 and H_4), 4.54 – 4.44 (AB, 2H, $\underline{CH_2OH}$), 4.31 – 4.16 (m, 2H, $\underline{CH_2CH_3}$), 4.12 (d, $J = 21.7$ Hz, 1H, H_1), 4.08 – 3.98 (m, 1H, $\underline{CH_2CH_3}$), 3.94 – 3.82 (m, 2H, $\underline{CH_2CH_3}$ and $Ph\dot{C}HCH_3$), 1.35 (t, $J = 7.1$ Hz, 3H, $CH_2\dot{C}H_3$), 1.33 (t, $J = 6.5$ Hz, 3H, $PhCH\dot{C}H_3$) 1.19 (t, $J = 7.0$ Hz, 3H, $CH_2\dot{C}H_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6 (d, $^4J = 3$ Hz, C_5), 149.7 (d, $^2J = 2$ Hz, C_2), 145.0 ($C_{1'}$), 128.5 ($2CH_{Ph}$), 127.2 ($C_{4'}$), 126.8 ($2CH_{Ph}$), 109.5 (d, $^3J = 8$ Hz, C_3), 108.4 (d, $^4J = 2$ Hz, C_4), 63.5 (d, $^2J = 7$ Hz, $\underline{CH_2CH_3}$), 63.1 (d, $^2J = 7$ Hz, $\underline{CH_2CH_3}$), 57.2 ($\underline{CH_2OH}$), 56.1 (d, $^3J = 12$ Hz, $Ph\dot{C}HCH_3$), 52.3 (d, $^1J = 159$ Hz, C_1), 22.9 ($PhCH\dot{C}H_3$), 16.6 (d, $^3J = 6$ Hz, $CH_2\dot{C}H_3$), 16.4 (d, $^3J = 6$ Hz, $CH_2\dot{C}H_3$). ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.8.

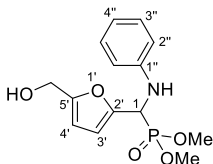
HRMS (ESI) m/z : Calcd for $[M+H]^+$ $C_{18}H_{27}NO_5P$ 368.1621; Found 368.1612.

Diastereoisomer B: Minor product, pale yellow sticky syrup. 1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 5H, H_{Ph}), 6.26 (d, $J = 3.0$ Hz, 1H, H_4), 6.16 (dd, $J = 3.2$ Hz, 1H, H_3), 4.64 – 4.52 (AB,

2H, $\underline{\text{CH}_2\text{OH}}$), 4.29 – 4.12 (m, 2H, $\underline{\text{CH}_2\text{CH}_3}$), 4.02 – 3.92 (m, 1H, $\underline{\text{CH}_2\text{CH}_3}$), 3.85 – 3.74 (m, $J = 24.1$ Hz, 2H, $\underline{\text{CH}_2\text{CH}_3}$ and H_1), 3.72 – 3.65 (m, 1H, PhCHCH_3), 1.35 (td, $J = 7.1, 0.6$ Hz, 3H, $\underline{\text{CH}_2\text{CH}_3}$), 1.33 (t, $J = 6.4$ Hz, 3H, PhCHCH_3) 1.14 (td, $J = 7.1, 0.6$ Hz, 3H, $\underline{\text{CH}_2\text{CH}_3}$). ^{13}C NMR (100 MHz, CDCl_3) δ 154.9 (d, $^4J = 3$ Hz, C_5'), 149.5 (d, $^2J = 4$ Hz, C_2'), 144.0 ($\text{C}_{1''}$), 128.6 (2CH_{Ph}), 127.4 ($\text{C}_{4''}$), 127.3 (2CH_{Ph}), 110.4 (d, $^3J = 9$ Hz, C_3'), 108.4 (d, $^4J = 2$ Hz, C_4'), 63.5 (d, $^2J = 7$ Hz, $\underline{\text{CH}_2\text{CH}_3}$), 62.9 (d, $^2J = 7$ Hz, $\underline{\text{CH}_2\text{CH}_3}$), 57.3 ($\underline{\text{CH}_2\text{OH}}$), 55.7 (d, $^3J = 17$ Hz, PhCHCH_3), 51.9 (d, $^1J = 163$ Hz, C_1), 25.1 (PhCHCH_3), 16.6 (d, $^3J = 6$ Hz, $\underline{\text{CH}_2\text{CH}_3}$), 16.4 (d, $^3J = 6$ Hz, $\underline{\text{CH}_2\text{CH}_3}$). ^{31}P NMR (162 MHz, CDCl_3) δ 21.3.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{H}]^+ \text{C}_{18}\text{H}_{27}\text{NO}_5\text{P}$ 368.1621; Found 368.1611.

Dimethyl ((5-(hydroxymethyl)furan-2-yl)(phenylamino)methyl)phosphonate (207t)

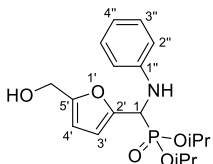


The title compound was obtained in 89% yield as a pale yellow sticky syrup after column chromatography (pentane: ethyl acetate = 1: 4 to 1: 8).

^1H NMR (400 MHz, CDCl_3) δ 7.17 – 7.08 (m, 2H, $\text{H}_{3''}$), 6.78 – 6.69 (m, 1H, $\text{H}_{4''}$), 6.71 – 6.63 (m, 2H, $\text{H}_{2''}$), 6.30 (dd, $J = 3.2$ Hz, 1H, $\text{H}_{3'}$), 6.18 (d, $J = 3.2$ Hz, 1H, $\text{H}_{4'}$), 4.90 (d, $J = 23.6$ Hz, 1H, H_1), 4.49 (s, 2H, $\underline{\text{CH}_2\text{OH}}$), 3.75 (d, $J = 10.6$ Hz, 3H, $\underline{\text{CH}_3}$), 3.58 (d, $J = 10.7$ Hz, 3H, $\underline{\text{CH}_3}$). ^{13}C NMR (100 MHz, CDCl_3) δ 155.1 (d, $^4J = 3$ Hz, C_5'), 148.2 (d, $^2J = 2$ Hz, C_2'), 145.8 (d, $^3J = 12$ Hz, $\text{C}_{1''}$), 129.2 ($2\text{C}_{3''}$), 119.0 ($\text{C}_{4''}$), 114.0 ($2\text{C}_{2''}$), 109.8 (d, $^3J = 8$ Hz, C_3'), 108.5 (d, $^4J = 2$ Hz, C_4'), 56.8 ($\underline{\text{CH}_2\text{OH}}$), 54.1 (d, $^2J = 7$ Hz, $\underline{\text{CH}_3}$), 53.8 (d, $^2J = 7$ Hz, $\underline{\text{CH}_3}$), 49.8 (d, $^1J = 161$ Hz, C_1). ^{31}P NMR (162 MHz, CDCl_3) δ 22.8.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+ \text{C}_{14}\text{H}_{18}\text{NNaO}_5\text{P}$ 334.0815; Found 334.0808.

