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DIPLOMARBEIT

WASTE TO VALUE – IONIC LIQUID STRATEGIES FOR THE VALORIZATION OF SPENT COFFEE GROUNDS

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unter Anleitung von
Ao.Univ.Prof. Dipl.-Ing. Dr. techn. Peter Gärtner
und
Univ.Ass. Dipl.-Ing. Dr. techn. Katharina Bica

durch
Diana Khlan BSc.
Viktor-Kaplan-Strasse 11/307
2700 Wiener Neustadt

Datum

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Deutsche Kurzfassung

Im Rahmen dieser Diplomarbeit sollten alternative Lösungsmittel zur Extraktion von pharmazeutisch wichtigen Wertstoffen aus Kaffeeabfall gefunden werden.

Im ersten Teil wurden verschiedene ionische Flüssigkeiten als Extraktionsmedium synthetisiert. Konventionelle ionische Flüssigkeiten wurden auf Basis von Imidazolium- oder Pyridiniumkationen durch Alkylierungs- und gegebenfalls durch Ionenaustauschreaktionen hergestellt. Destillierbare ionische Flüssigkeiten auf Basis von 1,1,3,3-Tetramethylguanidin und ionische Flüssigkeiten mit umschaltbarer Polarität basierend auf Guanidin wurden ebenfalls synthetisiert.

Anschließend wurde Koffein, Chlorogensäure sowie Phenole und Flavonoide mit den synthetisierten ionischen Flüssigkeiten als auch mit konventionellen Lösungsmitteln unter verschiedene Bedingungen aus Kaffeesatz extrahiert. Es konnte gezeigt werden, dass durch Verwendung der ionischen Flüssigkeit 1-Ethyl-3-methylimidazolium Acetat Phenole und Flavonoide mit höherer Ausbeute als mit konventionellen Lösungsmitteln extrahiert werden. Koffein wurde am besten mit einem Gemisch aus 1-Ethyl-3-methylimidazolium Acetat/Wasser extrahiert während Chlorogensäure ausschließlich mit Wasser extrahiert werden konnte.

Im letzten Teil der Diplomarbeit wurde die Membrantrennung von Mischungen aus 1-Ethyl-3-methylimidazolium Acetat und Wasser bzw. Ethanol mit vier unterschiedlichen Membranen untersucht. Zur Auswertung der Versuche wurden entsprechende chromatographische Techniken entwickelt. Es konnte jedoch keine Trennung der Stoffgemische durch die Membranfiltration beobachtet werden.

Short abstract

This thesis focuses on the development of alternative solvent systems for the improved extraction of pharmaceutically active components from waste coffee.

Different types of ionic liquids including conventional ionic liquids based on imidazolium or pyridinium cations, distillable ionic liquids or switchable ionic liquids were successfully synthesized, characterized and applied for spent coffee grounds dissolution. These ionic liquids as well as mixtures of 1-ethyl-3-methylimidazolium acetate ($[C_2mim]OAc$) with conventional solvents such as water or ethanol were used for the extraction of active ingredients including caffeine, chlorogenic acid, phenols and flavonoids. After evaluation of different extraction conditions, caffeine was extracted in the greatest yield with the mixture of $[C_2mim]OAc/H_2O$ (50 wt%), total phenols and flavonoids could be extracted with the best yields with pure $[C_2mim]OAc$ whereas chlorogenic acid could only be extracted with pure water.

The last part of this thesis focuses on the membrane separation of solvent mixtures used for the extraction of spent coffee grounds. Analytical strategies to determine the composition of $[C_2mim]OAc/H_2O$, $[C_2mim]OAc/EtOH$ and $EtOH/H_2O$ binary mixtures were developed. The separation of these binary mixtures was investigated using a stirred cell membrane set-up with four different membranes; however no separation could be observed.

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1 Introduction

1.1 Ionic liquids – properties and applications

Ionic liquids are commonly defined as organic salts or eutectic mixtures of organic and inorganic salts that have melting points or glass transition temperatures below 100 °C.[1] In particular, many salts are already molten at ambient temperature and are therefore called room-temperature ionic liquids.

