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HMF: multi-gram synthesis, upgrading and comparative environmental evaluation

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ABBREVIATIONS

AE	Atom economy
AMF	5-alcoxymethylfurfural
Ag ₁ H ₂ PW	Silver-exchanged phosphotungstic acid
Al-TUD-1	Mesoporous aluminosilicate with Al ³⁺ ions
BAMFs	2,5-bis(alcoxymethyl)furan
BHMF	2,5-bis(hydroxymethyl)furan
BHMTHF	2,5-bis(hydroxymethyl)tetrahydrofuran
[BMIM][Cl]	Butyl methyl imidazolium chloride
[BMIM][BF ₄]	Butyl methyl imidazolium boron tetrafluoride
[BMIMSO ₃ H] ₃ PW ₁₂ O ₄₀	Heteropolyacid-based ionic liquid, namely methylimidazolebutylsulfate phosphotungstate
BTC	Benzene-1,3,5-tricarboxylate
CB	Amorphous carbon black
CFCs	Chlorofluorocarbons
CN	Cetane number
CNT	Carbon nanotubes
Cs ₂ STA	Caesium-containing Silicotungstic acid
C/SBA	SBA functionalized with SO ₃ H groups
C/MCF	Mesostructured cellular foam functionalized with SO ₃ H groups
CTH	Catalytic transfer hydrogenation
[Cu-BTC][HPM]	Benzene-1,3,5-tricarboxylate on copper nanoparticles heteropolyacid material
DES	Deep eutectic solvent
DMA	N,N-dimethylacetamide
[DMA] ⁺ [CH ₃ SO ₃] ⁻	N,N-dimethylacetamide and methyl sulfonic acid ionic liquid
DMC	Dimethylcarbonate
DMF	2,5-dimethylfuran
DMFDCA	Dimethyl-2,5-furandicarboxylic acid
DMSO	Dimethyl sulfoxide
DOE	Department of Energy
E-f	Environmental factor
EIA	Energy Information Administration
EL	Ethyl levulinate
EMF	5-ethoxymethylfurfural
EMF-DEA	5-(ethoxymethyl)furfural diethylacetal
EMF-EH	5-(ethoxymethyl)furfural ethylhemiacetal
[EMIM][Cl]	Ethyl methyl imidazolium chloride
FA	Formic acid
Fe ₃ O ₄ @C- SO ₃ H	Sulfonic acid functionalized carbonaceous shell magnetic Fe ₃ O ₄ nanoparticles
Fe ₃ O ₄ @SiO ₂ -HPW	Phosphotungstic acid supported on Silica-coated magnetic Fe ₃ O ₄ nanoparticles
Fe ₃ O ₄ @SiO ₂ -SH-Im-HSO ₄	Polymeric ionic liquid supported on mercaptopropyl-modified silica-coated magnetic Fe ₃ O ₄ nanoparticles
FDCA	2,5-Furandicarboxylic acid
GC	Gas Chromatography
GHSs	Greenhouse gases
Glu-Fe ₃ O ₄ -SO ₃ H	Glucose-derived iron nanoparticles functionalizes with sulfonic acid groups
Glu-TsOH-Ti	Sulfonated carbocatalyst containing Brønsted acidic sulfonic acid group and Lewis acidic as Ti ⁴⁺
GO	Graphene oxide

GWP	Global Warming Potential
H ₂ BDC-SO ₃ H	2-sulphoterephthalic acid
HMF	5-hydroxymethylfurfural
HMFA	5-(hydroxymethyl)furan-2-carboxylic acid
HPW	Phosphotungstic acid
HR-MS	High resolution mass spectroscopy
HSAB	Hars-Soft Acid-Base
ICP	Inductively coupled mass
IEA	International Energy Agency
IEAB	International Energy Agency Bioenergy
K-10-clay-HPW	Phosphotungstic acid supported on montmorillonite K-10 clay
LA	Levulinic acid
MCM	Mesoporous molecular sieves
MCM-41-HPW	Phosphotungstic acid supported on mesoporous molecular sieves
MCS	Mesostructured cellular foam
MDGs	Millennium Development Goals
ML	Methyl levulinate
MMF	5-(methoxymethyl)furfural
MRP	Material recovery parameter
MS	Mass spectroscopy
MW	Microwave
NHC	1,3-bis(2,6-diisopropylbenzyl)imidazolyldiene
NMP	N-methyl-2-pyrrolidone
OBMF	5,5'-(oxy-bis(methylene))-2-furfural
ON	Octane number
PCP	Porous coordination polymer
PCP(Cr)-BA	Porous coordination polymer with Cr ³⁺ ions and H ₂ BDC-SO ₃ H linkers
PDVTA-SO ₃ H	Organic porous co-polymer of Divinylbenzene and Thioacetic acid functionalized with sulfonic acid
PEEK	Polyether ether ketone
PEF	Polyethylene Furanoate
PET	Polyethylene Terephthalate
PMF	5-(propylmethyl)furfural
PMI	Process mass intensity
[PPFPy][HSO ₄]	Polypropylene fiber supported 3-sulfopropylpyridinium hydrogensulfate
PTSA (or <i>p</i> -TSA)	<i>p</i> -toluensulfonic acid
RGO	Reduced graphene oxide
RME	Reaction mass efficiency
s-CB	Amorphous carbon black functionalized with sulfuric acid
s-CNT	Carbon nanotubes functionalized with sulfuric acid
SDGs	Sustainable Development Goals
SF	Stoichiometric factor
s-RGO	Reduced graphene oxide functionalized with sulfuric acid
STA	Silicotungstic acid
TaTPA/SnO ₂	Tantalum-exchanged Tungstophosphoric acid supported on SnO ₂
TBME	Tert-butyl methyl ether
TEAB	Tetraethylammonium bromide
TEAC	Tetraethylammonium chloride
THF	Tetrahydrofuran
TPA	Tungstophosphoric acid
UN	United Nations
UNCCC	United Nations Climate Change Conference
UNEP	United Nations Environmental Programme
UNFCCC	United Nations Framework Convention on Climate Change

1. INTRODUCTION

1.1. Climate change: origins and international actions

The fragility of our fossil-based industrial society has manifested itself dramatically in these years as drought, ocean acidification, epidemics. All these events belong to the well-known phenomenon of climate change, whose roots grow from the intense exploitation of non-renewable resources such as oil, coal and natural gas.¹ Since the 18th century, when the industrial revolution started in Great Britain and then spread in Europe in the 19th century,² fossil resources played a fundamental role in the development of new technologies. The steam train, the internal-combustion engine, the telegraph are just few examples of technologies that opened new possibilities and alternatives; travelling was faster, easier and cheaper, industries were able to increase production and facilities were more accessible.² This newly discovered source of energy gave a boost to the people lifestyle, but it also led to several drastic effects on the environment. The increase of greenhouse gases (GHGs) emissions in the atmosphere, such as carbon dioxide (CO₂), methane (CH₄) and nitrous oxide (N₂O) is just one example.³

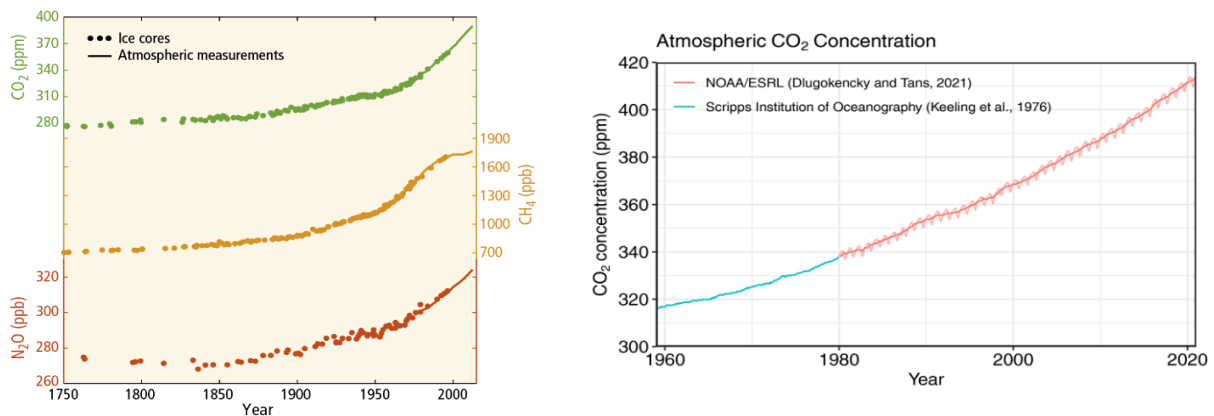


Figure 1.1. (Left) Atmospheric concentration trend of important greenhouse gases; (Right) CO₂ atmospheric concentration from 1960 to nowadays.

In Fig. 1.1 (left) is reported the atmospheric concentration of CO₂, CH₄ and N₂O over the last 200 years. The first evident increase in their trends started in the 19th century, and it was predominantly caused by anthropic activities. Since then, the increasing trend has never stopped, and it still persists in recent years (Fig. 1.1 (right)). The huge and rapid consumption of non-renewable resources has caused, and is still causing, several other problems: environmental pollution is affecting air, ground and water, jeopardizing animals and plants

¹ (a) [greenhouse effect | Definition, Diagram, Causes, & Facts | Britannica](#) ; (b) [Climate Change | United Nations](#)

² [Industrial Revolution | Definition, History, Dates, Summary, & Facts | Britannica](#)

³ [Climate Change Indicators: Atmospheric Concentrations of Greenhouse Gases | US EPA](#)

health.⁴ Moreover, the need to find alternative solutions to fossil sources is becoming more and more pressing since scientists have estimated that, with this rate of consumption, petroleum will last for less than 50 years.⁵ To overcome these problems, several international actions have been taken in the past 30 years (Fig. 1.2). In 1987 the Montreal Protocol imposed to all the countries that ratified the treaty to stop producing substances that were damaging the ozone layer, *i.e.*, chlorofluorocarbons (CFCs).⁶ In 1992 the United Nations Framework Convention on Climate Change (UNFCCC), held in Rio, pointed out the need to stabilize the GHGs emission in the atmosphere, and adopted the Agenda 21, an international plan with goals and measures to reach a sustainable development in a faster way.⁷ However, no quantitative threshold was given to limit GHGs emissions.⁷ This lack of restrictions led to the Kyoto Protocol, adopted in 1997 and entered into force in 2005. For the first time a treaty stated that countries had to reduce emissions by an average of 5% below 1990 levels.⁷ Unfortunately, the major carbon emitters (China, India and United States) didn't adhere to the treaty.



Figure 1.2. Fundamental stages of international agreements and treaty.

In 2000, at UN Headquarters in New York, the Millennium Declaration was adopted and signed by the Member States. In the same occasion, the Millennium Development Goals (MDGs) were elaborated to reduce poverty by 2015.⁷ In 2012, the United Nations Conference on Sustainable Development held in Rio decided to “update” the MDGs by starting the negotiates on the Sustainable Development Goals (SDGs). This culminated in September 2015 with the approval of the 2030 Agenda for the Sustainable Development: a list of 17 targets that comprise equality, sustainable energy, health, peace, actions to combat climate change and so on (Fig. 1.3).⁸ The SDGs underline that climate change impacts not only environmental pollution and global warming, but also water and food resources, human and animal health, poverty, education and many other fields.



Figure 1.3. The 17 Sustainable Development Goals (SDGs).

⁴ UNEP Annual Report 2021.

⁵ [World Oil Statistics - Worldometer \(worldometers.info\)](https://www.worldometers.info/world-oil-statistics/)

⁶ [About Montreal Protocol \(unep.org\)](https://www.unep.org/about-montreal-protocol)

⁷ [THE 17 GOALS | Sustainable Development \(un.org\)](https://www.un.org/sustainabledevelopment/the-17-goals/)

⁸ [Transforming our world: the 2030 Agenda for Sustainable Development | Department of Economic and Social Affairs \(un.org\)](https://www.un.org/sustainabledevelopment/transforming-our-world-the-2030-agenda-for-sustainable-development/)

In 2015 there was another fundamental key step for the regulation of emissions: the Paris Agreement. A milestone in global climate agreement, stated that signing countries had to design national emission-reduction pledges with the aim to limit global warming to 2.0 °C, possibly 1.5 °C with respect to the pre-industrial period, for this century.⁹ More recently, the Glasgow UN Climate Change Conference (UNCCC, 2021) remarked the importance of following as fast as possible the 17 SDGs and set other goals to tackle climate crisis, *i.e.* helping fragile realities to adapt to the changing world.¹⁰

International agreements and politics weren't the only areas to experience the rising wind of sustainability. Chemistry is still today associated by the society to environmental pollution and health risk, due to the well-known disasters happened over the last two centuries; Minamata Bay in 1945, Seveso in 1976, Bhopal in 1984 and the current problem of microplastics are only few recent examples.¹¹ The need to develop more sustainable processes and products started pushing chemists to find alternative solutions to the well-established old procedures that involved toxic and dangerous reagents or produced much waste. Guidelines to achieve this change were traced by the “12 Principles of Green Chemistry” (Fig. 1.4), proposed by Paul Anastas and John Warner: with them in 1998 Green Chemistry was officially born.¹²

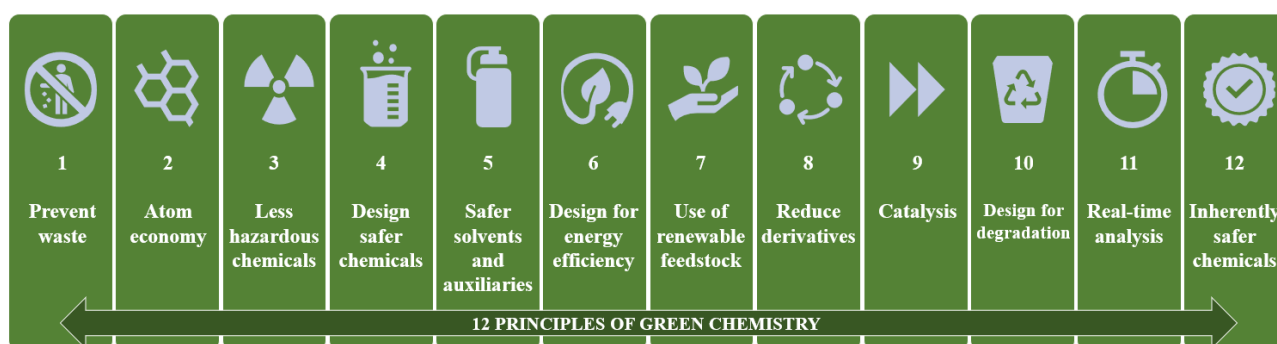


Figure 1.4. The twelve principles of Green Chemistry.

1.2. Renewables resources: refinery vs. biorefinery

As the International Energy Agency (IEA) reports,¹³ nowadays the biggest percentage of energy is produced from oil, coal and natural gas. Moreover, the products that use petroleum as feedstock are culpable of the major consumption of the total final energy.¹³ These data underline how much our society relies on the fossil-based energy and materials and how much effort is still required to switch from non-renewable resources to more sustainable ones in order to achieve the SDG 7: “Ensure access to affordable, reliable, sustainable and modern energy for all” and SDG 9 “Built resilient infrastructures, promote inclusive and sustainable industrialization

⁹ [The Paris Agreement | United Nations](#)

¹⁰ [COP26 Goals - UN Climate Change Conference \(COP26\) at the SEC – Glasgow 2021 \(ukcop26.org\)](#)

¹¹ (a) A. Kudo, S. Miyahara, *Water Sci. Technol.*, **1991**, 23, 283-290; (b) P. A. Bertazzi, *Sci. Total Environ.*, **1991**, 5-20; (c) Britannica, The Editors of Encyclopaedia. "Bhopal disaster". *Encyclopedia Britannica*, 30, **2021**; (d) Y. Loganathan, M. P. J. Kizhakedathil, *Biointerface Research in Applied Chemistry*, **2022**, 13(2), 126-144.

¹² P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, **1998**.

¹³ [Data & Statistics - IEA](#)

and foster innovation”.⁷ The awareness that non-renewables won’t last forever is pressing heavily on the urge to change from fossil to renewable alternative resources: not only as energy supplies, but also as new feedstocks to produce materials and goods. In this prospect, energy production can already count on several sustainable alternatives: solar power, wind, geothermic, hydroelectric:¹⁴ they are still a small percentage (less than 12%) in the energy final consumption, but the value is increasing year by year.

1.2.1. Petrorefinery versus Biorefinery

As above stated, if we consider the feedstocks used to produce most of our daily life goods, crude oil is the dominant starting material. Indeed, it’s the major source of aliphatic, aromatic and naphthenic hydrocarbons that can be chemically transformed in a wide array of materials, chemicals, fuels, energy, etc. through the well-known refinery process.¹⁵ This technology, started in the 19th century, is based on the fractional distillation and had plenty of time to evolve, develop and maximize yield, quality and variety of products (Fig. 1.5 (a)). From a single U.S. barrel of crude oil, usually 42 gallons (190 L), almost 50% of the product obtained is gasoline (Fig. 1.5 (b)).¹⁶

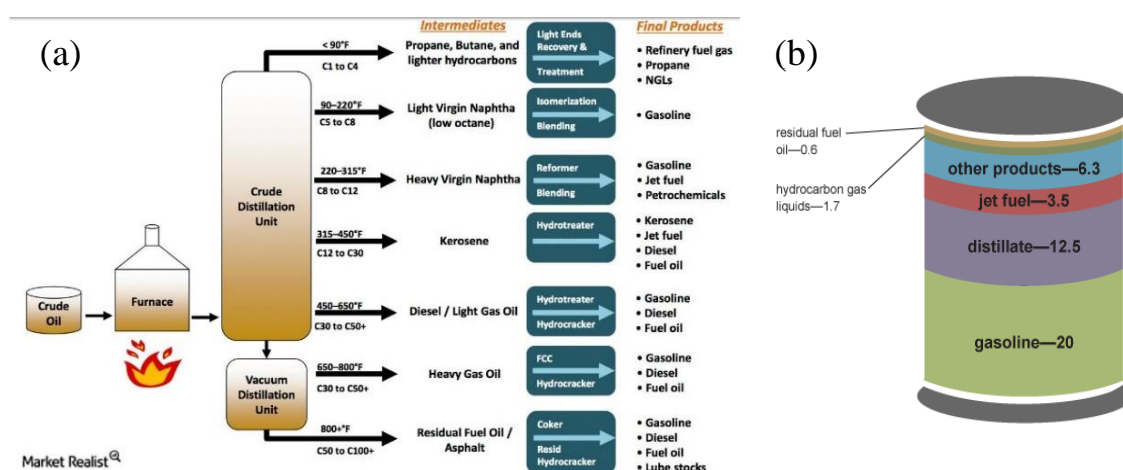


Figure 1.5. (a) Schematic representation of the refinery process starting from crude oil; (b) Gallons of different products obtained from crude oil, in 2021.

However, in recent years the urge to change starting material led to the development of another type of refinery, based on renewable resources: the biorefinery.¹⁷ This idea was born in 2007 from the International Energy Agency Bioenergy (IEAB), a branch of IEA, that set tasks and goals to support bioenergy development. In particular, task 42 defines biorefinery as “The sustainable synergetic processing of biomass into a spectrum of marketable food and feed ingredients, products (chemicals, materials) and energy (fuels, power, heat)”.¹⁷

¹⁴ N. L. Panwar, S. C. Kaushik, S. Kothari, *Renew. Sustainable Energy Rev.*, **2011**, 15(3), 1513-1524.

¹⁵ T. Olsen, *Chem. Eng. Prog.*, **2014**, 8, 16-22.

¹⁶ U.S Energy Information Administration, *Petroleum Supply Monthly*, Match **2022**, preliminary data.

¹⁷ IEA Bioenergy, *Task42 biorefining*, Wageningen, the Netherlands, August **2014**.

The biomass represents the starting material derived from renewable resources: trees, plants, agricultural and urban waste.¹⁸ The main difference between refinery and biorefinery is the type of feedstock rather than the final outcomes that in both cases are energy, materials and fuels. In fact, crude oil is an “homogeneous” starting material, thus its chemical composition is averagely constant; this implies that petrochemical industrial plants are comparable all over the world, and processes can be applied without virtually any changes in the production lines. Biomass, on the other hand, is an “heterogeneous” substrate, therefore different types of biomasses have distinct chemical composition and need different treatments. This is the major drawback as, around the world, biorefinery plants must adapt to the specific biomass available, and processes to achieve high-value products must be optimized for the individual starting substrate.¹⁷ As a consequence, biorefinery relies on chemical, biochemical, enzymatic, thermic, thermochemical and mechanical steps, while refinery is based only on chemical and thermochemical protocols.

Another issue that differentiates refinery from biorefinery is the variety of intermediate molecules that is possible to achieve. Petrochemical refinery can provide a wide range of molecules: from short-chain hydrocarbons to aromatics, whose intermediates can be further converted into fuels, polymers and chemicals.¹⁵ Biorefinery at the moment relies on a limited number of compounds, the so-called “Top 10 Bio-Based Platform Chemicals”. These molecules have been identified in 2004 by the U. S. Department Of Energy (DOE) as the “*substrate for the production of various higher value-added products obtained from the biomass*” both via chemical or biochemical conversion (Fig 1.6).¹⁹ In 2010 the list was updated following different criteria with respect to 2004: indeed, the list of platform chemicals is steadily evolving and increasing over time.¹⁹

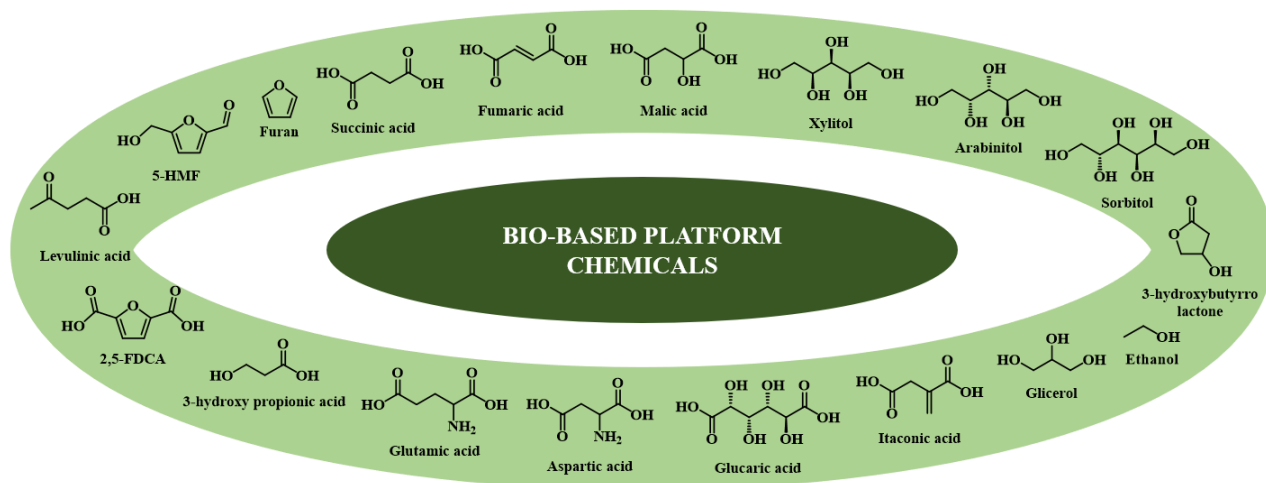


Figure 1.6. The “Bio-Based Platform Chemicals” from the U.S. Department Of Energy.

It should be pointed out that Biorefinery has the advantage of follows a circular economy model. In fact, while petrochemical refinery relies on linear economy, the “take-make-dispose” model, biorefinery is based on the

¹⁸ [Biomass \(europa.eu\)](http://biomass.europa.eu)

¹⁹ (a) S. Takkellapati, T. Li, M. A. Gonzalez, *Clean Technol. Environ. Policy*, **2018**, 20(7), 1615-1630; (b) J. J. Bozell, G. R. Petersen, *Green. Chem.*, **2010**, 12, 539-554; (c) T. Werpy, G. Petersen, *Top Value Added Chemicals from Biomass: Volume 1 -- Results of Screening for Potential Candidates from Sugars and Synthesis Gas*. United States, **2004**.

“make-use-recycle” slogan; waste is considered a precious feedstock and processes are designed to maximize its exploitation and to a reduced production of waste.²⁰ As a conclusion, a general comparison between refinery and biorefinery is reported in Table 1.1.

Table 1.1. Comparison between petrochemical refinery and biorefinery.

Petrochemical refinery	Biorefinery
Homogeneous feedstock (crude oil, natural gas)	Heterogeneous feedstock (biomass)
Many products obtained (fuels, chemicals, polymers...)	Many products obtained (fuels, chemicals, polymers...)
One step to obtain many products (fractional distillation)	Many steps to obtain many products (physical, chemical and biological treatments)
Standard, well-defined processes	New, developing processes
Many intermediates	Few intermediates (Bio-Based Platform Chemicals)
Linear economy	Circular economy

1.3. HMF and derivatives

1.3.1. 5-Hydroxymethylfurfural (HMF)

Among the Bio-Based Platform Chemicals, 5-hydroxymethylfurfural (HMF) is a promising biorefinery building block.²¹ It can be produced from renewable biomolecules such as hexose sugars, sucrose and inulin with chemical and/or biochemical processes. The starting sugars can be in turn obtained from cellulose and hemicellulose, fundamental components of biomass.²²

There are several processes that, starting from sugars, lead to HMF:²¹

1. Thermal and acid catalysis of sucrose and inulin;
2. Acid catalysed dehydration of hexoses;
3. Maillard reaction (with amino acids and reducing sugars as precursors).

Among the potential substrates, glucose is the cheapest as it can be easily obtained from (poly)carbohydrates such as maltose, sucrose, cellulose and starch.²³ The synthesis of HMF generally requires two steps: first the isomerization to fructose, which was demonstrated to be better catalysed by a base or a Lewis acid,²³ then a triple dehydration reaction to obtain the targeted molecule, which is mostly favoured by a Brønsted acid (Scheme 1.1).²³ The isomerization step is necessary because the hemiacetalic cyclic form of glucose is a six-

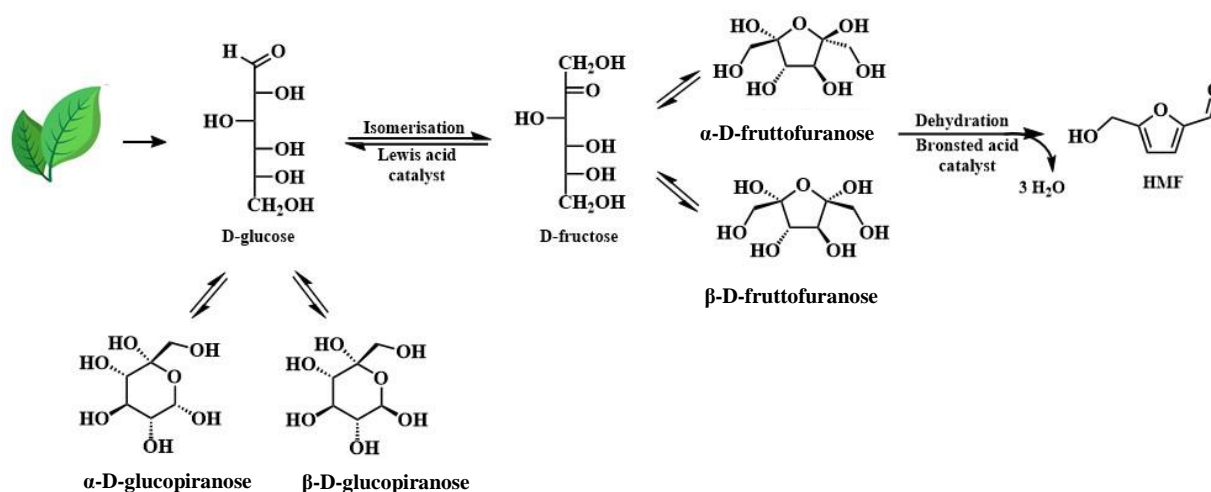
²⁰ (a) F. Sariatli, *Visegrad Journal on Bioeconomy and Sustainable Development*, **2017**, 6(1), 31-34; (b) Ellen MacArthur Foundation, Universal Circular Economy Policy Goals, **2021**.

²¹ (a) T. Klausli, *Green Process Synth.*, **2014**, 3, 235-236; (b) F. Menegazzo, E. Ghedini, M. Signoretto, *Molecules*, **2018**, 23, 2201; (c) K. Saikia, A. K. Rathankumar, P. S. Kumar, S. Varjani, M. Nizar, R. Lenin, J. George, V. K. Vaidyanathan, *J. Chem. Technol. Biotechnol.*, **2022**, 97(2), 409-419.

²² A. A. Houfani, N. Anders, A. C. Spiess, P. Baldrian, S. Benallaoua, *Biomass Bioenergy*, **2022**, 134, 105081.

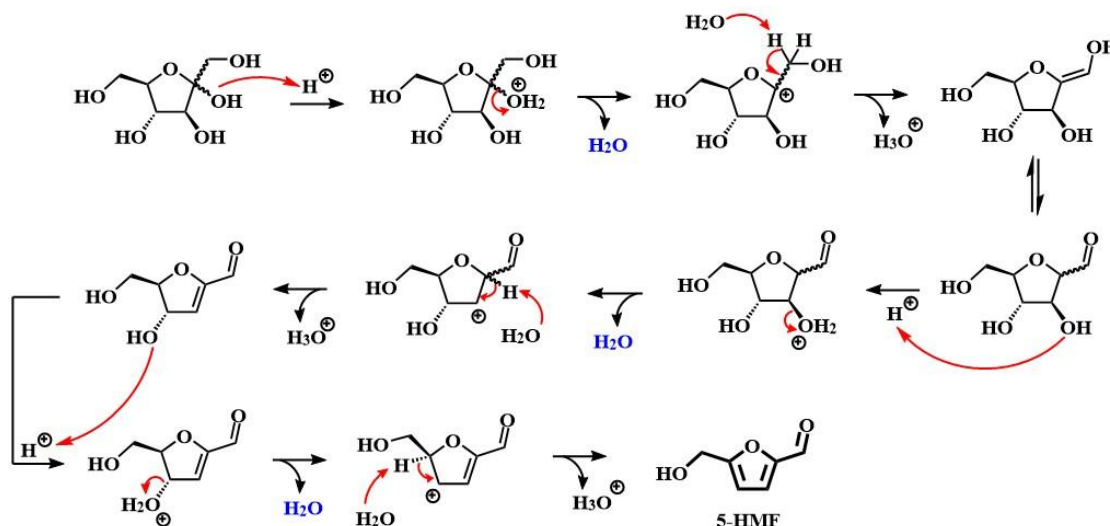
²³ B. Agarwal, K. Kailasam, R. S. Sangwan, S. Elumalai, *Renew. Sustainable Energy Rev.*, **2018**, 82(3), 2408-2425.

member ring, which would not lead by dehydration to HMF which is a 5-member ring. Overall, this two-steps path is characterised by numerous side reactions ultimately reducing the selectivity/yield towards HMF (averagely, 50-60% compared to 70-80% starting from D-fructose).²⁴



Scheme 1.1. Synthesis of HMF from D-glucose.

As a result glucose is generally a less favoured substrate for HMF respect D-fructose, which is more expensive but guarantees higher yields.²³ Indeed, the latter was demonstrated to undergo a faster acidic triple dehydration, compared to glucose, according to the mechanism reported in Scheme 1.2.²⁴



Scheme 1.2. Mechanism of the acid catalysed triple dehydration of fructose for the synthesis of HMF.

Chemists have studied and tested a wide array of heterogeneous and homogeneous acidic catalysts for the dehydration reaction of fructose (Tab. 1.2). Some of them are well-known, common catalysts: for instance, the transformation of D-fructose into HMF was performed by M. Ohara and co-workers with Amberlyst-15 – a commercial ionic exchange resin – in dimethylformamide for 3 hours at 100 °C; the final HMF yield achieved

²⁴ A. A. Rosatella, S. P. Simeonov, R. F. M. Frade, C. A. M. Afonso, *Green Chem.*, **2011**, 13, 754-793.

was 90%.²⁵ Other commonly used solid catalysts are zeolites (*i.e.*, H-Beta²⁶ and H-Y²⁷), oxides (*i.e.*, Nb₂O₃,²⁸ TiO₂,²⁹ ZrO₂³⁰), and heteropolyacids (*i.e.*, H₃PW₁₂O₄₀,³¹ CePW₁₂O₄₀,³² Ag₄[Si(W₃O₁₀)₄]•H₂O³³). Less frequent catalysts are functionalised silica (*i.e.*, SBA-15³⁴ and silica-supported boric acid³⁵) and carbon-based compounds (*i.e.*, phosphorylated carbon³⁶ and sulfonated carbon³⁷).

Homogeneous catalysts are less employed; many research groups have used HCl in a variety of different conditions. For instance, Y. Roman-Leshkov *et al.* worked on the triple dehydration of D-fructose into HMF catalysed by HCl in *n*-butanol at 150 °C for 35 minutes (69% conversion), in a mixture of aqueous KCl and *n*-butanol at 180 °C for 15 minutes (80% conversion), in THF at 150 °C for 35 minutes (71% conversion) and in many other conditions.³⁸ Other frequent catalysts are *p*-toluensulfonic acid,³⁹ H₂SO₄,⁴⁰ and H₃PO₄.⁴¹

As for the catalysts, a huge variety of solvents have been also utilized. However, reactions are preferably performed in ionic liquids instead of classic organic solvents such as propanol and butanol. In fact, many research groups developed procedures based on alkylmethylimidazolium chloride (*i.e.*, [BMIM][Cl]⁴² and [EMIM][Cl]⁴³) and on quaternary ammonium salts, such as tetraethylammonium bromide (TEAB).⁴⁴ Other common examples are reactions performed in water: for instance, F. Benvenuti and co-workers have developed a synthesis of HMF in presence of α -titanium phosphate,⁴⁵ while P. Vinke *et al.* worked with an ion-exchange resin catalyst at 90 °C for 48 hours.⁴⁶ Some articles focused also on the synthesis in dimethyl sulfoxide (DMSO).⁴⁷ Nevertheless, reactions conducted in a water- and alcohol-based solvent have lower yield. This result was ascribed to the tendency of HMF to hydrolyse to levulinic acid (LA) by a ring-opening rehydration and to undergo alcoholysis to form 5-(alcoymethyl)furfurals (AMFs) in an acidic environment (Scheme 1.3).⁴⁸

²⁵ M. Ohara, A. Takagaki, S. Nishimura, K. Ebitani, *Appl. Catal. A: Gen.*, **2010**, 383(1-2), 149-155.

²⁶ V. V. Ordonsky, J. Van Der Schaaf, J. C. Schouten, T. A. Nijhuis, *J. Catal.* **2012**, 287, 66-75.

²⁷ Y. Shi, X. Li, J. Hu, J. Lu, Y. Ma, Y. Zhang, Y. Tang, *J. Mater. Chem.*, **2011**, 21, 16223-16230.

²⁸ M. Marzo, *Chim Oggi-Chem Today*, **2012**, 30, 22-24.

²⁹ C. V. McNeff, D. T. Nowlan, L. C. McNeff, B. Yan, R. L. Fedie, *Appl. Catal. A: Gen.*, **2012**, 384, 65-69.

³⁰ X. Qi, M. Watanabe, T. M. Aida, R. L. Smith Jr., *Catal. Commun.*, **2008**, 9, 2244-2249.

³¹ Y. Zhang, V. Degirmenci, C. Li, E. J. M. Hensen, *ChemSusChem*, **2011**, 4, 59-64.

³² Y. Song, X. Wang, Y. Qu, C. Huangx, Y. Li, B. Chen, *Catalysts*, **2016**, 6(4), 49.

³³ A. H. Jadhav, H. Kim, T. Hwang, *Bioresour. Technol.*, **2013**, 132, 342-350.

³⁴ A. J. Crisci, M. H. Tucker, J. A. Dumesic, S. L. Scott, *Top. Catal.*, **2012**, 53, 1185-1192.

³⁵ M. Walia, U. Sharma, V. K. Agnihotri, B. Singh, *RSC Adv.*, **2014**, 4, 14414-14418.

³⁶ A. Villa, M. Schiavoni, P. F. Fulvio, S. M. Mahurin, S. Dai, R. T. Mayes, G. M. Veith, L. Prati, *J. Energy Chem.*, **2013**, 22, 305-311.

³⁷ J. Wang, J. Ren, X. Liu, G. Lu, Y. Wang, *AIChE J.*, **2013**, 59(7), 2558-2566.

³⁸ Y. Romàn-Leshkov, J. A. Dumesic, *Top. Catal.*, **2009**, 52, 297-303.

³⁹ H. E. Vandam, A. P. G. Kieboom, H. van Bekkum, *Starch/Staerke*, **1986**, 38(3), 95-101.

⁴⁰ J. D. Chen, B. F. M. Kuster, K. Van Der Wiele, *Biomass Bioenergy*, **1991**, 1, 217-223.

⁴¹ F. S. Asghari, H. Yoshida, *Ind. Eng. Chem.* **2006**, 45, 2163-2173.

⁴² (a) G. Yong, Y. Zhang, J. Y. Ying, *Angew. Chem., Int. Ed.*, **2008**, 47(48), 9345-9348; (b) X. H. Qi, M. Watanabe, T. M. Aida, R. L. Smith Jr, *Green Chem.*, **2009**, 11, 1327-1331.

⁴³ (a) J. Y. G. Chan, Y. Zhang, *ChemSusChem*, **2009**, 2, 731-734; (b) H. B. Zhao, J. E. Holladay, H. Brown, Z. C. Zhang, *Science*, **2007**, 316(5831), 1597-1600.

⁴⁴ S. P. Simeonov, C. A. M. Afonso, *J. Chem. Educ.*, **2013**, 90(10), 1373-1375.

⁴⁵ F. Benvenuti, C. Carlini, P. Patrono, A. M. Raspolli Galletti, G. Sbrana, M. A. Massucci, P. Galli, *Appl. Catal. A: Gen.*, **2000**, 193(1-2), 147-153.

⁴⁶ P. Vinke, H. Van Bekkum, *Starch/Staerke*, **1992**, 44, 90-96.

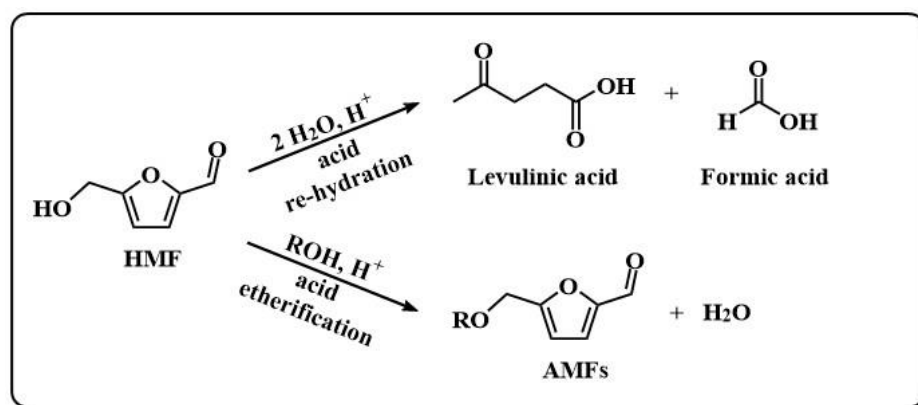
⁴⁷ (a) G. A. Halliday, R. J. Young, V. V. Grushin, *Org. Lett.*, **2003**, 5, 2003-2005; (b) R. M. Musau, R. M. Munavu, *Biomass*, **1987**, 13, 67-74.

⁴⁸ B. F. M. Kuster, *Starch-Stärke*, **1990**, 42(8), 314-321.

Table 1.2. Examples of synthetic procedures to HMF with heterogeneous and homogeneous catalysts.

	Catalyst	Solvent system	Time (h)	Temp (°C)	HMF yield %	Ref
Heterogeneous	Amberlyst-15	DMF	1	100	90	25
	H-Beta zeolite	Water-MIBK	5	165	45	26
	H-Y zeolite	DMSO	2	120	76	27
	Nb ₂ O ₃	Water	/	100	7	28
	TiO ₂ ,	Water	3 min	200	18	29
	ZrO ₂	Water	5 min	200	31	30
	H ₃ PW ₁₂ O ₄₀	[EMIM][Cl]	1	80	80	31
	CePW ₁₂ O ₄₀	<i>sec</i> -butanol	2	158	98	32
	Ag ₄ [Si(W ₃ O ₁₀) ₄]nH ₂ O	Superheated water	2	120	86	33
	SBA-15	Butanol	2	180	31	34
	Si ² O-supported boric acid	[BMIM][HSO ₄]	1.5	120	88	35
	Phosphorylated carbon	Water	8	120	43	36
	Sulfonated carbon	THF+DMSO	1	160	98	37
	Homogeneous		<i>n</i> -butanol	35 min	150	69 ^a
HCl		Sat.aq. KCl- <i>n</i> -butanol	15 min	180	80 ^a	
		THF	35 min	150	71 ^a	
PTSA		Water	3.3	88	20 ^a	39
H ₂ SO ₄		Ethylene glycol/dimethyl ether	3.3	200	70 ^a	40
H ₃ PO ₄		Subcritical H ₂ O	2 min	200	65 ^a	41

^a Value refers to HMF selectivity, not yield.



Scheme 1.3. HMF rehydration to LA and alcoholysis to AMFs.