Diisopropyl ((5-(hydroxymethyl)furan-2-yl)(phenylamino)methyl)phosphonate (207u)



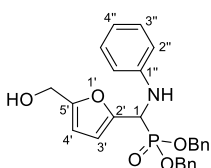
The title compound was obtained in 87% yield as a pale yellow sticky syrup after column chromatography (pentane: ethyl acetate = 1: 4 to 1: 8).

^1H NMR (400 MHz, CDCl_3) δ 7.15 – 7.09 (m, 2H, $\text{H}_{3''}$), 6.74 – 6.68 (m, 1H, $\text{H}_{4''}$), 6.68 – 6.63 (m, 2H, $\text{H}_{2''}$), 6.28 (dd, $J = 3.2$ Hz, 1H, $\text{H}_{3'}$), 6.18 (d, $J = 3.1$ Hz, 1H, $\text{H}_{4'}$), 4.86 – 4.69 (m, 2H, H_1 and

$\text{CH}(\text{CH}_3)_2$), 4.61 – 4.52 (m, 2H, $\text{CH}(\text{CH}_3)_2$ and NH), 4.50 (s, 2H, CH_2OH), 1.31 (d, $J = 6.2$ Hz, 3H, CH_3), 1.28 (d, $J = 6.2$ Hz, 3H, CH_3), 1.22 (d, $J = 6.2$ Hz, 3H, CH_3), 1.07 (d, $J = 6.2$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 154.8 (d, $^4J = 3$ Hz, C_5), 149.1 (d, $^2J = 2$ Hz, C_2), 146.3 (d, $^3J = 13$ Hz, $\text{C}_{1'}$), 129.2 ($2\text{C}_{3'}$), 118.7 ($\text{C}_{4'}$), 114.0 ($2\text{C}_{2'}$), 109.4 (d, $^3J = 7$ Hz, $\text{C}_{3'}$), 108.3 (d, $^4J = 2$ Hz, C_4), 72.45 (d, $^2J = 7$ Hz, $\text{CH}(\text{CH}_3)_2$), 72.38 (d, $^2J = 7$ Hz, $\text{CH}(\text{CH}_3)_2$), 57.1 (CH_2OH), 50.7 (d, $^1J = 161$ Hz, C_1), 24.3 (d, $^3J = 3$ Hz, CH_3), 24.2 (d, $^3J = 3$ Hz, CH_3), 23.7 (d, $^3J = 5$ Hz, CH_3), 23.5 (d, $^3J = 5$ Hz, CH_3). ^{31}P NMR (162 MHz, CDCl_3) δ 18.2.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{H}]^+ \text{C}_{18}\text{H}_{27}\text{NO}_5\text{P}$ 368.1621; Found 368.1612.

Dibenzyl ((5-(hydroxymethyl)furan-2-yl)(phenylamino)methyl)phosphonate (207v)

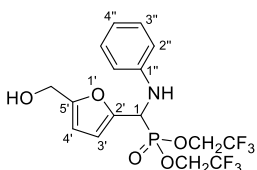


The title compound was obtained in 86% yield as a pale yellow sticky syrup after column chromatography (pentane: ethyl acetate = 2: 3).

^1H NMR (400 MHz, CDCl_3) δ 7.31 – 7.15 (m, 10H, H_{Ph}), 7.12 – 7.05 (m, 2H, $\text{H}_{3'}$), 6.74 – 6.67 (m, 1H, $\text{H}_{4'}$), 6.63 – 6.57 (m, 2H, $\text{H}_{2'}$), 6.25 (dd, $J = 3.2$ Hz, 1H, $\text{H}_{3'}$), 6.14 (d, $J = 3.1$ Hz, 1H, $\text{H}_{4'}$), 5.08 – 4.98 (m, 2H, CH_2Ph), 4.97 – 4.87 (m, 2H, CH_2Ph and H_1), 4.84 – 4.76 (m, 1H, CH_2Ph), 4.44 (s, 2H, CH_2OH). ^{13}C NMR (100 MHz, CDCl_3) δ 155.0 (d, $^4J = 3$ Hz, C_5), 148.4 (d, $^2J = 2$ Hz, C_2), 145.9 (d, $^3J = 12$ Hz, $\text{C}_{1'}$), 135.9 (d, $^3J = 6$ Hz, C_{Ph}), 135.8 (d, $^3J = 6$ Hz, C_{Ph}), 129.2 ($2\text{C}_{3'}$), 128.54 (2CH_{Ph}), 128.52 (2CH_{Ph}), 128.48 (CH_{Ph}), 128.43 (CH_{Ph}), 128.1 (2CH_{Ph}), 127.9 (2CH_{Ph}), 119.0 ($\text{C}_{4'}$), 114.0 ($2\text{C}_{2'}$), 109.8 (d, $^3J = 8$ Hz, $\text{C}_{3'}$), 108.5 (d, $^4J = 3$ Hz, C_4), 68.9 (d, $^2J = 7$ Hz, CH_2Ph), 68.6 (d, $^2J = 7$ Hz, CH_2Ph), 57.0 (CH_2OH), 50.5 (d, $^1J = 160$ Hz, C_1). ^{31}P NMR (162 MHz, CDCl_3) δ 20.9.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{H}]^+ \text{C}_{26}\text{H}_{27}\text{NO}_5\text{P}$ 464.1621; Found 464.1617.