The history of ionic liquids dates back to the second half of the nineteenth century, when it was noticed that two layers were formed during the addition small quantities of anhydrous aluminum chloride to amyl chloride in Friedel Crafts reactions.[2] In 1888, Gabriel reported the isolation of the low melting salt ethanolammonium nitrate with a melting point of 52-55 °C.[3] The room-temperature liquid salt ethylammonium nitrate with a melting point of 12.5 °C was described by Walden 1914, which is nowadays often considered as the first ionic liquid.

Initially, ionic liquids were mainly studied for electrochemical applications with a particular focus on Lewis-acidic chlorometallate salts. In 1951, Hurley and Wier applied low melting salts with chloroaluminate ions for electroplating of Aluminum.[4] The introduction of air- and water stable ionic liquids by Wilkes *et al.* in 1992 opened a considerably broader application range, and ionic liquids were proposed as solvents for synthesis and catalysis.[5] Later on room-temperature ionic liquids started to be widely applied as solvents, materials or electrolytes and research interest started to grow substantially.

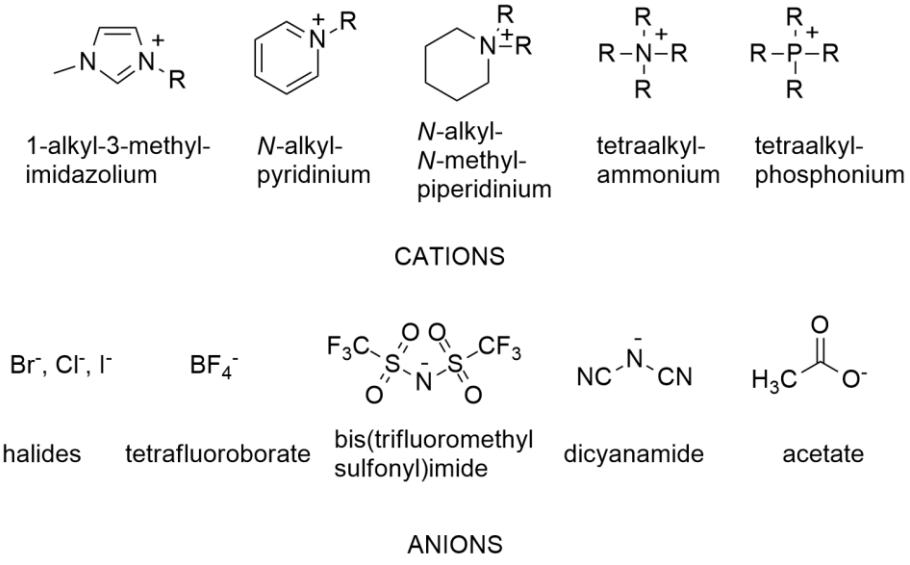

Figure 1: Commonly used cations and anionsfor ionic liquids

[1] ed. M. Freemantle, *An Introduction to Ionic Liquids*. Cambridge, UK: RSC Publishing, **2009**, p. 281.
[2] Wilkes, J. S. *Green Chem.*, **2002**, *4*, 73.
[3] Weiner, J.; Gabriel, S. *Ber.*, **1888**, *21*, 2669.
[4] Plechkova, N. V.; Seddon, K. R. *Chem. Soc. Rev.*, **2008**, *37*, 123.
[5] Wilkes, J. S.; Zaworotko, M. J. *Chem. Commun.*, **1992**, *13*, 965.

In the past years ionic liquids gained great interest due to their unique properties which can be varied on large scales to fit for the intended purpose. Some typical cations and anions are shown in Figure 1. With the variation of cations and anions, ionic liquids can be acidic, basic or neutral, water miscible or immiscible, toxic or non-toxic. A comparison of properties of ionic liquids and conventional organic solvents can be found in Table 1.