This problem can be in part solved by a biphasic solvent system. The combination is usually a water-based phase, for the dissolution of the sugar, and an organic-based phase, for HMF extraction, such as water-methyl isobutyl ketone (MIBK)⁴⁹ or water-supercritical acetone (20 MPa at 180 °C),⁵⁰ but it can also involve ionic

⁴⁹ X. Qi, M. Watanabe, T. M. Aida, R. L. Smith Jr., *Ind. Eng. Chem. Res.*, **2008**, 47(23), 9234-9239.

⁵⁰ M. Bicker, J. Hirth, H. Vogel, *Green Chem.*, **2003**, 5, 280-284.

liquids (i.e., [BMIM][Cl]-acetone and [BMIM][BF₄]-DMSO)⁴⁷ or two organic phases, such as DMSO and acetone.⁴² Other synthesis report a quaternary ammonium salt, i.e., tetraethylammonium bromide⁵¹ or chloride⁵² (TEAC), as solvent for sugar solubilization in combination with dimethyl carbonate (DMC) or THF, respectively, as the extracting phase.

A critical step of the HMF synthesis is the purification/isolation: HMF intrinsic reactivity makes it harsh to purify from the reaction crude. Indeed, apart from Simeonov and co-workers,⁴⁴ all the reactions reported in Table 1.2 and most of the papers in literature focus on HMF synthesis, and its quantification is performed *via* gas or liquid chromatography, or some other analytical technique. In order to have a general idea on the state of the art for HMF synthesis and purification reported in literature, in Figure 1.7 are depicted all the articles published since 2007 - when the concept of biorefinery was developed – that isolate HMF via extraction, column chromatography and crystallization/precipitation (in green). Overall, they represent less than 10% of the total literature on HMF synthesis (in violet).

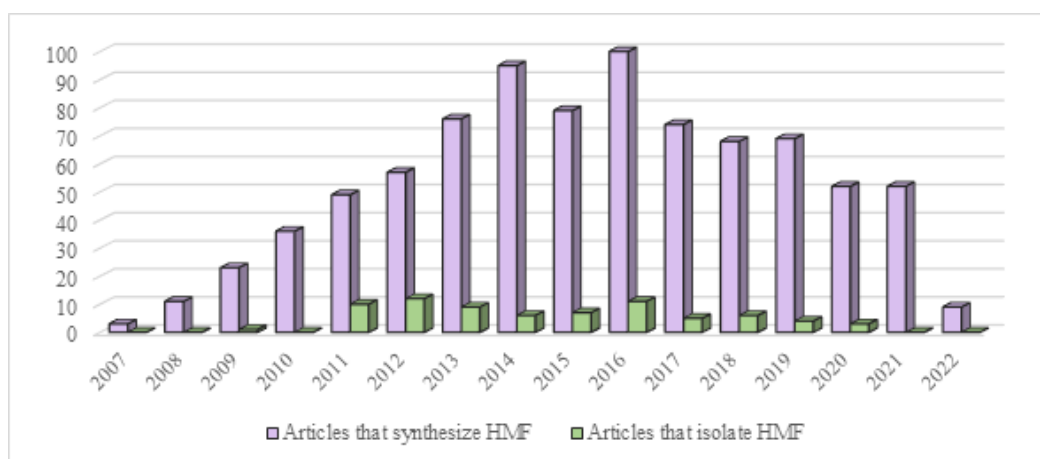


Figure 1.7. Number of published articles regarding synthesis (violet) and isolation (green) of HMF.

In Table 3.9 (Results and discussion chapter) are presented and discussed all the procedures that isolate HMF *via* different methodologies – to the best of my knowledge – starting from at least 0.5 g of D-fructose.

All the efforts made to synthesize HMF are connected to its high derivatization potential. Indeed, the aldehydic group, the hydroxyl group and the furan ring render this molecule very suitable to further chemical modifications and functionalizations such as (Fig. 1.8):

- **Oxidation:** selective oxidation of the aldehydic group leads to 5-(hydroxymethyl)furan-2-carboxylic acid (HMFCFA), while the oxidation of both aldehydic and hydroxyl groups produces 2,5-Furandicarboxylic acid (FDCA), a strategic biomonomer employed for the synthesis of Polyethylene Furanoate (PEF), identified as a green alternative to terephthalic acid and to Polyethylene Terephthalate (PET) as well as other polyesters;²¹

⁵¹ (a) G. Trapasso, G. Mazzi, B. Chicharo, M. Annatelli, D. Dalla Torre, F. Aricò, *Org. Process. Res. Dev.*, <https://pubs.acs.org/doi/10.1021/acs.oprd.2c00196>. (in press).

⁵² Q. Cao, X. Guo, J. Guan, X. Mu, D. Zhang, *Appl. Catal. A: Gen.*, **2011**, 403, 98-103.

- **Reduction:** reducing the HMF formyl group to a primary alcohol leads to 2,5-bis(hydroxymethyl)furan (BHMF). BHMF is a platform chemical used in polymers, fuel additives and solvents manufacturing.²¹ It can undergo etherification reaction with various alcohols to produce 2,5-bis(alcoxymethyl)furan (BAMFs) used as biodiesel additives;⁵³
- **Hydrogenation:** This reaction leads to 2,5-dimethylfuran (DMF), a precursor for biofuel production and a food additive;⁵⁴
- **Hydrolysis:** produces levulinic acid (LA), a platform chemical which can undergo esterification reaction to achieve a wide variety of alkyl levulinates, fuel additives candidates;⁵⁵
- **Etherification** with various alcohols (ethanol, isopropanol, t-butanol...) leads to the 5-alcoxymethyl furfural (AMFs) family, interesting biodiesel additives;⁵⁶
- **Self-etherification:** produces oxy-bis(methylene)bis-2-furfural (OBMF, or cirsumaldehyde), an emerging biomonomer. The two aldehydic functionalities can be further converted in other functional groups (alcohol, carboxylic acid, esters, etc..) leading to a wide range of biopolymers.⁵⁷

Indeed, HMF has applications in different sectors: bioplastics, automotive, chemicals, pharma and food and its derivatives include biopolymers, fuel additives, resins, coatings, paints, artificial fibres, surfactants and food additives.²¹

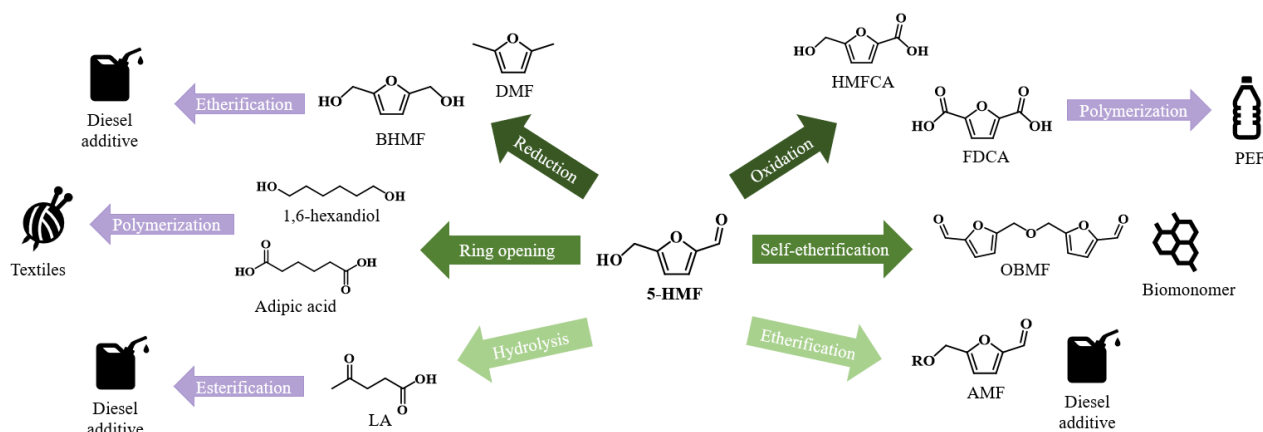


Figure 1.8. Some possible derivatives of 5-HMF.

However, some drawbacks to the great potentials of HMF owed to this molecule the name of “sleeping giant”. Among them we can list the low melting point (35 °C), the preferred solubility in water rather than organic solvents, the intrinsic reactivity and the already mentioned tendency to react with water to form levulinic acid: these issues make HMF hard to handle. For instance, in the triple dehydration of fructose, three molecules of water are formed for each target molecule: this opens HMF to a possible degradation pathway. Typical by-

⁵³ M. Musolino, M. J. Ginés-Molina, R. Moreno-Tost, F. Aricò, *ASC Sustain.*, **2019**, 7(12), 10221-10226.

⁵⁴ N. A. Endot, R. Junid, M. S. S. Jamil, *Molecules*, **2021**, 26(22), 6848.

⁵⁵ M. Annatelli, G. Trapasso, L. Lena, F. Aricò, *Sustain. Chem.*, **2021**, 2 (3), 493-505.

⁵⁶ S. Alipour, H. Omidvarborna, D. S. Kim, *Renew. Sustainable Energy Rev.*, **2017**, 71, 908-926.

⁵⁷ G. M. Averochkin, E. G. Gordeev, M. K. Skorobogatko, F. A. Kucherov, V. P. Ananikov, *ChemSusChem*, **2021**, 14, 3110-3123.

products of HMF synthesis are LA (through hydrolysis reaction), OBMF, (by self-etherification reaction) and humins: dark and complex polymeric structures caused by cross-polymerization.⁵⁸ Although humins are usually intended as a waste, some research groups have worked on their valorisation: for instance, M. El Fergani and co-workers have employed humins as a starting material to produce a carbonaceous graphite-like carbon catalyst,⁵⁹ while T. M. C. Hoang *et al.* did the steam reforming of this material to produce sustainable hydrogen.⁶⁰

The great potential of HMF is somehow limited also from its high cost: on Sigma-Merk website, prices vary from 29.00 € for 250 mg of 99% pure HMF⁶¹ to 104.00 € for 100 mg of analytical standard.⁶²

At the industrial level, currently, the Swiss company AVA Biochem is the main HMF producer and employs fructose as feedstock.²¹ In Table 1.3 are summarized the main physical and chemical HMF properties.

Table 1.3. *Some properties of HMF.*⁶³

Physical chemical properties of HMF	
Aspect	Yellow-white solid (to store in freezer). It is said to taste like caramel and to smell like chamomile flowers.
Melting Point (°C, 1 atm)	30-35 °C
Boiling Point (°C, 1 mmHg)	115 °C
Solubility	In many organic solvents and in water
GHS pictogram	Exclamation point. It can cause skin, respiratory and eye irritation.
LD50 (mg/Kg, rat)	2500
Note	It can be spontaneously found in food containing sugars and subjected to heat. ⁶⁴

1.3.2. 2,5-bis(hydroxymethyl)furan (BHMF)

Another promising bio-based platform chemical is 2,5-bis(hydroxymethyl)furan (BHMF), easily obtained by the reduction of HMF via several approaches (Tab. 1.4).⁶⁵ A common reducing reagent is H₂: Q. Cao and co-workers obtained BHMF (97% yield) using silica-supported copper (Cu/SiO₂) as catalyst, in pressure of H₂ (2.5 MPa),⁶⁶ while S. Fulignati *et al.* employed a Ru/C catalyst to reach a 93% yield.⁶⁷ Also Avantium industry

⁵⁸ (a) L. Filiciotto, A. M. Balu, A. A. Romero, C. Angelici, J. C. Van Der Waal, R. Luque, *Mol. Cat.*, **2019**, 479, 110564; (b) M. E. Zakrzewska, E. B. Lukasik, R. B. Lukasik, *Chem. Rev.*, **2011**, 111(2), 397-417.

⁵⁹ M. El Fergani, N. Candu, M. Tudorache, C. Bucur, N. Djelal, P. Granger, S. M. Coman, *Appl. Catal. A: Gen.*, **2021**, 618, 118130.

⁶⁰ T. M. C. Hoang, L. Lefferts, K. Seshan, *ChemSusChem*, **2013**, 6(9), 1651-1658.

⁶¹ [5-Hydroxymethyl-2-furaldehyde 99 67-47-0 \(sigmaaldrich.com\)](https://www.sigmaaldrich.com)

⁶² [5-\(Hydroxymethyl\)furfural analytical standard 67-47-0 \(sigmaaldrich.com\)](https://www.sigmaaldrich.com)

⁶³ National Center for Biotechnology Information. PubChem Compound Summary for CID 234332, 5-hydroxymethylfurfural, *PubChem*, **2022**.

⁶⁴ T. Husøy, M. Haugen, M. Murkovic, D. Jöbstl, L. H. Stølen, T. Bjellaas, C. Rønningborg, H. Glatt, J. Alexander, *Food Chem Toxicol*, **2008**, 46(12), 3697-3702.

⁶⁵ F. Aricò, *Pure Appl. Chem.*, **2021**, 93(5), 551-560.

⁶⁶ Q. Cao, W. Liang, J. Guan, L. Wang, Q. Qu, X. Zhang, X. Wang, X. Mu, *Appl. Catal. A: Gen.*, **2014**, 481, 49-53

⁶⁷ S. Fulignati, C. Antonietti, D. Licursi, M. Pieraccioni, E. Wilbers, H. J. Heers, A. M. Raspolli Galletti, *Appl. Catal. A: Gen.*, **2019**, 578, 122-133.

reported to use H₂ for the reduction of HMF into BHMF, in presence of a carbon-supported platinum catalyst (Pt/C) in ethanol (quantitative yield).⁶⁸ Although H₂ is an efficient reductive agent, many research groups exploited the efficiency of NaBH₄, indeed it was tested in a wide range of reaction conditions. F. A. Kucherov *et al.* reduced HMF to BHMF in water with a 99% yield of pure product,⁶⁹ R. S. Galaverna and co-workers performed the same reaction in methanol and obtained a 95% isolated yield,⁷⁰ while the research group of B. Saha used ethanol as reaction solvent and achieved a 90% yield.⁷¹ A particular application of NaBH₄ is in deep eutectic solvents (DES): T. Wang *et al.* obtained the platform molecule in a 80% yield employing a choline chloride-glycerol DES (ChCl-glycerol).⁷² It should be mentioned that these procedures are just few examples among the numerous BHMF syntheses reported in literature. Other less common methodologies include catalytic transfer hydrogenation (CTH), which was exploited by T. Wang *et al.* by using *i*-propanol as hydrogen source and Ru/Co₃O₄ as catalyst,⁷³ and biological reducing agents (*i.e.*, *E. coli* CCZU-K14 or *Meyerozyma guilliermondii* SC1103).⁷⁴

Table 1.4 Examples of synthetic procedures to produce BHMF using various reducing agents.

Catalyst	Reducing agent	Solvent system	Time (h)	Temp. (°C)	BHMF yield %	Ref.
Cu /SiO ₂	H ₂ (2.5 MPa)	Methanol	8	100	97 (isol.)	66
Ru/C	H ₂ (30 bar)	Water	4	50	93 (isol.)	67
Pt/C	H ₂ (5 bar)	Ethanol	48	r.t.	100 (isol.)	68
/	NaBH ₄	water	1	24	99 (isol.)	69
/		MeOH	4	0-25	95 (isol.)	70
/		EtOH	Over night	0-25	90 (isol.)	71
/		ChCl-glycerol	3	25	80 (isol)	72
Ru/Co ₃ O ₄	<i>i</i> -propanol	<i>i</i> -propanol	66	190	82 (isol)	73
/	<i>E. coli</i> CCZU-K14	Buffer	24	30	100 (HPLC)	74
/	<i>Meyerozyma guilliermondii</i> SC1103	Phosphate buffer	12	35	86 (HPLC)	75

To note that BHMF, compared to HMF, can be isolated more easily by extraction with ethyl acetate or recrystallization in methanol; indeed almost all the research groups reported the isolated yield. Moreover, it has a higher thermal stability, thus it can be easily handled.⁷⁶ In Table 1.5 are listed some of its properties.

⁶⁸ Avantium N. V., WO2009/30509, **2009**.

⁶⁹ F. A. Kucherov, K. I. Galkin, E. G. Gordeev, V. P. Ananikov, *Green Chem.*, **2017**, 19, 4858-4864.

⁷⁰ R. S. Galaverna, L. P. Fernandes, V. H. Mendez de Silva, A. de Siervo, J. C. Pastre, *Eur. J. Org. Chem.*, **2022**, 2022(24), e202200376.

⁷¹ B. Saha, C. M. Bohn, M. M. Abu-Omar, *ChemSusChem*, **2014**, 7(11), 3095-3101.

⁷² T. Wang, J. Wei, H. Liu, Y. Feng, X. Tang, X. Zeng, Y. Sun, T. Lei, L. Lin, *J. Ind. Eng. Chem.*, **2020**, 81(25), 93-98.

⁷³ T. Wang, J. Zhang, W. Xie, Y. Tang, D. Guo, Y. Ni, *Catalysis*, **2017**, 7(3), 92.

⁷⁴ Y. He, C. X. Jiang, G. G. Chong, J. H. Di, C. L. Ma, *Bioresour. Technol.*, **2018**, 247, 1215-1220.

⁷⁵ Y. Li, *ChemSusChem*, **2016**, 10(2), 372-378.

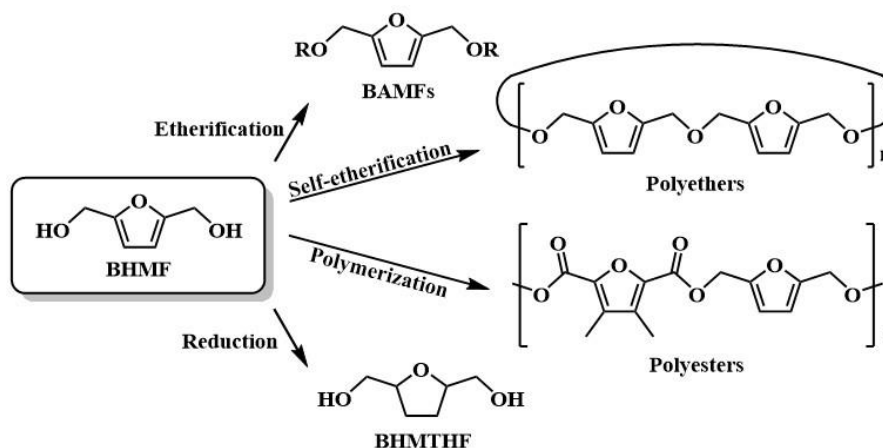
⁷⁶ X. Liu, D. C. Y. Leong, Y. Sun, *Green Chem.*, **2020**, 22, 6531-6539.

Table 1.5. Some properties of BHMf.⁷⁷

Physical chemical properties of BHMf	
Aspect	Yellow-white solid (to store in fridge, at +2-4 °C)
Melting Point (°C, 1 atm)	72-77
Boiling Point (°C, 1 atm)	275
Solubility	In many organic solvents and in water
GHS pictogram	Exclamation point. Harmful if swallowed, it can cause skin, respiratory and eye irritation.

The main reactions involving BHMf as starting material are (Scheme 1.4):

- **Etherification** with alcohols, as already mentioned, to obtain BAMFs;⁵³
- **Self-etherification**: to obtain polyethers (crown ethers);⁷⁸
- **Polymerization**: BHMf can be employed in copolymerization reactions, for instance with the biomonomer dimethyl-2,5-furandicarboxylic acid (DMFDCA) to produce polyesters;⁷⁹
- **Hydrogenation**: to achieve 2,5-bis(hydroxymethyl)tetrahydrofuran (BHMTHF): this compound can ultimately lead to 1,6-hexandiol, a precursor of Nylon 6,6 and other polyamides;⁷⁸



Scheme 1.4. Some of the main products from BHMf.

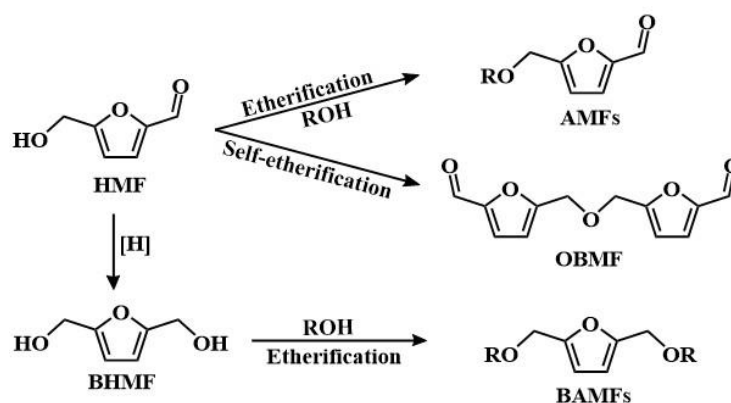
1.3.3. 5-Alcoxymethylfurfural (AMFs) and 2,5-Bis(alcoxymethyl)furan (BAMFs)

As mentioned above, HMF can undergo several etherification reactions to produce different by-products (Scheme 1.5); a similar behaviour is displayed by its reduced analogous, BHMf.

⁷⁷ National Center for Biotechnology Information. PubChem Compound Summary for CID 74663, 2,5-furandimethanol, *PubChem*, **2022**.

⁷⁸ J. Zhang, T. Wang, X. Tang, L. Peng, J. Wei, L. Lin, *BioRes.*, **2018**, 13(3), 7137-7154.

⁷⁹ D. Maniar, Y. Jiang, A. J. J. Woortman, J. van Dijken, K. Loos, *ChemSusChem*, **2019**, 12(5), 990-999.



Scheme 1.5. HMF and BHMf etherification reactions.

Specifically, 5-alkoxymethylfurfural (AMFs) and 2,5-bis(alkoxymethyl)furan (BAMFs) can be obtained by an acid-catalysed etherification of HMF and BHMf with primary, secondary and tertiary alcohols, *i.e.*, methanol, *i*-propanol, *t*-butanol etc. These molecules are promising diesel additives, used to increase the cetane number CN. The CN is a parameter employed to evaluate the performance of a diesel fuel. It is related to the content of linear molecules (*i.e.* n-hexadecane C₁₆H₃₄) in the diesel and it indicates how fast the fuel will combust. The higher the CN, the better the performance of the fuel. CN value ranges generally between 0 and 100;⁸⁰ fossil diesel has 40-55, a good alternative should have at least 50.⁸¹

The U.S. Energy Information Administration (EIA) defines biofuels as “*liquid fuels and blending components produced from biomass*”.⁸² Biofuels are a growing branch in the energy tree, as non-renewables feedstocks are running out. In particular, 5-ethylmethylfurfural (EMF) is a high boiling point liquid (235 °C) and an excellent additive for diesel due to its high CN, according to Avantium.⁸³ It has an energy density of 8.7 kWh/L, which is a great value if compared with the ones of gasoline (8.8 kWh/L) and diesel (9.7 kWh/L). The company tested an EMF-diesel blend in an engine and proved that there is a significant reduction in SO₂ and fine particulates emissions.⁸³ According to these results, other AMFs could perform as good additive candidates and for this reason several synthetic approaches to AMFs have been developed over the years.⁸⁴

Many different reaction conditions are reported in literature for the synthesis of EMF (Tab. 6.1, Appendix) via ethanolysis of HMF, which are mainly based on heterogeneous catalysis.⁵⁶ For instance, Balakrishnan *et al.* tested, for the HMF conversion into EMF, five different solid catalysts (Amberlyst-15, Amberlite IR 120, Dowex 50WX8, Dowex DR2030 and silica sulfuric acid) and two homogeneous catalysts (H₂SO₄ and PTSA) at 75 °C for 24 hours.⁸⁴ The resulting yields, that refer to the non-isolated compound, were higher for the homogeneous (75-81%) catalysts compared to the solid ones (33-57%). Lanzafame and co-workers found out that, among the eight heterogeneous catalysts investigated (HY-zeolite, SBA-15, ZrO₂-SBA-15, Sulfate-ZrO₂-SBA-15, Al-MCM-41 (25), Al-MCM-41 (50) and Al-MCM-41 (75)) the best-performing one at 140 °C was

⁸⁰ Edurete.org

⁸¹ R. Estevez, L. Aguado-Deblas, F. J. Lopez-Tenllado, C. Luna, J. Calero, A. A. Romero, F. M. Bautista, D. Luna, *Engines*, **2022**, 15(9), 3173.

⁸² [Biofuels explained - U.S. Energy Information Administration \(EIA\)](https://www.eia.gov/biofuels/)

⁸³ P. Imhof, A. S. Dias, E. De Jong, G. J. Gruter, *Furanics: versatile molecules for biofuels and bulk chemicals application*, Avantium Technologies BV.

⁸⁴ M. Balakrishnan, E. R. Sacia, A. T. Bell, *Green Chem.*, **2012**, 14, 1626-1634.

ZrO₂-SBA-15, leading to a 76% yield.⁸⁵ The best-performing reactions among all the procedures listed in Table 6.1 (Appendix), in term of EMF selectivity and yield, starting from at least 0.126 g (1.0 mmol) of HMF, are collected in the following Table 1.6.

Table 1.6. Best reaction conditions for the synthesis of EMF from HMF.

HMF (g)	Method	Solvent (mL)	Catalyst	Cat. amount	T (°C)	Time (h)	Yield %		Ref.
							EMF	EL	
0.126	B	EtOH 2.2	H ₂ SO ₄	5% mol	75	24	81	16	84
0.126	B	EtOH 5.0	AlCl ₃	10% mol	100	5	93	detected	86
0.126	A	EtOH 5.0	PDVTA-SO ₃ H	43 mg	110	0.5	88	n/a	87
0.126	Ace pressure tube	EtOH 5.0	(SO ₄ ²⁻ /Al ₁ Zr ₅ /KIT-6) S _{0.5} A ₁ Z ₅ -K	75 mg	120	2.5	90	n/a	88
0.126	Sealed tube	EtOH 2.5	Cs ₂ STA	30 mg	120	2.5	91	n/a	89
0.126	Sealed tube	EtOH 2.0	TPA/NbP	3.8% with respect to reaction mixture	120	1	89	n/a	90
0.126	B	EtOH 5.0	Glu-TsOH-Ti	50 mg	90	6	91 74 ^a	n/a	91
0.126	B	EtOH 5.0	Cellulose sulfuric acid	50 mg	100	10	84	n/a	92
0.126	B	EtOH 5.0	MCM-41-HPW	40% wt.	100	12	83	n/a	93
0.126	A	EtOH 5.0	K-10 clay-HPW	160 mg	100	10	91	n/a	94
0.126	B	EtOH 5.0	Silica-SO ₃ H	200 mg	100	10	84	n/a	95
0.126	B	EtOH 5.0	Fe ₃ O ₄ @SiO ₂ -HPW	150 mg	100	11	84	n/a	96
0.126	B	EtOH 5.0	Fe ₃ O ₄ @SiO ₂ -SO ₃ H	100 mg	100	10	89	n/a	97
0.126	A	EtOH 5.0	Fe ₃ O ₄ @C-SO ₃ H	100 mg	100	12	88	n/a	98
0.126	A	EtOH 5.0	Fe ₃ O ₄ @SiO ₂ -SH-Im-HSO ₄	150 mg	100	12	90	n/a	99
0.126	A	EtOH 5.0	Ag ₁ H ₂ PW	24.5 mg	100	10	89	n/a	100
0.126	B	EtOH 5.0	[BMIMSO ₃ H] ₃ PW ₁₂ O ₄₀	5% mol.	70	24	91 ^a	n/a	101
0.3	B	EtOH 6.0	[DMA] ⁺ [CH ₃ SO ₃] ⁻	10% wt.	120	2	84 ^a	n/a	102
0.315	A	EtOH 3.5	ZrO ₂ -SBA-15	-	140	5	76	23	85
0.378	B	EtOH 1.8	H ₄ SiW ₁₂ O ₄₀ /MCM-41	-	90	4	77	3	103

^a Isolation via column chromatography.

⁸⁵ P. Lanzafame, D. M. Temi, S. Perathoner, G. Centi, A. Macariom A. Aloise, G. Giordano, *Cat. Today*, **2011**, 175(1), 435-441.

⁸⁶ B. Liu, Z. Zhang, K. Huang, Z. Fang, *Fuel*, **2013**, 112, 625-631.

⁸⁷ Y. Xiang, S. Wen, Y. Tian, K. Zhao, D. Guo, F. Cheng, Q. Xu, X. Liu, D. Yin, *RSC Adv.*, **2021**, 11, 3585-3595.

⁸⁸ H. Hafizi, G. Walker, J. Iqbal, J. J. Leahy, M. N. Collins, *Mol. Cat.*, **2020**, 496, 111176.

⁸⁹ G. Raveendra, A. Rajasekhar, M. Srinivas, P. S. Sai Prasad, N. Lingaiah, *Appl. Catal. A: Gen.*, **2016**, 520, 105-113.

⁹⁰ P. Krishna Kumari, S. Srinivasa Rao, D. Padmakar, N. Pasha, N. Lingaiah, *Mol. Cat.*, **2018**, 448, 108-115.

⁹¹ D. Gupta, B. Saha, *Catal. Commun.*, **2018**, 110, 46-50.

⁹² B. Liu, Z. Zhang, K. Huang, *Cellulose*, **2013**, 20, 2081-2089.

⁹³ A. Liu, Z. Zhang, Z. Fang, B. Liu, K. Huang, *J. Ind. Eng. Chem.*, **2014**, 20, 1977-1984.

⁹⁴ A. Liu, B. Liu, Y. Wang, R. Ren, Z. Zhang, *Fuel*, **2014**, 117, 68-73.

⁹⁵ B. Liu, Z. Zhang, *RSC Adv.*, **2013**, 1, 12313-12319.

⁹⁶ S. Wang, Z. Zhang, B. Liu, J. Li, *Catal. Sci. Technol.*, **2013**, 3, 2104-2112.

⁹⁷ Z. Zhang, Y. Wang, Z. Fang, B. Liu, *ChemPlusChem*, **2014**, 79, 233-240.

⁹⁸ Z. Yuan, Z. Zhang, J. Zheng, J. Lin, *Fuel*, **2013**, 150, 263-242.

⁹⁹ S. Yin, J. Sun, B. Liu, Z. Zhang, *J. Mater. Chem. A*, **2015**, 3, 4992-4999.

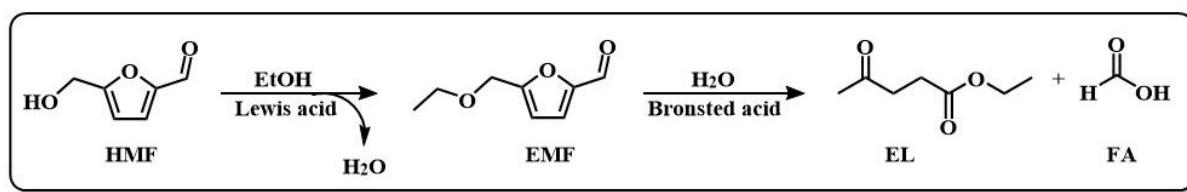
¹⁰⁰ Y. Ren, B. Liu, Z. Zheng, J. Lin, *J. Ind. Eng. Chem.*, **2015**, 21, 1127-1131

¹⁰¹ L. Bing, Z. Zhang, K. Deng, *Ind. Chem. Eng. Res.*, **2012**, 51, 15331-15336

¹⁰² M. I. Alam, S. De, S. Dutta, B. Saha, *RSC Adv.*, **2012**, 2, 6890-6896

¹⁰³ P. Che, F. Lu, J. Zhang, Y. Huang, X. Nie, J. Gao, J. Xu, *Bioresour. Technol.*, **2012**, 119, 433-436.

As can be seen, the method for obtaining EMF is based on autoclave (A), batch (B) or sealed tube conditions. Overall, the amount of starting HMF used is quite low, in fact it rarely exceeds one mmol. This is a huge limit in the spreading of EMF as additive fuel, since its production can't rely on larger reaction scales. Beside H_2SO_4 employed by Balakrishnan *et al.*,⁸⁴ acid catalysts employed in the etherification reactions are all heterogeneous. Among them, many are home-made compounds: for instance, Y. Xiang and co-workers developed a divinylbenzene-triallylamine co-polymer structure (PDVTA- SO_3H).⁸⁷ The research group of A. Liu synthesized a phosphotungstic acid supported on montmorillonite K-10 clay (K-10 clay-HPW),⁹⁴ while P. Che *et al.* produced a silicotungstic acid supported on a mesoporous material ($\text{H}_4\text{SiW}_{12}\text{O}_{40}/\text{MCM-41}$).¹⁰³ Although they can be recovered and reused several times, they generally require many steps and reagents to be prepared. Beside the variety of acidic catalysts employed and the wide range of time (0.5-24 h) and temperatures (75-140 °C) displayed by Table 1.6, yields are quite similar. In the reported procedures a frequent by-product is ethyl levulinate (EL). It has been suggested that strong Lewis acid sites promote EMF production, while Brønsted sites promote the ring-opening reaction leading to EL, which is also considered a good diesel fuel additive (Scheme 1.6).⁵⁶



Scheme 1.6. Re-hydration of EMF to EL.

Another important information that is evident from Tab 3.15 (Results and discussion chapter) is that almost none of the procedures isolate EMF. Its identification and quantification are reported mostly according to data collected by High Performance Liquid Chromatography (HPLC), or Gas Chromatography (GC) coupled with Mass Spectrometer (MS) and Inductively Coupled Plasma (ICP). This can be ascribed to the fact that EMF and EL are very difficult to separate.

Similarly, numerous works have been also reported on the etherification of BHMF to achieve BAMFs in acidic conditions, with heterogeneous and homogeneous catalysts.¹⁰⁴ Compared to AMFs, BAMFs have the advantage of not having the aldehydic group which is the major responsible of side-reactions and by-products formation. Moreover, the cetane numbers of these compounds is reported as higher as AMFs.¹⁰⁵

It must be highlighted that, even after a deep search in literature, it was not possible to find data on cetane numbers of AMFs and BAMFs blends with diesel fuels.

¹⁰⁴ (a) I. Elsayed, M. A. Jackson, E. Barbary Hassan, *Fuel Process. Technol.*, **2021**, 213, 106672; (b) J. Wei, T. Wang, X. Cao, H. Liu, X. Tang, Y. Sun, X. Zeng, Y. Lei, S. Liu, L. Lin, *Appl. Catal. B*, **2019**, 258, 117793; (c) J. Wei, X. Cao, T. Wang, H. Liu, X. Tang, X. Zeng, Y. Sun, T. Lei, S. Liu, L. Lin, *Catal., Sci., Technol.*, **2018**, 8, 4474-4484.

¹⁰⁵ J. Han, Y. H. Kim, B. Y. Jung, S. H. Hwang, J. Jegal, J. W. Kim, Y. S. Lee, *Synlett*, **2017**, 28(17), 2299-2302.

1.4. Tools for a green evaluation

Within the framework of Green Chemistry, over the last 30 years several quantitative and qualitative tools have been launched to better understand how much a certain reaction adheres to the 12 Principles of Green Chemistry. Examples are the Green Metrics: mathematical formulas developed to calculate different green aspects of a single reaction (Tab. 1.7).

- **Atom Economy:** (AE, #1; Table 1.7). Introduced by M. Trost in 1991,¹⁰⁶ it represents the ratio between the molecular weight of the target molecule and the sum of reagents molecular weight, expressed in percentage unit. The aim is to understand how many atoms constituting the reagents have been incorporated into the final product(s) structure; the ideal value is 100%. AE is a qualitative metric based on stoichiometric information of the reaction; it doesn't take into account yield, conversion and/or selectivity.
- **Environmental-factor** (E-factor, E-f or E-total, #2; Table 1.7). Theorized in the 1992 by R. A. Sheldon,¹⁰⁷ it is a quantitative evaluation of the waste produced by a reaction and it is calculated as the ratio between the kilograms of waste mass – intended as everything that is not the target molecule – on 1 kilogram of product. It was initially employed especially for pharmaceutical syntheses, but it became helpful for all industrial fields. In 2017 Sheldon published an update of his metric, due to the changings occurred in 25 years of Sustainable Chemistry.¹⁰⁸ For instance, in the first version water was not included as waste, although it was an important solvent in pharmaceutical industries, therefore it was added in the updated version of the metric. E-factor can be broken in several contributes, depending on the specific feature assessed; more information can be found in the Appendix.
- **Process Mass Intensity** (PMI, #3 Table 1.7).¹⁰⁹ It is a quantitative metric calculated as the ratio between the fraction of the total input mass that is not recovered and the mass of the product; the ideal value is 1. It must be mentioned that the amount of water used is excluded from the total input mass. If none of the materials used in the reaction is recovered, PMI is calculated as the E-factor plus 1 (intended as 1 Kg of product); otherwise, the PMI is inferior to the E-total.
- **Reaction Mass Efficiency** (RME, #4; Table 1.7) is a quantitative parameter, similar to the AE, used to assess how many kilograms of reagents end up in the product.¹⁰⁹ It is calculated as the ratio between the mass of the product and the sum of the mass of all reagents, expressed in percentage unit; the ideal value is 100%. Compared to AE, RME includes intrinsically the yield.
- **Stoichiometric Factor** (SF, #5; Table 1.7),¹¹⁰ calculated as the ratio between the excess kilograms of reagents (with respect to the limiting reagent) and the stoichiometric mass of reagents, plus one. It evaluates how large is the excess of non-limiting reagents compared to the limiting one since it

¹⁰⁶ B. M. Trost, *Science*, **1991**, 254(5037), 1471-1477.

¹⁰⁷ R. A. Sheldon, *Chem. Ind.*, **1992**, 930-906.

¹⁰⁸ R. A. Sheldon, *Green Chem.*, **2017**, 19(1), 18-43.

¹⁰⁹ D. J. C. Constable, A. D. Curzons, V. L. Cunningham, *Green Chem.*, **2002**, 4, 521-527.

¹¹⁰ A. Albini, S. Protti, *Green Metrics, an Abridged Glossary. In: Paradigms in Green Chemistry and Technology. SpringerBriefs in Molecular Science*, **2016**, Springer.

includes the stoichiometric coefficients of the reagents and their masses, but it does not consider any information on the product(s). This metric is considered a semi-quantitative one.

- **Material Recovery Parameter (MRP, #6; Table 1.7)**, a more comprehensive measure that collects data from reaction, work-up and purification steps.¹¹⁰ The formula includes yield (referred as ϵ , which is the yield in the range 0-1 instead of 0-100%), AE, mass of catalyst (c), mass of reaction solvent (s), mass of work-up and purification materials (ω), mass of target product and the SF. It ranges from 0 to 1, where 1 corresponds to the recovery of all the materials employed.

Table 1.7. Some of the most used green metrics.

#	Metric	Formula
1	Atom Economy (AE)	$\frac{MW \text{ of product}}{\sum MW \text{ of reagents}} * 100$
2	Environmental-factor (E-factor, E-f or E-total)	$\frac{Kg \text{ of waste}}{Kg \text{ of product}}$
3	Process Mass Intensity (PMI)	$\frac{(total \text{ input mass (Kg)} - Kg \text{ recovered materials})}{Kg \text{ of product}}$
4	Reaction Mass Efficiency (RME)	$\frac{Kg \text{ of product}}{\sum Kg \text{ of reagents}} * 100$
5	Stoichiometric Factor (SF)	$\frac{Kg \text{ of excess reagents}}{\sum \text{stoichiometric mass of reagents}} + 1$
6	Material Recovery Parameter (MRP)	$\frac{1}{1 + \frac{\epsilon * AE * (c + s + \omega)}{SF * kg \text{ of product}}}$

These metrics however present some limitations:

1. Toxicity, time, temperature and costs are not considered in most of the Metrics;
2. The amount of water is usually not included in the calculations;
3. Since they are comparative metrics, at least two reactions are required to obtain meaningful results;
4. It is difficult to find a relation among the many metrics, since they evaluate different aspects.

A partial solution to the third and fourth limitations can be found in J. Andraos radial pentagon,¹¹¹ which is a cumulative assessment of five different parameters: AE, Yield (ϵ), RME, MRP and SF⁻¹. Indeed, the pentagon allows the comparison between the target reaction and an ideal one, which has all the parameters at their maximum values, giving an immediate visual impact on the reaction green performances. This allows to easily see where the procedure can be implemented or which among different processes is the most sustainable. An example is given in Figure 1.9.

¹¹¹ J. Andraos, M. Sayed, *J. Chem. Educ.*, **2007**, 84(6), 1004-1010.



Figure 1.9. Example of the J. Andraos radial pentagon.

A simpler alternative to compare synthesis is the EcoScale algorithm, a semi-quantitative tool developed in 2006 by K. V. Aken and co-workers. EcoScale assesses materials toxicity and hazards, costs, time, amount of reagents, products and waste, temperature, reaction set-up and work-up/purification steps.¹¹² Its usage is quite simple: the chemist is only required to fill reagents and products boxes, together with the experimental set-up. The algorithm works by subtracting points (penalties) from an initial score of 100. The more the reaction is time consuming, or works with high temperatures, or employs hazardous materials, the more the algorithm will subtract points. At the end of the calculations, a final score is given; the higher the number (up to 100), the greener the reaction. In Figure 6.1 (Appendix) is shown the EcoScale calculator window. However, it must be pointed out that EcoScale recognizes substances through their CAS number, thus some reagents and/or custom-made catalysts cannot be included in the evaluation. In addition, recyclability of catalyst and/or solvents are not taken into account by the algorithm.