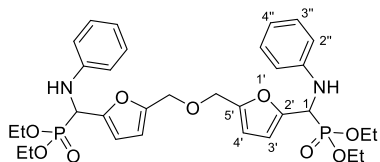
Bis(2,2,2-trifluoroethyl) ((5-(hydroxymethyl)furan-2-yl)(phenylamino)methyl)phosphonate (207w)



The title compound was obtained in 54% yield as a pale yellow sticky syrup after column chromatography (pentane: ethyl acetate = 2: 1 to 3:2).

^1H NMR (400 MHz, CDCl_3) δ 7.21 – 7.14 (m, 2H, $\text{H}_{3''}$), 6.84 – 6.78 (m, 1H, $\text{H}_{4''}$), 6.75 – 6.69 (m, 2H, $\text{H}_{2''}$), 6.35 (dd, $J = 3.4$ Hz, 1H, $\text{H}_{3'}$), 6.21 (d, $J = 3.1$ Hz, 1H, $\text{H}_{4'}$), 5.09 (d, $J = 23.0$ Hz, 1H, H_1), 4.49 (s, 2H, CH_2OH), 4.48 – 4.09 (m, 4H, CH_2CF_3). ^{13}C NMR (100 MHz, CDCl_3) δ 155.5 (d, $^4J = 3$ Hz, $\text{C}_{5'}$), 146.7 ($\text{C}_{2'}$), 145.3 (d, $^3J = 12$ Hz, $\text{C}_{1''}$), 129.5 ($2\text{C}_{3''}$), 127.4 – 117.5 (2CF_3), 120.0 ($\text{C}_{4''}$), 114.5 ($2\text{C}_{2''}$), 110.7 (d, $^3J = 9$ Hz, $\text{C}_{3'}$), 108.8 (d, $^4J = 2$ Hz, $\text{C}_{4'}$), 63.2 and 63.0 (qd, $J = 38$, 6 Hz, $2\text{CH}_2\text{CF}_3$), 56.9 (CH_2OH), 50.7 (d, $^1J = 166$ Hz, C_1). ^{31}P NMR (122 MHz, CDCl_3) δ 22.5. HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+$ $\text{C}_{16}\text{H}_{16}\text{F}_6\text{NNaO}_5\text{P}$ 470.0562; Found 470.0542.

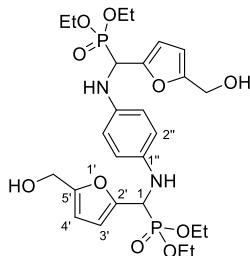
Diethyl ((5-(hydroxymethyl)furan-2-yl)(phenylamino)methyl)phosphonate dimer (207x)



The title compound was obtained in 86% yield as a pale yellow sticky syrup after column chromatography (pentane: ethyl acetate = 1: 5 to 1: 10).

^1H NMR (400 MHz, CDCl_3) δ 7.13 (t, $J = 7.8$ Hz, 4H, $\text{H}_{3''}$), 6.72 (t, $J = 7.3$ Hz, 2H, $\text{H}_{4''}$), 6.67 (d, $J = 8.1$ Hz, 4H, $\text{H}_{2''}$), 6.34 (t, $J = 3.3$ Hz, 2H, $\text{H}_{3'}$), 6.23 (d, $J = 3.3$ Hz, 2H, $\text{H}_{4'}$), 4.89 (dd, $J = 24.0$, 7.7 Hz, 2H, H_1), 4.65 (q, $J = 7.7$ Hz, 2H, NH), 4.40 – 4.32 (m, 4H, CH_2OCH_2), 4.23 – 4.12 (m, 4H, CH_2CH_3), 4.10 – 4.01 (m, 2H, CH_2CH_3), 3.96 – 3.84 (m, 2H, CH_2CH_3), 1.28 (t, $J = 7.1$ Hz, 6H, CH_2CH_3), 1.19 (t, $J = 7.1$ Hz, 6H, CH_2CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 151.2 (dd, $J = 3$, 2 Hz, $2\text{C}_{5'}$), 149.8 ($2\text{C}_{2'}$), 146.0 (dd, $J = 13$, 2 Hz, $2\text{C}_{1''}$), 129.1 ($4\text{C}_{3''}$), 118.8 ($J = 2$ Hz, $2\text{C}_{4''}$), 113.8 ($4\text{C}_{2''}$), 110.9 (d, $^4J = 3$ Hz, $2\text{C}_{4'}$), 109.4 (dd, $J = 7$, 2 Hz, $2\text{C}_{3'}$), 63.5 (d, $^2J = 7$ Hz, $2\text{CH}_2\text{CH}_3$), 63.3 (d, $^2J = 7$ Hz, $2\text{CH}_2\text{CH}_3$), 63.1 and 63.0 (CH_2OCH_2), 50.1 (d, $^1J = 159$ Hz, 2C_1), 16.4 (d, $^3J = 6$ Hz, $2\text{CH}_2\text{CH}_3$), 16.2 (d, $^3J = 6$ Hz, $2\text{CH}_2\text{CH}_3$). ^{31}P NMR (162 MHz, CDCl_3) δ 20.0. HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+$ $\text{C}_{32}\text{H}_{42}\text{N}_2\text{NaO}_9\text{P}_2$ 683.2258; Found 683.2223.

Diethyl (((4-(((diethoxyphosphoryl)(5-(hydroxymethyl)furan-2-yl)methyl)amino)phenyl)amino)(5-(hydroxymethyl)furan-2-yl)methyl)phosphonate (207y)

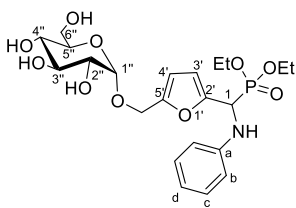


The title compound was obtained in 72% yield as a brown sticky syrup after column chromatography (ethyl acetate: methanol = 40:1 to 20:1).