The melting points of room-temperature ionic liquids tend to decrease with increase of cation and anion size. The symmetry of the cations also has a large influence on the melting point, as non-symmetrical cations, *e.g.* 1-alkyl-3-methylimidazolium cations often result in a dramatic reduction of melting points due to inefficient packing. In general, ionic liquids are more viscous than conventional solvents. The range of viscosity of ionic liquids lies between 10-500 cP, which can be also modified with a variation of cations and anions. [6]

One very important characteristic of ionic liquids is their exceptionally low vapor pressure that makes them ideally suited as a solvent for applications where they are not supposed to evaporate or boil at high temperatures. Many ionic liquids have high thermal decomposition temperatures and can therefore be used in high-temperature applications without evaporation or significant degradation.[1]

Moreover ionic liquids have inherent conductivity, making them potential candidates for electrolytes. The electrochemical potential window of ionic liquids can be varied based on cations and anions chemistry, and therefore can be widener or narrower to create the desired potential window ranges.[7,8]

Another important characteristic of ionic liquids is their high solubility power of organic and inorganic compounds, including biomass that largely depends on hydrogen-bond accepting ability of the involved anions.[9]

[6] Marsh, K. N.; Boxall, J. A.; Lichtenthaler, R. *Fluid Phase Equilib.* **2004,** *219*, 93.
[7] Murugesan, S.; Quintero, O. A.; Chou, B. P.; Xiao, P.; Park, K.; Hall, J. W.; Jones, R. A.; Henkelman, G.; Goodenough, G. B.; Stevenson, K. J. *J. Mater. Chem. A*. **2014**, *2*, 2194.
[8] Galinski, M.; Lewandowski, A.; Stepniak, I. *Electrochim. Acta.* **2006***, 26,* 5567.
[9] Freire, M. G.; Teles, A. R. R.; Rocha, A. A.; Schröder, B.; Neves, C. M. S. S.; Carvalho, P. J.; Evtuguin, D. V.; Santos, L. M. B. F.; Coutinho, J, A. P. *J. Chem. Eng. Data* **2011***, 56,* 4813.

Property	Organic solvent	Ionic liquids
Number of solvents	> 1000	>1000000
Applicability	Single function	Multifunction
Catalytic ability	Rare	Common and tuneable
Chirality	Rare	Common and tuneable
Vapour pressure	Obeys the Clausius-Clapeyron equation	Negligible vapour pressure under normal conditions
Flammability	Usually flammable	Usually nonflammable
Solvation	Weakly solvating	Strongly solvating
Polarity	Conventional polarity concepts apply	Polarity concepts questionable
Tuneability	Limited range of solvents available	Virtually unlimited range means "designer solvents"
Cost	Normally cheap	Typically between 2 and 100 times the cost of organic solvents
Recyclability	Green imperative	Economic imperative
Viscosity/ cP	0.2-100	22-40000
Density/ cm^{-3}	0.6-1.7	0.8-3.3
Refractive index	1.3-1.6	1.5-2.2

Table 1: Comparison of conventional solvents with ionic liquid[4]

Based on their attractive properties, ionic liquids were soon recognized as valuable alternatives in order to replace highly flammable and toxic conventional solvents. Consequently, ionic liquids were potentially considered as “green solvents”, although their toxicity was only sparely investigated. While the risk of air pollution through evaporation of ionic liquids is limited due to their low volatility, some ionic liquids are significantly soluble in water, indicating that release in the environment might occur through this media. The studies of ionic liquid toxicity showed that some candidates have considerable aquatoxicity towards aquatic microorganisms and animals, particularly when long-chain alkylammonium cations are involved. The use of perfluorinated anions is also not eco-friendly, because of their unstable properties that might lead to the release of hydrogen fluoride under some conditions. Additionally, the biodegradability of many ionic liquids raises problems, as especially long-chain imidazolium salts show poor biodegradability. However there are some ways to increase the biodegradability of ionic liquids by introduction of polar groups or by the increase of alkyl-chain length. As a conclusion it should be noted that ionic liquids for large scale applications must be designed with consideration of the data received from the toxicity and biodegradation studies.[10,11]

The outstanding properties of ionic liquids resulted in many applications so that they are nowadays widely available. Currently ionic liquids can be easily bought by major suppliers, *e.g.* Merck, BASF, IoLiTec, ACROS, Sigma Aldrich and many others. One of the most notable examples for industrial processes using ionic

[10] Pham, T. P. T.; Cho, S.-W.; Yun, Y.-S. *Water Res.* **2010**, *44*, 352.
[11] Zhao, D.; Liao, Y.; Zhang, Z. *Clean* **2007**, *35*, 42.