1.5. Unconventional heating technologies

1.5.1. Microwave

Many chemical reactions require heat to occur. The traditional way implies heat to pass from the outside to the inside, through the solution container, and some time is required before the reagents are heated up (Fig. 1.10 (a)). Due to the impellent necessity to maximise energy efficiency, as stated by the 6th Principle of Green Chemistry, unconventional energy sources could represent promising alternatives to conventional heating systems. An example is the use of microwave irradiation (MW).

¹¹² (a) K. V. Aken, L. Strekowski, L. Patiny, *Beilstein J. Org. Chem.* **2006**, 2, 3; (b) The EcoScale website (<http://ecoscale.cheminfo.org/calculator>), access date: October 2022.

MWs are able to heat the solution from the inside to the outside: this cuts reaction times, enhances selectivity, saves energy and reduces side reactions (Fig. 1.10 (b)); thus, representing a good Green Chemistry ally.

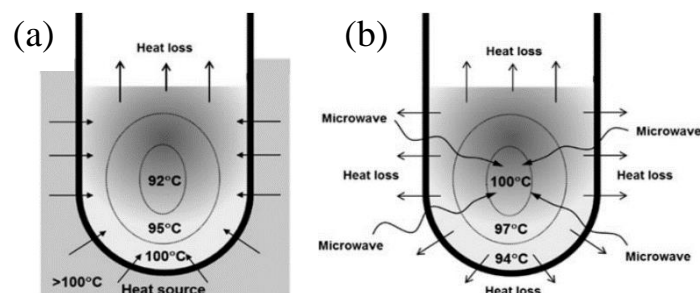


Figure 1.10. Conventional versus microwave heating.

Microwave (also called centimetre wave) radiations have a low energy content and their frequency ranges between 300 GHz and 300 MHz. Generally, both domestic and industrial MWs operate at a frequency of 2.45 GHz (corresponding wavelength of 12.24 cm) or 915 MHz (corresponding wavelength 32.8 cm).¹¹³

The process behind the efficient heating is called radiative heat transfer as it doesn't involve contact between objects; heat is instead transmitted through space by thermal radiation. Radiative energy is absorbed, reflected and partially transmitted through the object.¹¹³ Microwave heating, or dielectric heating, relies on the interaction between the electric component **E** of the electromagnetic wave and the electric dipole moment of the molecules in the solution. When **E** is applied, every dipole moment will try to align to the electric field, causing the rotation of the molecule.¹¹³ Since the field oscillates, molecules continuously change direction; this is the dipolar rotation. Rotating molecules collide and crash, thus energy is transferred to other molecules and heat is produced.¹¹³ The loss tangent ($\text{Tan } \delta$) determines the ability of a solvent or material to convert MW energy into heat: the higher the $\text{Tan } \delta$, the higher the MW absorbance. Organic solvents are usually classified in high ($\text{Tan } \delta > 0.5$), medium ($0.1 < \text{Tan } \delta < 0.5$) and low ($\text{Tan } \delta < 0.1$) microwave absorbing. Some of the commonly employed solvents as well as their $\text{Tan } \delta$ values are collected in Table 1.8.¹¹³

Table 1.8. Common organic solvents and their loss tangent δ values.

Solvent	Tan δ	Solvent	Tan δ	Solvent	Tan δ
Ethylene glicole	1.350	Acetic acid	0.174	Acetonitrile	0.062
Ethanol	0.941	DMF	0.161	Tetrahydrofuran	0.047
Dimethyl sulfoxide	0.825	1,2-dichloroethane	0.127	Dichloromethane	0.042
Methanol	0.659	Water	0.123	Toluene	0.040
1,2-dichlorobenzene	0.280	Chloroform	0.091	Hexane	0.020

¹¹³ (a) S. Horikoshi, R. F. Schiffmann, J. Fukushima, N. Serpone, *Microwave Chemical and Materials Processing*, Springer, **2018**; (b) M. B. Gawande, S. N. Shelke, R. Zboril, R. S. Varma, *Acc. Chem. Res.*, **2014**, 47(4), 1338-1348.

It's evident that only molecules with a permanent dielectric moment will react to microwave irradiation: thus, reactors are usually made by Teflon, quartz and polyether ether ketone (PEEK).¹¹³

Nevertheless, MW presents some issues: it can cause hotspots, if the solution is inhomogeneous (Fig. 1.11). It can also produce superheating: a metastable state of the solvent that, even if at higher temperature than the boiling point, shows no bubbling. But, if the solvent is disturbed, it can easily explode.

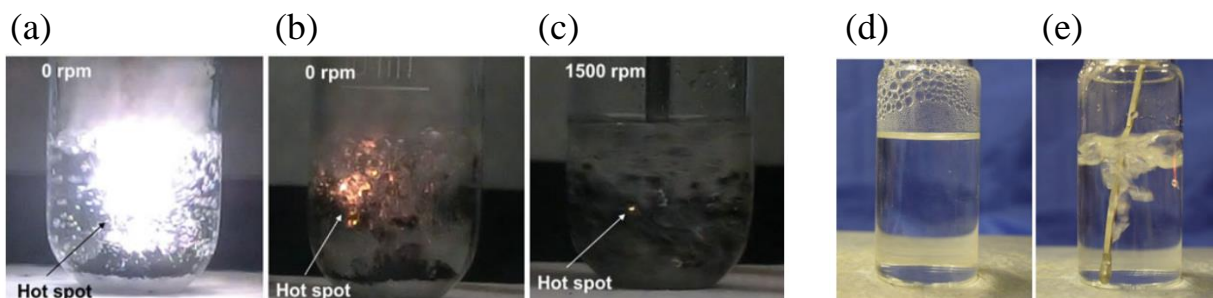


Figure 1.11. Example of hotspots in (a) and (b) non stirred solution and (c) stirred solution; example of superheating: (d) methanol under superheating conditions and (e) its eruption caused by a spatula.

Another issue is the penetration depth: the more energetic the microwave radiation, the deeper the penetration into the solution. But if the reactor is too large, the centre will be much hotter than the sides.¹¹³

The first MW machine was developed by the Raytheon Company and commercialized in 1952. The first reported MW application in organic synthesis is the aqueous emulsion polymerization of butyl acrylate, acrylic acid and methacrylic acid.¹¹⁴ Since then, many improvements have been made and numerous reactions were successfully tested: from Diels Alder reaction,¹¹⁵ to oxidation,¹¹⁶ reduction,¹¹⁷ alkylation,¹¹⁸ hydrolysis,¹¹⁹ halogenation,¹²⁰ polymerization,¹²¹ acid digestion,¹²² solvent free reactions,¹²³ and many others.¹²⁴

1.5.2. Sonicator

The energy needed to make molecules collide and thus react can come from many sources: high-frequency (> 20 kHz) sound waves, which manifest themselves as vibrations, are an unconventional heating system utilized by the sonicator.¹²⁵ There are two types of sonicating systems (Fig. 1.12):¹²⁶ the bath type, where ultrasound waves are delivered to the reagents through water, and the probe type, which is sharp metallic object that is inserted into the desired mixture, and ultrasound waves are delivered directly to the reagents.¹²⁷ Compared to

¹¹⁴ M. A. Surati, S. Jauhari, K. R. Desai, *Arch. Appl. Sci. Res.*, **2012**, 4(1), 645-661.

¹¹⁵ J. A. Mavoral, C. Cativiela, J. I. Garcia, E. Pires, A. J. Roivo, F. Figueras, *Appl. Catal. A*, **1995**, 131, 159-166.

¹¹⁶ A. R. Kiasat, F. Kazemi, M. Rafati, *Synth. Commun.*, **2003**, 33(4), 601-605.

¹¹⁷ T. N. Danks, *Microwave-assisted reductions*. In: J. P. Tierney and P. Lindstrom, Eds., *Microwave Assisted Organic Synthesis*, **2005**, Blackwell Publishing Ltd., Oxford.

¹¹⁸ R. A. Abramovitch, Q. Shi, D. Bogdal, *Synth. Commun.*, **1995**, 25(1), 1-8.

¹¹⁹ T. E. Nielsen, *Angew. Chem. Int. Ed.*, **2007**, 47, 48-56.

¹²⁰ T. Jnagaki, *Synthesis*, **2003**, 8, 1157-1159.

¹²¹ Z. T. Vu, *J. Polym. Sci., Part A: Polym Chem.*, **2003**, 41, 13-21.

¹²² B. L. Hayes, *Aldrichimica Acta*, **2004**, 37(2), 66-77.

¹²³ A. Laurent, P. Jacquault, J. L. Di Martino, J. Hamelin, *J. Chem. Soc., Chem. Commun.*, **1995**, 11, 1101.

¹²⁴ K. K. Rana, S. Rana, *Open Access Library Journal*, **2014**, 1, e686.

¹²⁵ [Sonicators: How these agitating lab instruments work \(laboratory-equipment.com\)](http://laboratory-equipment.com)

¹²⁶ J. H. Warner, F. Schaffel, A. Bachmatiuk, M. H. Rummeli, *Graphene: fundamentals and emergent applications*, Elsevier, Waltham (USA), **2013**.

¹²⁷ J. Ampofo, M. Ngadi, *Ultrason. Sonochem.*, **2022**, 84, 105955.

the bath sonicator method, the probe sonication can provide more acoustic power, a more uniform distribution of sound waves and a major reproducibility.¹²⁸ However, the bath sonicator allows the use of closed vials, while the most common probe sonicator forces to use open systems.

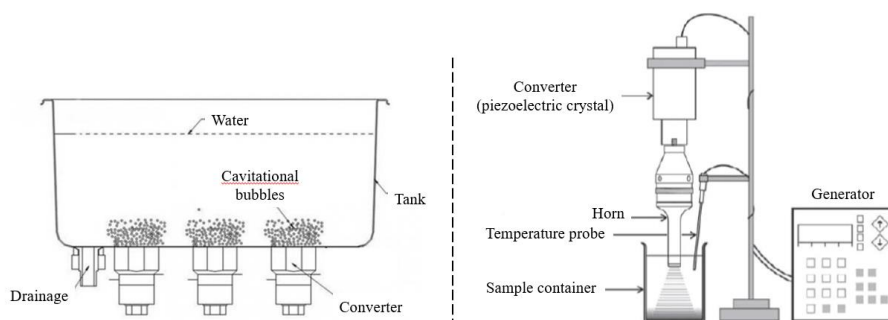


Figure 1.12. Water bath sonicator and probe sonicator.

The phenomenon behind the sonicator systems is cavitation: particles, as sound waves pass through them, experience continuous cycles of high (compression) and low (rarefaction) pressure. During the low-pressure moment, microscopic air bubbles are formed in the solution; during the high-pressure stage, bubbles are compressed; the subsequent rarefaction step allows bubbles to grow and the process repeats cyclically (Fig. 1.17). At a certain point, bubbles become too unstable because of their dimension, so they collapse during the high-pressure stage. The implosion of the bubble leads to extremely high local temperature (up to 5000 K) and pressure (up to 2000 atm).¹²⁹ This liberates huge amount of energy in the reaction mixture, leading to favourable reaction condition. Moreover, a constant mixing of the solution is provided.

The cavitation effect can also occur in other circumstances: indeed, it's a major problem in water turbine engines because changes in flow velocity can lead to pressure fluctuation and formation of bubbles, that will eventually hit on the turbine and implode.¹³⁰ Thus, the metal is damaged, and the turbine performances can drop after 2-3 years of work (Fig. 1.13).

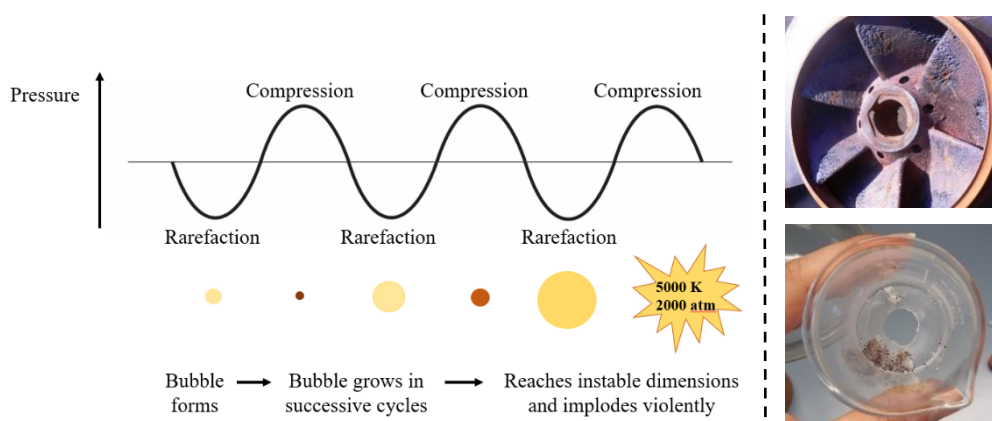


Figure 1.13. Cavitation phenomenon and its damages.

¹²⁸ A. Asadi, F. Pourfattah, I. M. Szilágyi, M. Afrand, G. Zyla, H. S. Ahn, S. Wongwises, H. M. Nguyen, A. Arabkoohsar, O. Mahian, *Ultrason. Sonochem.*, **2019**, 58, 104701.

¹²⁹ K. S. Suslick, Y. Didenko, M. M. Fang, T. Hyeon, K. J. Kolbeck, W. B. McNamara, M. Mdleleni, M. Wong, *Phil. Trans. R. Soc. A*, **1999**, 357, 335–353.

¹³⁰ P. Kumar, R. P. Saini, *Renew. Sustainable Energy Rev.*, **2010**, 14(1), 374–383.

Although this unconventional technique can provide many advantages, *i.e.*, extremely high local temperatures and pressures, inadequate equipment can be damaged by these harsh conditions: indeed, glass can easily break (Fig. 1.13). Moreover, reaction reproducibility is strictly connected to the dimensions of the reactor: the outcome of the same reaction will be different if the beaker employed is larger or tighter.

Sonochemistry can be used for many reactions, such as the preparation of heterocycles via multicomponent synthesis in water,¹³¹ or for a one-step reduction and self-assembly of carbon dots-reduced graphene oxide,¹³² nevertheless it is highly used in other fields such as protein extraction,¹³³ nanotubes dispersion in water,¹³⁴ and medicine.¹³⁵ Also food industry takes advantage of the sonicator power, for instance to produce emulsions.¹³⁶

¹³¹ R. Pagadala, V. Kasi, N. G. Shabalala, S. B. Jonnalagadda, *Arab. J. Chem.*, **2022**, 15(1), 103544.

¹³² S. Xu, H. Liu, C. Chen, S. Feng, J. Fan, *Chem. Eng. J.*, **2023**, 451, 138569.

¹³³ (a) A. Patel, *Synth. Commun.*, **2021**, 51(2), 163-190; (b) X. Liu, Z. Wu, R. Cavalli, G. Cravotto, *Ind. Eng. Chem. Res.*, **2021**, 60(28), 10011-10032.

¹³⁴ K. Yang, *Chin. Sci. Bull.*, **2013**, 58(17), 2082-2090.

¹³⁵ (a) P. Palanisamy, M. Alam, S. Li, S. K. H. Chow, Y. P. Zheng, *J. Ultrasound Med.*, **2022**, 41(3), 547-563; (b) S. J. Radford, C. Clarke, B. Shinkins, P. Leighton, S. Taylor, G. Moran, *Frontline Gastroenterol.*, **2022**, 13(4), 280-286; (c) S. Schoen, M. S. Kilinc, H. Lee, Y. Guo, F. L. Degertekin, G. F. Woodworth, *Adv. Drug Deliv.*, **2022**, 180, 114043.

¹³⁶ L. Zhou, J. Zhang, L. Xing, W. Zhang, *Trends Food Sci. Technol.*, **2021**, 110, 493-512.

2. SCOPE

The urge to expand and implement biorefinery is pressing on the research field, as problems and limitations connected to the fossil resources and the petroleum refinery are increasing exponentially. As already mentioned in the introduction, HMF is a promising Bio-Based Platform Chemical and a fundamental intermediate for many products with various applications, *i.e.*, chemical intermediates, fuel additives and monomers for polymers. However, it has several drawbacks mainly connected to its stability and isolation; indeed, it is a solid that melts at 35 °C, thus it must be stored in freezer (-30 °C), and it can easily react with water to form levulinic acid and other by-products. These issues are the causes of the lack of large-scale synthetic procedures, as well as of isolation/purification methods, ultimately leading to its high price. Indeed, in literature there are only few articles that report a multi-gram synthesis of HMF, including also the purification step.

In this prospect, the first aim of this thesis project was to develop a high yielding and scalable synthesis of HMF starting from the promising preliminary results already published by this research group,¹³⁷ and on the design of an efficient purification/isolation procedure. The idea was also to define the greenness of the new procedure when compared to the published procedures already reported in the literature using several Green Metrics and the semi-quantitative algorithm EcoScale. The second goal was to employ the HMF produced in this way to design a microwave-assisted etherification with various alcohols to obtain the corresponding fuel additives AMFs and eventually BAMFs (from BHMF). Indeed, the literature showed a lack in synthetic pathways that employ this alternative heating technique. A green comparative evaluation would also be performed for the HMF etherification in order to define the greenness of the novel proposed procedure.

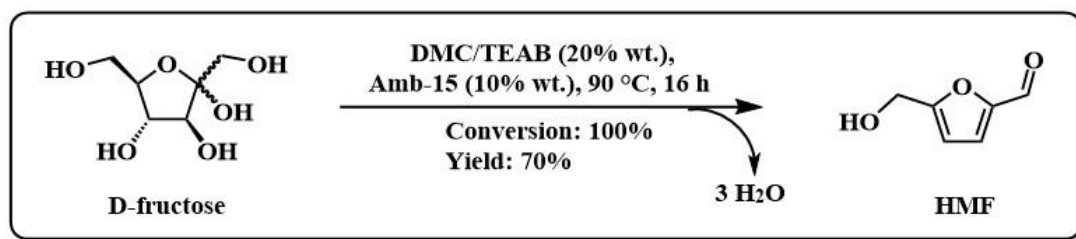
¹³⁷ M. Musolino, J. Andraos, F. Aricò, *ChemistrySelect*, **2018**, 3, 2359-2365.

3. RESULTS AND DISCUSSION

3.1. HMF synthesis in autoclave

3.1.1. Optimization of the HMF synthesis in autoclave

Previous investigations conducted in this research group led to a new procedure for the synthesis of HMF via D-fructose triple dehydration in mild conditions.¹³⁷ In particular, D-fructose was dissolved in a dimethyl carbonate (DMC)/tetraethylammonium bromide (TEAB) biphasic system, in the presence of an heterogeneous acidic catalyst, Amberlyst-15 (Amb-15). The reaction was conducted at 90 °C for 5-24 hours depending on the amount of substrate employed, *i.e.*, 10 grams of D-fructose required 24 hours to achieve HMF in *ca.* 70% isolated yield. Scheme 3.1 depicts the D-fructose chemical transformation as well as the reaction conditions. Fructose is poorly soluble in organic solvent, due to its numerous hydroxy groups, thus polar solvents such as water or alcohols that are the preferred media for this reaction.¹³⁸ Furthermore, HMF displays a hydrophilic behaviour, thus its subsequent separation from a reaction media such as water is very challenging, and distillation can become problematic because of its thermal instability. In this prospect, it was decided to base the improved synthetic procedure on the biphasic system previously adopted, *i.e.*, DMC/TEAB. The quaternary ammonium salt (ionic liquid) TEAB allows dissolution of the starting sugar meanwhile DMC acts as the extracting medium for the product.¹³⁸ An important feature to underline is the employment of DMC, a non-toxic and green solvent.¹³⁹



Scheme 3.1. HMF synthesis reported in the previous reported article.

This previously published article was used as a trampoline to explore the synthesis of HMF. The aim was to study if the reaction time as well as the amount of the solvent system could be reduced while enhancing the product yield. To this end, it was decided to carry out the reaction in an autoclave as its close environment generally enables reactions to be conducted at higher temperature than the solvent boiling point, thus allowing a greater reaction rate.

¹³⁸ S. P. Simeonov, J. A. S. Coelho, C. A. M. Afonso, *Org. Synth.*, **2016**, 93, 29-36.

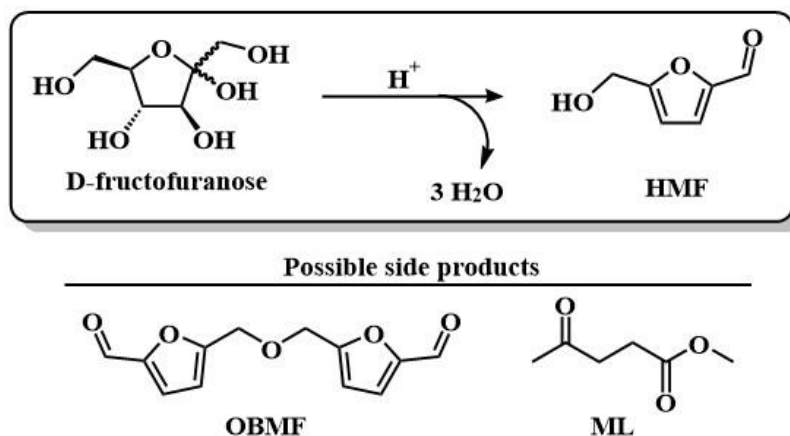
¹³⁹ F. Aricò, P. Tundo, *Russ Chem. Rev.*, **2010**, 79(6), 479.

For this case study, a temperature of 110 °C was chosen as well as a reaction time of 2 hours as starting parameters. The preliminary optimization step was a screening of several heterogeneous acidic catalysts, in order to find the best performing one; Table 3.1 reports the results achieved.

A typical reaction was performed as follows: D-fructose (3.75 g), the selected catalyst (10% wt.), TEAB (20% wt.) and DMC (30 mL) were added in the autoclave, equipped with a magnetic stirrer and a thermocouple. Reagents concentrations employed in the research group previous investigation were maintained for these initial trials. The system was then sealed and warmed to 110 °C; in all of the experiments the autogenous pressure never exceeded 2 bar.

After 2 hours the autoclave was let to cool down and opened; the reaction solution was filtered on a gooch packed with basic alumina and celite to remove the exhausted catalyst and the TEAB. The autoclave was then rinsed with the smallest amount of hot ethyl acetate (AcOEt). To note that on the bottom of the autoclave there was always a small amount of a dark, solid residue, mostly residual catalyst mixed with humins and, most probably, burnt sugar. High resolution mass spectrometry (HR-MS) analysis was performed to better understand the nature of this dark residue, however the results were inconclusive (cfr. Appendix).

The solution recovered after filtration was dried under vacuum leading to a dark-brown, viscous oil. ¹H-NMR analysis was employed to confirm the presence of the targeted HMF and to calculate both selectivity and yield. A frequent observed by-product was OBMF, from the self-etherification promoted by an acidic environment. In few trials methyl levulinate (ML) was also observed in small amount; its formation, which leads also to formic acid (FA), can be ascribed to the acid reaction conditions which activate DMC as methylating agent (Scheme 3.2).¹⁴⁰



Scheme 3.2. Common by-products in the synthesis of HMF.

It must be noted that conversion is not reported in Table 3.1 since AcOEt used during the work-up does not solubilize the starting sugar, thus only product and by-products could be recovered. As a result D-fructose signals were never detected in the NMR spectra of the reaction mixture. Another important information regards the yield. Its value, calculated following Eq. 1, is the combination between the weight of the crude product and

¹⁴⁰ D. Dalla Torre, M. Annatelli, F. Aricò, *Catal. Today*, **2022** (in press). <https://doi.org/10.1016/j.cattod.2022.08.034>

the selectivity, determined via ¹H-NMR and calculated following the Eq. 2. It was decided to not employ an internal standard for the calculations because the final aim was to eventually isolate the compound.

$$\text{Yield \%} = \text{Weight of the crude product} * \text{selectivity \%} \quad \text{Eq. 1}$$

$$\text{Selectivity \%} = \frac{\text{Area of the product peak}}{\sum \text{Area of all the compounds peaks}} \quad \text{Eq. 2}$$

Table 3.1. Screening of several acidic catalysts. ^a

#	Catalyst	Selectivity % ^b		Yield % ^b
		HMF	OBFM	
1	Amb-15	98	2	64
2	Amb-36	98	2	65
3	Pur. CT151	94	6	66
4	Pur. CT269	97	3	67
5	Pur. CT275	96	4	63
6	Pur. CT275DR	98	2	73

^a Reaction conditions: 3.75 g of D-fructose were dissolved in 30 mL of DMC/TEAB (20% wt.) biphasic system, in presence of 10% wt. of heterogeneous acidic catalyst, in an autoclave at 110 °C for 2 h; ^b Estimated via ¹H-NMR.

The tested catalysts belong to two types of heterogeneous proton-exchange resins: Amberlysts (#1,2; Table 3.1) and Purolites (#3-6; Table 3.1). Briefly, they are spherical beads made of polystyrene crosslinked with divinylbenzene and functionalised with sulfonic acid; particle size ranges from less than 300 μm to 1200 μm, and surface area from 15 m²/g to 53 m²/g. Detailed properties for each type of the herein investigated catalyst are summarized in Table 6.2 in the Appendix. Purolites CT275 and CT275DR display the same properties, beside the moisture retention which is 51-59% and < 5% respectively.

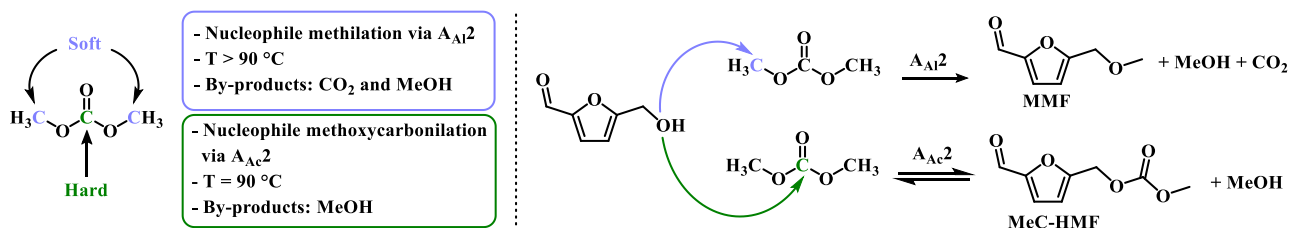
As can be seen from Tab. 3.1, Amberlyst-15 (#1; Table 3.1), Amberlyst-36 (#2; Table 3.1) and Purolite CT275DR (#6; Table 3.1) showed almost quantitative selectivity towards HMF, with very small quantities of OBFM, which resulted from HMF self-etherification. The great performance of Purolite CT275DR compared with the others (#3-5; Table 3.1) can be ascribed to its high acidity in combination with its large average pore diameter, that might make the acidic sites more accessible. Since Purolite CT275DR gave the highest yield (73%), it was chosen as catalyst for further trials.

An important question to be answered was if the extracting solvent, DMC, participated somehow to the reaction, as it was recently found in the synthesis of 2,5-furandicarboxylic acid dimethyl ester (FDME) from galactaric acid.¹⁴¹ DMC is an organic carbonate, with two soft nucleophilic sites and one hard nucleophilic site, with respect to the Hard-Soft Acid Base (HSAB) theory of Pearson.¹⁴² Thus, HMF can be involved in two possible reaction pathways via methoxycarbonylation (A_{Ac}2 mechanism) or methylation (A_{Al}2 mechanism) as shown in Scheme 3.3.¹⁴³

¹⁴¹ G. Trapasso, M. Annatelli, D. Dalla Torre, F. Aricò, *Green Chem.* **2022**, 24, 2766-2771.

¹⁴² R. G. Pearson, *J. Am. Chem. Soc.*, **1963**, 85, 3533.

¹⁴³ P. Tundo, M. Musolino, F. Aricò, *Green Chem.* **2018**, 20, 28-85.



Scheme 3.3. DMC and possible interactions during the reaction.

To understand the role of DMC, the reaction was conducted with the optimized conditions (#6; Table 3.1) and stopped at different time intervals. The reaction mixture was then filtered on a paper filter, the autoclave was washed with hot AcOEt and everything was collected in a round-bottom flask. After rotavapor and vacuum drying, samples were taken from the reaction mixture and dissolved in DMSO- d_6 . $^1\text{H-NMR}$ spectra can be found in the Appendix. The information that could be extrapolated from these data were:

- HMF begins to form in the first 30 minutes of the reaction;
- No methylated or methoxycarbonyl product could be detected, suggesting that DMC is not involved in the reaction mechanism;

Therefore, DMC acts only as the extracting solvent.

For the successive optimization steps, the amount of starting D-fructose was directly increased to 10.0 g since the previous attempts with 3.75 g performed greatly.

The first parameter assessed was the reaction time (Tab. 3.2). The experiment stopped after 1 hour gave already good results, with more than 90% selectivity and almost 70% yield (#1; Table 3.2). A longer reaction time (3 hours) produced up to 75% yield (#3, Table 3.2). However, the selectivity towards HMF decreased to 94% in these conditions, compared to the 98% of the two hours reaction (#2; Table 3.2). Longer reaction times led to similar or worse results probably because they favour the formation of humins, ultimately reducing selectivity and yield of HMF.¹⁴⁴ Overall, a two hours reaction was the best compromise between high selectivity and high yield.

Table 3.2. Evaluation of reaction time and Purolite CT275DR amount.^a

#	CT275DR (% wt.)	Time (h)	Selectivity % ^b		Yield % ^b
			HMF	OBFM	
1	10	1	91	9	68
2	10	2	98	2	73
3	10	3	94	6	75
4	5	2	100	0	70
5	2.5	2	100	0	53

^a Reaction conditions: 10 g of D-fructose were dissolved in 80 mL of DMC/TEAB (20% wt.) biphasic system, in presence of heterogeneous acidic catalyst Purolite CT275DR, in an autoclave at 110 °C; ^b Estimated via $^1\text{H-NMR}$.

¹⁴⁴ S. Liu, Y. Zhu, Y. Liao, H. Wang, Q. Liu, L. Ma, C. Wang, *Appl. En. Combust. Sci.*, **2022**, 10, 100062.

The second parameter investigated was the catalyst amount (Tab. 3.2). The trial performed using half of the usual amount of Purolite CT275DR (from 10 to 5% wt., #4; Table 3.2) gave a quantitative selectivity and a yield comparable with previous results (70%), while lower amounts (#5; Table 3.2) caused a decrease in HMF yield (53%). This highlighted that 5% wt. was the lowest amount of catalyst that could guarantee good outcomes.

The effect of the amount of ionic liquid TEAB on the HMF formation was next studied (Tab. 3.3). By halving the usual amount (from 20 to 10% wt., #1; Table 3.3), the product selectivity resulted quantitative and the yield was comparable to the previous reactions (70%). Lower quantities of TEAB didn't perform as good: this is probably due to the lower solubilization of D-fructose in the reaction medium, which led to a lower conversion to HMF. The last trial was performed in absence of TEAB in the reaction mixture (#4; Table 3.3) to ensure that the biphasic system was a requirement. Even though the reaction occurred and HMF selectivity was good (94%), HMF yield was just moderate (55%).

Table 3.3. Evaluation of the amount of the ionic liquid TEAB.^a

#	TEAB (% wt.)	DMC (mL)	Selectivity % ^b		Yield % ^b
			HMF	OBF	
1	10	80	100	0	70
2	5	80	95	5	66
3	2	80	95	5	58
4	---	80	94	6	55
5	10	50	98	2	70
6	10	40	98	2	73

^a Reaction conditions: 10 g of D-fructose were dissolved in a DMC/TEAB biphasic system, in presence of 5% wt. of heterogeneous acidic catalyst Purolite CT275DR, in an autoclave at 110 °C, for 2 hours; ^b Estimated via ¹H-NMR.

The effect of the DMC amount on the reaction outcome was also studied. For all the abovementioned reactions, the ratio between D-fructose and DMC was 1:8 (1:17 mol eq.). Following our main scope to reduce the waste production (E-factor) in this procedure, several experiments were carried out in more concentrated conditions, *i.e.*, limiting the solvent excess, thus employing 50 mL (#5; Table 3.3) and 40 mL (#6; Table 3.3) of DMC (instead of 80 mL). Once again, the trials were conducted on 10 g of D-fructose. Both trials gave excellent results, allowing to reduce the initial volume of DMC by half and to lower the ratio D-fructose:DMC to 1:4 (*ca.* 1:8 mol eq.).

The last adjustment regarded the reaction temperature (Table 3.4): tests conducted at temperatures up to 150 °C produced similar or worse results in terms of HMF selectivity and yield. Methyl levulinate (ML) and several by-product peaks started to appear in the ¹H-NMR spectrum (*cf.* Appendix) because of side reactions and product degradation. Moreover, a higher amount of humins was visibly produced, in accordance with previous published works suggesting that the formation of humins is dependent on reaction temperature.¹⁴⁵

¹⁴⁵ I. van Zandvoort, Y. Wang, C. B. Rasrendra, E. R. H. van Eck, P. C. A. Bruijninx, H. J. Heeres, B. M. Weckhuysen, *ChemSusChem*, **2013**, 6(9), 1745-1758.

Another issue for the trials conducted at higher temperature was related to the Purolites thermal stability, in fact these heterogeneous catalysts cannot withstand temperatures much higher than 120-130 °C, otherwise their catalytic activity is reduced, and their physical structure compromised.

Table 3.4. Optimization of the reaction temperature.^a

#	T (°C)	Selectivity % ^b			Yield % ^b
		HMF	ML	Other	
1	120	97	3	0	68
2	130	96	4	0	70
3	150	68	18	16	46

^a Reaction conditions: 10 g of D-fructose were dissolved in 40 mL of DMC/TEAB (10% wt.) biphasic system, in presence of 5% wt. of heterogeneous acidic catalyst Purolite CT275DR, in an autoclave for 2 hours; ^b Estimated via ¹H-NMR.

3.1.2. Crystallization procedure and BHMF synthesis




After obtaining good results in terms of selectivity and yield in the new reaction conditions, an important issue to overcome was the isolation and purification of HMF. Indeed, after the vacuum drying step, the remaining crude appeared as a dense, viscous dark-brown oil, quite far from the yellow crystals described as the pure product.⁶³ In our case, the dark colour of HMF was probably caused by some insoluble humins transported from the autoclave into the final crude.

In this view, a crystallization procedure was tailored starting from a protocol reported in a published article.¹⁴⁶ Indeed, the main difference is the amount of crystallization solvent utilized and the time required for the crystals to form.

The main idea was to dissolve the dark crude HMF in an appropriate solvent and to store the solution in freezer (-30 °C) for a certain amount of time, to allow crystals formation and to prevent HMF thermal degradation. To find the most efficient crystallization medium, common organic solvents, and some mixtures, were tested (Tab. 3.5). The pure HMF yield column reported in Table 3.5 refers to the amount of pure HMF (in the form of crystals) obtained compared to the starting D-fructose.

¹⁴⁶ K. I. Galkin, E. A. Krivodaeva, L. V. Romashov, S. S. Zalessiky, V. V. Kachala, J. V. Burykina, V. P. Ananikov, *Angew. Chem.* **2016**, 29, 8478-8482.

Table 3.5. Screening of several organic solvents for the crystallization process.^a

#	Solvent	Dissolution of crude oil	HMF crystals	Pure HMF yield %	Crystals	
1 ^b	Et ₂ O	Partial	✓	ca. 50	Yellow crystals	
2 ^{b,c}	Et ₂ O + Hexane	Partial	✓	ca. 30	Needle-shape, yellow-orange crystals	
3	TBME	Total	✗	/	/	/
4	THF	Total	✗	/	/	/
5	2-MeTHF	Total	✗	/	/	/
6	Hexane	None	✗	/	/	/
7 ^{b,c}	Acetone + Hexane	Partial	✗	/	/	/
8 ^{b,c}	AcOEt + Hexane	Partial	✓	ca. 30	Needle-shape, yellow-orange. They melt faster.	
9	AcOEt	Total	✗	/	/	/

^a After obtaining the dark brown reaction crude, solvent(s) was added, the organic phase was collected in a beaker and put in freezer for 48h; ^b Separation between organic phase and dark brown oil; ^c 10 mL of Et₂O, acetone or AcOEt were poured in the reaction crude, then hexane was added until the formation of a white-yellow powder; this procedure was repeated two more times, the recovered organic phase were then put in the freezer for 48h.

Among all media evaluated, Et₂O was found to be the best solvent with a final yield of HMF bubble-shape yellow crystals of ca. 50% (#1; Table 3.5); the mixture diethyl ether/hexane (#2; Table 3.5) and ethyl acetate/hexane (#8; Table 3.5) gave a lower yield, around 30%, but the crystals were beautifully needle-shape and transparent.

The resulting purification procedure can be so summarized:

1. the dark-brown crude was dissolved in Et₂O as much as possible; however ca. a 30% of the crude oil remained insoluble.
2. The organic fraction was separated from the insoluble one by decantation, then both were kept in freezer at - 30 °C for 48 h.
3. The bubble-shape light-yellow crystals of pure HMF were recovered by filtration from the diethyl ether solution. The HMF structure was confirmed by ¹H-NMR analysis (Appendix).

According to NMR analysis the insoluble fraction, stored in the freezer to avoid degradation, was still rich in HMF (cfr. Appendix), mostly trapped in a gluey humins mixture. To maximise the efficiency of the overall procedure, it was decided to combine the residual crystallization water with the insoluble oil. After the evaporation of the solvent, the residual HMF-rich oil was dissolved in THF and subject to reduction by addition of sodium borohydride (NaBH_4). This led to the synthesis of BHMF, isolated as a pale-yellow powder with a 75% yield calculated with respect to the initial amount of residual HMF-rich oil (#1; Table 3.6). It should also be mentioned that, also in this case, a certain quantity of insoluble black tar material, probably humins, was present at the end of the reaction. The graphical scheme of the complete procedure is given in Figure 3.1.

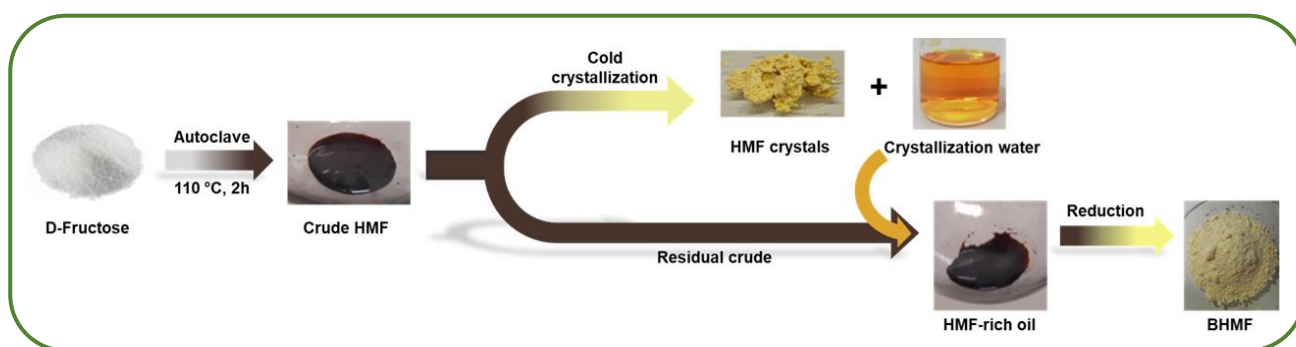


Figure 3.1. Graphical representation of the complete procedure.

3.1.3. Scale up synthesis of HMF in autoclave

The highest amount of D-fructose employed so far for the reactions, was 10.0 g – already an improvement compared to the initial 3.75 g used for the catalyst screening. Results, in term of selectivity and yield, were very satisfactory, thus it was decided to scale up the procedure to the maximum amount possible considering the autoclave volume. The maximum volume of liquid that the autoclave can contain safely is 200.0 mL, thus the maximum amount of DMC that could be tested was 160.0 mL, considering also the amount of the starting sugar (40.0 g), the ionic liquid TEAB (10.0 g) and the catalyst Purolite CT275DR (5.0 g). Overall, the reaction was tested on a 20.0 g, 30.0 g and 40.0 g scale; results are reported in Table 3.6.

Table 3.6. Scale up synthesis of HMF in autoclave.^a

D-fruct. (g)	DMC (mL)	Crude HMF (g)	Selectivity % ^b		HMF yield % ^b	HMF cryst. %	HMF rich oil (g)	BHMF yield % ^c	Total yield % ^d
			HMF	OBMF					
10	40	5.37	98	2	73	47 (3.2 g)	1.86	75 (18)	65
20	80	11.21	98	2	76	44 (6.2 g)	4.61	78 (21)	65
30	120	17.08	97	2	77	45 (9.4 g)	6.72	70 (19)	64
40	160	22.76	96	4	72	46 (12.9 g)	7.92	73 (17)	63

^a Reaction conditions: D-fructose was dissolved in DMC/TEAB in the presence of Purolite CT275DR (5% wt.) at 110 °C for 2h; ^b Evaluated via ¹H NMR spectroscopy; ^c Isolated yield calculated with respect to the HMF contained in the residual oil; in parenthesis, yield calculated with respect to the starting amount of D-fructose; ^d Considered as HMF crystals + BHMF yield.

Results of the scale up confirmed the intrinsic potential of this procedure: selectivity towards HMF was almost quantitative for all the reactions (*ca.* 98%) except for the 40.0 g scale one, which slightly decreased to 96%. HMF crystals yields were all comparable with the previous 10-gram scale reactions. The cumulative yields of pure HMF and pure BHMF were around 65%, a value consistent with the yield evaluated via ¹H-NMR. To highlight the improvements achieved in the optimized procedure herein discussed with respect to the one previously published by this research group, in Table 3.7 is reported a complete comparison.