^1H NMR (400 MHz, CDCl_3) δ 6.52 (s, 4H, H_{Ph}), 6.23 (t, $J = 3.2$ Hz, 2H, $\text{H}_{3'}$), 6.14 (d, $J = 3.2$ Hz, 2H, $\text{H}_{4'}$), 4.71 (d, $J = 23.6$ Hz, 2H, H_1), 4.47 (s, 4H, CH_2OH), 4.19 – 4.06 (m, 4H, CH_2CH_3), 4.06 – 3.94 (m, 2H, CH_2CH_3), 3.89 – 3.78 (m, 2H, CH_2CH_3), 1.24 (t, $J = 7.0$ Hz, 6H, CH_2CH_3), 1.16 (t, $J = 7.1$ Hz, 6H, CH_2CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 154.7 (d, $^4J = 3$ Hz, $2\text{C}_{5'}$), 148.8 (d, $^2J = 3$ Hz, $2\text{C}_{2'}$), 139.2 (dd, $J = 14, 4$ Hz, $2\text{C}_{1'}$), 115.9 (d, $J = 5$ Hz, $4\text{C}_{2''}$), 109.7 (d, $^3J = 8$ Hz, $2\text{C}_{3'}$), 108.4 (d, $^4J = 2$ Hz, $2\text{C}_{4'}$), 63.8 (d, $^2J = 7$ Hz, $2\text{CH}_2\text{CH}_3$), 63.5 (d, $^2J = 7$ Hz, $2\text{CH}_2\text{CH}_3$), 56.8 ($2\text{CH}_2\text{OH}$), 51.3 (dd, $^1J = 160, 8$ Hz, 2C_1), 16.4 (d, $^3J = 6$ Hz, $2\text{CH}_2\text{CH}_3$), 16.3 (d, $^3J = 6$ Hz, $2\text{CH}_2\text{CH}_3$). ^{31}P NMR (162 MHz, CDCl_3) δ 20.5.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+ \text{C}_{26}\text{H}_{38}\text{N}_2\text{NaO}_{10}\text{P}_2$ 623.1894; Found 623.1868.

Diethyl ((5-(α -D-glucosyloxymethyl)furan-2-yl)(phenylamino)methyl)phosphonate (207z)

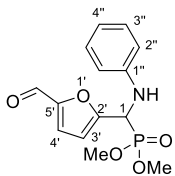


The title compound was obtained in 78% yield as a white solid after column chromatography (Dichloromethane: methanol = 10:1).

^1H NMR (400 MHz, MeOD) δ 7.11 – 7.05 (m, 2H, H_c), 6.76 – 6.71 (m, 2H, H_b), 6.68 – 6.62 (m, 1H, H_d), 6.37 (dd, $J = 3.2$ Hz, 1H, $\text{H}_{3'}$), 6.35 – 6.32 (m, 1H, $\text{H}_{4'}$), 5.06 (d, $J = 23.6$ Hz, 1H, H_1), 4.85 (dd, $J = 3.8$ Hz, 1H, $\text{H}_{1''}$), 4.81 (br, 1H, NH), 4.69 – 4.42 (AB, 2H, $\text{C}_{5'}$ - CH_2O), 4.18 – 3.90 (m, 4H, CH_2CH_3), 3.80 – 3.74 (m, 1H, $\text{H}_{6''}$), 3.68 – 3.56 (m, 3H, $\text{H}_{6''} + \text{H}_{5''} + \text{H}_{3''}$), 3.37 (dd, $J = 9.7, 3.8$ Hz, 1H, $\text{H}_{2''}$), 3.29 – 3.25 (m, 1H, $\text{H}_{4''}$), 1.23 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 1.19 (t, $J = 7.1$ Hz, 3H, CH_2CH_3). ^{13}C NMR (100 MHz, MeOD) δ 152.8 (2d, $^4J = 3$ Hz, $\text{H}_{5'}$), 151.0 (d, $^2J = 2$ Hz, $\text{C}_{2'}$), 147.9 (d, $^3J = 12$ Hz, C_a), 130.0 (C_c), 119.6 (2s, C_d), 115.1 (2s, C_b), 111.8 (2d, $^4J = 2$ Hz, $\text{C}_{4'}$), 110.8 (d, $^3J = 8$ Hz, $\text{C}_{3'}$), 99.1 (2s, $\text{C}_{1'}$), 75.0 (2s, $\text{C}_{3''}$), 73.8 ($\text{C}_{5''}$), 73.4 ($\text{C}_{2''}$), 71.7 (2s, $\text{C}_{4''}$), 65.0 (d, $^2J = 7.2$ Hz, CH_2CH_3), 64.8 (d, $^2J = 7.2$ Hz, CH_2CH_3), 62.6 ($\text{C}_{6''}$), 61.9 (2s, $\text{OCH}_2\text{-C}_{5'}$), 51.0 (2d, $^1J = 161$ Hz, C_1), 16.8 (d, $^3J = 5$ Hz, CH_2CH_3), 16.7 ($^3J = 5$ Hz, CH_2CH_3). ^{31}P NMR (162 MHz, MeOD) δ 20.66, 20.63.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+ \text{C}_{22}\text{H}_{32}\text{NNaO}_{10}\text{P}$ 524.1656; Found 524.1645.

Dimethyl ((5-formylfuran-2-yl)(phenylamino)methyl)phosphonate (207aa)

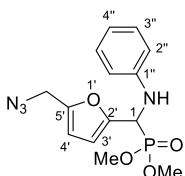


To the solution of K-F product **207t** (0.353 mmol, 110 mg) in DCM (3 mL), Dess–Martin periodinane (1.1 equiv., 0.388 mmol) was added. The suspension was stirred at room temperature for 2 h. Then 10 wt% Na₂S₂O₃ solution (10 mL) was added to quench the reaction. The mixture was extracted with DCM (20 mL). The organic layer was washed with saturated aqueous NaHCO₃ solution (10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (pentane: EA = 2:3 – 1:2) affording final product as a white solid (95 mg, 87% yield).