liquids is the BASIL™ process owned by BASF Company. This process is used for production of the photoinitiator precursors alkoxyphenylphosphines and presented below. (Figure 2)

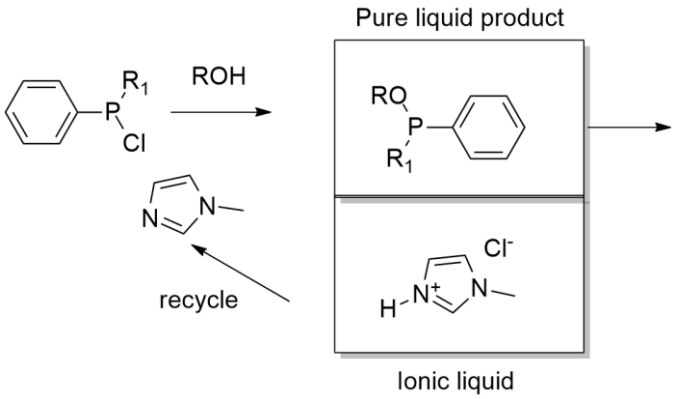

Figure 2: BASIL™ process[4]

In the previous process version, triethylamine was used as a base for the formation of alkoxyphenylphosphines from chlorophenylphosphines and various alcohols. The by-product triethylammonium chloride had to be removed by a difficult filtration step. In the current BASIL process, 1-methylimidazole scavenges the acid and the protic ionic liquid 1-methylimidazolium chloride is formed that can be easily separated and recycled. Additionally, the use 1-methylimidazole resulted in increased yields compared to triethylamine, as the base 1-methylimidazole acts as a nucleophilic catalyst.[4]

A further example of the application of ionic liquids on industrial scale is Eastman Chemical Company's process for the isomerization of 3,4-epoxybut-1-ene to 2,5-dihydrofuran which has been running since 1996. (Figure 3)

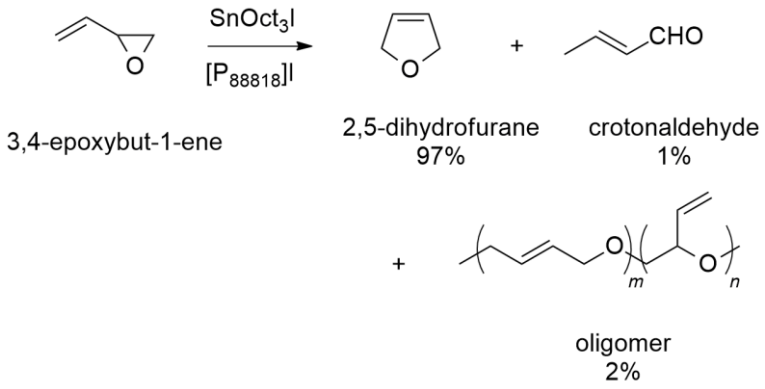

Figure 3: Isomerisation of 3,4-epoxy-1-butene to 2,5-dihydrofurane[4]

In the synthesis of 2,5-dihydrofurane a trialkyltin iodide is used as a Lewis acid catalyst whereas a Lewis basic tetraalkylphosphonium iodide ionic liquid acts as a co-catalyst. The continuous process of isomerization requires nonvolatile catalysts that do not contaminate the product by distillation. High selectivity for 2,5-dihydrofuran is usually achieved by the co-catalyst system that also provides an efficient

strategy for catalyst recovery.[12] A plant at Longview, Texas by Texas Eastman Devision was working with annual capacity of 1400 metric tons from 1996 to 2004 and then shut down because the need for the product decreased.[4]

Currently the largest industrial application of ionic liquids is PetroChina's Ionikylation process. This refinery process used in the alkylation of C_4-olefins with isobutene results in the formation of the most desirable product trimethylpentane having an octane number greater than 100 for high-quality gasoline production. The application of a Lewis-acidic chloroaluminate (III) copper chloride composite ionic liquid as a homogenous catalyst provides trimethylpentane with high selectivity at ambient temperature and pressure.