Table 3.7. Comparison between the previous procedure and the one herein proposed.^a

Method ^a	DMC (mL)	TEAB (% wt.)	Catalyst (% wt.)	T (°C)	Time (h)	HMF Yield %		Maximum reaction scale ^b	
						Oil	Crystals		
Prev. article	Reflux	80	20	Amb-15 (10)	90	16	70	/	20 g
This thesis	Autoclave	40	10	CT275DR (5)	110	2	73	47	40 g

^a Data refer to a typical D-fructose 10-gram scale procedure; ^b Maximum amount of D-fructose used.

Both procedures are based upon a DMC/TEAB biphasic system and on commercially available reagents, solvents and catalysts; nevertheless, for the autoclave conditions, Purolite CT275DR performed better than Amberlyst-15, with a dramatically decrease in the reaction time (2 hours instead of 16). It was also possible to lower the DMC, catalyst and TEAB amount without affecting the final outcome. In addition, both DMC and ethyl acetate could be recovered and reused (see chapter 3.1.5 on the greenness evaluation), and a custom-made purification procedure was developed following the waste-minimization principle developed by P. Anastas.¹²

3.1.4. MW- and sonicator-assisted synthesis of HMF

In the introduction chapter, basic principles on MW and sonicator have been introduced. Since they both have great potentiality, it was tested if the procedure for the synthesis of HMF, developed and optimized in the autoclave conditions, could be successful also via MW or sonification.

The first alternative method tested was the microwave. The instrument parameters that could be tuned are maximum dispensed power (0 – 1900 W), the spinning of the magnetic stirrer (0 - 100%), temperature and time, with the possibility to build a controlled ramp.

A typical reaction was conducted as follows: all the reagents and the magnetic stirrer were placed into the quartz vessel, which was then sealed into a PEEK (polyetheretherketone) cylinder, inserted in the Teflon support, and placed in the MW; in Figure 3.2 is shown the equipment used to perform the MW reaction.

The conditions of the first reaction mimicked the best ones of the autoclave despite being conducted in a lower scale (#1; Table 3.8): 2.0 g of D-fructose, 10% wt. of TEAB, 5% wt. of Purolite CT275DR and 8.0 mL of DMC were added in the quartz vessel and kept at 110 °C for 15 minutes.

Once the reaction was finished, the system was opened, the mixture was poured into a flask and the quartz vessel was rinsed with the minimum volume of hot ethyl acetate. The solution was then filtered on a gooch packed with basic alumina and celite and dried under vacuum. In Table 3.8 is reported the optimization of the HMF MW-assisted synthesis. As displayed by Table 3.8, there is a consistent discrepancy between selectivity and yield. This issue is mostly attributable to both carbonization of sugar and formation of humins, indeed at the end of the reactions there was always a certain amount of dark, gluey material on the bottom of the quartz vessel that was not solubilized during the work-up by hot ethyl acetate. This involves the loss of material, ultimately leading to a decrease in yield.



Figure 3.2. Microwave equipment. From left to right: quartz vessel with magnetic stirrer, PEEK cylinder with screw cap, Teflon support.

Table 3.8. Optimization of the MW-assisted synthesis of HMF.^a

#	Temp. Ramp ^b (°C/min)	T (°C)	Time (min)	Selectivity % ^c				Yield % ^c
				HMF	OBFM	MMF	FMF	
1 ^d	22	110	15	90	4	5	1	20
2	22	110	15	87	8	5	1	27
3	28	140	15	73	20	5	2	35
4	21	170	15	90	5	3	2	35
5	20	200	15	47	6	20	27	Traces
6	21	170	5	95	5	< 1	< 1	41
7	21	170	7	95	3	1	1	46
8	21	170	10	91	4	3	2	35
9	17	170	7	90	4	3	3	35
10	11	170	7	90	10	/	/	48
11	8.5	170	7	88	12	/	/	47
12 ^e	21	170	7	97	3	< 1	< 1	38

^a Reaction conditions: 1 g of D-fructose was dissolved in 8 mL of DMC/TEAB (10% wt.) biphasic system in presence of 5% wt. of heterogeneous acidic catalyst Purolite CT275DR, with a spinning of 75% and a maximum power of 800 W; ^b Temperature ramp, it represents how fast the instrument reaches the selected temperature; ^c Estimated via ¹H-NMR; ^d 2 g of D-fructose; ^e Maximum power 1200 W.

Despite the high selectivity towards HMF (90%), the ¹H-NMR yield evaluated (21%) was not comparable to the autoclave trials (#1; Table 3.8). A possible explanation could be ascribed to the difficulty to keep such

concentrated solution evenly mixed by employing a small stirring bar. Therefore, the amount of D-fructose was halved to 1.0 gram both to facilitate the solubility of D-fructose and to prevent its thermal decomposition before having the chance to dehydrate to HMF (#2; Table 3.8). As a result, a little increase in the yield (27%) was observed while the product selectivity was not affected (87%).

Reaction temperature was then varied (#3-5; Table 3.8): even though a similar yield was obtained for both the reactions conducted at 140 °C and 170 °C, an evident increase in selectivity was achieved at the higher temperature (from 73% to 90%, respectively). This result aided to explain the low yield of the first reaction (#1, Table 3.8), conducted for 15 minutes at 110 °C. Most probably, in the first trial the temperature was too low to promote efficiently the conversion of the starting sugar. On the other hand, temperature higher than 170 °C (#5; Table 3.8) resulted in the formation of a dark, solid residue that was hard to treat and analyse; indeed, only traces of HMF could be detected. This is mostly caused by the carbonization of the starting sugar at very high temperatures, together with the catalyst breakdown and the formation of humins.

In few experiments, the formation of some by-products (Fig. 3.3) were also observed. These compounds were identified to be OBMF, 5-(methoxymethyl)furfural (MMF) and (5-formyl-2-furanyl)methylformate (FMF) (¹H-NMR can be found in the Appendix chapter).

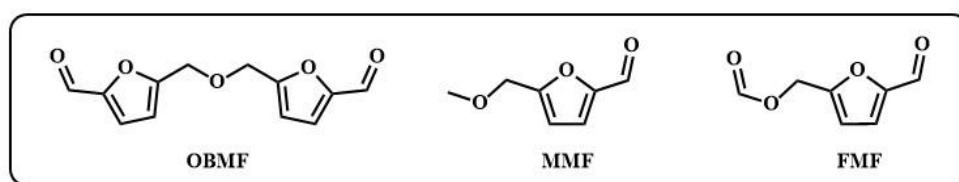


Figure 3.3. By-products detected after the reaction at 200 °C (#5, Tab. 3.8).

These preliminary experiments seem to indicate that in MW conditions side reactions are favoured by the combination of long reaction time and high temperatures.

To increase the greenness of this approach, and with the aim to limit by-products formation, the reaction time was reduced (#6-8; Table 3.8). Reaction conducted for 5 minutes showed an enhanced HMF selectivity and yield (95% and 41% respectively). Furthermore when the reactions were carried out for 7 minutes, it was possible to achieve a 46% yield while maintaining the selectivity unaltered (95%). When the reaction was kept for 10 minutes, results were comparable with the 15 minutes reaction (#4; Table 3.8), and no improvements were detected.

Another parameter taken into account was the temperature ramp. To avoid the initial burning of the sugar caused by a sudden heating, slower temperature ramps were tested (#9-11; Table 3.8). Among the trials, the best outcome was achieved by almost halving the °C/min ratio (#10; Table 3.8). However, the yield remained unvaried (48%) and the HMF selectivity diminished (90%) with respect to the experiment #7, Table 3.8.

Finally, the best MW conditions (#7; Table 3.8) were tested with a maximum power of 1200 W (#12; Table 3.8). While the selectivity remained unaltered (97%), the yield decreased (38%). A higher power caused the solution to heat faster leading to a higher degradation of both HMF and D-fructose. In addition, it must be mentioned that since the solvent employed for the work-up (ethyl acetate) does not dissolve the initial sugar,

conversion of the reagent could not be calculated; however, it is possible to assume that conversion was far from quantitative.

Overall, a final yield of ca. 50% was achieved for the MW-assisted synthesis of HMF. Results are not comparable with the autoclave outcome, however they highlight the adaptability of this new developed autoclave procedure.

The second alternative heating technique tested was ultrasounds. In a typical sonicator-assisted reaction, 3.75 g of D-fructose were dissolved in 30.0 mL of DMC/ TEAB (10% wt.) biphasic system in presence of 5% wt. of the heterogeneous acidic catalyst Purolite CT275DR, at 90 °C for 1 hour. The reaction was conducted in a narrow beaker, to guarantee an even mixing, and the tip of the sonicator was inserted into the solution at about ½ of the total height. The amplitude of the probe was kept at 40%. The work-up and the purification steps were the same as for the autoclave reaction.

Although the good premises found in literature,¹⁴⁷ the best-performing autoclave reaction didn't work with this new setting, leading to a maximum NMR yield of 11%. It was noticed that, since the instrument wasn't equipped with a specific container and being the sonicating phenomenon dependant on the longitudinal and horizontal distance from the tip, the shape of the beaker used for the reaction had a great influence on the final results. Moreover, the system was open, allowing the solvent to freely evaporate during the experiment, and temperature control wasn't always precise. Overall, there was a high degree of irreproducibility that negatively affected the reaction.

Finally it must be noted that the quantities that can be used with these two systems (in the apparatus at our disposal) are much lower than the autoclave. For instance, the 50 mL quartz vessel of the MW can contain safely a maximum volume of 12 mL. Therefore, we can conclude that the best reaction conditions for HMF production and scale-up were obtained via triple dehydration of D-fructose in autoclave conditions.

3.2. *Green metrics and Ecoscale evaluation of the HMF synthesis*

A fundamental part of this thesis was devoted to develop not just a standard organic chemistry procedure, but a sustainable one following the most prominent green chemistry principles. Thus, to evaluate these aspects, two tools have been employed: the Green Metrics using the J. Andraos radial pentagon and the EcoScale algorithm, both already discussed in the introduction. An important requirement was to find proper synthetic pathways to compare to the one herein proposed. At this scope, it was decided to select among all the procedures reported in the literature only the ones that employ as starting material at least 0.5 g of D-fructose and isolate HMF through crystallization, extraction or column chromatography, either as a solid or as an oil (see Table 3.9).

¹⁴⁷ (a) Z. Babaei, A. N. Chermahini, M. Dinari, M. Saraji, A. Shahvar, *J. Clean.*, **2018**, 198, 381-388; (b) A. Sarwono, Z. Man, N. Muhammad, A. S. Khan, W. S. W. Hamzah, A. H. A. Rahim, Z. Ullah, C. D. Wilfred, *Ultrason. Sonochem.*, **2017**, 37, 310-319; (c) P. H. Hoang, N. M. Dat, T. D. Cuong, D. T. Tung, *RSC Adv.*, **2020**, 10, 13489-13495; (d) N. Esmacili, M. J. Zohuriaan-Mehr, H. Bouhendi, G. Bagheri-Marandi, *Korean J. Chem. Eng.*, **2016**, 33(6), 1964-1970.

3.2.1. Green metrics evaluation

All the synthetic routes found in literature with the abovementioned features – to the best of my knowledge – were evaluated. Table 3.9 collects these heterogeneous results, divided in two parts: procedures with PMI lower than 100 (#1-18; Table 3.9) and PMI higher than 100 (#19-22; Table 3.9). This division was the most practical for a discussion and a graphical representation (Fig. 3.4-3.5). All the abbreviations used in Table 3.9 are in the Abbreviation table. The methods employed for the triple dehydration of D-fructose were labeled autoclave (A), batch (B) or continuous flow (C).

For each procedure the J. Andraos radial pentagon was applied, all the representation are included in the Appendix. The results are comprehensive of reaction, work-up and purification procedure, although not all the procedures reported the amounts of all materials employed, thus some of the Green Metrics related to these synthetic approaches are not very accurate.

Table 3.9. Environmental assessment of procedures with PMI lower (#1-18) and higher (#19-22) than 100.^a

#	Method	D-Fruct (g)	Catalyst	Rxn solvent	Yield (%)	E-ker	E- rxn solv.	E-cat	E-workup	E-purif	E-f	PMI	Ref.
1	B ^b	0.64	CeP ₃ ^c	DMC/water	68 (solid)	1.11	44.43	0.33	39.6	0	85.47	86.47	148
2	C ^d	1	HCl 0.25M	MIBK	74 (oil)	0.92	23.02	21.5 4	0	0	45.48	46.48	149
3	B ^b	1	FeCl ₃ /Et ₄ NBr	NMP	78	0.83	18.83	0.55	67.29	0	87.13	88.13	150
4	B ^e	1.8	HBr/silica	THF	95 (oil)	0.5	88.8	4.01	0.83	0	94.14	95.14	151
5	B ^{b,d}	2.1	Ti/Si500	water/TEAC	95	0.5	7.14	0.14	5.64	0	13.42	14.42	152
6	B	5	[PPFPy][HSO ₄]	DMSO	83 (oil)	0.73	30.4	0.92	7.6	0	39.65	4.17 ^f	153
7	B	5	[PPFPy][HSO ₄]	DMSO	84 (oil)	0.69	29.79	0.9	59.58	0	90.97	57.34	153
8	B	5	[PPFPy][HSO ₄]	MIBK/water	83 (oil)	0.72	28.86	0.92	5.49	0	35.99	36.99	153
9	A ^{e,g}	5	CO ₂	H ₂ O	92 (oil)	0.55	5.59	0	0	0	6.14	7.14	154
10	B ^{d,e}	10	H ₂ SO ₄ /LiBr	DMAc	45 (oil)	2.15	29.56	3.26	21.34	0	56.31	57.31	155
11	A	10	Pur CT275DR	DMC	50 (cryst.)	2.03	12.96	0.45	27.3	6.49	49.24	14.25	This thesis (With purif.)

¹⁴⁸ A. Dibenedetto, M. Aresta, L. di Bitorno, C. Pastore, *ChemSusChem*, **2016**, 9, 118.

¹⁴⁹ M. Brasholtz, K. Von Kanel, C. H. Hornung, S. Saubern, J. Tsanaktsidis, *Green Chem.*, **2011**, 12, 1114-1117.

¹⁵⁰ X. Tong, M. Li, N. Yan, Y. Ma, P. J. Dyson, Y. Li, *Catal. Today*, **2011**, 175-524.

¹⁵¹ R. Rajmohan, S. Gayathri, P. Vairaprakash, *RSC Adv.*, **2015**, 5, 100401.

¹⁵² L. Capuzzi, F. Digioia, G. Carotenuto, WO2014/180879 A1, **2014**.

¹⁵³ X. L. Shi, M. Zhang, Y. Li, W. Zhang, *Green Chem.*, **2013**, 12, 3438-3445.

¹⁵⁴ S. Motokucho, H. Morikawa, H. Nakatani, B. A. J. Noorderover, *Tetrahedron Lett.*, **2016**, 57, 4742-4745.

¹⁵⁵ C. C. Kovash Jr., E. Pavlacky, S. Selvakumar, M. P. Sibi, D. C. Webster, *ChemSusChem*, **2014**, 7, 2289-2294.

- Continued -

#	Method	D-Fruct (g)	Catalyst	Rxn solvent	Yield (%)	E-ker	E- rxn solv.	E-cat	E-workup	E-purif	E-f	PMI	Ref.
12	A ^b	10	Pur CT275DR	DMC	72 (oil)	0.98	8.45	0.3	17.8	0	27.53	5.13	This thesis (No purif.)
13	B	10	Amb-15	CH ₃ CN/TEAC	78 (oil)	0.82	21.27	2.18	7.19	13.15	44.61	45.61	¹⁵⁶
14	B	20	Amb-15	DMC/TEAB	70 (oil)	1.04	17.45	0.61	5.52	0	24.62	25.62	¹³⁷
15	B	20	Amb-15	water	91 (oil)	0.57	0.7	7.28	86.84	0	95.39	96.39	¹⁵⁷
16	B	20	BF ₃ OEt ₂	DMC	76 (oil)	0.89	16.14	0.53	2.55	0	20.11	21.11	¹³⁷
17	A	40	Purolite CT275DR	DMC	47 (cryst.)	2.03	12.96	0.45	27.3	5.41	48.15	17.36	This thesis (With purif.)
18	A ^b	40	Purolite CT275DR	DMC	72 (oil)	0.99	8.50	0.3	17.9	0	27.7	7.84	This thesis (No purif.)
19	B ⁱ	1.5	H ₂ SO ₄	[BMIM][Cl]	78 (cryst.)	0.83	8.55	0.02	605.74	34.68	649.81	646.41	¹⁴⁶
20	B	18	BF ₃ OEt ₂	DMSO-toluene	60 (oil)	1.37	26.41	0.29	67.74	153.79	249.60	250.60	¹⁵⁸
21	B ⁱ	18	H ₂ SO ₄	[BMIM][Cl]	73 (cryst.)	0.96	7.83	0.02	647.79	37.03	693.69	694.69	¹⁴⁶
22	C ^l	70	WCl ₆ /HY	[BMIM][Cl]/THF	55	1.62	170.04	0.27	0	0	171.93	172.93	¹⁵⁹

^a The reported metrics do not consider the preparation of the catalyst; ^b Recovery of catalyst not included; ^c CeP₃ is Cerium Phosphate catalyst with formula [(Ce(PO₄)_{1.5}(H₂O)(H₃O)_{0.5}(H₂O)_{0.5}]; ^d Amounts of work-up and/or purification materials are not reported in the original article; ^e Column chromatography is excluded from calculations for absence of data in the original article; ^f DMSO is partially recovered; ^g Reaction conducted for 158 h; ^h Excluding purification; ⁱ Aqueous solution of NaCl/NaHCO₃ not included; ^l Reaction conducted in continuous biphasic system over a 42 h period where 7 cycles of 10 g each of D-fructose run at 6 h intervals were combined.

Regarding the Green metrics evaluations, we can briefly summarize that to achieve a green/sustainable procedure the key parameters are high yield, low E-f and low PMI. This combination guarantees a well design synthesis of the target molecule, with a limited waste production; moreover, it renders the synthesis (in theory) industrially feasible.

According to the data collected, HMF yields range from moderate (45%, #10, Table 3.9) to almost quantitative (95%, #5, Table 3.9), and are independent from the amount of starting material employed.

For what concerns waste-related metrics, in 1992, R. A. Sheldon published the first article on E-factor that comprised also a general classification of industries based on waste production.¹⁰⁸ The “cleanest” was

¹⁵⁶ D. W. Brown, A. J. Floyd, R. G. Kinsman, Y. Roshan-Ali, *J. Chem. Tech. Biotech.*, **1982**, 32, 920.

¹⁵⁷ S. P. Simeonov, J. A. S. Coelho, C. A. M. Afonso, *ChemSusChem*, **2012**, 5, 1388.

¹⁵⁸ R. M. Musau, R. M. Munavu, *Biomass*, **1987**, 13, 67.

¹⁵⁹ J. Y. G. Chen, Y. Zhang, *ChemSusChem*, **2009**, 2, 731.

petrochemical refinery, with an E-f lower than 0.1 Kg/Kg; the second was bulk chemicals industry, with a maximum of 5.0 Kg/Kg. Then fine chemicals industry (5-50 Kg/Kg) and lastly pharmaceuticals industry (25->100 Kg/Kg). This enables to objectively evaluate the procedures listed in Table 3.9. Moreover, the several contributes to the E-total allow to understand which is the major wasting step.

The highest E-f procedure comes from Galkin and co-workers (#21; Table 3.9), with a value far beyond 100 Kg/Kg (693.69 Kg/Kg). The enormous waste production is influenced by the work-up and purification steps, as can be seen from the E-workup and E-purification columns in Table 3.9. Indeed, liters of solvent are utilized and not recycled – thus, the PMI value is 1 point more than E-total. Despite these issues, this procedure is one of the few that reports a successful large-scale production and isolation of HMF (73% yield). Similarly, other procedures (#19, 21, 22; Table 3.9) display very high E-factor and PMI values, with moderate and high yields (Figure 3.4).

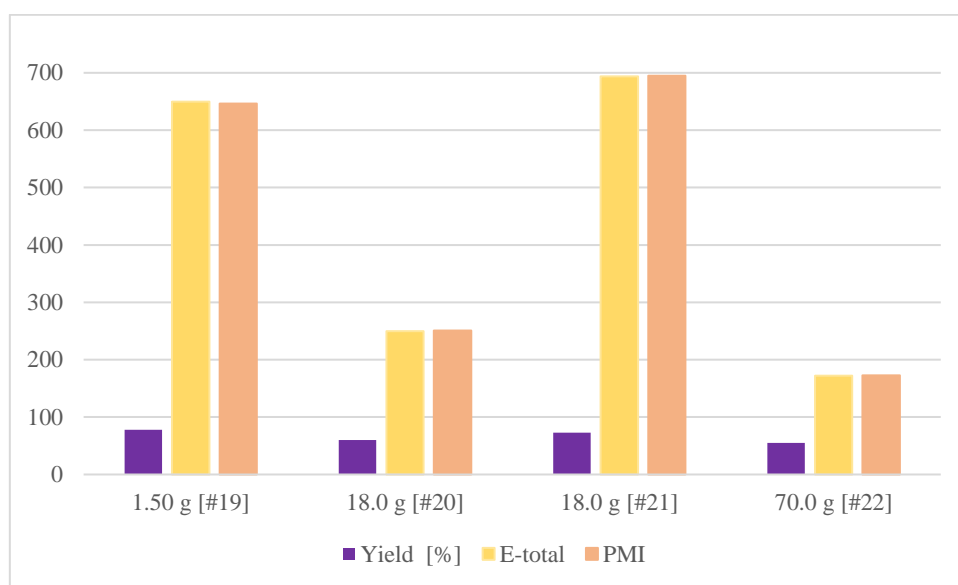


Figure 3.4. Yield, E-factor, and PMI values of procedures with PMI higher than 100; D-fructose initial amount rises from left to right.

On the contrary, the lowest E-f belongs to Motokucho *et al.* (6.14 Kg/Kg), who employ CO₂ as catalyst and water as solvent (#9; Table 3.9). Even if this synthetic procedure appears very efficient, with a yield of 92%, the purification step requires column chromatography with an unspecified amount of CHCl₃, which leads to an incomplete green evaluation. In addition, the reaction is conducted for 168 hours (7 days) in autoclave, at 90 °C, under CO₂ pressure (7.0 MPa). This is an example of green metrics limitations: the toxicity of chloroform, the very long reaction time and the unknown quantity of liquid CO₂ employed are issues not considered by the metrics and thus limit their efficiency.

The procedure herein proposed for the synthesis of HMF has an E-factor of 49.24 Kg/Kg (#11; Table 3.9), being within the fine chemicals range. Notably, it was possible to recover 88% of DMC (35 mL) and 75% of AcOEt (90 mL) by rotary evaporation, for a typical 10-gram scale reaction: this led to a PMI value of 14.25, one of the lowest among all the procedures of Table 3.9. Moreover, if the purification step is not included in the calculations the PMI value reaches 5.13, almost in the range of bulk chemicals, with a final yield of 72%.

All the other procedures displayed heterogeneous results, but most of them had an E-factor around 25-40 Kg/Kg, as shown in Figure 3.5 (D-fructose amount increases from left to right). The best-performing one, considering the combination of yield (95%) and PMI (14.42), is the Novamont synthesis (#5; Table 3.9). It starts from 2.1 g of D-fructose and employs a distilled water/tetraethylammonium chloride (TEAC) biphasic system, at 80-100 °C for *ca.* 45 minutes.¹⁵² The acid catalyst used for the triple dehydration of the sugar is titanium supported on silica (Ti/Si₅₀₀) and its synthesis is reported in the same patent. During the work-up both TEAC (via precipitation and filtration) and the catalyst (via filtration) were recovered. The remaining liquid phase was then filtered on silica gel and concentrated to give HMF in a yield of 93%. The solid mixture of TEAC and catalyst was recycled three times, and the last cycle gave HMF in a 82% yield.¹⁵²

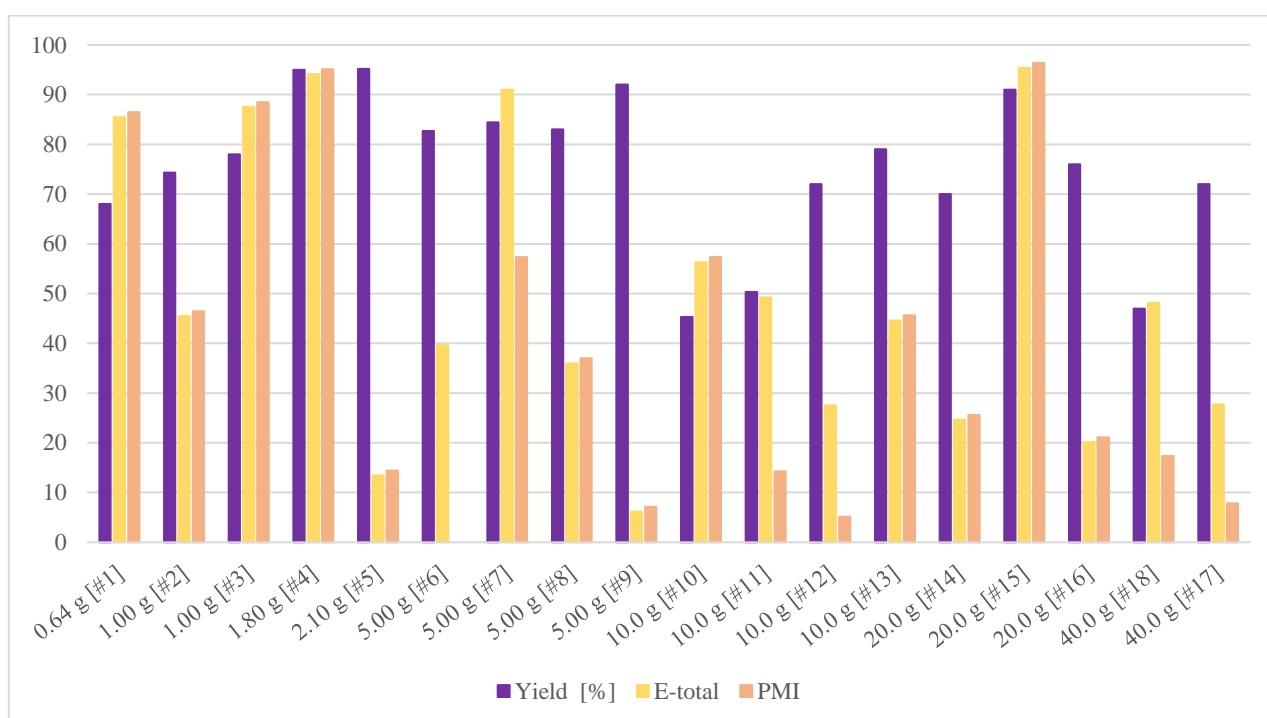


Figure 3.5. Yield, E-factor and PMI values of procedures with PMI lower than 100; D-fructose initial amount rises from left to right.

This first evaluation highlights the potential of the procedure here proposed; indeed, it has several benefits compared to the other processes:

- DMC and AcOEt can be recovered, leading to a low PMI value;
- Waste production (E-f) is in the fine chemicals scale, but is lower than many other processes;
- Amount of catalyst required is low.

3.2.2. EcoScale evaluation

A simpler evaluation of the greenness of a synthetic procedure can be conducted using the semi-quantitative algorithm called EcoScale (see section 1.4 for further details). All the procedures listed in Tab. 3.9 have been

studied with this easy-to-use tool and the outcomes are reported in Table 3.10, with comments regarding the calculations and notes of eventual inaccuracies.

Table 3.10. *EcoScale* evaluation of procedures reported in Table 3.9.

#	Reference	D-fruct. (g)	Pure HMF yield %	EcoScale value	Comments
1	¹⁴⁸	0.64	68	59	Recovery of catalyst not included
2	¹⁴⁹	1.00	74	56	Continuous flow reaction
3	¹⁵⁰	1.00	78	65	Recovery of catalyst not included
4	¹⁵¹	1.8	95	51	Purification by filtration on silica pad with unknown volume of AtOAc/Hex 1:4
5	¹⁵²	2.10	95	89	Ti/Si 500 (catalyst) not included
				67	Reagent for catalyst synthesis included
6		5.00	83	83	Catalyst not included. DMSO recovered by distillation.
				36	Reagent for catalyst synthesis included
7	¹⁵³	5.00	84	81	Catalyst not included. DMSO recovered by distillation. Purification by AcOEt/H ₂ O extraction.
				34	Reagent for catalyst synthesis included
8		5.00	83	82	MIBK/water extraction
				32	Reagent for catalyst synthesis included
9	¹⁵⁴	5.00	92	80	Reaction performed for 168 h in autoclave; amount of CO ₂ employed not specified
10	¹⁵⁵	10	45	43	HMF isolated as yellow liquid
11	This thesis	10	50	60	Catalyst not included (Purolite not present in the database)
12	This thesis (no purif.)	10	72	71	Catalyst not included (Purolite not present in the database)
13	¹⁵⁶	10	78	66	Recovery of catalyst not included. Purification by 100 mL of Et ₂ O:AcCN 5:1, then filtration and evaporation
14	¹³⁷	20	70	64	Ambetlyst-15 not included (algorithm doesn't recognize) purification not performed – only work up
15	¹⁵⁷	20	92	86	Work-up/purification with 1.2 L of AcOEt
16	¹³⁷	20	76	62	Purification not performed – only work up
17	This thesis	40	46	54	Catalyst not included (Purolite not present in the database)
18	This thesis (no purif.)	40	72	67	Catalyst not included (Purolite not present in the database)
19	¹⁴⁶	1.5	78	76	Purification included
20	¹⁵⁸	18	60	52	
21	¹⁴⁶	18	73	71	Large-scale reaction in rotatory evaporator
22	¹⁵⁹	70	55	55	Continuous biphasic reaction; yield refers to product after 42 h of reaction. Zeolite HY (5.0 g) not included. Recovery of reaction solvent (THF), ionic liquid (BMIMCl) and catalyst (UH-Y) not included. Purification by evaporation of solvent.

EcoScale recognizes substances through their CAS number, thus exotic and/or custom-made catalysts may not be identified. For the procedures that have this issue, reagents used for the catalyst synthesis were included in the calculations (#5-8; Table 3.10). Just as an example Kovash and co-workers synthesis has a very low final rating, indeed it is severely influenced by the toxicity of reagents (*i.e.* sulfuric acid, N,N-dimethylacetamide and lithium bromide).

The highest score belongs once again to Novamont (#5; Table 3.10), that reaches 89. This result confirms the sustainability of this procedure. Nevertheless, if the reagents used to synthesise the catalyst are included, the score drops to 67 because of reagent cost (dioxan) and silica toxicity. An advantage of EcoScale algorithm is that in the assessment are included both reagents price and toxicity, which usually are not evaluated by the Green Metrics.

The Motokucho *et al.* procedure reaches 80, a very high score, but as already mentioned in the Green Metrics section, reaction conditions (168 h, unprecise amount of CO₂) and purification (via column chromatography with chloroform as eluent) are all parameters not assessed in the calculations of the algorithm, leading to a rough estimation of the greenness of this pathway. The 10-gram scale procedure proposed in this thesis work (#11-12; Table 3.10) reached a final score of 71 (60 when considering the purification step), one of the highest score in the table, although catalyst was not included because it was not present in the algorithm database. The scores for the 40-grams scale reaction (#17-18; Table 3.10) are lower, however they are still competitive with the other procedures.

In Figure 3.6 are displayed the final scores listed in Tab. 3.10; the columns profiled in black refer to the 10-gram and 40-gram reactions, with and without purification.

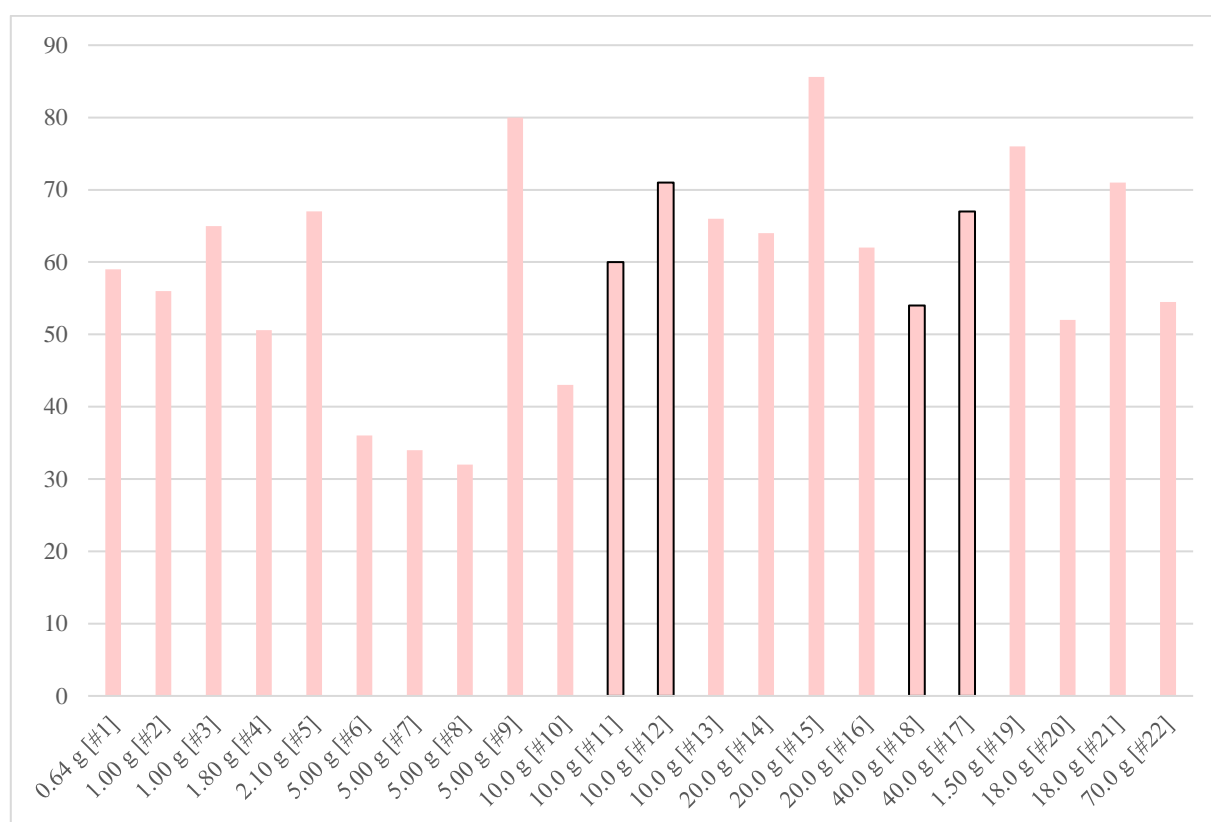


Figure 3.6. Histogram of the EcoScale final score for procedures of Table 3.9. Bars with a dark profile refer to the procedures proposed in this thesis.

It should be mentioned that EcoScale has several limitations:

- i. recyclability is not accounted;
- ii. there are very few options regarding the reaction conditions (*i.e.* heating can be set only as higher or lower than one hour, thus a two hours reaction at 90 °C will score the same as a reaction that requires heating to 200 °C for one day);
- iii. work-up and purification steps are restricted to very few examples of common techniques while the amount of solvent needed does not count.

Indeed, the Simeonov and co-workers' procedure has an incredible final score (86), but the algorithm doesn't take into account the work-up/purification step: more than one litre of AcOEt are required for an initial amount of D-fructose of 20.0 g, and a final filtration on silica pad is performed. Moreover, over 90.0 g of TEAB are utilized for the reaction.

With the EcoScale evaluation it was possible to confirm other interesting features of this new procedure for the synthesis of HMF presented in this thesis work:

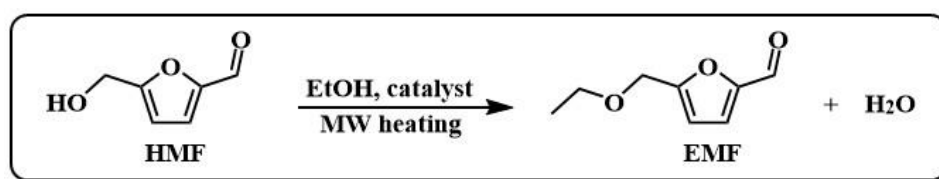
- Short reaction time and temperature
- Cheap and non-toxic reagents
- Simple set-up

3.3. Upgrading of HMF through etherification with alcohols in microwave

Among the various HMF functionalization reactions, it was chosen to explore its etherification with different alcohols to obtain 5-alkylmethylfurans (AMFs), excellent diesel fuel additives. As a starting point, it was decided to focus on the synthesis of 5-ethoxymethylfurfural (EMF). Consistent bibliographic research was carried out to study the various methodologies to produce EMF: the best reactions are reported in Table 1.6 in the Introduction, while the complete literature table can be found in Table 6.1 in the Appendix.

Beside the variety of acidic catalysts employed and the wide range of time and temperatures, it was evident that the typical synthetic methods included batch, autoclave or sealed tube conditions. Thus, it was decided to test the reaction in MW conditions, willing to reduce time and/or temperature, while reaching a good yield.

In a typical MW-assisted reaction (Scheme 3.4), HMF, ethanol, the catalyst and the magnetic stirrer were placed in the quartz MW vessel, which was then sealed and inserted in the MW chamber. Once the reaction was completed, the mixture was filtered on paper filter, washed with 10.0 mL of EtOH and dried via rotary evaporation under vacuum.



Scheme 3.4. Synthesis of EMF from HMF in MW conditions.

The first parameter optimized was the catalyst, as displayed in Table 3.11. It was decided to use only heterogeneous catalysts to allow a more facile separation from the reaction mixture, in accordance with the green chemistry principles of waste minimization. A previous work of our research group focused on the synthesis of BAMFs by etherification of BHMF with various alcohols, using Purolite CT269 as acid catalyst (10% wt.), at 40 °C for 24 h.⁵³ Since BHMF has two hydroxyl functionalities, the reaction for the etherification of HMF with ethanol was first tested with half of the catalyst employed for BHMF. Thus, Purolite CT269 (5% wt.) was used at 40 °C. As a comparison, the reaction was performed both in MW and in batch conditions (#1-2; Table 3.11). The only parameter that differentiated the two reactions was time: 24 hours for the batch *versus* 1 hour for the MW assisted. Outcomes were the same, in terms of conversion (33%), selectivity (50%) and yield (8%): this pointed out how much the reaction rate can be increased by MW.

Table 3.11. Catalyst optimization.^a

#	Catalyst	Conversion % ^b	Selectivity % ^b		Yield % ^b
			EMF	OBMF	
1 ^c	CT269	33	50	50	8
2 ^{d,c}	CT269	33	50	50	8
3	CT275DR	< 1	Traces	Traces	Traces
4 ^c	CT275	40	55	45	14
5 ^c	CT151	31	55	45	10
6	Amberlyst-15	7	43	67	Traces
7 ^c	Amberlyst-36	33	50	50	7
8	Dowex 50WX8	< 1	Traces	Traces	Traces
9	β-NH ₄ ⁺ :38	< 1	Traces	Traces	Traces
10 ^e	KW2000 (calcin.)	4	0	100	0
11 ^e	KW500 (calcin.)	5	0	100	0
12^{c,f}	Fe₂(SO₄)₃ (dry)	50	56	44	17
13 ^f	Fe ₂ O ₃	2	0	100	0
14 ^f	Fe(III)citrate	< 1%	Traces	Traces	Traces

^a Reaction conditions: in the MW quartz vessel were added 0.5 g of HMF, 3 mL of EtOH and 5% wt. of catalyst, then it was sealed and heated at 40 °C for 1 hour; ^b Estimated via ¹H-NMR; ^c Catalyst kept in oven at 100 °C overnight before reaction; ^d Reaction performed at reflux for 24 hours; ^e Catalyst calcinated at 400 °C for 4 hours before reaction; ^f Used 5% mol. instead of 5% wt. of catalyst.

Nevertheless, results weren't satisfactory, thus other Purolites (#3-5; Table 3.11) were tested. Among all, CT275 gave the highest conversion (40%) and yield (14%); a possible explanation for this behavior could be the bigger pores, that allowed reagents molecules to reach the acidic active sites more easily, compared to CT269 and CT151. Strangely, CT275DR gave only traces of EMF.

Amberlyst-type catalysts (#6,7; Table 3.11) were also tried, but once again they gave unsatisfactory results. The last ionic exchange resin tested was Dowex 50WX8 (#8; Table 3.11), a styrene-divinylbenzene backbone structure functionalized by sulfonic acid functional groups. Similarly to CT275DR resin, this catalyst produced EMF only in traces.

All these tested catalysts were Brønsted-type acids, due to the $-\text{SO}_3\text{H}$ functionalization. Some experimental evidence have demonstrated that in these conditions the etherification is generally less favored compared to the formation of levulinates by a ring-opening reaction.⁸⁵ However, this alternative pathway does not occur probably because of the low temperature. A competitive reaction – and sometimes more favored – is the self-etherification to OBMF.