¹H NMR (300 MHz, CDCl₃) δ 9.55 (s, 1H, CHO), 7.26 – 7.03 (m, 3H, H_{4'} and 2H_{3''}), 6.80 – 6.72 (m, 1H, H_{4''}), 6.68 – 6.56 (m, 2H, H_{2''}), 6.59 (dd, *J* = 3.4 Hz, 1H, H_{3'}), 5.01 (d, *J* = 24.9 Hz, 1H, H₁), 3.83 (d, *J* = 10.8 Hz, 3H, CH₃), 3.69 (d, *J* = 10.8 Hz, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 177.4 (CHO), 156.5 (d, ²*J* = 2 Hz, C_{2'}), 152.7 (d, ⁴*J* = 3 Hz, C_{5'}), 145.4 (d, ³*J* = 13 Hz, C_{1''}), 129.4 (2C_{3''}), 122.5 (C_{4'}), 119.5 (C_{4''}), 113.9 (2C_{2''}), 111.6 (d, ³*J* = 6 Hz, C_{3'}), 54.5 (d, ²*J* = 7 Hz, CH₃), 53.9 (d, ²*J* = 7 Hz, CH₃), 50.2 (d, ¹*J* = 157 Hz, C₁). ³¹P NMR (162 MHz, CDCl₃) δ 21.0.

HRMS (ESI) *m/z*: Calcd for [M+Na]⁺ C₁₄H₁₆NNaO₅P 332.0658; Found 332.0663.

Dimethyl ((5-(azidomethyl)furan-2-yl)(phenylamino)methyl)phosphonate (**207ab**)

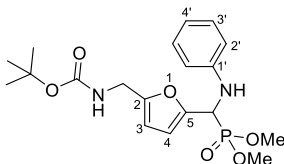


Under N₂ atmosphere, diphenylphosphoryl azide (1.5 equiv., 0.581 mmol) was added to a solution of K-F product **207t** (0.387 mmol, 120 mg) in toluene (3 mL). After stirring at room temperature for 10 min, the reaction mixture was cooled to 0 °C and DBU (1.5 equiv., 0.581 mmol) was added dropwise. The mixture was stirred at 0 °C for 1.5 h, and then at room temperature for 18 h. Subsequently water (10 mL) was added and the mixture was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (pentane: acetone = 5: 1 – 3: 1) affording the corresponding azide as a pale yellow solid. (55 mg, 42% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.19 – 7.13 (m, 2H, $\text{H}_{3'}$), 6.79 – 6.73 (m, 1H, $\text{H}_{4'}$), 6.69 – 6.64 (m, 2H, $\text{H}_{2'}$), 6.37 (dd, $J = 3.3$ Hz, 1H, $\text{H}_{3'}$), 6.29 (d, $J = 3.3$ Hz, 1H, $\text{H}_{4'}$), 4.91 (d, $J = 24.0$ Hz, 1H, H_1), 4.25 (s, 2H, CH_2N_3), 3.82 (d, $J = 10.7$ Hz, 3H, CH_3), 3.67 (d, $J = 10.7$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 150.2 (d, $^2J = 2$ Hz, $\text{C}_{2'}$), 149.2 (d, $^4J = 3$ Hz, C_5), 145.8 (d, $^3J = 13$ Hz, $\text{C}_{1'}$), 129.4 ($2\text{C}_{3'}$), 119.3 ($\text{C}_{4'}$), 114.1 ($2\text{C}_{2'}$), 110.9 (d, $^4J = 3$ Hz, $\text{C}_{4'}$), 109.9 (d, $^3J = 7$ Hz, $\text{C}_{3'}$), 54.1 (d, $^2J = 7$ Hz, CH_3), 53.9 (d, $^2J = 7$ Hz, CH_3), 50.0 (d, $^1J = 160$ Hz, H_1), 47.0 (CH_2N_3). ^{31}P NMR (162 MHz, CDCl_3) δ 22.3.

HRMS (ESI) m/z : Calcd for $[\text{M}+\text{Na}]^+ \text{C}_{14}\text{H}_{17}\text{N}_4\text{NaO}_4\text{P}$ 359.0880; Found 359.0877.

***tert*-Butyl ((5-((dimethoxyphosphoryl)(phenylamino)methyl)furan-2-yl)methyl)carbamate (207ac)**



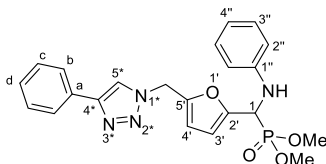
To the solution of azide **207ab** (0.15 mmol, 50.4 mg) in MeOH (3 mL), $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (0.45 mmol) was added. The mixture was stirred under nitrogen atmosphere at room temperature for 6 h. After the reaction completion, MeOH was removed under reduced pressure. 5 mL of DCM and 10 mL of saturated NaHCO_3 solution were added. The organic layer was separated and the aqueous was extracted with DCM (2×15 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 . The obtained murky suspension was filtered to remove insoluble Sn species and Na_2SO_4 . Removing the solvent provided the crude amine, which was dissolved in DCM (2 mL) immediately for Boc protection procedure. Boc_2O (0.225 mmol) and TEA (0.3 mmol) were added to DCM solution at 0 $^\circ\text{C}$. The solution was stirred at room temperature overnight. When the reaction was complete, the mixture was diluted with DCM (5 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with DCM (2×15 mL). The combined organic layer was washed with brine and dried over Na_2SO_4 , concentrated under reduced pressure. The residue was purified by column chromatography (pentane: ethyl acetate = 2 : 3) affording the **207ac** as a white solid (39.6 mg, 64%).

^1H NMR (400 MHz, CDCl_3) δ 7.19 – 7.12 (m, 2H, $\text{H}_{3'}$), 6.78 – 6.72 (m, 1H, $\text{H}_{4'}$), 6.69 – 6.64 (m, 2H, $\text{H}_{2'}$), 6.31 (dd, $J = 3.3$ Hz, 1H, $\text{H}_{4'}$), 6.14 (d, $J = 3.3$ Hz, 1H, $\text{H}_{3'}$), 4.87 (d, $J = 23.9$ Hz, 2H, $\text{CHP} + \text{NH}$), 4.25 (d, $J = 4.7$ Hz, 2H, CH_2NH), 3.80 (d, $J = 10.6$ Hz, 3H, OCH_3), 3.63 (d, $J = 10.6$ Hz, 3H, OCH_3), 1.43 (s, 9H, $\text{C}(\text{CH}_3)_3$). ^{13}C NMR (100 MHz, CDCl_3) δ 155.6 (CO), 152.5 (C_2), 148.6 (d, $^2J = 2$ Hz, C_5), 145.9 (d, $^3J = 13$ Hz, $\text{C}_{1'}$), 129.4 ($\text{C}_{3'}$), 119.2 ($\text{C}_{4'}$), 114.1 ($\text{C}_{2'}$),

109.9 (d, $^3J = 7$ Hz, C₄), 108.3 (C₃), 79.8 (C(CH₃)₃), 54.1 (d, $^2J = 7$ Hz, OCH₃), 53.8 (d, $^2J = 7$ Hz, OCH₃), 49.9 (d, $^1J = 160$ Hz, CHP), 37.9 (CH₂NH), 28.5 ((C(CH₃)₃). ^{31}P NMR (162 MHz, CDCl₃) δ 22.5.