The conventional alkylation uses sulfuric acid or anhydrous hydrofluoric acid as catalyst, which are not safe and environmentally hazardous. PetroChina's Ionikylation process based on ionic liquids was tested at a pilot plant and integrated into the current 65000 tons a year sulfuric acid alkylation unit, what increased not only the yield of process compared to the sulfuric acid catalyzed process, but the process unit capacity as well.[4,13]

Apart from the use as solvent or catalyst in these industrial processes, ionic liquids provide novel opportunities for many fields, and more possible applications for ionic liquids can be found in Table 2.

[12] Meindersma, G. W.; Maase, M.; De Haan, A. B. *Ionic Liquids. Ullmann's Encyclopedia of Industrial Chemistry* **2007**, *Vol. 19*, 547.
[13] Zhang, R., Xu, C., Xia, R., Liu, Z. *Oil Gas J.* **2006**, 23.

Applications of ionic liquids					
Engineering	**Solvents and catalysts**	**Analytics**	**Biological Uses**	**Electrochemistry**	**Physical chemistry**
• Coatings • Lubricants • Plasticisers • Dispersing agents • Compatibilisers	• Synthesis • Catalysis • Microwave chemistry • Nanomaterials • Multiphasic reactions and extractions	• Matrices for mass spectroscopy • Gas chromatography columns • Stationary phase for HPLC	• Biomass processing • Drug delivery • Biocides • Personal care • Embalming	• Electrolyte in batteries • Metal plating • Solar Panels • Fuel Cells • Electro-optics • Ion propulsion	• Refractive index • Thermodynamics • Binary and ternary systems

Table 2: Possible applications of ionic liquids[4]

2 State of the art

2.1 Biomass processing with ionic liquids

Utilization of biomass is topic of current importance, because of the decreasing number of fossil fuels as well as the danger of global health warnings caused by greenhouse gas emissions. One of the examples for biomass with multiple uses is lignocellulose, which comprises cellulose, hemicellulose and lignin.

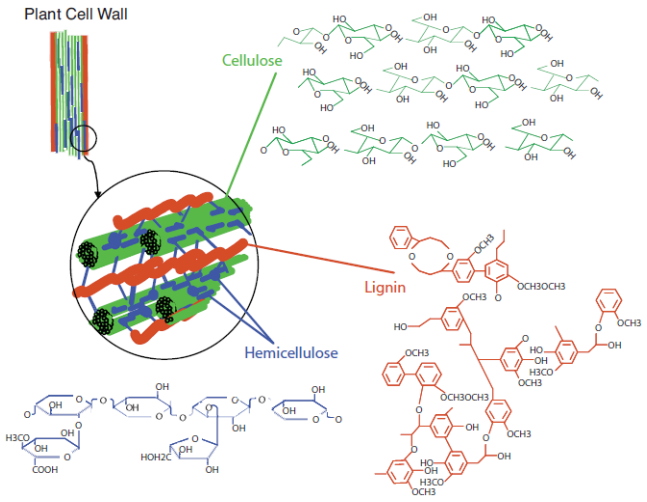

Figure 4: Lignocellulose structure[14]

The rigid structure of lignocellulose is explained by several covalent and non-covalent interactions, thereby making its fractionation a difficult and energy-intense process. Usually the compounds from lignocellulose fractionation are separated by thermochemical and physical methods; however there are several drawbacks such as the low selectivity and high price of the process and partial degradation of desired products. That is the reason why ionic liquids were recently taken into consideration of biomass dissolution, particularly in the light lignocellulose fractionation and valorization.[15,16] While processing of (ligno-)cellulose with ionic liquids is the most prominent research area, other examples for biomass processing with ionic liquids in literature also include biopolymers such as silk fibroin, starch, protein, chitin/chitosan and others.[17]

Dissolution of cellulose with ionic liquids was first mentioned by Graenacher who suggested in 1934 that molten N-ethylpyridinium chloride in presence of *N*-containing bases could be used for cellulose treatment.[18] In the 2000's, the dissolution of cellulose with various ionic liquids and their use under different conditions gained again much interest. It was noted that some ionic liquids, including 1-butyl-3-methylimidazolium chloride ([C_4mim]Cl), 1-ethyl-3-methylimidazolium acetate [C_2mim]OAc,

[14] https://microbewiki.kenyon.edu/, last accessed 09-03-2015.
[15] da Costa Lopes, A. M.; Joao, K. G.; Morais, A. R. C.; Bogel-Luukasik, E.; Bogel-Lukasik, R. *Sustain. Chem. Process.* **2013**, 1.
[16] Mäki-Arvela, P.; Anugwom, I.; Virtanen, P.; Sjöholm, R.; Mikkola, J.P. *Ind. Crops. Prod.* **2010**, *32*, 175.
[17] Passos, H.; Freire, M. G.; Coutinho, J. A. P. *Green Chem.* **2014**, *16*, 4786.
[18] Graenacher, C., 1943176, **1934**.