K. Barbera and coworkers have demonstrated that, for the synthesis of EMF in autoclave at 140 °C for 5 hours, NH_4^+ -exchanged zeolites (*i.e.*, NH_4^+ -BEA) perform better in term of selectivity and yield compared to the corresponding H^+ -exchanged catalyst.¹⁶⁰ Thus, it was decided to include a zeolite-based catalyst in the optimization in order to explore its behavior in MW conditions. At this end, a β -zeolite with NH_4^+ as counterion and $\text{SiO}_2/\text{Al}_2\text{O}_3$ molar ratio equal to 38 was investigated (#9; Table 3.11). In our reaction conditions HMF conversion was less than 1% and only traces of the product were found in the NMR spectrum. This can be ascribed to the lower temperature employed (40 °C) and the shorter reaction time (1 hour) and possibly to the smaller average pore diameter. It must be said that the zeolite was not calcinated before the reaction: indeed, it was noted that already at 100 °C the white powder turned dark, as it was burned.

Another family of heterogeneous catalyst tested was hydrotalcites (#10,11; Table 3.11), a magnesium/aluminum hydroxycarbonate porous material. Specifically, KW2000 and KW500 were used – both after calcination at 400 °C for 4 hours – but NMR analysis showed the only presence of OBMF after the reaction, thus they were not further investigated.

Since the reactions with the abovementioned catalysts did not show any concrete results, it was decided to investigate some iron-based Lewis acid catalysts (#12-14; Table 3.11). Indeed, iron(III) sulfate was recently employed in our research group for the high yielding self-etherification reaction of HMF to OBMF. The experiment (#12) confirmed the efficiency of this catalyst for the acid etherification reactions by leading to the highest HMF conversion (50%), EMF selectivity (56%) and yield (17%). An on-going research is currently focused on the understanding the behavior of the catalyst during the etherification reaction. Other iron-based catalysts were tried (#13, 14; Table 3.11), however only traces of the targeted EMF were detected.

The second parameter tuned was the concentration of the reaction mixture; indeed literature procedures employed quite diluted solutions compared to the one that was used for the catalyst optimization described above. Reducing the concentration employed in Table 3.11 (167 g/L) to 21 g/L (#1; Table 3.12) and to 42 g/L (#2; Table 3.12), gave results comparable with the best reaction of Table 3.11 (#12). Nevertheless, when the concentration was halved (83 g/L), the outcome displayed an increment in EMF selectivity (68%) and yield (23%).

¹⁶⁰ K. Barbera, P. Lanzafame, S. Perathoner, G. Centi, M. Migliori, A. Aloise, G. Giordano, *New J. Chem.*, **2016**, 40, 4300-4306.

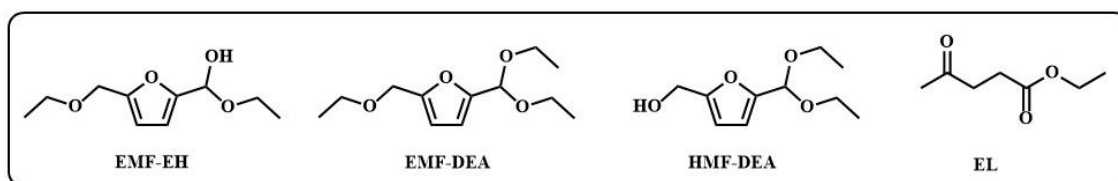
Table 3.12. Optimization of concentration and temperature.^a

#	HMF (g)	T (°C)	Conversion % ^b	Selectivity % ^b			Yield % ^b
				EMF	OBMF	EL	
1	0.125	40	40	60	40	0	14
2	0.25	40	40	60	40	0	17
3	0.5	40	50	68	32	0	23
4	0.5	80	47	73	27	0	21
5	0.5	100	70	78	9	13	38

^a Reaction conditions: in the MW quartz vessel were added HMF, 6 mL of EtOH and 5% mol. of Fe₂(SO₄)₃, then it was sealed and heated for 1 hour; ^b Estimated via ¹H-NMR.

The temperature optimization (#4, 5; Table 3.12) was a turning point in the experiments: as soon as the temperature was increased to 100 °C, conversion had a spike, reaching 70%, as well as selectivity (78%) and yield (38%); nevertheless, ethyl levulinate (EL) started to appear as side product (Fig. 3.7). As expected, the combination of the acid environment, the high reaction temperature and the presence of water produced by the etherification with ethanol, promoted the ring-opening side reaction, leading to ethyl levulinate.

It was chosen to not exceed 100 °C in order to avoid other possible side reactions. Thus, to enhance conversion, selectivity and yield it was decided to test different amounts of catalyst (Table 3.13). When the catalyst amount was increased to 7.5% mol (#1; Table 3.13), all the parameters increased notably; however, EL selectivity remained constant. By doubling the amount (#2; Table 3.13) it was possible to reach a quantitative conversion and the highest EMF selectivity and yield (84% and 65% respectively); the reaction crude was a dark-reddish oily liquid. The same reaction was performed twice to confirm the results (#3; Table 3.13). Notably, no peaks of potential by-products such as 5-ethoxymethylfurfural ethylhemiacetal (EMF-EH), 5-ethoxymethylfurfural diethylacetal (EMF-DEA) and 5-hydroxymethylfurfural diethylacetal (HMF-DEA) were detected in the ¹H NMR spectrum (Fig. 3.7). Moreover, of the 16.0 mL of ethanol employed (6.0 mL for the reaction and 10.0 mL for the work-up), almost 12.0 could be recovered by rotary evaporation.

**Figure 3.7.** Possible by-products in the EMF synthesis.

The final parameter tuned was the reaction time (#4, 5; Table 3.13). When the time was halved (30 minutes, #4; Table 3.13), conversion reached only 80%, while EMF selectivity decreased to 78% and the final yield was just above 50%. Small improvements, compared to the 30 minutes reaction, were achieved by increasing the time to 45 minutes (#5; Table 3.13). The yield trend reveals that most of the product is formed within the first 30 minutes. Since the EL selectivity incremented the more the reaction was prolonged, it was decided to keep the reaction time at 1 hour: with these conditions HMF is completely converted and the least amount of by-product is formed.

Table 3.13. Optimization of amount of catalyst and time.^a

#	Cat. (% mol.)	Time (h)	Conversion % ^b	Selectivity % ^b			Yield % ^b
				EMF	OBMF	EL	
1	7.5	1	90	83	6	11	52
2	10	1	100	84	5	11	65
3	10	1	97	80	6	14	64
4	10	0.5	80	78	13	9	51
5	10	0.75	86	81	8	11	53
6 ^c	10	1	85	80	6	14	42

^a Reaction conditions: in the MW quartz vessel were added 0.5 g of HMF, 6 mL of EtOH and Fe₂(SO₄)₃, then it was sealed and heated at 100 °C; ^b Estimated via ¹H-NMR; ^c Reaction crude obtained with the best-performing conditions was neutralized with Na₂CO₃ before the rotary evaporation step.

An important issue discovered while working with this compound was that the reaction crude, if stored for few days without any treatment, formed a dark, gluey and insoluble plastic which was impossible to process or analyse. This phenomenon was also reported in a previous work.⁵⁵ The plausible explanation is that the presence of acid in the crude mixture (indeed, no neutralization was tested so far) catalyses some kind of polymerisation (and or degradation) reaction. To avoid the formation of this plastic solid due to the acidic environment, a literature procedure that reported the treatment of reaction crude with Na₂CO₃⁸⁴ as neutralizing agent was followed. This treatment led to a light-brown oily liquid after the vacuum drying step, that NMR spectrum confirmed to be EMF. However, HMF was also present in the product, indeed conversion resulted incomplete (85%), and a final yield of 42% was calculated.

Isolation was a critical step. As some literature articles report,¹⁶¹ a major challenge to overcome is the separation of EMF from EL since they have similar properties; moreover, in this case the presence of OBMF complicated the purification process. Gradient column chromatography was the first purification method tested; the eluent composition was gradually varied from 9:1 to 6:4 mixture of hexane and ethyl acetate. As a result, a clean, yellow mixture of EMF-EL was obtained in a 46% yield. Although EMF was not isolated, the mixture with EL can also be used as diesel fuel additive since both the components enhance the fuel performance in an internal combustion engine.

The next step was focused on the isolation of EMF from the reaction crude, trying to avoid the alkyl levulinate presence. Following the Balakrishnan *et al.* methodology,⁸⁴ it was firstly tried a simple washing of reaction crude with AcOEt (15.0 mL x 3), nevertheless the final product contained both EMF and EL.

Results were far from satisfying, so it was decided to follow a different protocol:¹⁶² addition of water into the reaction crude, and subsequent extraction with ethyl acetate. However, as soon as the water was poured (5.0 mL), an insoluble brown material deposited on the inside of the round-bottom flask. The water phase was extracted with the organic solvent (15.0 mL x 3), which was dried with Mg₂SO₄, filtered, evaporated with a rotavapor and analysed. Also in this case protonic NMR spectrum highlighted the presence of EL.

Better results were obtained with purification by column chromatography, using a mixture of dichloromethane and ethyl acetate 98:2 as eluent. The final product was isolated as a yellow-amber oil in *ca.* 35% yield.

¹⁶¹ (a) A. Bredihhin, U. Mäerog, L. Vares, *Carbohydr. Res.*, **2013**, 375, 63-67; (b) G. A. Kraus, T. Guney, *Green Chem.*, **2012**, 14, 1593-1596.

¹⁶² I. Viil, A. Bredihhin, U. Mäerog, L. Vares, *RSC Adv.*, **2014**, 5, 5689-5693.

Since the separation of the mixture EMF-EL resulted problematic, and being EL favoured by high temperatures, it was decided to test the best-performing reaction (#2; Table 3.13) at 80 °C instead of 100 °C, with the aim to reduce the ring-opening reaction and, thus, to avoid column chromatography. Nevertheless, HMF conversion reached only 80% and EMF selectivity decreased to 76%; EL was still present (8%), as well as OBMF (16%). This suggests that even if the temperature was lower than 100 °C, the higher amount of acidic catalyst favoured the side-reaction anyway. In conclusion, the complete conversion of the starting D-fructose and the increment in selectivity and yield of EMF are intrinsically connected to the formation of EL when performing the reaction in MW.

The best reaction conditions (#2; Table 3.14) were also tested with the conventional oil bath heating technique. The proceeding of the reaction was monitored via TLC. After 1 hour at 100 °C, the mixture displayed traces of EMF, and HMF was still the major compound; a similar situation was noted after 4 hours. It required 24 hours to have a complete conversion of HMF into the alkylated derivative. Nevertheless, during the rotary evaporation step the mixture turned into an insoluble, dark plastic. This behaviour suggests that long reaction time in presence of an acidic environment promotes a polymerization reaction, causing the formation of the plastic-like material.

The scope of the reaction was evaluated by testing the applicability of this brand-new MW-assisted reaction to other HMF alkylated derivatives – namely, using different alcohols (Table 3.14).

Table 3.14. *Synthesis of different AMFs in MW.*^a

#	Alcohol	Conversion % ^b	Selectivity % ^b			Yield % ^b	Isolated Yield %
			AMF	OBMF	Alkyl Lev		
1	Methanol	92	83	0	17	66	44
2	Ethanol	100	84	5	11	65	35
2	<i>n</i> -propanol	100	86	0	14	34	12
3	<i>n</i> -butanol	< 5	Traces	0	Traces	0	0

^a Reaction conditions: in the MW quartz vessel were added 0.5 g of HMF, 6 mL of corresponding alcohol and 10% mol. of Fe₂(SO₄)₃, then it was sealed and heated at 100 °C for 1 hour; ^b Estimated via ¹H-NMR.

Despite the initial mistrust on methanol as reagent due to previous discouraging results, the methylation reaction took place in moderate yield (#1; Table 3.14), displaying results comparable with the alkylation with ethanol (#2; Table 3.14). Preliminary TLC showed the presence of separated MMF and ML spots when dichloromethane was employed as eluent. Reaction crude was purified via silica gel column chromatography, nevertheless ¹H-NMR analysis of the MMF fraction showed the presence of ML also. Formation of the latter compound can be ascribed to the acidity of silica gel which promotes the ring-opening reaction.

However, when the alcohol chain was increased to 3 carbon atoms (#3; Table 3.14), the yield began to decrease (34%); this trend was confirmed by the results of *n*-butanol alkylation, which formed the corresponding product only in traces (#4; Table 3.14). The goal was to test primary, secondary and tertiary alcohols, however during these last experiments the MW did not work properly, preventing the prosecution of the experiments. For the same reason it was not possible to test BAMFs synthesis.

3.4. Green Metrics and EcoScale evaluation for the synthesis of EMF

3.4.1. Green Metrics evaluation

As for HMF synthesis, the Green Metrics and the EcoScale algorithm were utilized to evaluate the greenness of this EMF MW-assisted synthesis and of the other synthetic procedures that started from at least 0.126 g of HMF. The outcome of the evaluation is reported in Table 3.15. Synthesis and recovery of the catalyst were not included in the calculations, as well as purification of reaction crude, since the majority of the procedures quantified EMF via GC or HPLC. Since ethanol is both solvent and reagent, for the Green Metrics calculation it was necessary to split its amount in two contributes: a stoichiometric amount, with respect to the starting HMF, was included in the reagent section, while the remaining was evaluated in the solvent section.

Although the Lanzafame *et al.* procedure (Tab. 6.1 Appendix) started with 0.315 g of HMF, it was not included in the assessment because the amount of catalyst required for the reaction was not given. A similar decision was taken for the P. Che and *et al.* protocol, which starts from 0.378 g of HMF but reports only the moles of $\text{H}_4\text{SiW}_{12}\text{O}_{40}$ (0.007 mmol, corresponding to 0.028 mmol H^+) for the solid catalyst $\text{H}_4\text{SiW}_{12}\text{O}_{40}/\text{MCM-41}$.

As a general overview of the procedures, the methods used for this reaction are in an autoclave (A), in batch (B) or in microwave (MW). Yields are high and the E-factor rarely exceeds 30 Kg/Kg; nevertheless, the starting HMF amount is quite low and catalysts are mostly heterogeneous and homemade – sometimes exotic. Among them, supported heteropoly acids (HPA) are very common, especially on iron nanoparticles. Although these catalysts are efficient, as displayed by the data in Table 3.15, their synthesis sometimes require a lot of reagents, synthetic steps and time. All the catalyst abbreviations are reported in the Abbreviation table, unless specified. The procedure proposed by Balakrishnan and co-workers (#1; Table 3.15) has a very low E-catalyst (0.04), nevertheless it displays the highest E-factor (and PMI) surpassing the 200 Kg of waste per Kg of product. This result is ascribed to the work-up step that requires 30.0 mL of AcOEt for a final product amount of 125 mg. However, it must be noted that all the other procedures did not perform any work-up since qualification and quantification were performed via GC or HPLC analysis of diluted samples of reaction mixture, at different reaction times. The only other procedure that comprised a work-up is the MW-assisted herein proposed (#19; Table 3.15).

Beside B. Liu *et al.* procedure, that employed AlCl_3 as catalyst, (#2; Table 3.15), all the other utilize self-made catalyst that are difficult to evaluate (#3-18; Table 3.15). As mentioned above, catalyst synthesis wasn't included in the calculations, although they can be quite time and reagent consuming. For instance, PDVTA- SO_3H (#3; Table 3.15) requires a two-steps synthesis: first the polymeric PDVTA structure is formed by copolymerization of divinylbenzene (DVB) and triallylamine (TAA) with a radical initiator for 12 hours at 40 °C, then it undergoes the sulfonation process by addition of chlorosulfonic acid, under nitrogen atmosphere, for 4 h; not to mention the numerous washing steps, with unclear amount of acetone and ethanol, and the drying steps under vacuum.

Table 3.15. Comparative environmental evaluation using the Green Metrics.

#	Method	D-fruct (g)	Catalyst	Yield %	E-ker	E-rnx solv	E-cat	E-workup	E-f	PMI	Ref
1	B	0.126	H ₂ SO ₄	81	0.38	13.77	0.04	216.88	231.07	232.07	84
2	B	0.126	AlCl ₃	93	0.20	27.27	0.09	0	27.56	28.56	86
3	A	0.126	PDVTA-SO ₃ H	87	0.28	28.95	0.32	0	29.54	30.54	87
4 ^a	A	0.126	SO ₄ ²⁻ /Al ₁ -Zr ₅ /KIT-6	90	0.25	28.26	0.36	0	28.86	29.86	88
5	B	0.126	C ₅ S ₂ STA	91	0.23	13.96	0.21	0	14.40	15.40	89
6	B	0.126	30% TaTPA/SnO ₂	90	0.24	14.06	0.05	0	14.34	15.34	90
7 ^b	B	0.126	Glu-TsOH-Ti	74	0.51	34.20	0.44	0	35.15	36.15	91
8	B	0.126	Cellulose sulfuric acid	84	0.32	29.99	0.38	0	30.70	31.70	92
9	B	0.126	MCM-41-HPW (40% wt.)	83	0.34	30.34	0.78	0	31.46	32.46	93
10	A	0.126	K-10-clay-HPW (30% wt.)	91	0.22	27.65	1.13	0	29.01	30.01	94
11	B	0.126	Silica-SO ₃ H	84	0.33	30.23	1.94	0	32.50	33.50	95
12	B	0.126	Fe ₃ O ₄ @SiO ₂ -HPW	84	0.34	30.30	1.17	0	31.80	32.80	96
13	B	0.126	Fe ₃ O ₄ @SiO ₂ -SO ₃ H	90	0.25	28.36	0.73	0	29.34	30.34	97
14	A	0.126	Fe ₃ O ₄ @C-SO ₃ H	88	0.26	28.67	0.74	0	29.67	30.67	98
15	A	0.126	Fe ₃ O ₄ @SiO ₂ -SH-Im-HSO ₄	90	0.25	28.26	0.72	0	29.23	30.23	99
16	A	0.126	Ag ₁ H ₂ PW	89	0.26	28.57	0.73	0	29.56	30.56	100
17	B	0.126	[BMIMSO ₃ H] ₃ PW ₁₂ O ₄₀	91	0.23	27.93	1.26	0	29.42	30.42	101
18	B	0.3	[DMA] ⁺ [CH ₃ SO ₃] ⁻	84	0.32	14.19	0.10	0	15.34	16.34	102
19	MW	0.5	Fe ₂ (SO ₄) ₃	65	0.75	11.67	0.41	20.23	33.06	9.7	This thesis
20	MW	0.5	Fe ₂ (SO ₄) ₃	65	0.75	11.67	0.41	0	12.83	3.57	This thesis (no work-up)

^a SO₄²⁻/Al₁-Zr₅/KIT-6 is a ZrO₂- and Al₂O₃-based Lewis catalyst; ^b yield refers to the isolated product.

It must be underlined, however, that usually catalysts are recovered from the reaction mixture, washed, dried and utilized again for at least 3 times without losing in efficiency.

As can be seen from Figure 3.8 and from Table 3.15, the MW synthesis here discussed (#19; Table 3.15) has the lowest yield (65%), quite distant from all the other procedures, nevertheless the recovery of EtOH leads to the lowest value of PMI, *i.e.*, 9.7. This is an important feature for a green synthesis. In addition, the work-up is included in the assessment, which influences in the final outcome. If the work-up step is not included, PMI decreases to 3.57 (#20; Table 3.15). The graphical representation of the Metrics, given in Figure 3.8, has a vertical axes restricted to 100, even though the first procedure has the E-f and the PMI values over 200. This interval was chosen to allow a better vision of the other procedures.

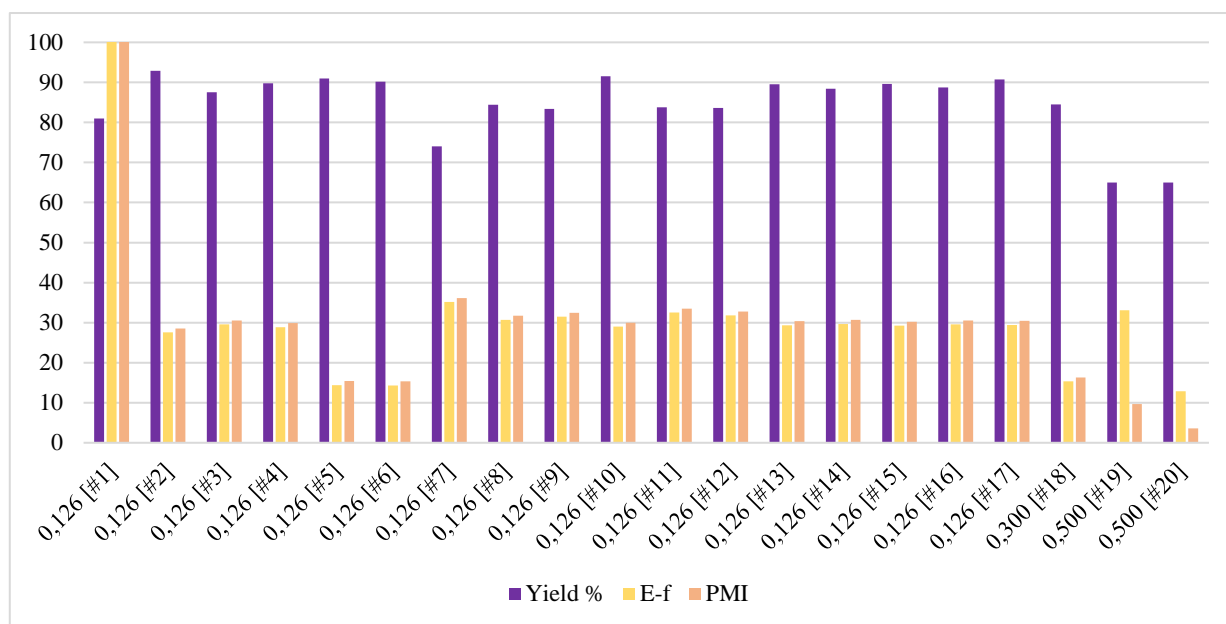


Figure 3.8. Graphical comparison of the procedures reported in Table 3.15.

3.4.2. EcoScale evaluation

A well-known limit of the common Metrics is that toxicity is not considered, as well as reaction time, temperature and solvents/reagents costs. In this perspective, the EcoScale algorithm can be a useful tool to fill up these Green Metrics flaws. Table 3.16 reports the final scores of the best procedures (already reported in Table 1.6 in the Introduction chapter) calculated using the algorithm. As mentioned in the HMF EcoScale assessment, this programme recognizes compounds through the CAS number; since most of the catalysts were self-made, thus nonregistered in the database of the programme, the synthesis of EMF from HMF were assessed including the reagents to produce the catalyst when specified and excluded otherwise. This issue, however, gives the opportunity to see how much the synthesis of a self-made catalyst can influence the final score. For instance, the Y. Xiang *et al.* score drops from 75.45 to 32 (#3; Table 3.16) when the catalyst production is included; this is mainly caused by price/availability of reagents, that subtracted 32 points from the total, and safety, which caused an additional 20 points loss.

To note that in some cases the precise amount of the reagents and/or solvents was not made explicit by the authors, thus the present evaluation includes some inaccuracies.

Overall, all the procedures lose at least 30-35 points when the catalyst preparation is included. However, some synthesis impact more heavily on the final score, *i.e.* in the procedures reported by S. Wang *et al.* (#12; Table 3.16), Z. Yuan *et al.* (#14; Table 3.16) and S. Yin *et al.* (#15; Table 3.16) the final outcome of the EcoScale resulted zero. Indeed all of them have a functionalized iron nanoparticles coated with silica (SiO₂) which require many reagents and solvents. The major problem is connected to the many steps, the safety/toxicity of compounds and to their price/availability.

Table 3.16. *EcoScale values of procedures reported in Table 3.15.*

#	HMF amount (g)	EMF Yield %	EcoScale value	Comments	Ref
1	0.126	81	73		84
2	0.126	92.9	79		86
3	0.126	87.5	75.45		87
			32	Synthesis of catalyst included	
4	0.126	89.9	72		88
			34	Synthesis of catalyst included	
			76		
5	0.126	91	64	Synthesis of catalyst included; specific amount of aqueous CsNO ₃ not given	89
6	0.126	90.2	77	EcoScale value with catalyst not calculated because of some missing data.	90
7	0.126	74	68		91
			51	Synthesis of catalyst included	
8	0.126	84.4	75		92
			54	Synthesis of catalyst included	
9	0.126	83.4	73		93
			29	Synthesis of catalyst included	
			76		
10	0.126	91.5	57	Synthesis of catalyst included; K-10 clay not included	94
11	0.126	83.8	76		95
			21	Synthesis of catalyst included	
			72		
12	0.126	83.6	0	Synthesis of catalyst included	96
13	0.126	89.5	78	EcoScale value with catalyst not calculated because of some missing data.	97
14	0.126	88.4	75		98
			0	Synthesis of catalyst included	
			76		
15	0.126	89.6	0	Synthesis of catalyst included	99
16	0.126	88.7	75	EcoScale value with catalyst not calculated because of some missing data.	100
17	0.126	90.7	89		101
			62	Synthesis of catalyst included	
			76		
18	0.3	84.5	52	Synthesis of catalyst included	102
19	0.5	64	61		This thesis

As an example, Z. Yuan and co-workers use a sulfonic acid functionalized silica-coated magnetic Fe₃O₄ nanoparticles (Fe₃O₄@C-SO₃H); the sole production of the starting iron-based nanoparticles requires to mix a very expensive FeCl₃·6H₂O, polyvinylpyrrolidone, sodium acetate and ethylene glycol for two hours at room temperature, then the homogeneous solution is transferred in an autoclave for 8 hours at 200 °C. The resulting black particles are collected by an external magnet, washed with ethanol several times and dried under vacuum at 60 °C for 24 hours. Two other time- and reagent-consuming steps are needed to produce the final catalyst.

A good procedure is the one developed by B. Liu *et al.* (#2; Table 3.16), which uses cheap reagents (excluding HMF) and relatively mild conditions (100 °C for 5 hours); with these features, a final EcoScale score of 79 is achieved. Similar conclusions can be made for the G. Raveendra *et al.* protocol (#5; Table 3.16) whose final score, that comprise also catalyst production, is 64. In fact, beside silicotungstic acid and HMF, all the other reagents are cheap. Moreover, the catalyst requires few steps to be prepared, and a very small amount of it (0.03 g) is employed in the synthesis of EMF starting from 0.126 g of HMF.

The MW-assisted production of EMF here proposed scored 61, a good result considering that it has the lowest yield among all the other articles and that this synthetic procedure still require further optimization. The use of a common compound such as $\text{Fe}_2(\text{SO}_4)_3$ as catalyst remarkably limits the price and ensures more safety. Compared to the catalyst-including evaluations, the goodness of the synthesis is confirmed. A graphical comparison is reported in Figure 3.9.

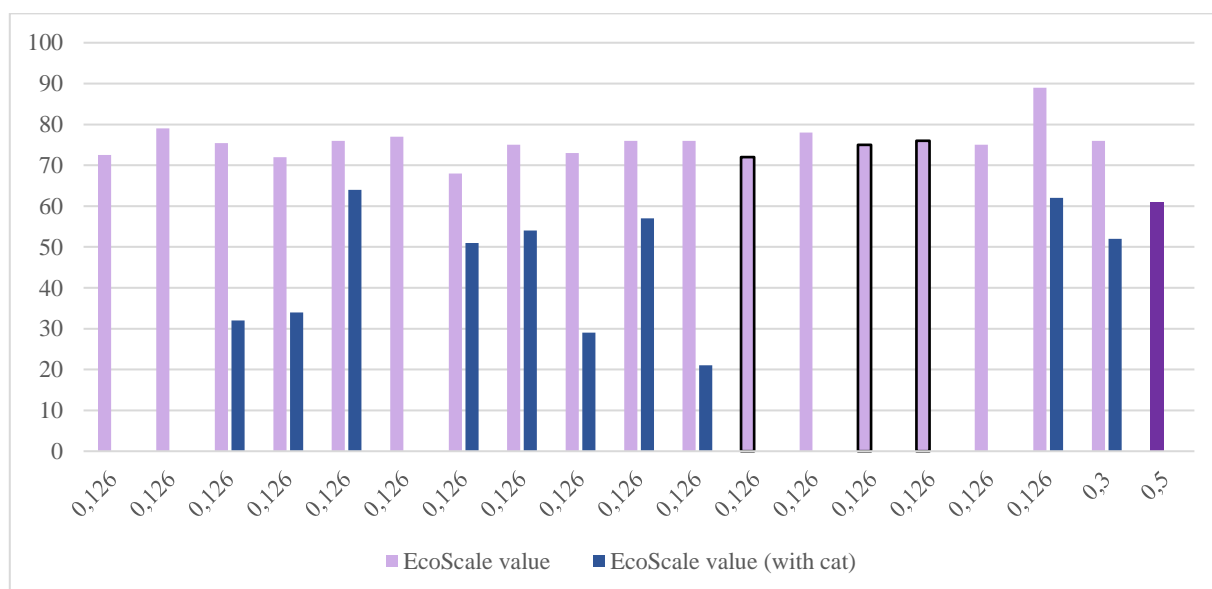


Figure 3.9. Graphical representation of the EcoScale score, without (light purple) and with (blue) catalyst preparation. In dark purple is highlighted the MW synthesis of EMF, while bars with a dark profile have a catalyst-including final score of 0.

Overall, this is the first MW-assisted synthesis of EMF starting from 0.5 g of D-fructose to the best of my knowledge. This procedure encloses many important features to underline:

- It employs a common, non-toxic catalyst ($\text{Fe}_2(\text{SO}_4)_3$)
- Reaction conditions are mild (1 hour at 100 °C)
- Conversion of the starting D-fructose is quantitative
- Works with medium concentrated solutions, compared of the more diluted literature procedures
- Ethanol (reaction and work-up solvent) can be recovered up to 75%, allowing to reach the lowest PMI value (9.7).

4. CONCLUSIONS

Environmental pollution, epidemics, drought and many other problematics are all faces of the same dice: climate change. Its roots grow from the Industrial Revolution in 18th century, when the exploitation of non-renewable resources such as carbon, petroleum and natural gas has begun, and its effects does not seem to extinguish. For this reason, it is important to switch from a fossil-based industry to a renewables-based one. A starting point is biorefinery, which relies on waste and biomass as feedstock, as opposed to refinery that depends on petroleum. Another difference is that refinery has many intermediates, while biorefinery has a limited range of platform molecules, the so called “Top 10 Bio-Based Platform Chemicals”. Among them, 5-hydroxymethylfurfural (HMF) encloses a high potential since it can undergo oxidation, reduction, etherification, self-etherification, ring opening reaction and polymerization. Nevertheless, its industrial exploitation is withdrawn by several problematics, such as its low melting point (35 °C), its thermal instability and its sensibility to water, which promotes the formation of levulinic acid. For these reasons, multi-gram synthesis of HMF are rare to find in literature; moreover, the isolation of HMF is usually not performed.

Knowing that, efforts were made to develop fast, high-yielding and scalable procedure to synthesize and crystallize HMF from D-fructose. The best reaction conditions employed a DMC/TEAB (10% wt.) biphasic system to dissolve the initial sugar, in presence of the heterogeneous acid catalyst Purolite CT275DR (5% wt.), in an autoclave, for 2 hours at 110 °C. For a typical 10-gram scale reaction it was achieved an HMF yield of 73%. Reaction crude was further purified following a custom-made procedure with Et₂O, and 47% yield of HMF crystals was reached. The procedure was successfully performed with up to 40 grams of D-fructose (72% yield of pure HMF and 42% yield of HMF crystals). The same procedure was further tested with alternative heating techniques (i.e., microwaves and sonicator), but results were not comparable with the autoclave one. A green evaluation was carried out, employing the well-known Green Metrics and the EcoScale algorithm in order to define the sustainability of the developed process compared to other procedures published in literature. Results confirmed the goodness of the methodology.

A successive step was the upgrading of HMF by etherification reaction with ethanol, in MW conditions, to obtain 5-(ethoxymethyl)furfural (EMF), a diesel additive. The best results were achieved when 0.5 g of HMF were reacted with 6 mL of ethanol in presence of 10% mol. of Fe₂(SO₄)₃ at 100 °C for 1 hour (100% conversion, 86% selectivity, 65% yield). Purification with column chromatography gave a 35% yield of the oily, light-yellow, pure product. The same reaction conditions were tested with three more alcohols, nevertheless the malfunction of the instrument prevented the investigation of other compounds.

Also, for this protocol, the Green Metrics and the EcoScale algorithm were used to evaluate its greenness. Although the yield is the lowest, the synthesis starts from the highest amount of HMF compared to the other procedures and requires mild reaction conditions. Moreover, the recovery of the reaction/work-up solvent decreases the PMI to the lowest.

It must be said that EMF synthesis in MW conditions is at a preliminary stage and further studies are necessary to enhance yield and purification procedure.

5. MATERIALS AND METHODS

5.1. *Materials and instruments*

All the solvents and reagents were purchased from Sigma-Merck and employed without any further purification. Purolite CT151, CT269, CT275 and CT275DR were kindly provided by Purolite®. Tetraethylammonium bromide (TEAB) and $\text{Fe}_2(\text{SO}_4)_3$ were dried in an oven overnight at 100 °C prior to use. Under pressure reactions have been conducted in a stainless-steel autoclave (220 mL of capacity) equipped with a thermocouple and a magnetic stirrer (1000 rpm). Reactions in microwave have been conducted in Ethos UP Milestone using a 50 mL quartz vessel, with a magnetic stir bar. Reactions with the sonicator have been conducted in a 5 cm diameter beaker using a 20 kHz Branson probe (digital sonifier model 450 L) connected to a 12 mm diameter tip and equipped with a thermocouple for the temperature control. NMR spectra were acquired using a Bruker 400 MHz in CDCl_3 and MeOD.

5.2. *General procedures*

5.2.1. Synthesis of HMF in autoclave

In a typical reaction in an autoclave, 10.0 g of D-fructose (55.0 mmol, 1 mol. eq.) were reacted with 0.5 g of Purolite CT275DR, 1.0 g of TEAB (10% wt.) and 40.0 mL of dimethyl carbonate (475.0 mmol, 8.6 mol. eq.), at 110 °C for 2 h. The autogenous pressure reached the value of 2 bar. After cooling, the reaction crude was filtered on a Gooch under vacuum packed with basic alumina (5.0 g) and celite (5.0 g) and washed with hot ethyl acetate (30.0 mL \times 4). The mixture was then evaporated and dried under vacuum to give a viscous dark-brown oil (5.3 g). HMF yield (73%) in the crude product was estimated by $^1\text{H-NMR}$. $^1\text{H-NMR}$ (400 MHz; CDCl_3) δ (ppm): 9.64 (s, 1H), 7.24 (d, 1H), 6.54 (d, 1H) and 4.75 (s, 2H). $^{13}\text{C-NMR}$ (100 MHz; CDCl_3) δ (ppm): 177.64, 160.47, 152.43, 122.61, 109.99, 57.68.

5.2.2. HMF Crystallization

The HMF-containing reaction crude was dissolved in 30.0 mL of Et_2O (10.0 mL \times 3). The organic yellow layer was separated from the insoluble dark-brown oil, and both were stored at -30 °C for 48 h. Orange-yellow crystals of HMF were filtered on a paper filter and dried under a vacuum to give pure HMF (3.8 g, 47%). The filtered mixture and the insoluble dark-brown oil obtained in the previous step were mixed together and dried under a vacuum.

5.2.3. Synthesis of HMF in an Autoclave: Large Scale

D-fructose (222.0 mmol, 1.0 mol. eq.) was reacted with 4.0 g of TEAB (10% wt.), 2.0 g of Purolite CT275DR (5% wt.), and 160.0 mL of dimethyl carbonate (1930 mmol, 8.6 mol. eq.), at 110 °C for 2 h. The autogenous pressure reached the value of 8 bar. After cooling, the reaction crude was filtered on a Gooch under vacuum with basic alumina (15.0 g) and celite (15.0 g) and washed with hot ethyl acetate (80.0 mL × 5). The mixture was then evaporated and dried under a vacuum to give the crude product as a viscous dark-brown oil (7.9 g). HMF yield (72%) in the crude product was estimated by ¹H-NMR.

5.2.4. HMF Crystallization: Large Scale

The HMF-containing reaction crude was dissolved in 90.0 mL of Et₂O (30.0 mL × 3). The organic yellow layer was separated from the insoluble dark-brown oil, and both were stored at -30 °C for 48 h. Orange-yellow crystals of HMF were filtered on a paper filter and dried under a vacuum to give pure HMF (12.9 g, 46%). The filtered Et₂O and the insoluble dark-brown oil obtained in the previous step were mixed together and dried under a vacuum.

5.2.5. Synthesis of 5-Bis(hydroxymethyl)furan (BHMF)

The dark-brown oily HMF mixture obtained in previous steps (4.6 g) was dissolved in 110.0 mL of THF; then 2.1 g (1.5 mol. eq.) of NaBH₄ were added slowly under stirring. The mixture was allowed to react at r.t. overnight, then it was quenched by the addition of water (20.0 mL), and the organic solvent was evaporated under vacuum. The aqueous mixture was transferred in a separatory funnel and extracted with AcOEt (30.0 mL × 3). The organic fractions were collected and dried with Na₂SO₄, filtered, and concentrated under vacuum to give 3.0 g of pure BHMF as a yellow solid (21% with respect to the initial 20.0 g of D-fructose). The product was further purified by grinding it in a mortar with a pestle in the presence of 15.0 mL of Et₂O; the solvent was then removed with a Pasteur pipette, obtaining a pale-yellow powder. ¹H-NMR (400 MHz; MeOD) δ (ppm): 6.25 (s, 2H), 4.51 (s, 4H). ¹³C-NMR (100 MHz; MeOD) δ (ppm): 154.36, 107.71, 56.08.

5.2.6. Synthesis of 5-hydroxymethylfurfural (HMF) in microwave

In a typical microwave-assisted reaction, 1.0 g of D-fructose (5.5 mmol, 1.0 mol. eq.) was reacted with 0.1 g of TEAB (10% wt.), 50 mg of Purolite CT275DR (5% wt.) and 8.0 mL of DMC (96.9 mmol, 17.5 mol. eq.), at 170 °C for 7 minutes, with a maximum power of 800 W and 75% of stirring intensity. After cooling, the reaction crude was filtered on a gooch packed with basic alumina and celite and washed with hot ethyl acetate (10.0 mL × 3). The mixture was then evaporated and dried under vacuum to give a viscous dark-brown oil (365 mg). HMF yield (46%) in the crude product was estimated by ¹H-NMR.

5.2.7. Synthesis of 5-hydroxymethylfurfural (HMF) under sonication

In a typical sonicator-assisted reaction, 1880 mg of D-fructose (10.5 mmol, 1.0 mol. eq.) were reacted with 188 mg of TEAB (10% wt), 94 mg of Purolite CT275DR (5% wt.) and 30.0 mL of dimethyl carbonate (363 mmol, 34.9 eq.mol) in a beaker (5.0 cm diameter) for 1 hour, with an amplitude of 40%. The tip of the sonicator was inserted into the solution at about half of the total height; the maximum temperature reached was 86.9 °C. After cooling, the reaction crude was filtered on a gooch packed with basic alumina and celite and washed with hot ethyl acetate (10 mL x 3). The mixture was then evaporated and dried under vacuum to give a viscous dark-brown oil (365 mg). HMF yield (46%) in the crude product was estimated by ¹H-NMR.

5.2.8. MW-assisted synthesis of AMFs

In a typical MW-assisted synthesis of AMFs, 500 mg of HMF (4.0 mmol, 1.0 mol. eq.) were reacted with 160 mg of Fe₂(SO₄)₃ (0.4 mmol, 0.1 mol. eq.) and 6.0 mL of the chosen alcohol in the MW quartz vessel, under magnetic stirring (100% stirring intensity) for 1 hour at 100 °C. Reaction mixture was then filtered on paper to separate the solid catalyst and dried under vacuum to give the crude product.

5-methoxymethylfurfural (MMF)

Light-yellow oil (44% yield, 1.7 mmol, 240 mg) obtained after silica gel column chromatography with 100% DCM as eluent. ¹H-NMR (400 MHz, CDCl₃) δ (ppm): 9.65 (s, 1H), 7.23 (d, 1H), 6.55 (d, 1H), 4.52 (s, 2H), 3.45 (s, 3H). ¹³C-NMR (100 MHz; CDCl₃) δ (ppm): 177.73, 158.28, 152.66, 121.83, 110.10, 66.54, 58.68.

Methyl levulinate (ML)

¹H-NMR (400 MHz, CDCl₃) δ (ppm): 3.70 (s, 3H), 2.78 (d, 2H), 2.60 (d, 2H), 2.21 (s, 3H). ¹³C-NMR (100 MHz; CDCl₃) δ (ppm): 206.55, 173.12, 51.75, 37.91, 29.83, 27.70.

5-ethoxymethylfurfural (EMF)

Yellow oil (3% yield, 1.4 mmol, 210 mg) after silica gel column chromatography (98:2 DCM:AcOEt) as eluent. ¹H-NMR (400 MHz, CDCl₃) δ (ppm): 9.64 (s, 1H), 7.23 (d, 1H), 6.54 (d, 2H), 4.55 (s, 2H), 3.61 (q, 2H), 1.26 (t, 3H). ¹³C-NMR (100 MHz; CDCl₃) δ (ppm): 177.71, 158.77, 121.89, 110.98, 66.65, 64.78, 15.08.

Ethyl levulinate (EL)

¹H-NMR (400 MHz, CDCl₃) δ (ppm): 4.14 (q, 2H), 2.76 (t, 2H), 2.57 (t, 2H), 2.20 (s, 3H), 1.26 (t, 3H). ¹³C-NMR (100 MHz; CDCl₃) δ (ppm): 206.69, 172.73, 60.61, 37.95, 29.85, 28.02, 14.15.