HRMS (ESI) m/z: Calcd for [M+Na]⁺ C₁₉H₂₇N₂NaO₆P 433.1499; Found 433.1497.

Dimethyl ((5-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)furan-2-yl)(phenylamino)methyl)phosphonate (207ad)

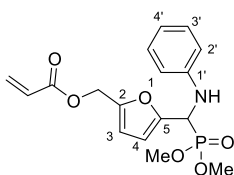


To the mixture of CuI (0.2 eq), DIPEA (0.4 eq) and AcOH (0.4 eq) in DCM (1 mL), phenylethyne (1.1 eq) and azide **207ab** (0.1 mmol, 1 eq, 33.6 mg) were added. The resultant mixture was stirred at room temperature until the azide disappeared (48 h). Once completion, the mixture was diluted with DCM (5 mL) and H₂O (10 mL). The organic layer was separated and the aqueous layer was extracted with DCM (2 × 15 mL). The combined organic layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (pentane : ethyl acetate = 1 : 2.5 to 1 : 5) to provide triazole **207ad** as a white solid (32.5 mg, 74% yield).

^1H NMR (400 MHz, CDCl₃) δ 7.79 – 7.75 (m, 2H, H_{Ar}), 7.72 (s, 1H, H_{5''}), 7.43 - 7.37 (m, 2H, H_{Ar}), 7.34 – 7.29 (m, 1H, H_d), 7.16 – 7.10 (m, 2H, H_{3''}), 6.77 – 6.71 (m, 1H, H_{4''}), 6.68 – 6.63 (m, 2H, H_{2''}), 6.43 – 6.38 (m, 2H, H_{3'} + H_{4'}), 5.52 (s, 2H, CH₂-C_{5'}), 4.92 (d, $J = 24.2$ Hz, 1H, H₁), 3.77 (d, $J = 10.6$ Hz, 3H, OCH₃), 3.57 (d, $J = 10.6$ Hz, 3H, OCH₃). ^{13}C NMR (100 MHz, CDCl₃) δ 150.7 (d, $^2J = 2$ Hz, C_{2'}), 148.2 (C_{4''}), 147.5 (d, $^4J = 3$ Hz, C_{5'}), 145.7 (d, $^3J = 13$ Hz, C_{1''}), 130.5 (C_a), 129.4 (C_{3''}), 128.9 (C_{Ar}), 128.3 (C_d), 125.8 (C_{Ar}), 119.5 (C_{4''} + C_{5''}), 114.1 (C_{2''}), 111.7 (d, $^4J = 3$ Hz, C_{4'}), 110.2 (d, $^3J = 7$ Hz, C_{3'}), 54.3 (d, $^2J = 7$ Hz, OCH₃), 53.8 (d, $^2J = 7$ Hz, OCH₃), 49.9 (d, $^1J = 160$ Hz, C₁), 46.8 (CH₂-C_{5'}). ^{31}P NMR (162 MHz, CDCl₃) δ 21.9.

HRMS (ESI) m/z: Calcd for [M+H]⁺ C₂₂H₂₄N₄O₄P 439.1530; Found 439.1526.

(5-((Dimethoxyphosphoryl)(phenylamino)methyl)furan-2-yl)methyl acrylate (207ae)



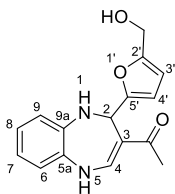
To the solution of K-F product **207t** (0.303 mmol, 94 mg) and triethylamine (1.25 equiv., 0.379 mmol) in THF (1.5 mL), acryloyl chloride (1 equiv., 0.303 mmol) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 2 h, then at room temperature for 3 h. As conversion followed by TLC was not complete, additional triethylamine (0.6 equiv., 0.182 mmol) and acryloyl chloride (0.5 equiv., 0.152 mmol) were added. The mixture was stirred overnight. After the reaction completion, the mixture was diluted with DCM (5 mL) and water (10 mL), then extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (10 mL), concentrated and dried over Na₂SO₄. The residue was purified by column chromatography (pentane: ethyl acetate = 1: 2) affording the corresponding acrylate as a white solid (93 mg, 84% yield).

¹H NMR (300 MHz, CDCl₃) δ 7.18 – 7.10 (m, 2H, H_{3'}), 6.78 – 6.70 (m, 1H, H_{4'}), 6.69 – 6.63 (m, 2H, H_{2'}), 6.44 – 6.33 (m, 3H, CH₂=CH, H₃ and H₄), 6.09 (dd, *J* = 17.3, 10.4 Hz, 1H, CH₂=CH), 5.82 (dd, *J* = 10.4, 1.5 Hz, 1H, CH₂=CH), 5.09 (s, 2H, CH₂O), 4.91 (d, *J* = 24.0 Hz, 1H, CHNH), 3.79 (d, *J* = 10.7 Hz, 3H, OCH₃), 3.62 (d, *J* = 10.7 Hz, 3H, OCH₃). ¹³C NMR (75 MHz, CDCl₃) δ 165.6 (CO), 150.0 (d, ²*J* = 2 Hz, C₅), 149.5 (d, ⁴*J* = 3 Hz, C₂), 145.8 (d, ³*J* = 13 Hz, C_{1'}), 131.4 (CH₂=CH), 129.3 (2C_{3'}), 128.0 (CH₂=CH), 119.1 (C_{4'}), 114.0 (2C_{2'}), 112.1 (d, ⁴*J* = 3 Hz, C₃), 109.9 (d, ³*J* = 7 Hz, C₄), 58.1 (CH₂O), 54.0 (d, ²*J* = 7 Hz, OCH₃), 53.8 (d, ²*J* = 7 Hz, OCH₃), 49.9 (d, ¹*J* = 160 Hz, CHNH). ³¹P NMR (122 MHz, CDCl₃) δ 22.3.