1-ethyl-3-methylimidazolium chloride [C_2mim]Cl, 1-allyl-3-methylimidazolium chloride ([amim]Cl) can dissolve high quantities of cellulose under mild conditions without the addition of derivatizing reagents.[19,20] Moreover, the use of microwave irradiation can greatly improve the fraction of dissolved cellulose, since microwave irradiation can be characterized as internal heating and can facilitate the breakdown of H-bonding networks between the microfibers.[21]

A tentative mechanisms of cellulose dissolution with ionic liquids 1-butyl-3-methylimidazolium chloride ([C_4mim]Cl) suggests that the oxygen and hydrogen atoms are forming electron donor and electron acceptor complexes with charged species of ionic liquids (Figure 5).[22] The interaction must occur between the C-6 and C-3 hydroxyl groups of the cellulose chains.

Figure 5: Dissolution mechanism of cellulose with [C_4mim]Cl[22]

Another mechanism of dissolution is based on nuclear magnetic resonance spectroscopy NMR investigations and shows that [C_2mim]OAc forms a covalent bond between C-1 of glucose and C-2 of imidazolium cation, due to the disappearance of the C-1 signal of glucose after dissolution with [C_2mim]OAc. (Figure 6)

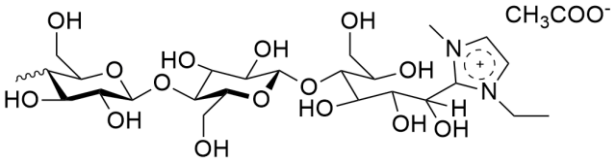

Figure 6: Dissolution mechanism of cellulose with [C_2mim]OAc based on NMR studies[22]

Key to efficient cellulose dissolution is the selection of appropriate ionic liquids. For instance, it was noted that ionic liquids with bulky cations and halide anions could decrease the activity of active chloride and thus the solubility of cellulose and lignin. In contrast, cations with smaller size could be more efficient, as the degree of interaction with the cellulose chain is higher. Dissolution of cellulose with smaller anions is also preferable, since they can diffuse faster in the lignocellulose matrix.[15]

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[19] Wang, H.; Gurau, G.; Rogers, R. D. *Chem. Soc. Rev.* **2012**, *41*, 1519.
[20] Zhu, S.; Wu, Y.; Chen, Q.; Yu, Z.; Wang, C.; Jin, S.; Ding, Y.; Wu, G. *Green Chem.* **2006**, *8*, 325.
[21] Ha, S. H.; Mai, N. L.; An, G.; Koo, Y.-M. *Bioresour. Technol.* **2011**, *102*, 1214.
[22] Pinkert, A.; Marsh, K. N.; Pang, S.; Staiger, M. P. *Chem. Rev.* **2009**, *109*, 6712.

Another important aspect for cellulose processing concerns the viscosity of the ionic liquid. The lower viscosity and melting point of $[C_2mim]OAc$ makes it more preferable for the dissolution process when compared to $[C_2mim]Cl$ and $[C_4mim]Cl$, due to easier handling and dissolution.