5-propoxymethylfurfural (PMF)

¹H-NMR (400 MHz, CDCl₃) δ (ppm): 9.64 (s, 1H), 7.23 (d, 2H), 6.54 (d, 2H), 3.64 (t, 2H), 1.63 (m, 2H), 0.96 (t, 3H).

6. APPENDIX

6.1. Comprehensive table of all literature procedures for the synthesis of EMF

Table 6.1. Published articles on the synthesis of EMF from HMF.^a

HMF (g)	Method	Solvent (mL)	Catalyst (amount)	T (°C)	Time (h)	Yield		EMF isolated yield	Ref.
						EMF	EL		
0.02	B	EtOH/H ₂ O 1.9/0.1	PCP(Cr)-BA 5 mg	140	4	63		No (n/a)	L. Zhang <i>et al.</i> , <i>RSC Advances</i> , 2021 , 11(54), 33969-33979
0.041	B	EtOH 1	CNT 10 g _{cat} /dm ³	140	24	36	3	No (GC)	M. M. Antunes <i>et al.</i> , <i>ChemSusChem</i> , 2014 , 7(3), 804-812.
0.041	B	EtOH 1	S-CNTs	140	24	52		No (GC)	
0.041	B	EtOH 1	CB	140	24	23		No (GC)	
0.041	B	EtOH 1	S-CB	140	24	55		No (GC)	
0.041	B	EtOH 1	RGO	140	24	33		No (GC)	
0.041	B	EtOH 1	S-RGO	140	24	42		No (GC)	
0.041	B	EtOH 1	Al-TUD-1 (21) 10 g _{cat} /dm ³	140	24	70	11	No (GC)	P. Neves <i>et al.</i> , <i>Green Chem.</i> , 2013 , 15, 3367-3376
0.041	B	EtOH 1	Al-TUD-1 (4) 10 g _{cat} /dm ³	140	24	65	7	No (GC)	P. A. Russo, <i>Green Chem.</i> , 2014 , 16, 4292-4305.
0.041	B	EtOH 1	C/SBA(45) 10 g _{cat} /dm ³	110	4	80	14	No (GC)	
0.041	B	EtOH 1	C/MFC(63) 10 g _{cat} /dm ³	110	4	78	18	No (GC)	
0.063	A	EtOH 4	[Cu-BTC][HPM] 40 mg	140	12	68	20.2	No (GC)	Z. Wang <i>et al.</i> , <i>Green Chem.</i> , 2016 , 18, 5884-5889
0.063	A	EtOH 1	GO 20 mg	100	12	92		Yes (Column chromat.)	H. Wang <i>et al.</i> , <i>Green Chem.</i> 2013 , 15, 2379-2383.
0.063	A	EtOH 1	p-TSA 3% mol.	100	12	61			
0.063	A	EtOH 1	H ₃ PW ₁₂ O ₄₀ 3% mol.	100	12	82			
0.063	A	EtOH 1	Amberlyst-15 10 mg	100	12	59			
0.063	A	EtOH 1	H ₂ SO ₄ 3% mol.	100	12	54			
0.1	B	EtOH 5	Glu-Fe ₃ O ₄ -SO ₃ H 30% wt.	80	2	92 (Isol.)	n/a	Yes (Column chromat.)	R. S. Thombal <i>et al.</i> , <i>Tetrahedron Lett.</i> , 2016 , 57(39), 4398-4400.
0.15	B	EtOH 5	H-USY(6) (75 mg) + Amb-15 (25 mg)	96	11	70	5	No	H. Li <i>et al.</i> , <i>Green Chem.</i> , 2016 , 18(3), 726-734
0.15	B	EtOH 5	DeAl-H-beta (12.5) -700	125	10	63	8	No	
0.122	B	AcCN 5 EtI 3 mmol	Cs ₂ CO ₃ 1.5 mmol	50	48	50		Yes (Column chromat.)	WO2018/18035 A1
0.126	B	EtOH 5	AlCl ₃ 13 mg, 10% mol.	100	5	93	detected	No (HPLC)	B. Liu <i>et al.</i>, <i>Fuel</i>, 2011, 113, 625-631
0.126	B	EtOH 2.5	H ₂ SO ₄ 5% mol.	75	24	81	16	No	M. Balakrishnan <i>et al.</i> , <i>Green Chem.</i> , 2012 , 14, 1626
0.126	B	EtOH 2.5	p-TSA 5% mol.	75	24	75	15	No	
0.126	B	EtOH 2.5	Amberlyst-15 5% mol.	75	24	55	8	No	
0.126	B	EtOH 2.5	Amberlite IR 120	75	24	33	7	No	
0.126	B	EtOH 2.5	Dowex 50WX8	75	24	45	9	No	
0.126	B	EtOH 2.5	Dowex DR 2030	75	24	57	8	No	

0.126	B	EtOH 2.5	Silica sulfuric acid	75	24	36	7	No	
0.126	A	EtOH 5	PDVTA-SO ₃ H 42.5 mg	110	0.5	88		No (GC)	Y. Xiang <i>et al.</i> , <i>RSC Adv.</i> , 2021 , 11(6), 3585-3595.
0.126	A	EtOH 5	(SO ₄ ²⁻ /Al ₁ Zr ₅ /KIT-6) S _{0.5} Al ₁ Zr ₅ -K 75 mg	120	2.5	90		No (HPLC)	H. Hafizi <i>et al.</i> , <i>Mol. Cat.</i> , 2020 , 496, 111176
0.126	A	EtOH 2.5	Cs ₂ STA 0.03 g	120	2.5	91	n/a	No (GC)	G. Raveendra <i>et al.</i> , <i>App. Catal. A: Gen.</i> , 2016 , 520, 105- 113
0.126	B	EtOH 5	Glu-TsOH-Ti 50 mg	90	6	91		Yes (74% yield) (method not specified)	D. Gupta <i>et al.</i> , <i>Catal. Comm.</i> , 2018 , 110, 46-50.
0.126	B	EtOH 5	p- TSA 5% mol.	70	18	81		Yes (Column chromat.)	L. Bing <i>et al.</i> , <i>Ind. Chem. Eng. Res.</i> , 2012 , 51, 15331-15336
0.126	B	EtOH 5	H ₂ SO ₄ 5% mol.	70	18	80			
0.126	B	EtOH 5	NKG-9 5% mol.	70	24	83			
0.126	B	EtOH 5	[BMIMSO ₃ H] ₃ PW ₁₂ O ₄₀ 5% mol.	70	24	91			
0.126	B	EtOH 5	H ₃ PW ₁₂ O ₄₀ 5% mol.	70	24	85			
0.3	B	EtOH 6	[NMP] ⁺ [CH ₃ SO ₃] ⁻ 10% wt.	120	2			Yes (Column chromat.)	M. I. Alam <i>et al.</i> , <i>RSC Adv.</i> , 2012 , 2, 6890-6896
0.3	B	EtOH 6	[DMA] ⁺ [CH ₃ SO ₃] ⁻ 10% wt.	120	2				
0.315	A	EtOH 3.5	NH ₄ -BEA	140	5	3.5 Mmol/h *g _{cat}	0.44 Mmo l/h*g _{cat}	No (GC- FID)	K. Barbera <i>et al.</i> , <i>New J. Chem.</i> , 2016 , 40, 4300
0.315	A	EtOH 3.5	H-BEA	140	5	3.1 Mmol/h *g _{cat}	0.62 Mmo l/h*g _{cat}	No (GC- FID)	
0.315	A	EtOH 3.5	NH ₄ -MFI	140	5	1.3 Mmol/h *g _{cat}	0.44 Mmo l/h*g _{cat}	No (GC- FID)	
0.315	A	EtOH 3.5	H-MFI	140	5	2.28 Mmol/h *g _{cat}	0.62 Mmo l/h*g _{cat}	No (GC- FID)	
0.315	A	EtOH 3.5	SBA-15	140	5	-	-	No (GC-MS)	Lanzafame <i>et al.</i> , <i>Cat. Today</i> , 2011 , 175, 435-441y.
0.315	A	EtOH 3.5	Zirconia-SBA-15	140	5	76	23	No (GC-MS)	
0.315	A	EtOH 3.5	Sulfate Zirconia-SBA-15	140	5	62	35	No (GC-MS)	
0.315	A	EtOH 3.5	H ₂ SO ₄	140	5	3	96	No (GC-MS)	
0.315	A	EtOH 3.5	Amb-15	140	5	-	99	No (GC-MS)	
0.315	A	EtOH 3.5	Al-MCM-41 (25)	140	5	37	47	No (GC-MS)	
0.315	A	EtOH 3.5	Al-MCM-41 (50)	140	5	68	10	No (GC-MS)	
0.315	A	EtOH 3.5	Al-MCM-41 (75)	140	5	-	-	No (GC-MS)	
0.378	B	EtOH 1.8	H ₄ SiW ₁₂ O ₄₀ / MCM-41 0.028 mmol H ⁺	90	4	77.4	5.3	No (GC)	P. Che <i>et al.</i> , <i>Bioresour. Technol.</i> , 2012 , 119, 433-436
0.378	B	EtOH 1.8	H ₃ PO ₄ 0.051 mmol H ⁺ (9.4 mmol/L)	90	2	0.5	-	No (GC)	
0.378	B	EtOH 1.8	p-TSA 0.051 mmol H ⁺ (28.3 mmol/L)	90	2	49	5.6	No (GC)	
0.378	B	EtOH 1.8	H ₃ PW ₁₂ O ₄₀ 0.051 mmol H ⁺ (9.4 mmol/L)	90	2	65.9	4.9	No (GC)	
0.378	B	EtOH 1.8	H ₄ SiW ₁₂ O ₄₀ 0.051 mmol H ⁺ (4.1 mmol/L)	90	2	76.3	4.8	No (GC)	
0.378	B	EtOH 1.8	H ₂ SO ₄ +NaSiW	90	2	60.2	3.9	No (GC)	

			0.051 mmol H ⁺						
0.378	B	EtOH 1.8	Amb-15 0.051 mmol H ⁺	90	2	15.9	1.3	No (GC)	
0.378	B	EtOH 1.8	H ₂ SO ₄ 0.051 mmol H ⁺ (14.2 mmol/L)	90	2	39.7	4.5	No (GC)	

^a Catalysts abbreviations are reported in the Abbreviations table.

6.2. Supporting information on Green Metrics and EcoScale

E-factor, as mentioned in the Introduction chapter, can be fractioned in several contributes depending on the specific waste evaluated (*i.e.*, waste from catalyst, reaction solvent, or purification). The contributes can be calculated using the following formulas:

- E-catalyst (E-cat), calculated as $\frac{\text{mass of catalyst}}{\text{mass of target product}}$;
- E-reaction solvent (E-rxn solv), calculated as $\frac{\text{mass of reaction solvent}}{\text{mass of target product}}$;
- E-work up, calculated as $\frac{\text{mass of work-up materials}}{\text{mass of target product}}$;
- E-purification (E-purif), calculated as $\frac{\text{mass of purification materials}}{\text{mass of target product}}$;
- E-excess, calculated as $\frac{\text{mass of excess reagents}}{\text{mass of target product}}$, where the excess reagents are measured with respect to the limiting reagent;
- E-kernel, calculated as $\frac{(\text{mass of reagents} - \text{mass of target product})}{\text{mass of target product}} - E \text{ excess}$, it represents the mass contribution of reaction by-products and unreacted starting materials to the total E-factor.

The EcoScale algorithm window appears as reported in Figure 6.1.

Figure 6.1. EcoScale calculator.

6.3. Mass analysis of the dark solid residue on the bottom of the autoclave

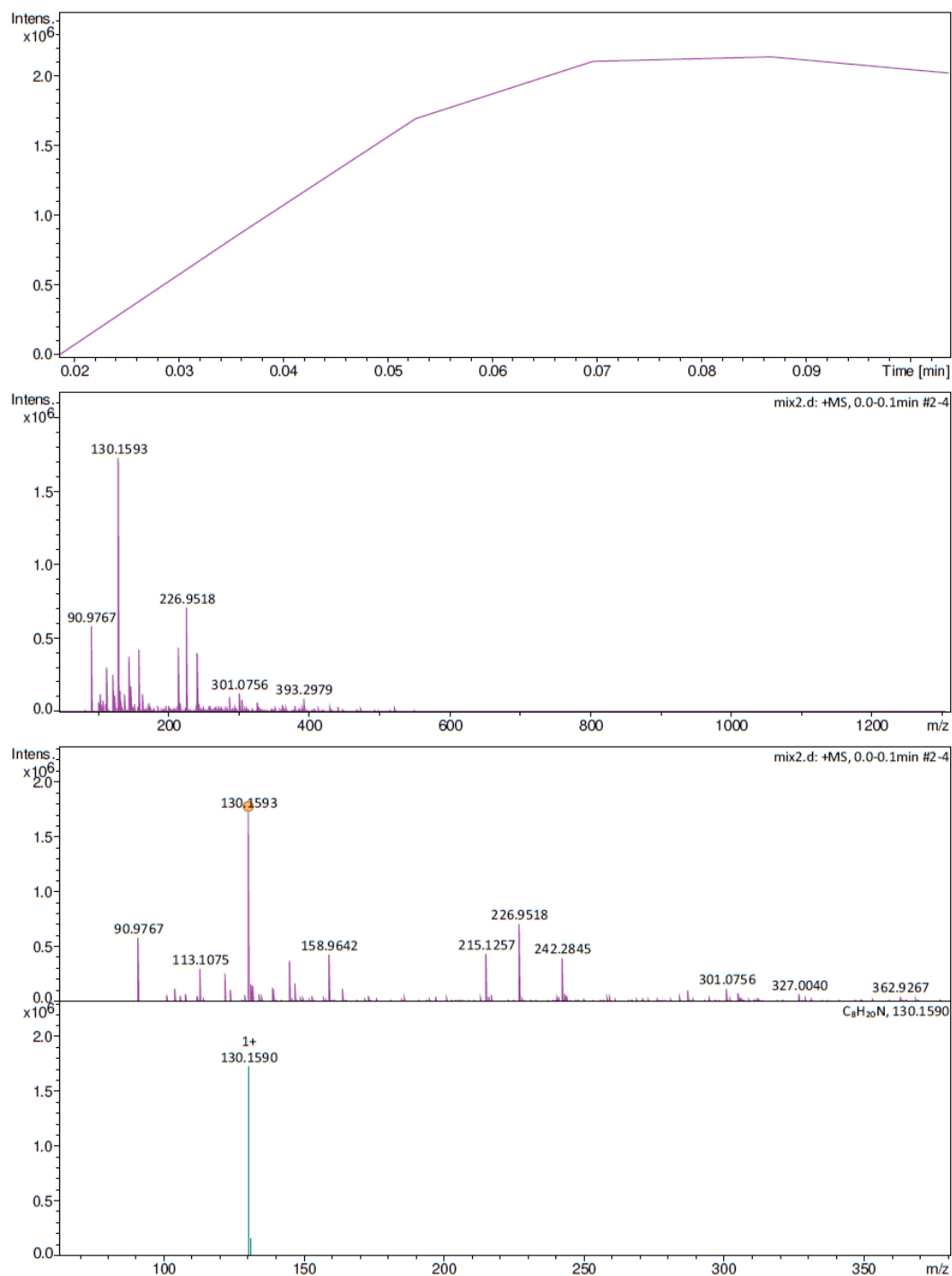


Figure 6.1. Mass analysis of the solid, dark residue in the autoclave.

6.4. Properties of Amberlysts and Purolites

Table 6.2. Properties of several Amberlysts and Purolites.^a

	Amberlyst-15	Amberlyst-36	CT151	CT269	CT275	CT275DR
Polymer structure	Macroporous polystyrene crosslinked with divinylbenzene					
Appearance	Spherical Beads					
Functional Group	Sulfonic Acid					
Ionic Form	H ⁺ form					
Particle Size Range μm	< 300	600-850	425 - 1200	425 - 1200	425 - 1200	425 - 1200
Dry Weight Capacity eq/kg (H ⁺ form)	≥ 4.7	≥ 5.4	5.1	5.2	5.2	5.2
Moisture Retention % (H ⁺ form)	≤ 1.6	51 - 57	54 - 59	51 - 57	51 - 59	< 5
Surface Area m ² /g	53	33	15 - 25	35 - 50	20 - 40	20 - 40
Pore Volume mL/g	0.40	0.20	0.15 - 0.30	0.30 - 0.50	0.40 - 0.60	0.40 - 0.60
Average Pore Diameter Å	300	240	250 - 400	250 - 425	400 - 700	400 - 700
Temperature Limit °C	120	150	150	130	130	130

^a All Purolite® information is available on <https://www.purolite.com/index>. All Amberlyst-15 information are available on the DuPont (<https://www.dupont.com/content/dam/dupont/amer/us/en/watersolutions/public/documents/en/45-D00927-en.pdf>).

6.5. ¹H-NMR spectra of reaction mixture for the synthesis of HMF at different times.

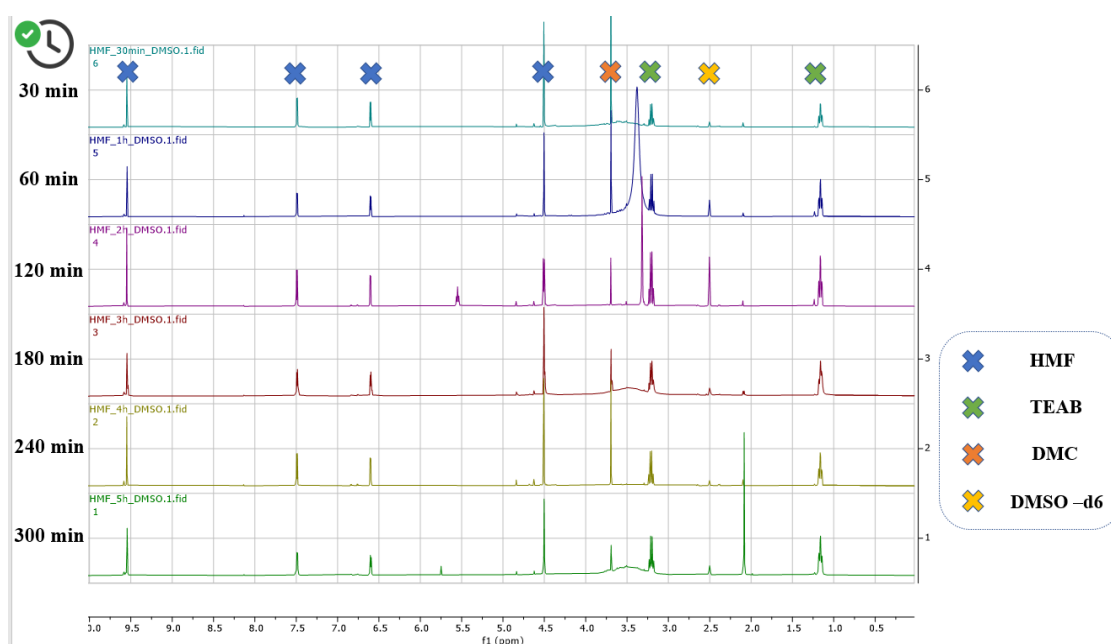


Figure 6.2. NMR spectra of the reaction mixture for the synthesis of HMF, at different times.

6.6. $^1\text{H-NMR}$ spectrum of the reaction #3 Table 3.4.

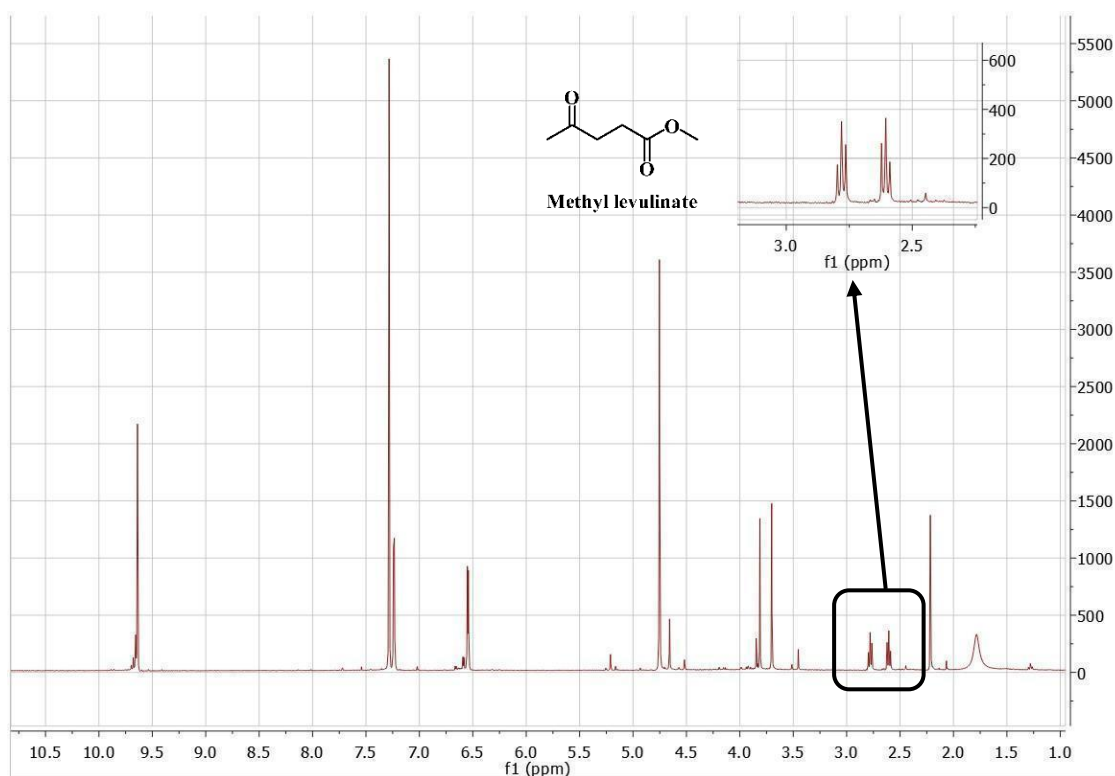


Figure 6.3. Protonic NMR spectrum of the reaction conducted at 150 °C for 2 hours, in CDCl_3 .

6.7. $^1\text{H-NMR}$ spectrum of the insoluble dark-brown oil after the purification step

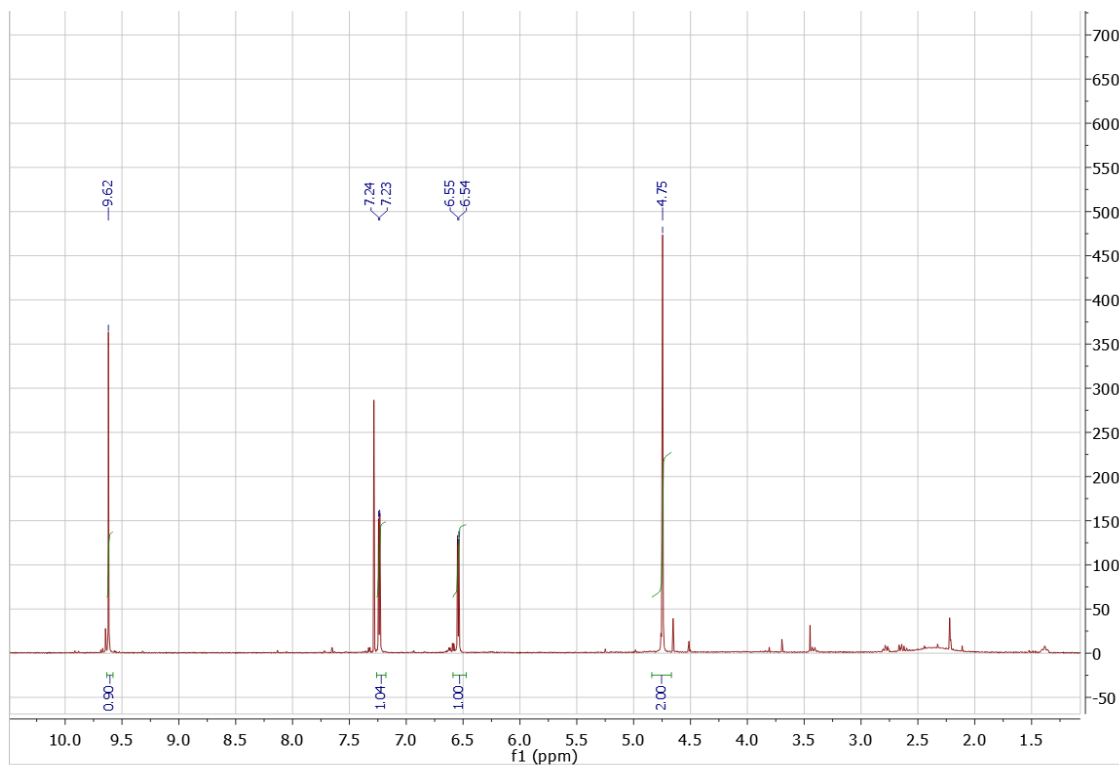
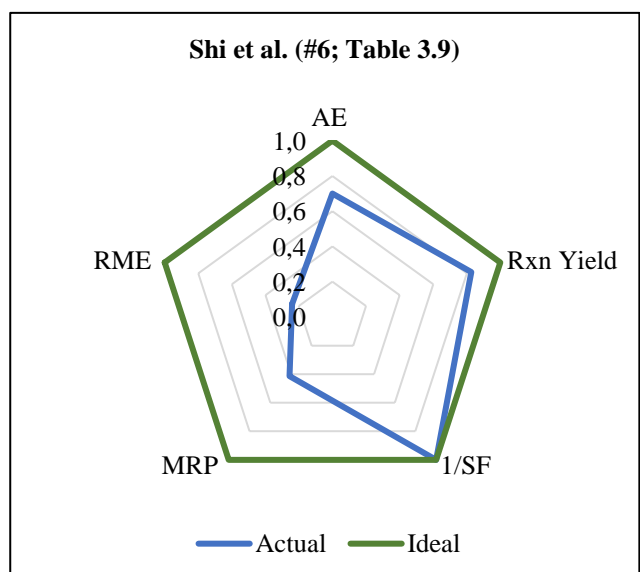
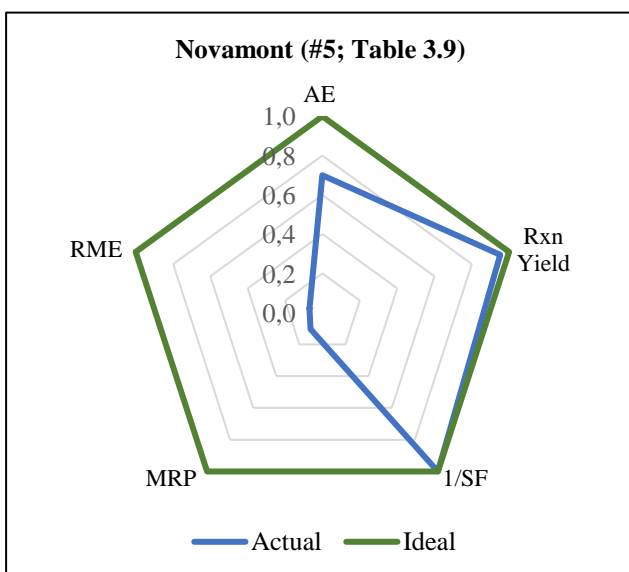
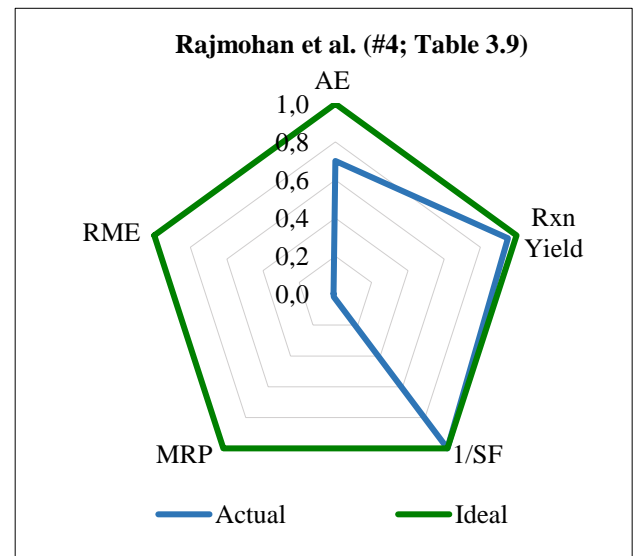
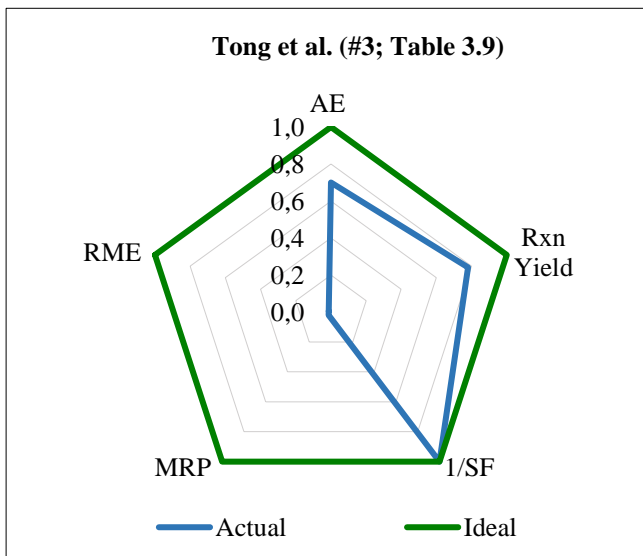
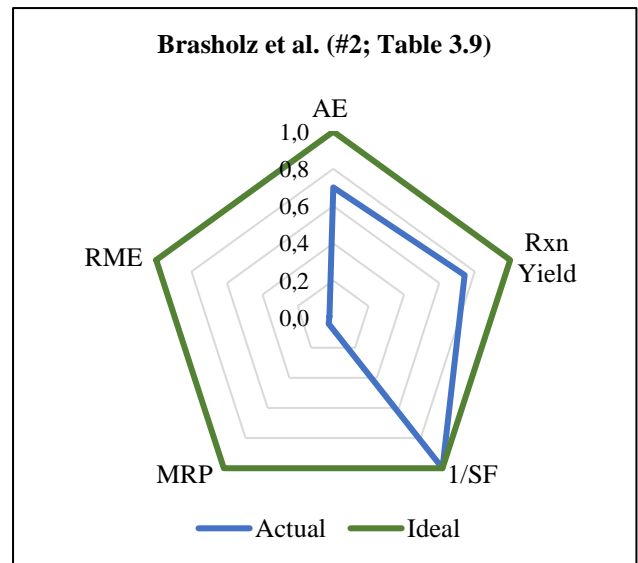
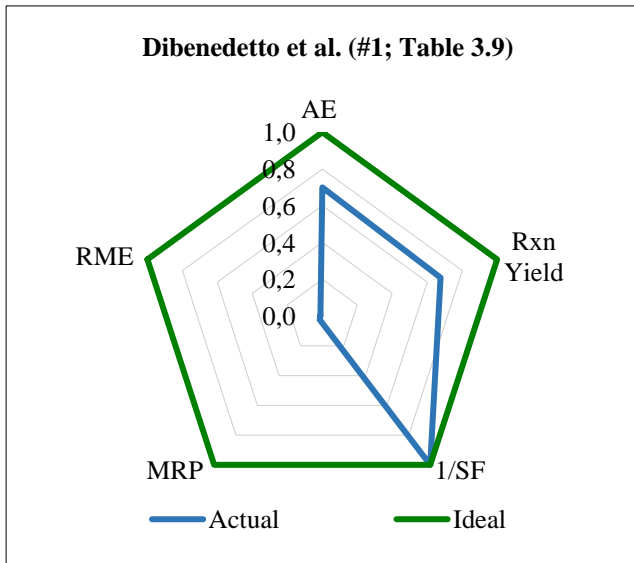
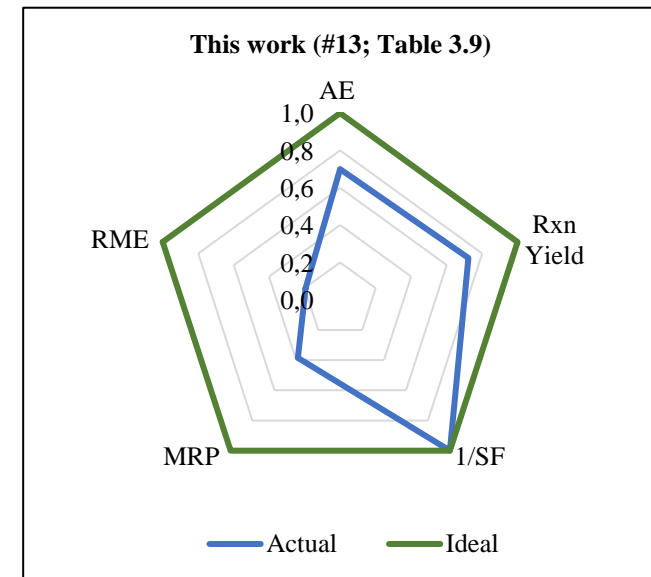
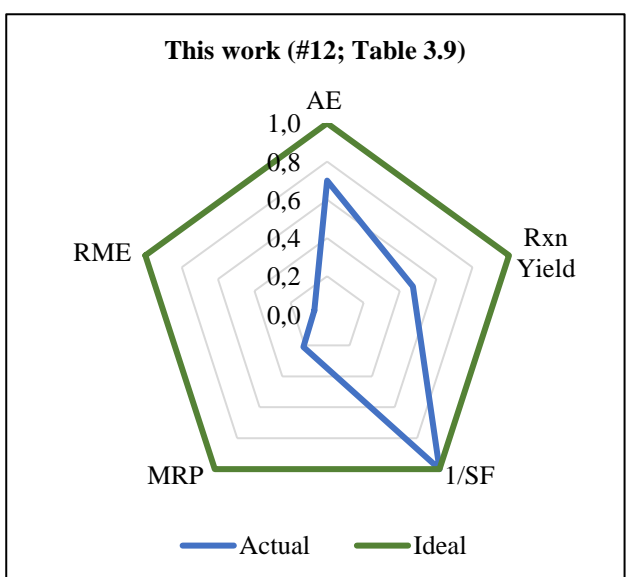
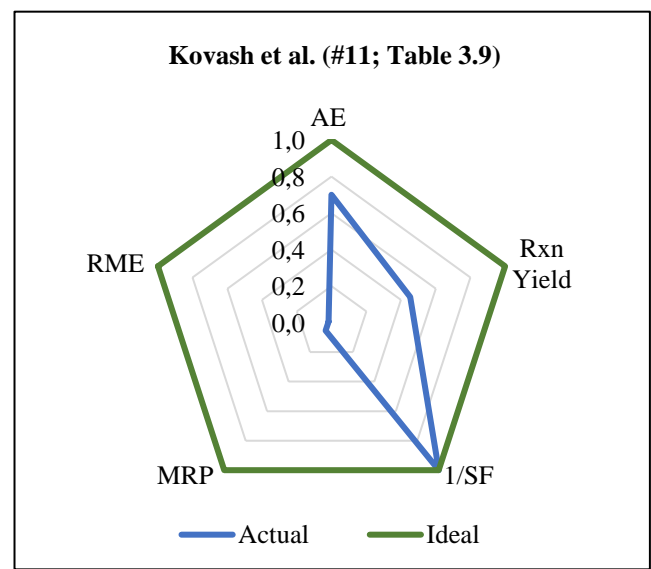
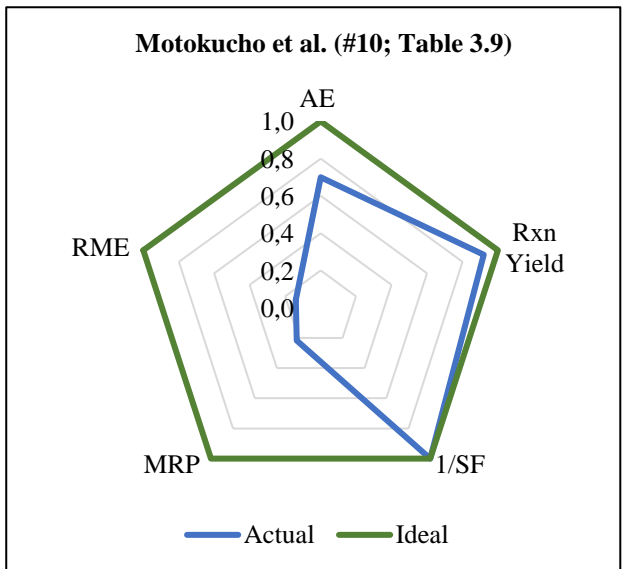
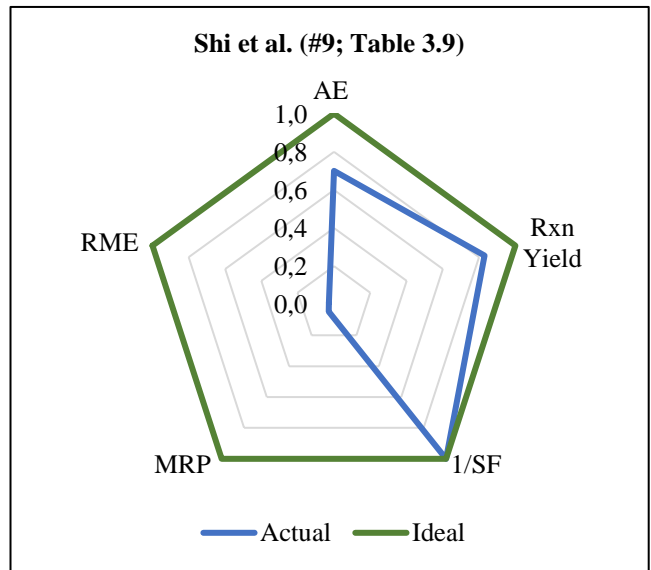
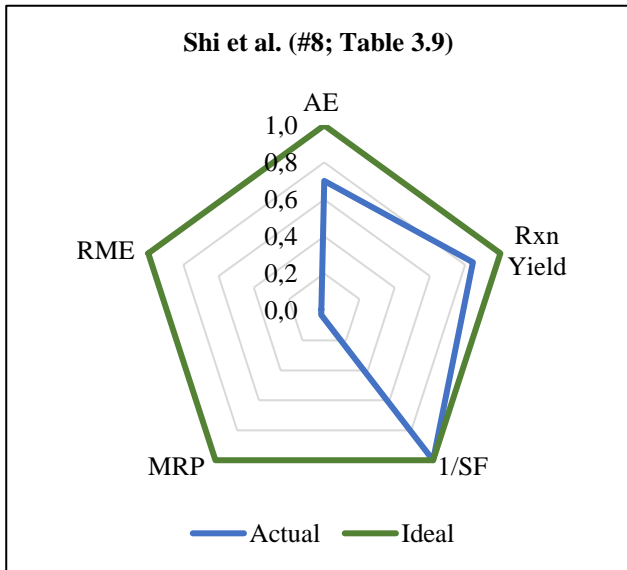
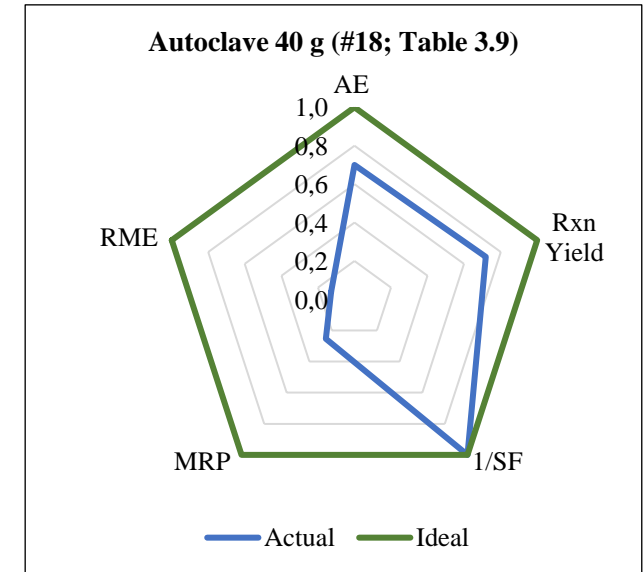
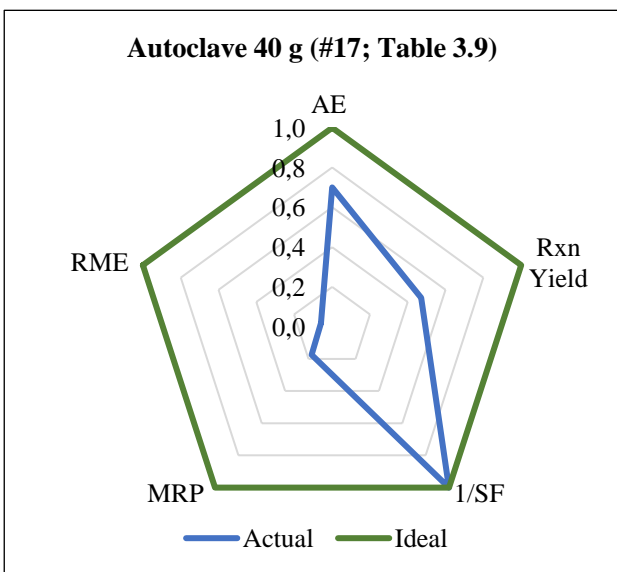
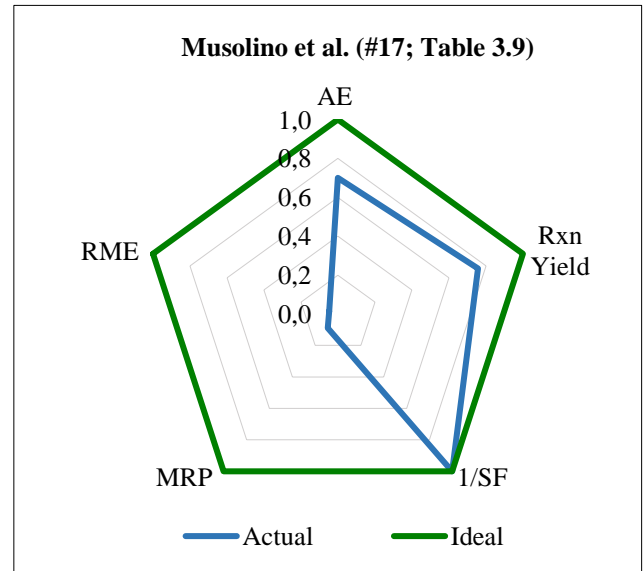
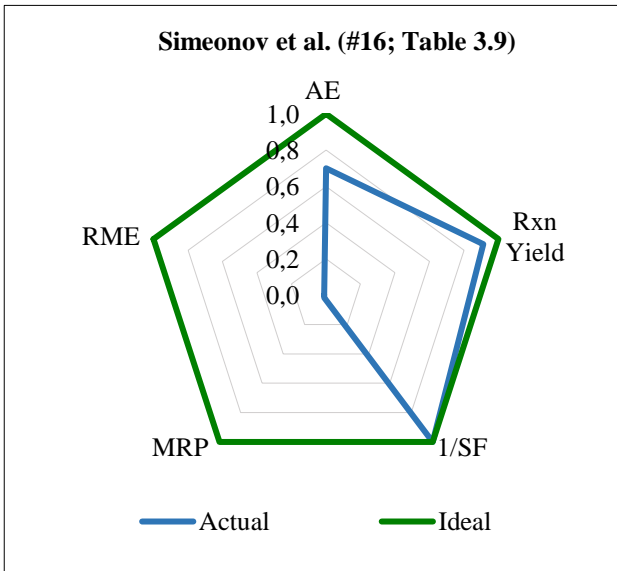
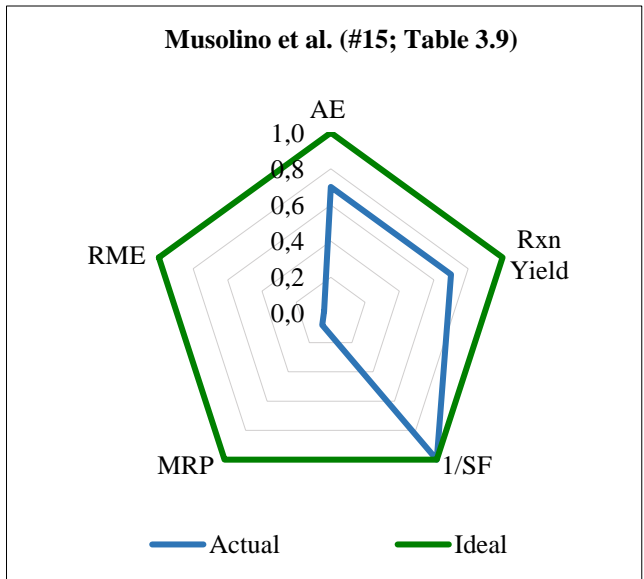
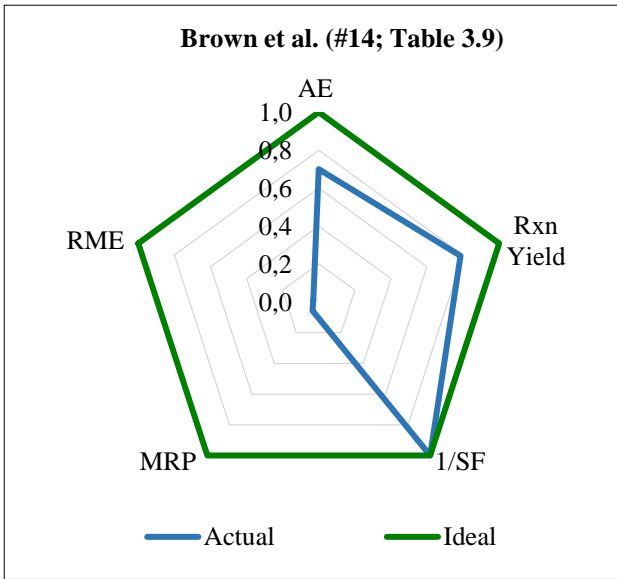