HRMS (ESI) *m/z*: Calcd for [M+Na]⁺ C₁₇H₂₀NNaO₆P 388.0920; Found 388.0914.

5. Experimental data in Perspectives part

1-(2-(5-(Hydroxymethyl)furan-2-yl)-2,5-dihydro-1H-benzo[b][1,4]diazepin-3-yl)ethan-1-one (212)

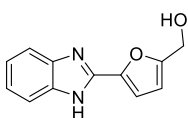


The solution of HMF (1 mmol), *o*-phenylenediamine (1 mmol), 3-buten-2-one (1 mmol) and Lewis acid (20 mol%) in EtOH (2 mL) was stirred at indicated temperature. After completion, the reaction mixture was diluted with water (20 mL). The mixture was extracted with ethyl acetate (4 × 30 mL). The organic phase was combined and washed with brine, dried over Na₂SO₄. The obtained residue was purified by column chromatography (DCM: MeOH = 25 : 1 to 15 : 1) to provide compound **212** as a pale yellow solid.

^1H NMR (400 MHz, DMSO- d_6) δ 9.30 (d, J = 8.0 Hz, 1H, H₅), 7.47 (d, J = 7.9 Hz, 1H, H₄), 6.91 – 6.77 (m, 1H, H_{Ph}), 6.71 – 6.62 (m, 3H, H_{Ph}), 6.13 (d, J = 5.8 Hz, 1H, H₁), 5.90 (d, J = 3.0 Hz, 1H, H_{4'}), 5.58 (dd, J = 3.0, 0.9 Hz, 1H, H_{3'}), 5.53 (d, J = 5.8 Hz, 1H, H₂), 5.03 (t, J = 5.6 Hz, 1H, OH), 4.22 (d, J = 5.6 Hz, 2H, CH₂OH), 2.19 (s, 3H, COCH₃). ^{13}C NMR (100 MHz, DMSO- d_6) δ 191.6 (C=O), 155.8 (C_{2'}), 153.9 (C_{5'}), 142.9 (C₄), 138.5 (C_{Ph}), 131.3 (C_{Ph}), 122.8 (C_{Ph}), 121.0 (C_{Ph}), 120.1 (C_{Ph}), 119.5 (C_{Ph}), 113.6 (C₃), 107.0 (C_{4'}), 106.2 (C_{3'}), 55.8 (CH₂OH), 51.5 (C₂), 24.4 (COCH₃).

MS (ESI) m/z : Calcd for $[\text{M}+\text{H}]^+$ C₁₆H₁₇N₂O₃ 285.12; Found 285.1.

(5-(1H-benzo[d]imidazol-2-yl)furan-2-yl)methanol (87)

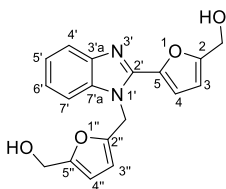


White solid.

^1H NMR (300 MHz, DMSO- d_6) δ 12.88 (s, 1H, NH), 7.60 (d, J = 7.3 Hz, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.23 – 7.15 (m, 2H), 7.12 (d, J = 3.5 Hz, 1H, H_{fur}), 6.54 (d, J = 3.5 Hz, 1H, H_{fur}), 5.41 (t, J = 5.7 Hz, 1H, OH), 4.52 (d, J = 5.7 Hz, 2H, CH₂OH).

MS (ESI) m/z : Calcd for $[\text{M}+\text{H}]^+$ C₁₂H₁₁N₂O₂ 215.08; Found 215.1.

(5-((2-(5-(Hydroxymethyl)furan-2-yl)-1H-benzo[d]imidazol-1-yl)methyl)furan-2-yl)methanol (213)

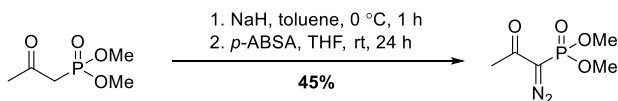


Pale yellow solid.

^1H NMR (400 MHz, DMSO- d_6) δ 7.77 – 7.72 (m, 1H, H_{Ph}), 7.66 – 7.61 (m, 1H, H_{Ph}), 7.34 – 7.22 (m, 2H, H_{Ph}), 7.18 (d, J = 3.4 Hz, 1H, H₄), 6.58 (d, J = 3.4 Hz, 1H, H₃), 6.45 (d, J = 3.2 Hz, 1H, H_{3''}), 6.20 (d, J = 3.2 Hz, 1H, H_{4''}), 5.74 (s, 2H, CH₂N), 5.51 (t, J = 5.7 Hz, 1H, C₂-CH₂OH), 5.13 (t, J = 5.7 Hz, 1H, C_{5''}-CH₂OH), 4.57 (d, J = 5.6 Hz, 2H, C₂-CH₂OH), 4.26 (d, J = 5.5 Hz, 2H, C_{5''}-CH₂OH). ^{13}C NMR (100 MHz, DMSO- d_6) δ 157.5 (C₂), 155.6 (C_{5''}), 149.1 (C_{2''}), 143.9 (C₅), 143.4 (C_{2'}), 142.5 (C_{Ph}), 135.4 (C_{Ph}), 122.8 (C_{Ph}), 122.5 (C_{Ph}), 118.9 (C_{Ph}), 113.5 (C₄), 110.9 (C_{Ph}), 109.6 (C_{3''}), 109.2 (C₃), 107.8 (C_{4''}), 55.8 (CH₂OH), 55.6 (CH₂OH) 41.1 (CH₂N).

MS (ESI) m/z : Calcd for $[\text{M}+\text{H}]^+$ C₁₈H₁₇N₂O₄ 325.12; Found 325.1.