The outstanding dissolution properties of ionic liquids for biopolymers are however not limited to cellulose solubilization. An impressive characteristic of ionic liquids is that they can fully dissolve wood. In 2007 Fort *et al.* investigated that $[C_4mim]Cl/DMSO\text{-}d_6$ (84/16 wt%) can partially dissolve wood chips.[23] In parallel, Kilpelainen *et al.* completely dissolved 8 wt% of dried wood sawdust samples in $[C_4mim]Cl$ and $[C_2mim]Cl$.[24] A great improvement of wood dissolution was achieved by Sun *et al*., who showed that both soft wood (southern yellow pine) and hardwood (red oak) could be dissolved with $[C_2mim]OAc$ after mild grinding at 110 °C for 16 hours with the yield of 90 w/w% yield.[25] So far, by comparison of various ionic liquids it was found that 1-allyl-3-methylimidazolium chloride ([amim]Cl) is the most suitable ionic liquid for dissolution of all tested wood.[15] However, dissolution of biomass is just an initial step and a further challenge is the biomass regeneration process and the separation and recovery of the ionic liquids. Usually biomass regeneration is done by addition of a precipitating solvent (or so-called anti-solvent), which can be water, ethanol, acetone, dichloromethane and others. It was verified by Wang *et al.* that the addition of water to cellulose dissolved in ionic liquids resulted in a brown gel that became colorless after washing with H_2O/DMSO for several times.[26] Singh *et al.* stated by microscopic observations, that the structure of the cellulose is fibrous after precipitation with water.[27] This regeneration process provides several problems, as ionic liquid traces have to be removed from the recovered biomass with excessive washings. Additionally, large amounts of ionic liquid-solvent mixtures are obtained that have to be separated before further use.

Recently, some other novel ionic liquids were investigated to overcome the separation problem of ionic liquid with water or another antisolvent after biomass regeneration. One alternative is the use of switchable ionic liquids, which are solvents that can switch its hydrophobicity due to transition from the neutral liquid to an ionic form. Usually switchable ionic liquids are formed by mixing equimolar amounts of water or alcohol and strong organic base (*e.g.* 1,8-diazabicyclo[5.4.0]undec-7-ene). By addition or removal of CO_2 or SO_2 gas, the solvent can be switched between neutral and its ionic form. The concept of switchable ionic liquids was initially reported by Jessop group and the schematic concept is shown in Figure 7.[28]

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[23] Fort, D. A.; Remsing, R. C.; Swatloski, R. P.; Moyna, P.; Moyna, G.; Rogers, R. D. *Green Chem*. **2007**, *9*, 63.
[24] Kilpeläinen, I.; Xie, H.; King, A.; Granstrom, M.; Heikkinen, S.; Argyropoulos, D. S., *J Agric. Food Chem*. **2007**, *55*, 9142.
[25] Sun, N.; Rahman, M.; Qin, Y.; Maxim, M. L.; Rodríguez, H.; Rogers, R. D. *Green Chem.* **2009**, *11*, 646.
[26] Wang, X.; Li, H.; Cao, Y.; Tang, Q. *Bioresour. Technol.* **2011**, *102*, 7959.
[27] Singh S.; Simmons, B. A.; Vogel, K. P. *Biotechnol Bioeng*. **2009**, *104*, 68.
[28] Jessop, P. G.; Heldebrant, D. J.; Li, X.; Eckert, C. A.; Liotta, C. L. *Nature* **2005**, *436*, 1102.

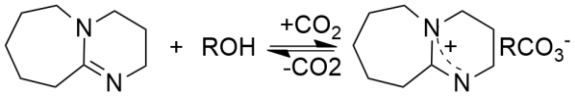


Figure 7: Switchable ionic liquids reported by Jessop group[28]

The strategy of switchable ionic liquids was already applied for selective extraction of hemicellulose from spruce wood. As a result lignin and cellulose remained suspended and were recovered as non-degraded material and xylanes were recovered by degassing with CO_2 to yield a conventional amine-alcohol solution.[29]

Switchable ionic liquids could be also used as alternative to the current industrial process for extraction of soybean oil from soybean flakes. The current process uses extraction of soybean oil with hexane and further distillation. The use of switchable ionic liquids could decrease vapor emissions of hexane, which contribute to smog formation. The scheme of switchable ionic liquids for extraction of soybean oil is presented in Figure 8.[30]