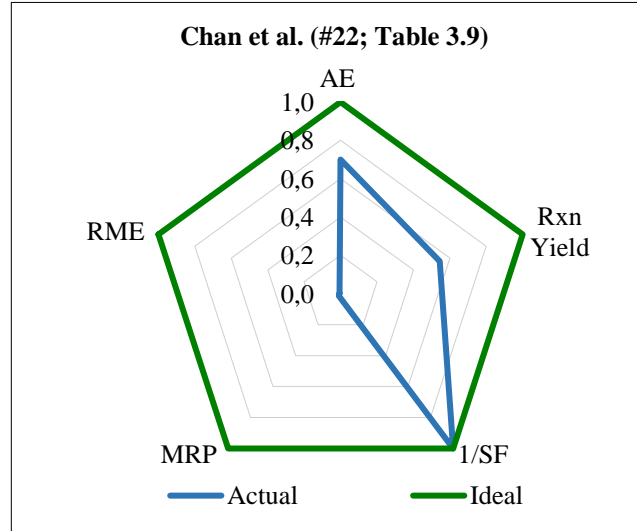
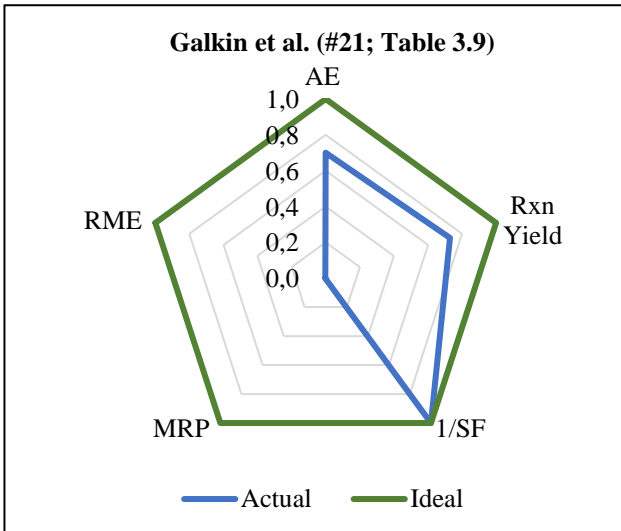
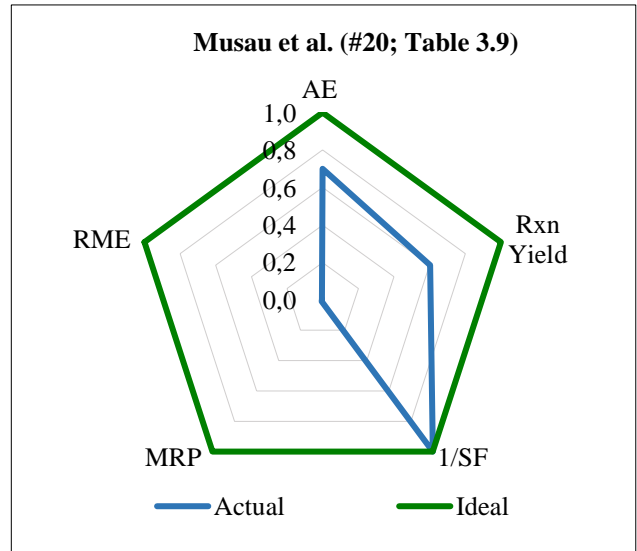
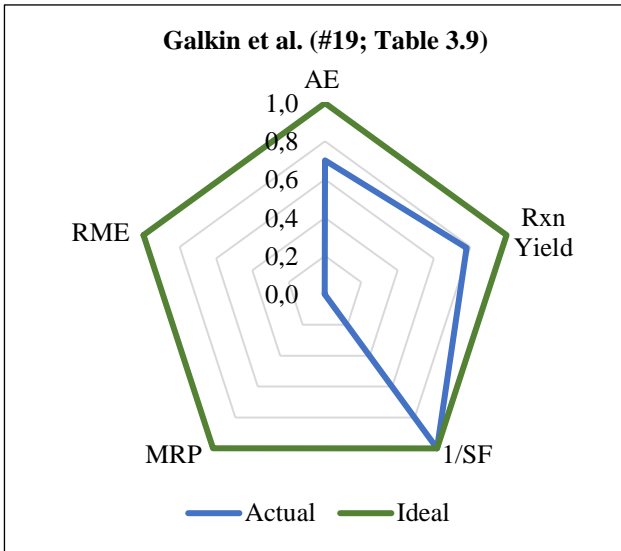
Figure 6.4. Protonic NMR spectrum of the insoluble dark-brown oil remained after purification protocol.

6.8. *J. Andraos radial pentagon for the HMF procedures*

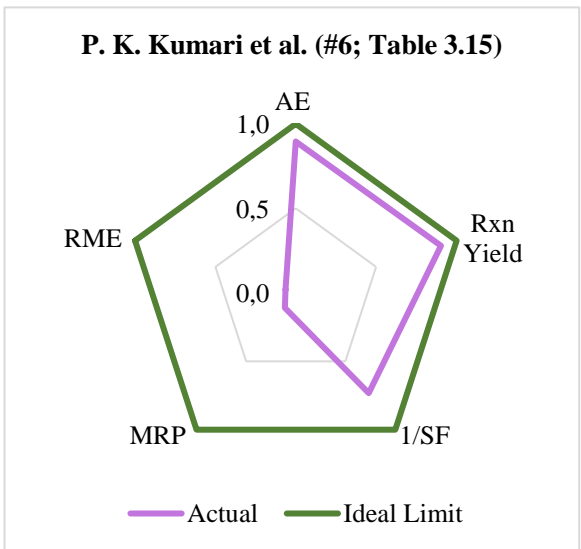
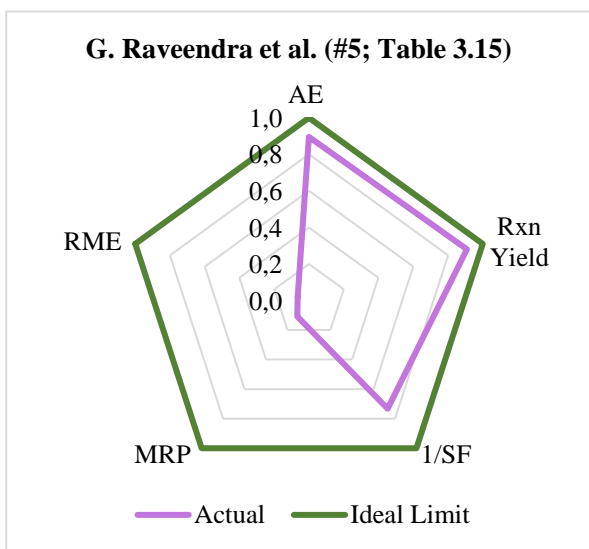
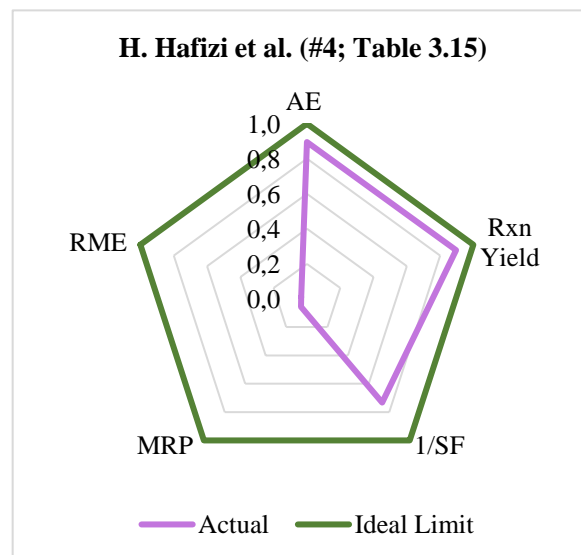
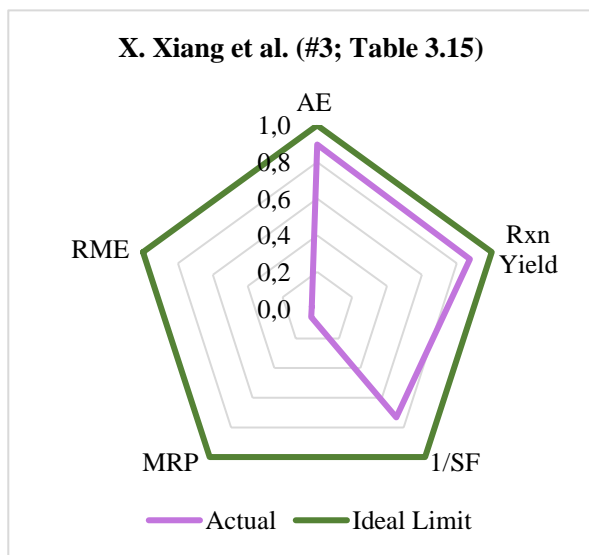
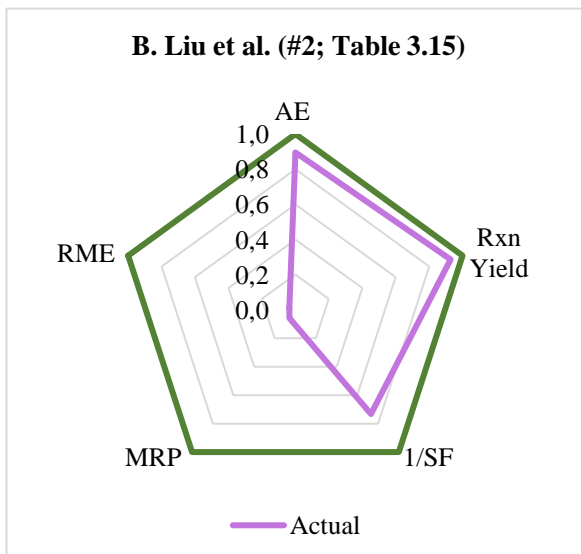
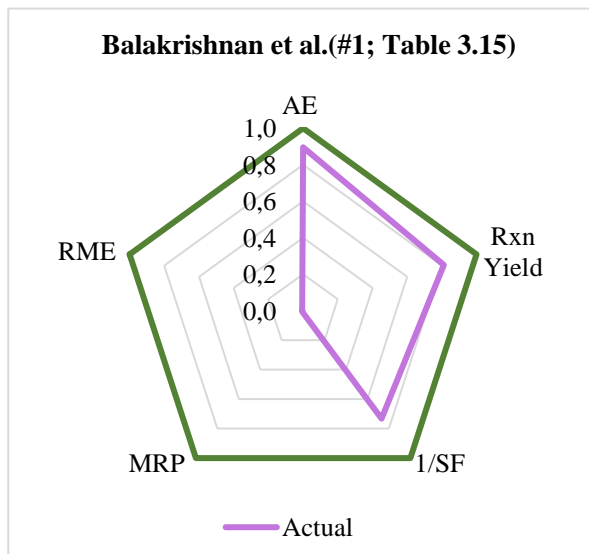




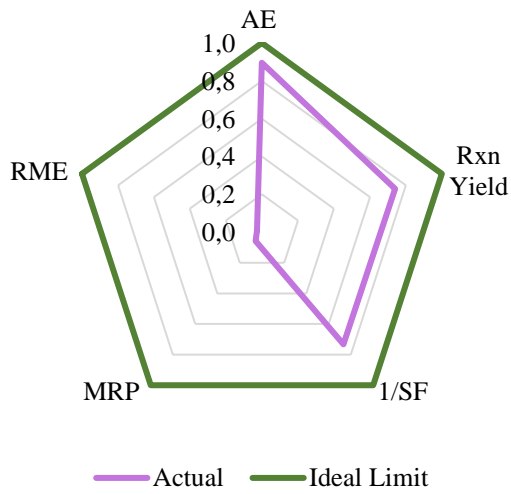




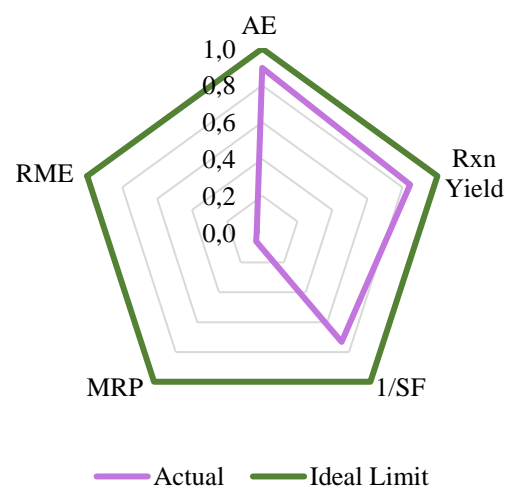
6.9. *J. Andraos radial pentagon of the EMF procedures*



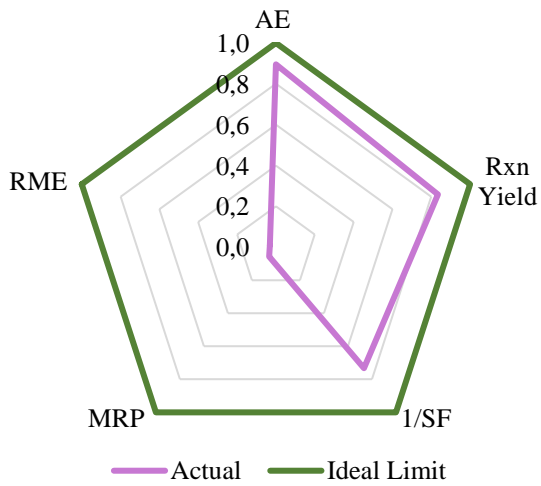
D. Gupta et al. (#7; Table 3.15)



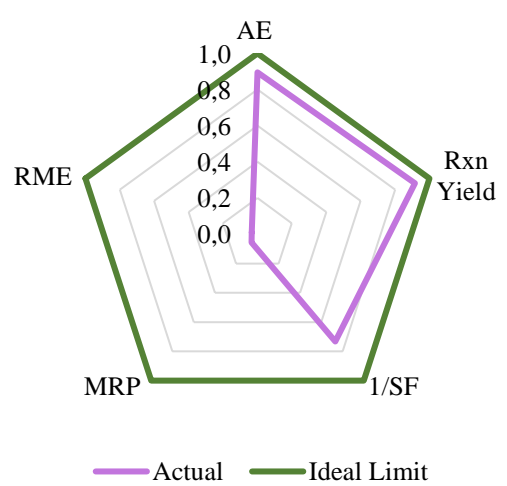
B. Liu et al. (#8; Table 3.15)



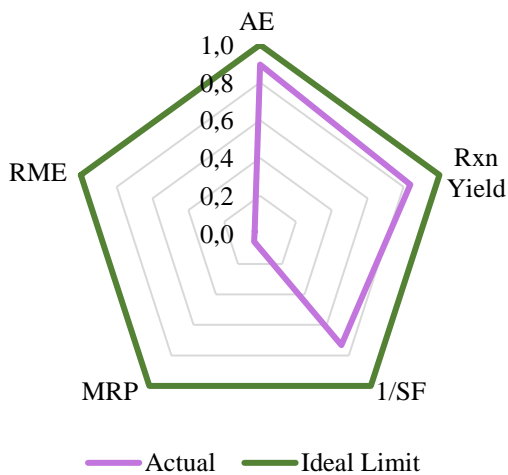
A. Liu et al. (#9; Table 3.15)



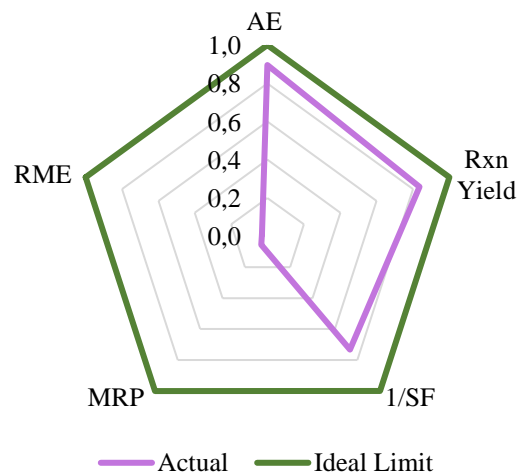
A. Liu et al. (#10; Table 3.15)



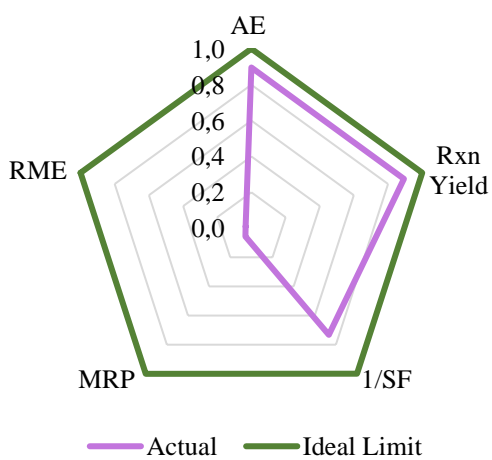
B. Liu et al. (#11; Table 3.15)



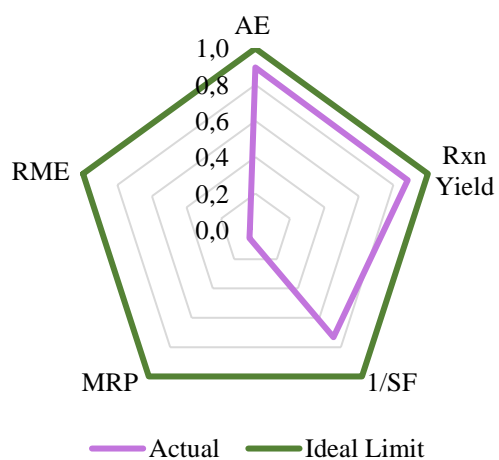
S. Wang et al. (#12; Table 3.15)



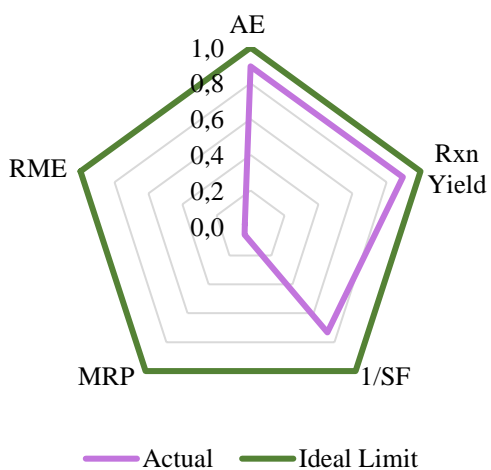
Z. Zhang *et al.* (#13; Table 3.15)



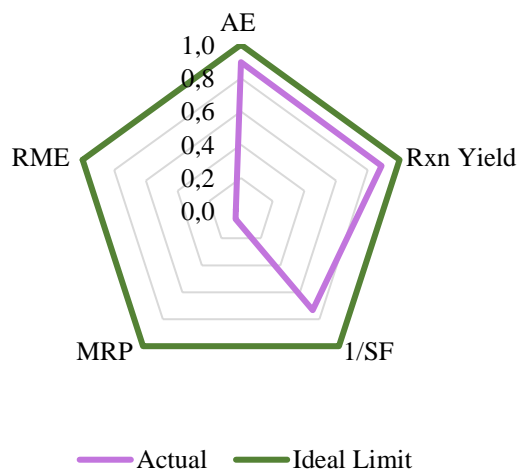
Z. Yuan *et al.* (#14; Table 3.15)



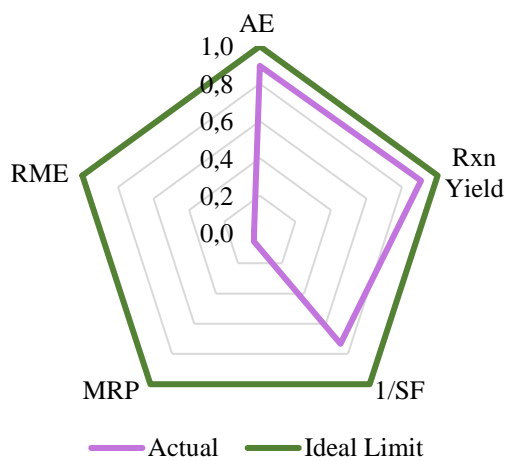
S. Yin *et al.* (#15; Table 3.15)



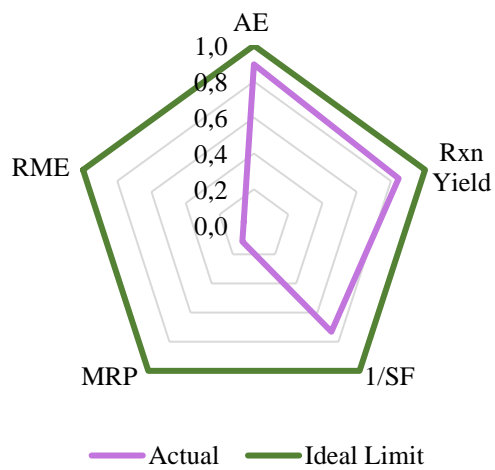
Y. Ren *et al.* (#16; Table 3.15)

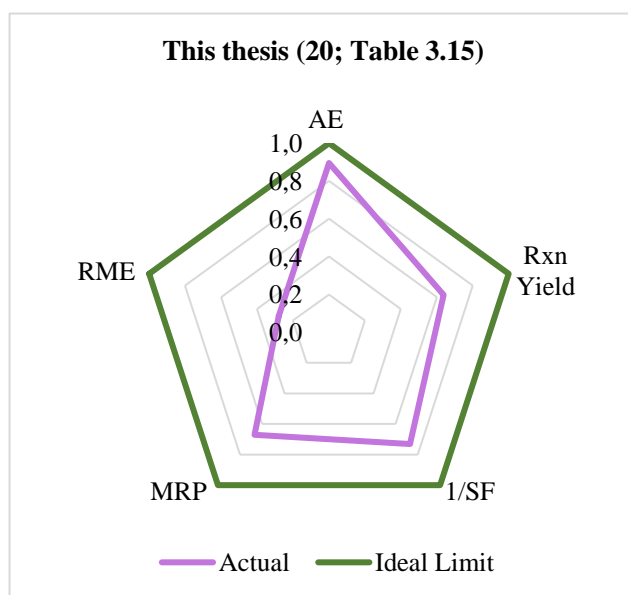
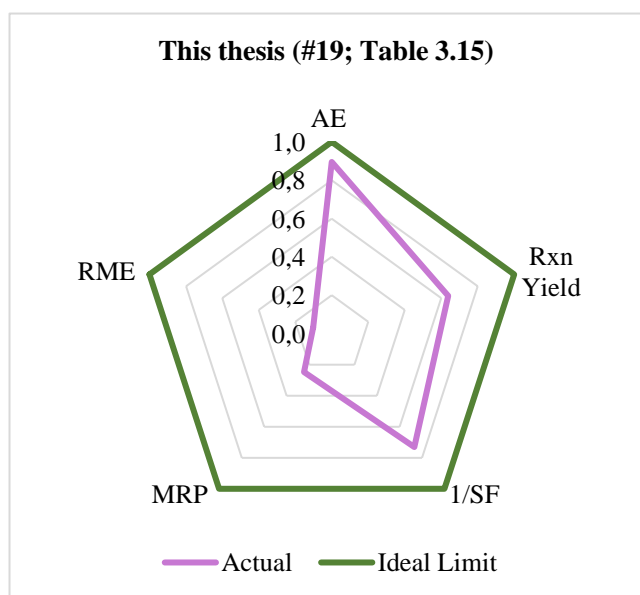


L. Bing *et al.* (#17; Table 3.15)



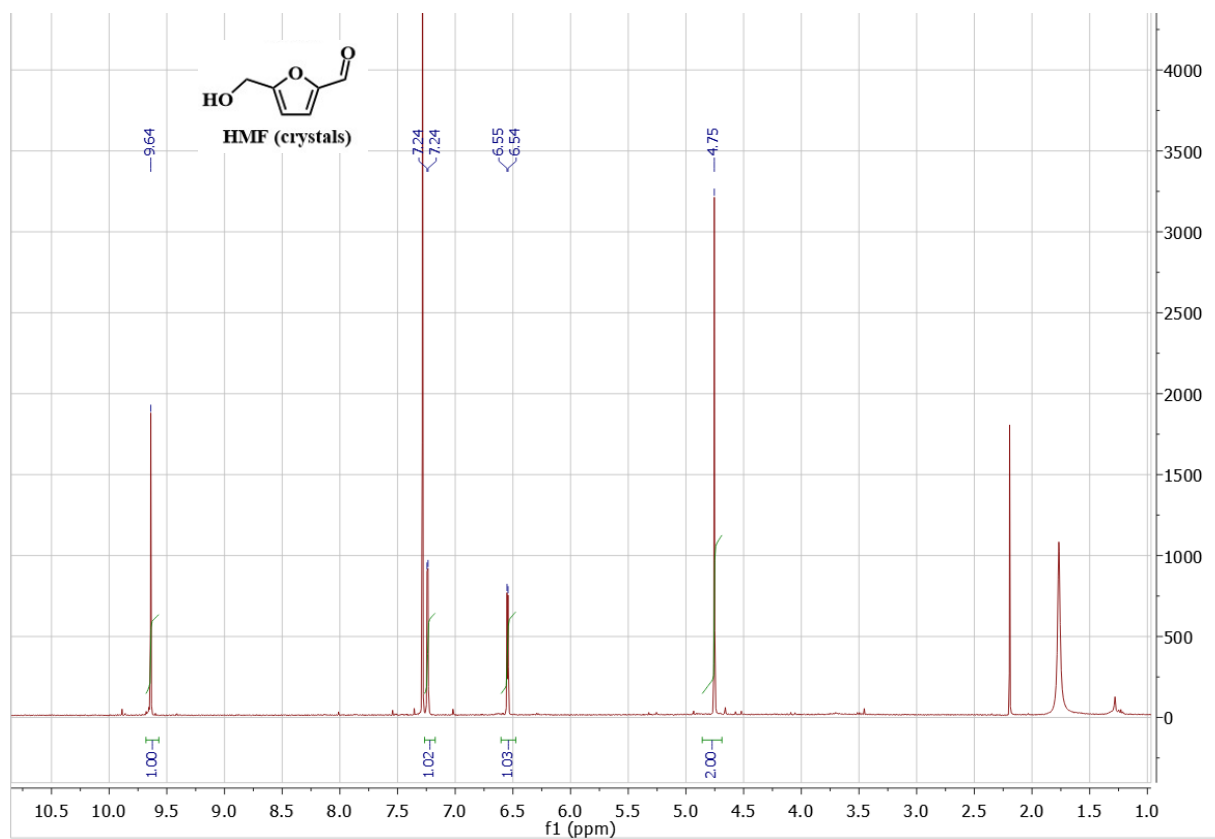
M. I. Alam *et al.* (#18; Table 3.15)