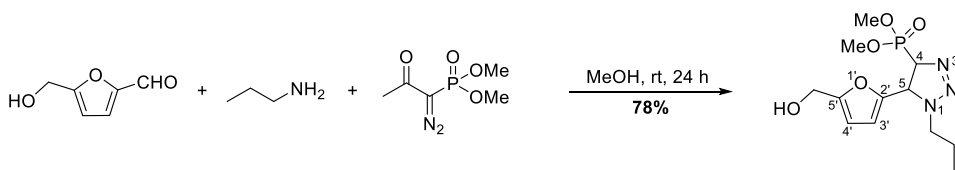
Synthesis of the Bestmann-Ohira reagent^[335]



To a solution of dimethyl 2-oxopropylphosphonate (5 mmol) in toluene (15 mL) at 0 °C, NaH (60 % dispersion in mineral oil, 6 mmol) was added in portions. After stirred for 1 h at the same temperature, a solution of *p*-ABSA (4.5 mmol) in THF (8 mL) was added dropwise. The reaction mixture was stirred at room temperature for 24 h. After the reaction was completed, 15 mL petroleum ether was added, then the precipitate was filtered off, and the filter cake was washed with diethyl ether (3 × 15 mL), the filtrate was evaporated and the residue was purified by column chromatography (pentane: ethyl acetate = 1: 2) to provide the Bestmann-Ohira reagent as yellow liquid (389 mg, 45% yield).

¹H NMR (300 MHz, CDCl₃) δ 3.82 (d, *J* = 11.9 Hz, 6H, OCH₃), 2.25 (s, 3H, CH₃CO). ¹³C NMR (75 MHz, CDCl₃) δ 190.0 (d, ²*J* = 13 Hz, CO), 53.7 (d, ²*J* = 6 Hz, OCH₃), 27.2 (CH₃CO).

Synetesis of HMF-derived 1,2,3-trizaoline (214)



To a solution of HMF (0.5 mmol, 63.1 mg) in MeOH (3 mL), *n*-propylamine (0.75 mmol, 62.9 uL) and the Bestmann-Ohira reagent (0.75 mmol, 144.1 mg) were added. The reaction mixture was stirred at room temperature for 24 h. After completion, MeOH was removed under reduced pressure and the residue was purified by column chromatography (pure ethyl acetate) to afford product **214** as yellowish oil (123.3 mg, 78%).

¹H NMR (400 MHz, CDCl₃) δ 6.22 (d, *J* = 3.2 Hz, 1H, H_{3'}), 6.17 (d, *J* = 3.2 Hz, 1H, H_{4'}), 4.84 – 4.64 (m, 2H, H₄ and H₅), 4.46 (s, 2H, CH₂OH), 3.77 (d, *J* = 10.7 Hz, 3H, OCH₃), 3.73 (d, *J* = 10.8 Hz, 3H, OCH₃), 3.56 – 3.46 (m, 1H, CH₂CH₂CH₃), 3.29 – 3.21 (m, 1H, CH₂CH₂CH₃), 1.60 – 1.50 (m, 2H, CH₂CH₂CH₃), 0.83 (t, *J* = 7.4 Hz, 3H, CH₂CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 155.8 (C_{5'}), 149.1 (d, ³*J* = 14 Hz, C_{2'}), 110.2 (C_{3'}), 108.3 (C_{4'}), 77.2 (d, ¹*J* = 161 Hz, C₄), 57.0 (CH₂OH), 56.1 (d, ²*J* = 2 Hz, C₅), 54.0 (d, ²*J* = 7 Hz, OCH₃), 53.5 (d, ²*J* = 7 Hz, OCH₃), 49.5 (CH₂CH₂CH₃), 21.2 (CH₂CH₂CH₃), 11.1 (CH₂CH₂CH₃).

HRMS (ESI) *m/z*: Calcd for [M+Na]⁺ C₁₂H₂₀N₃NaO₅P 340.1033; Found 340.1037

Reference

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FOLIO ADMINISTRATIF

THESE DE L'UNIVERSITE DE LYON OPEREE AU SEIN DE L'INSA LYON

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DATE de SOUTENANCE : 05 Avril 2019

Prénoms : Weigang

TITRE : Utilisation du HMF en réactions multicomposantes: accès rapide vers de nouvelles cibles en chimie fine

NATURE : Doctorat

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RESUME :

L'utilisation de matières premières renouvelables pour la production de produits chimiques est un enjeu majeur de l'industrie chimique. Elle vise à répondre aux contraintes environnementales et économiques de disponibilité des ressources fossiles et de limitation de l'empreinte carbone des produits chimiques.

Il existe une famille de molécules fonctionnelles directement issues de la biomasse dénommées « molécules plateforme ». Parmi elles, le 5-hydroxyméthylfurfural (HMF), porteur d'une fonction aldéhyde, un motif furanique et un groupe CH_2OH , est particulièrement intéressante. Cependant, sa stabilité modérée, notamment en conditions acides, est une forte limitation de sa chimie et son utilisation vers des cibles en chimie fine reste un défi.

Les réactions multi-composantes conduisent à des architectures élaborées à partir de briques simples de manière économe en temps et nombre d'étapes. Beaucoup de ces réactions concernent la fonction aldéhyde, ce qui rend intéressant de les appliquer au 5-HMF. Ceci est l'objet de cette thèse, qui porte sur deux réactions en particulier, Biginelli et Kabachnik-Fields.

La réaction de Biginelli est la condensation d'un aldéhyde, un composé dicarbonylé et une urée conduisant à des dihydropyrimidinones (DHPMs). Etant acido-catalysée, il a été nécessaire d'optimiser les conditions pour l'appliquer au HMF. Les meilleures conditions (réaction sans solvant, ZnCl_2) ont permis d'atteindre une large variété de nouvelles DHPMs dans des rendements convenables à très bons.

La réaction de Kabachnik-Fields est la condensation d'un aldéhyde avec une amine et un dialkyl phosphate, conduisant à des α -aminophosphonates. Les conditions optimales trouvées pour son application au 5-HMF sont l'utilisation d'iode comme catalyseur dans le solvant biosourcé 2-MeTHF à température ambiante ou modérément élevée. Une série de nouveaux α -aminophosphonates comportant le motif HMF a été préparé. Le groupe hydroxyméthyle issu du HMF persiste dans le produit, offrant de nombreuses possibilités de dérivation et démontrant son utilité comparativement à la chimie du furfural.

MOTS-CLÉS : 5-hydroxyméthylfurfural (HMF), réactions multicomposantes, chimie fine, biomasse, Biginelli, Kabachnik-Fields

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