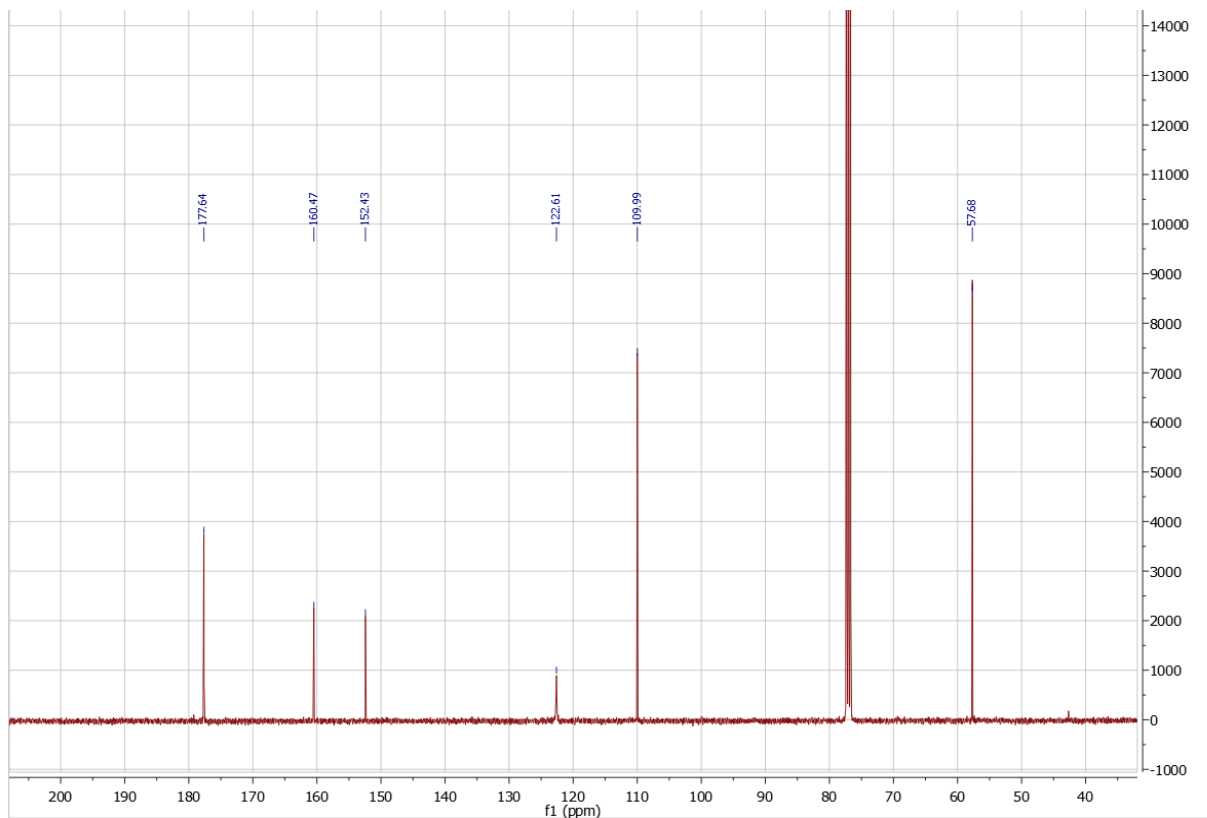




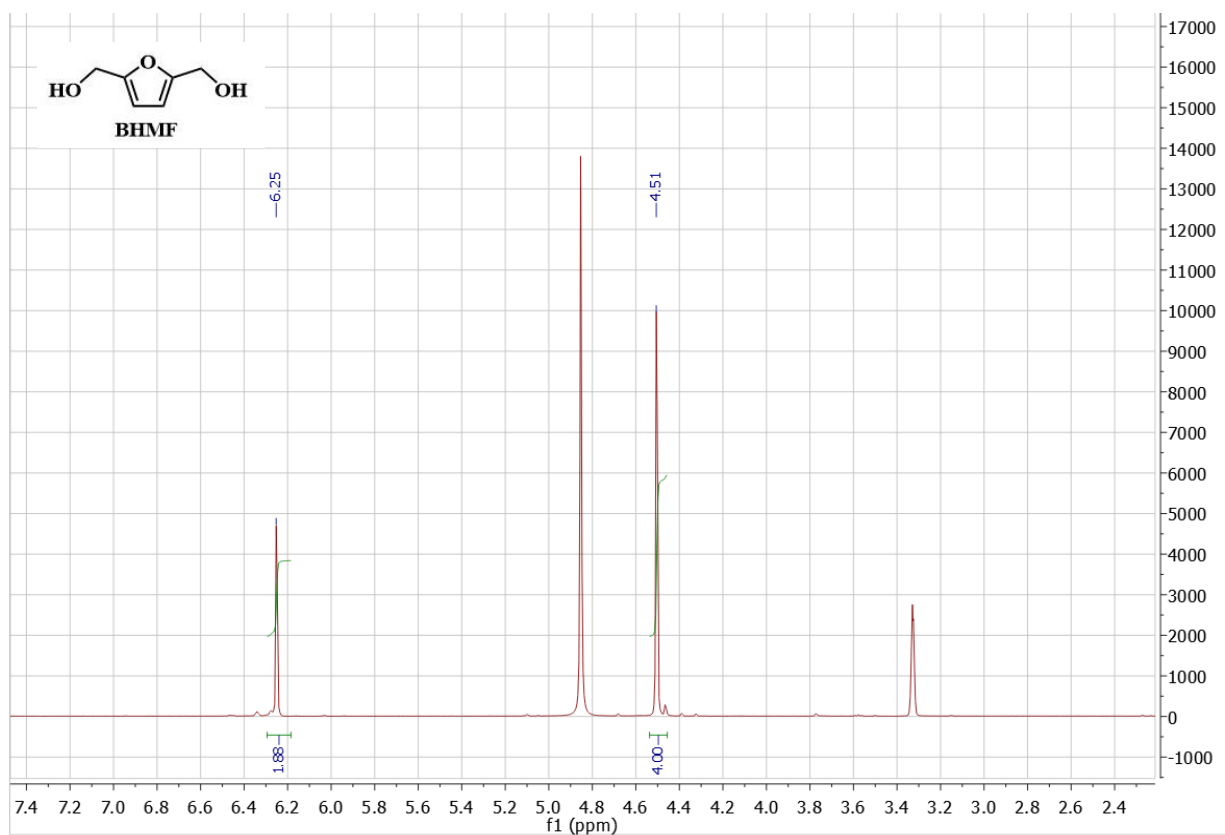
6.10. ^1H - and ^{13}C -NMR of products

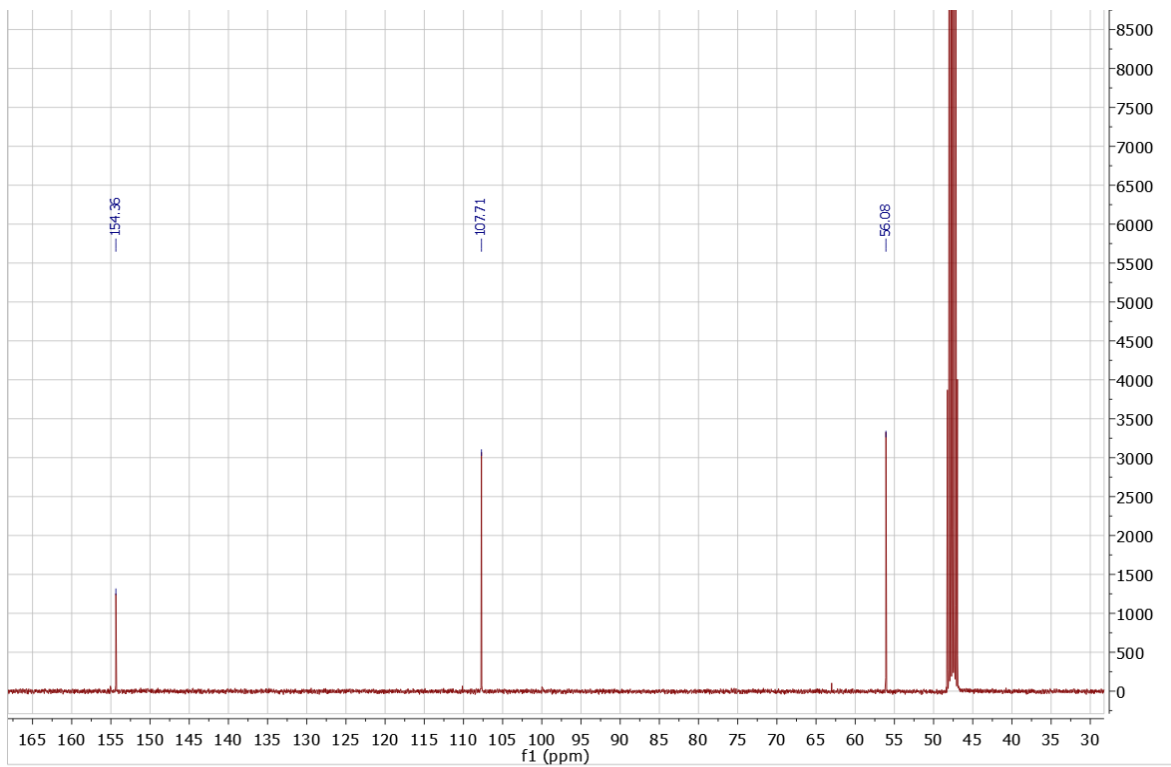
5-hydroxymethylfurfural (HMF) in CDCl_3



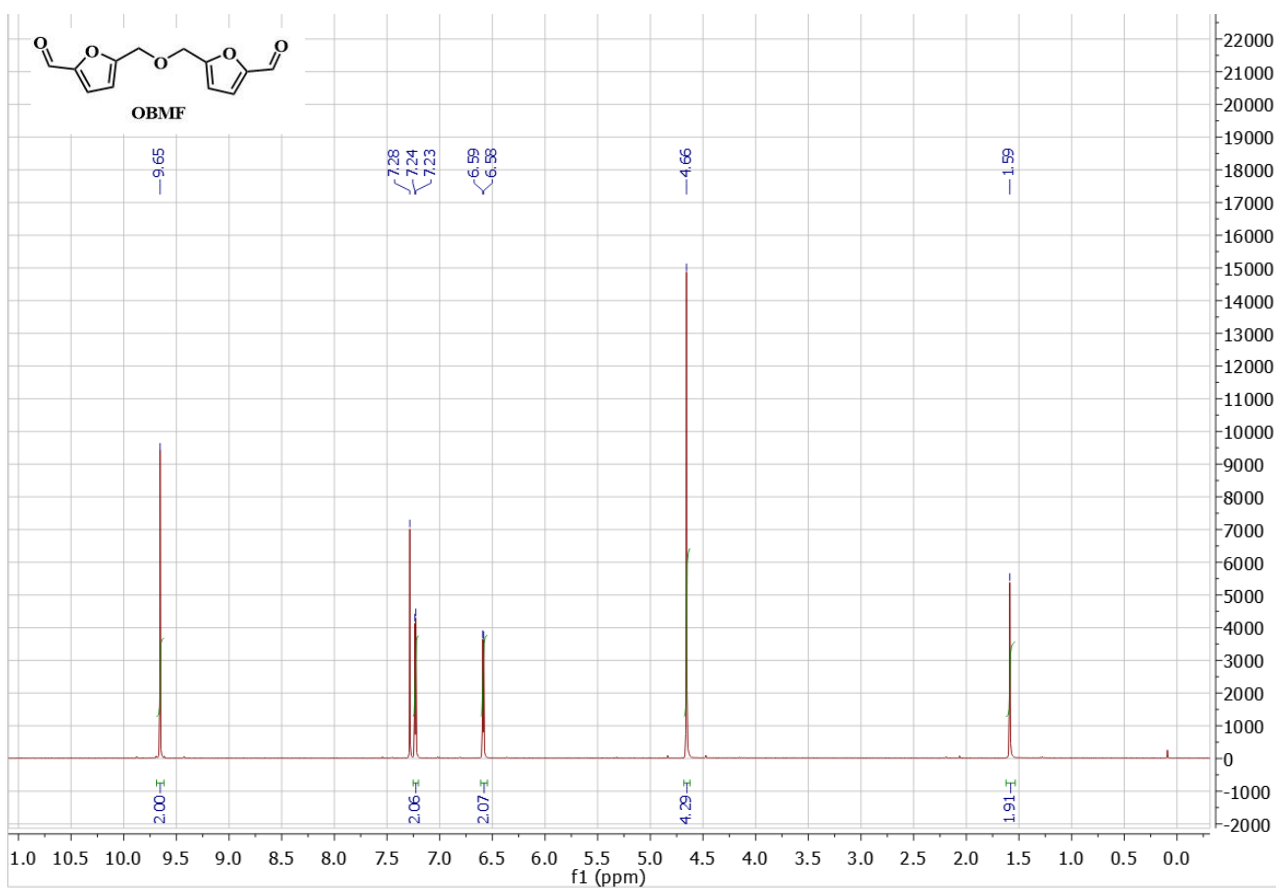


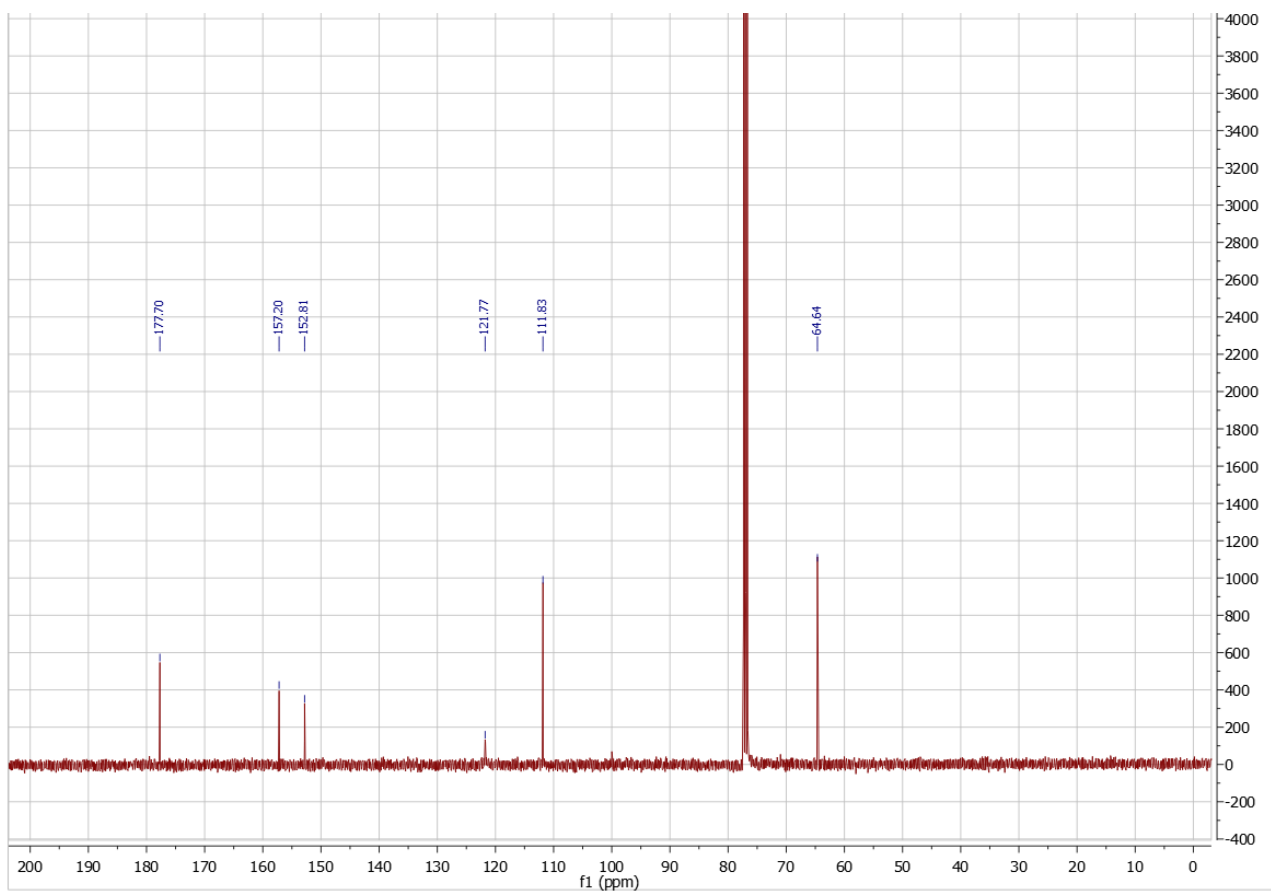
Bis-(hydroxymethyl)furan (BHMF) in MeOD



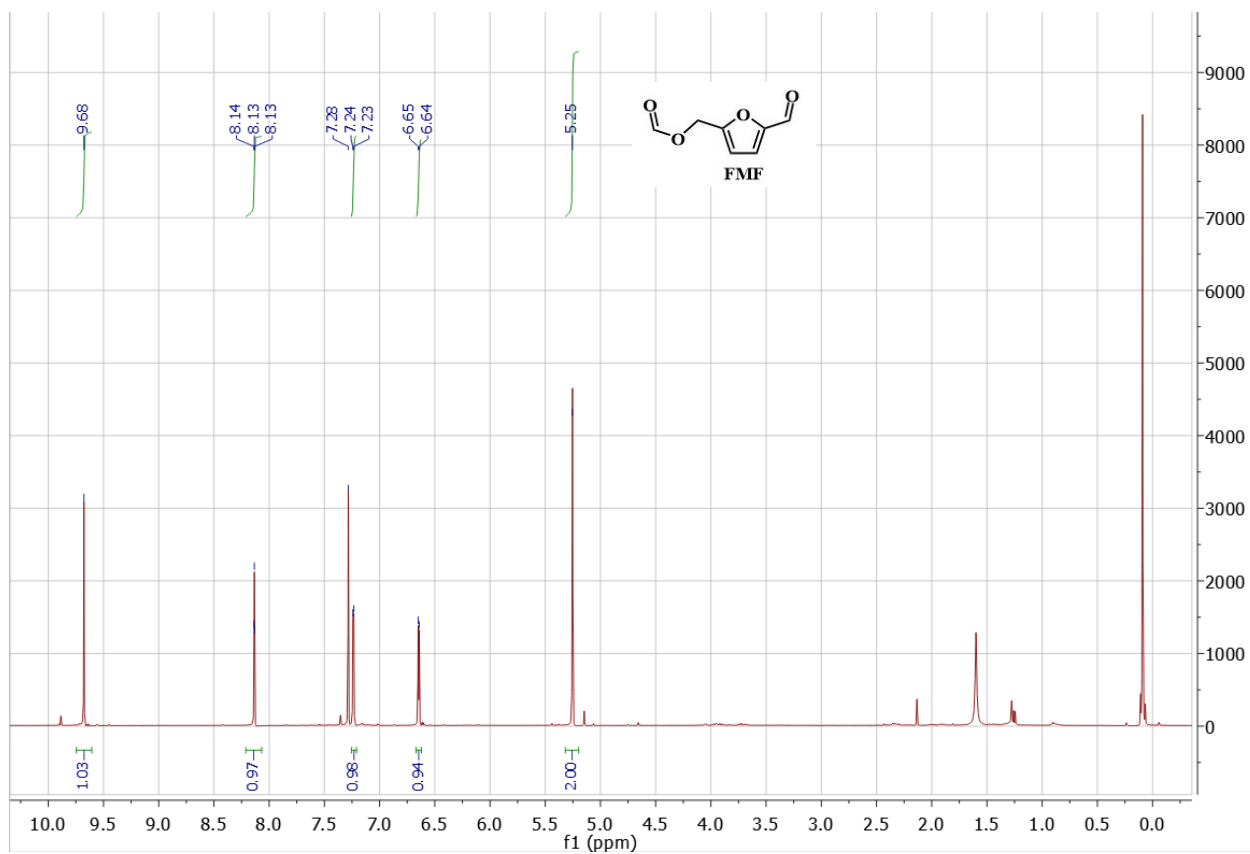


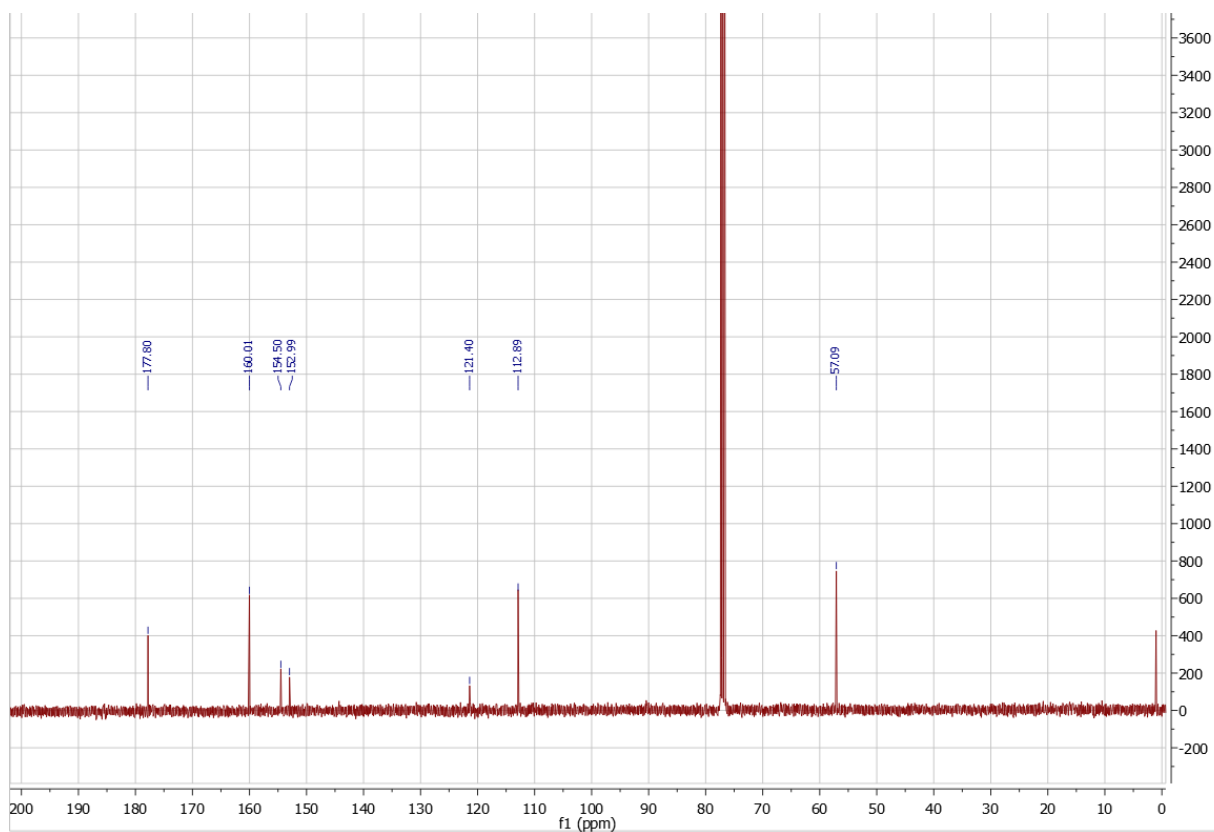
5,5'-(oxy-bis(methylene))-2-furfural (OBMF) in CDCl₃



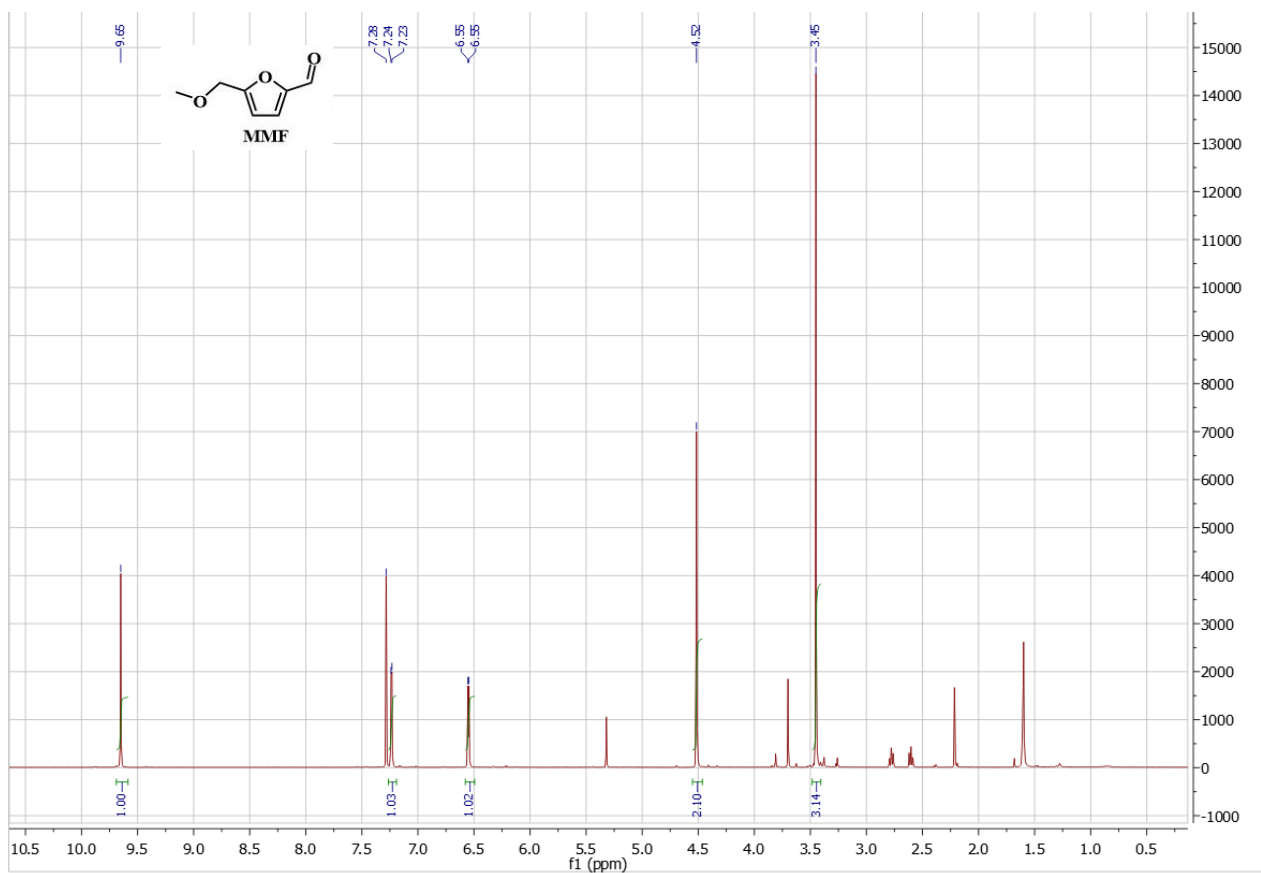


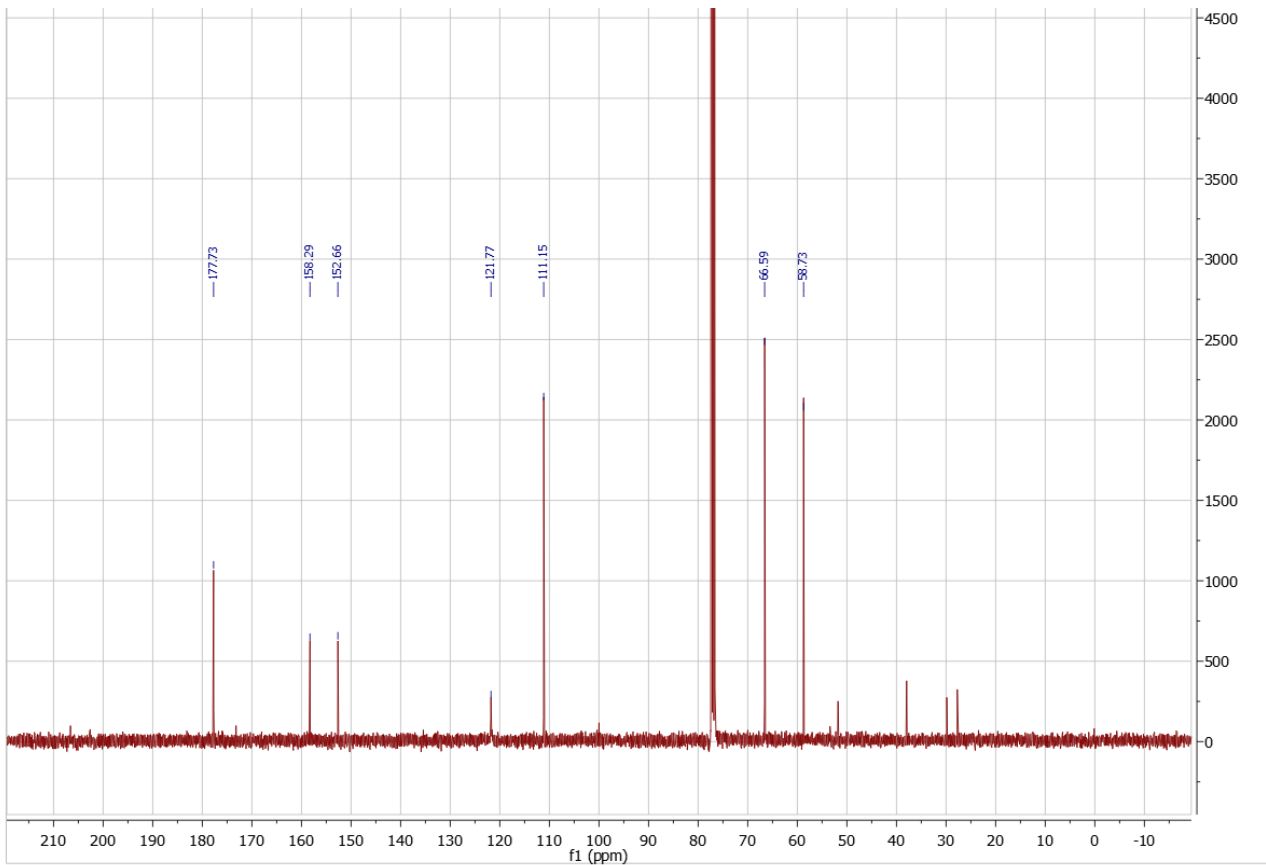
(5-formyl-2-furanyl)methylformate (FMF) in CDCl₃



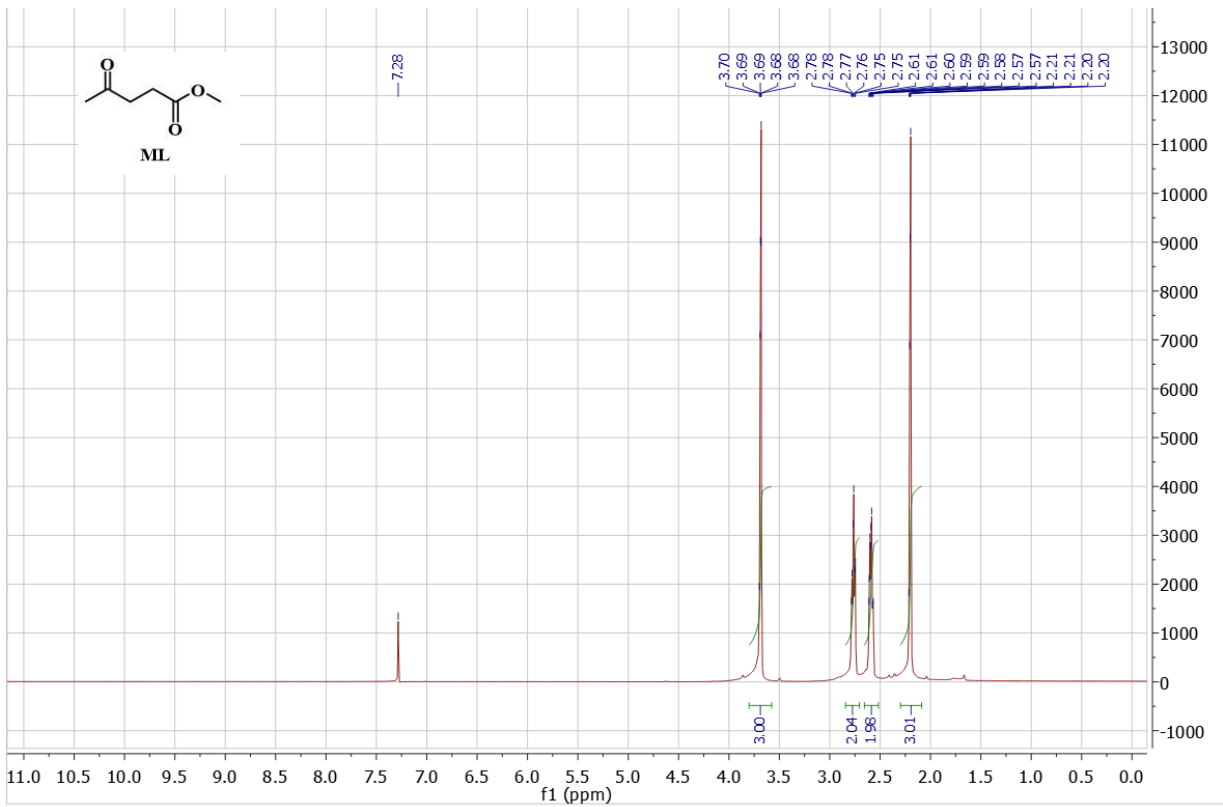


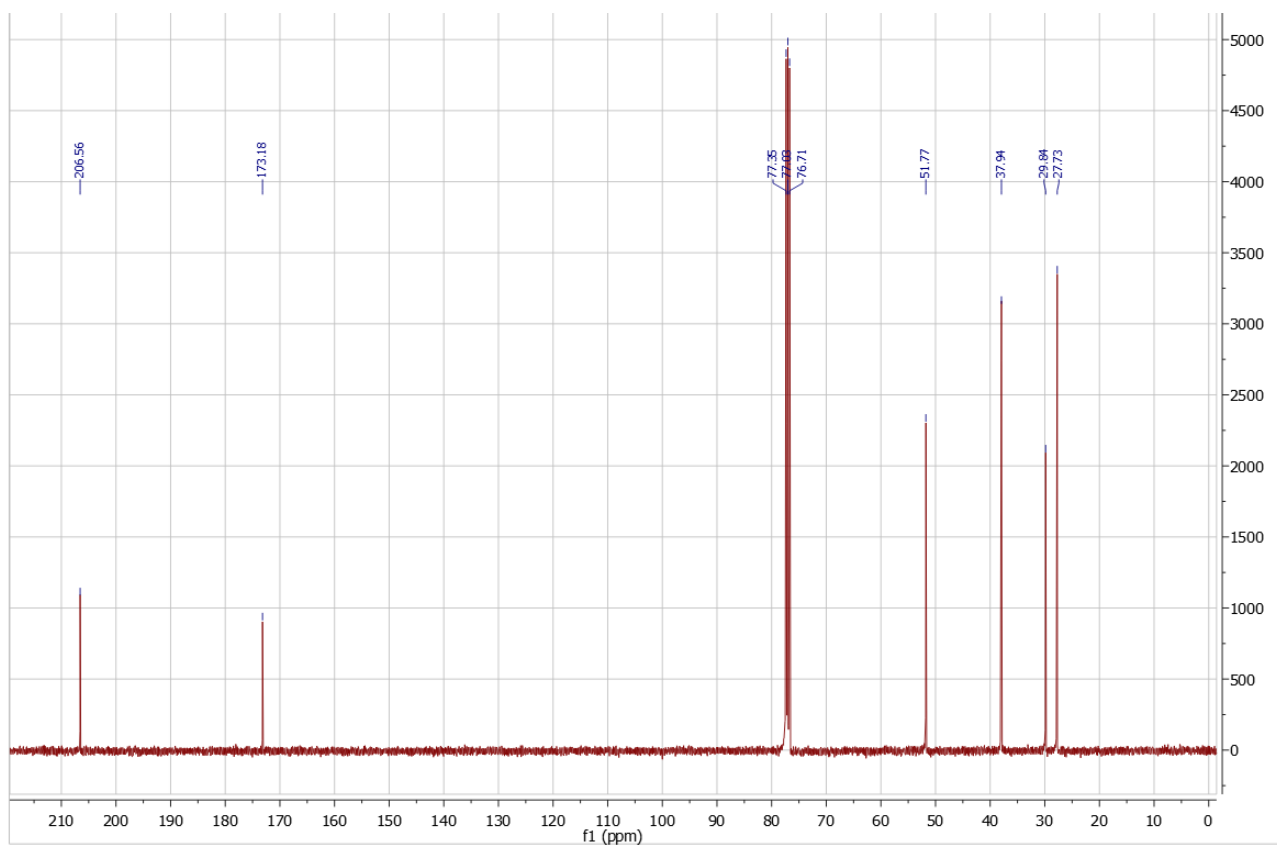
5-methoxymethylfurfural (MMF) in CDCl₃ (with residues of methyl levulinate)



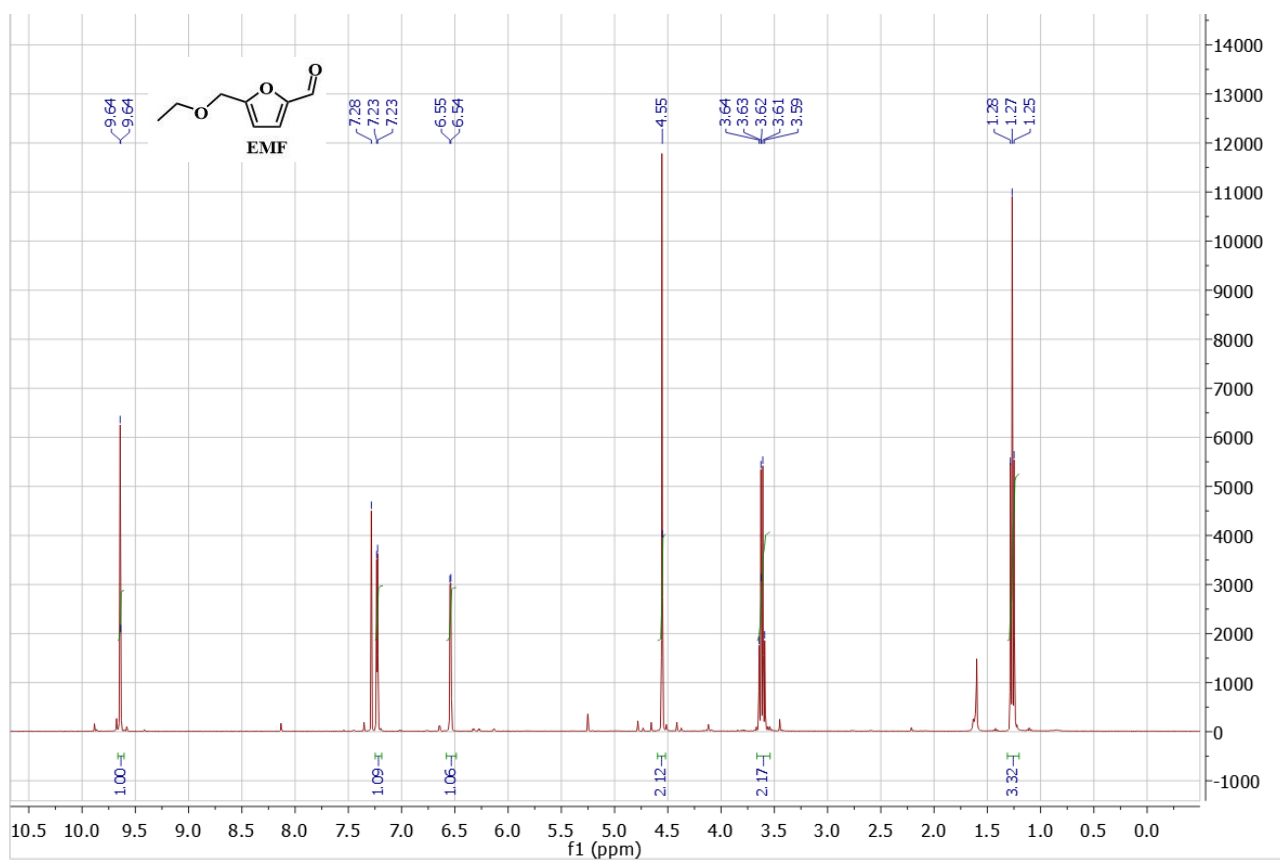


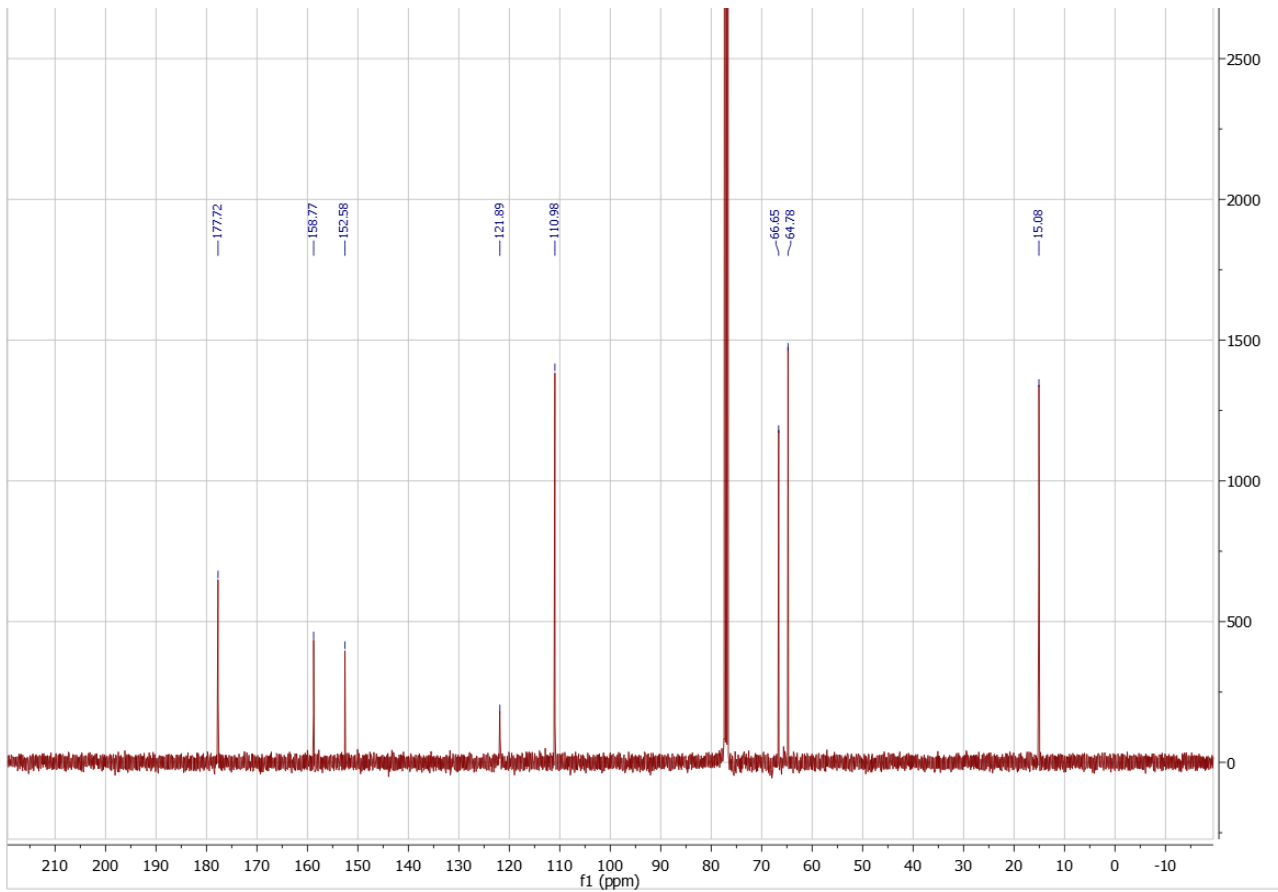
Methyl levulinate (ML) in CDCl₃



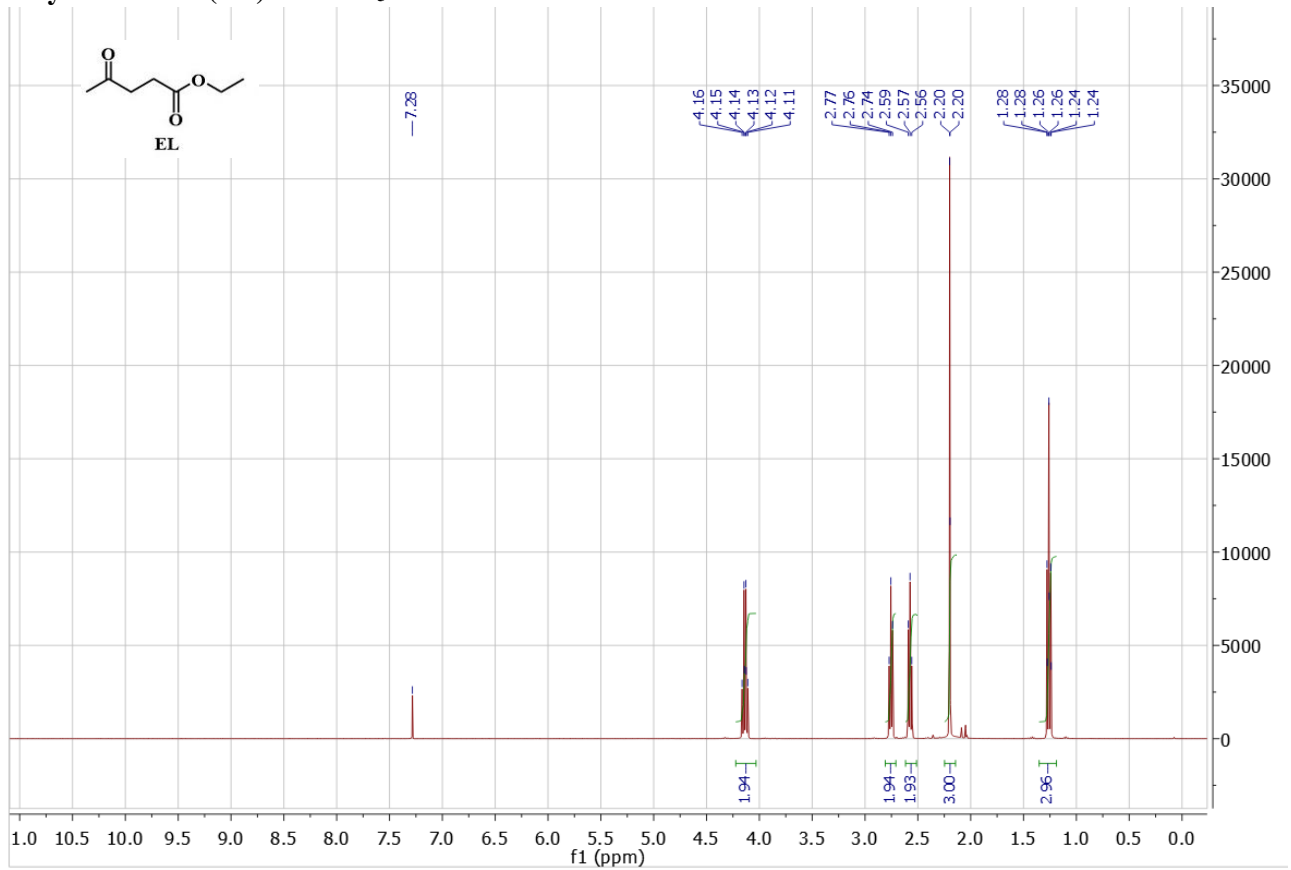


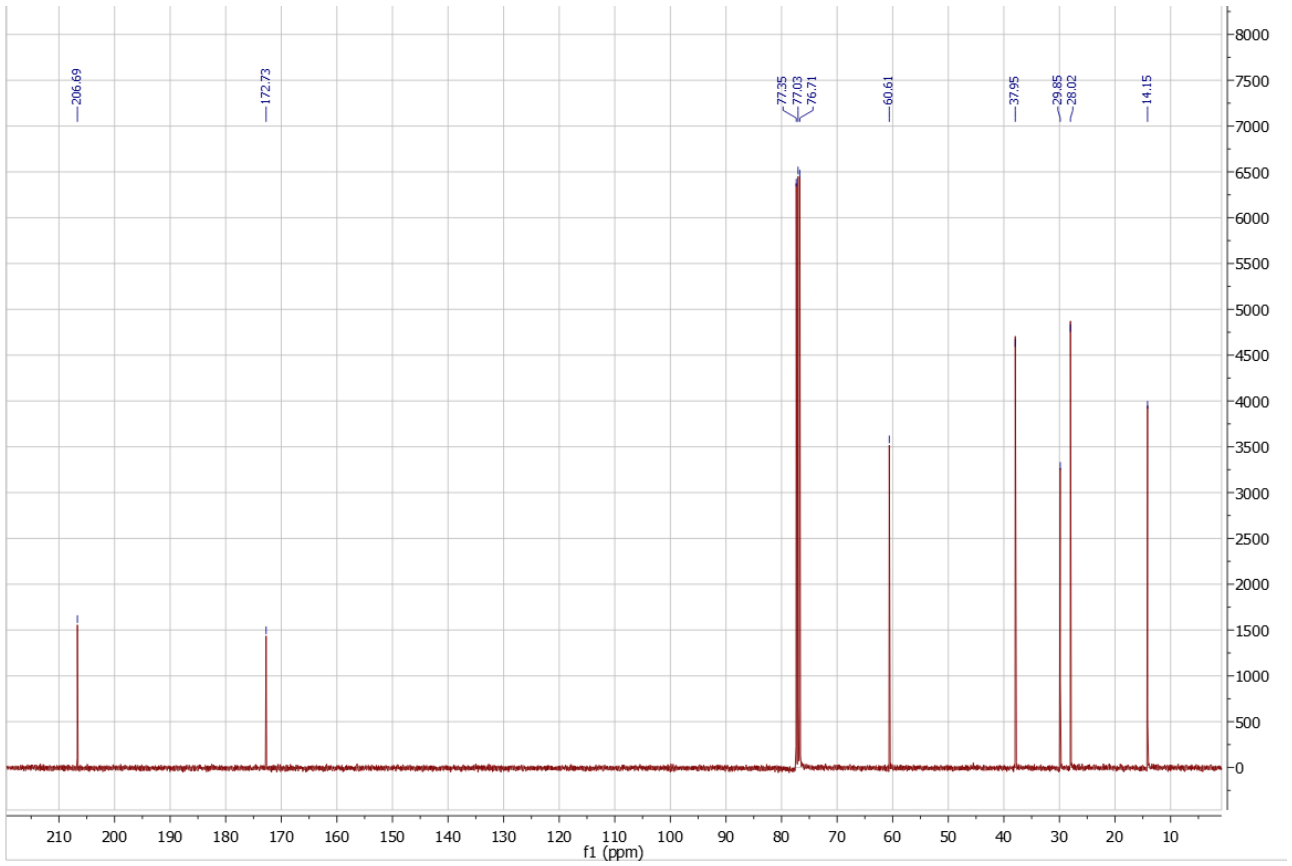
5-ethoxymethylfurfural (EMF) in CDCl₃





Ethyl levulinate (EL) in CDCl₃





5-propoxymethylfurfural (PMF) with impurities in CDCl₃