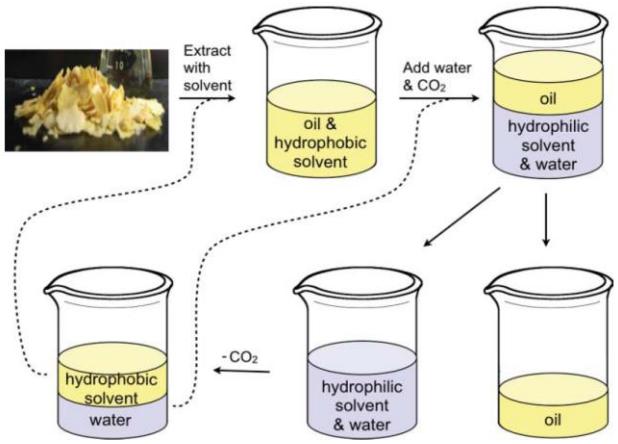


Figure 8: Switchable ionic for extraction of soybean oil from soybean flakes using switching ionic liquids[30]

Another very promising type of ionic liquid for biomass dissolution are distillable ionic liquids that are composed of a protonated salt. They can be distilled which is not the case for conventional ionic liquids that are known to have a very low vapor pressure and will decompose rather than evaporate. In contrast the reversible formation of protic ionic liquids *via* neutralization of acid and base makes them distillable. One of the latest examples of using distillable ionic liquids for cellulose dissolution was described by King *et al.* based on conjugation 1,1,3,3-tetramethylguanidine (TMG) and commercially available carboxylic acids. As the result $[TMGH]^+$ can rapidly dissolve cellulose. It was also shown that $[TMGH][CO_2Et]$ can be distilled and recovered in very high purity (99%), which was confirmed by NMR.[31]

[29] de María P. D. *J Chem. Technol. Biotechnol.* **2014**, *89*, 11.
[30] Jessop, P. G.; Phan, P.; Carrier, A.; Robinson, A.; Dürra, C. J.; Harjania, J. R. *Green Chem.* **2010**, *12*, 809.
[31] King, A. W. T.; Asikkala, J.; Mutikainen, I.; Jrvi, P., Kilpelinen, I. *Angew. Chem.* **2011**, *50*, 6301.

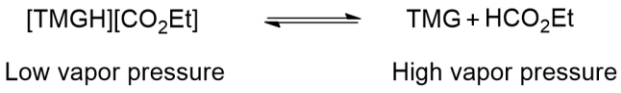


Figure 9: Equilibrium of distillable ionic liquids for cellulose dissolution[31]

2.2 Active ingredients extraction with ionic liquids

The use of ionic liquids can be beneficial not only for biomass dissolution, but also for active ingredients isolation from natural plant material. In general, the high dissolution capacity of ionic liquids for organic, inorganic or even polymeric materials makes them ideally suited as extraction medium. A selection of ionic liquid-assisted extraction processes for various organic substrates is given in Table 3.

Substances		Ionic liquid	Extractant	Ref.
Phenolic compounds	phthalic acid, aniline, 4-hydroxybenzoic acid, benzoic acid, *p*-toluic acid, benzene, chlorobenzene, 1,2,4-trichlorobenzene, 1,4-dichlorobenzene, 4,4'-dichlorobiphenyl,	$[C_4mim]PF_6$	None	Huddleston[32]
	Phenol, tyrosol, *p*-hydroxybenzoic acid	$[C_nmim]BF_4$ (*n* = 1, 3, 6, 8, 10) $[C_nmim]PF_6$ (*n* = 6, 10)	None	Vidal [33] Rogers[34]
	Chlorophenols	$[C_4mim]PF_6$, $[C_2mim]$Beti	None	
Amino acids	Tryptophan, glycine, alanine, leucine, lysine, arginine	$[C_4mim]PF_6$	DC18C6	Smirnova [35]
Carbohydrates	Xylose, fructose, glucose, sucrose	$[C_nmim]X$ (*n* = 4, 6, 8, 10; X = Cl^-, PF_6^-, BF_4^-)	None	Visser [36]
	Glucose, sucrose, lactose, cyclodextrin	$[C_4mim]N(CN)_2$ $[C_nmim]X$ (*n* = 4, 6, 8)	None	Liu [37]
	Cellulose		None	Spear [38]
Organic acids	Lactic acid, acetic acid, glycolic acid, propionic acid, pyruvic acid, butyric acid	$[C_nmim]PF_6$ (*n* = 4, 6, 8)	TBP (in some cases)	Mochiduki [39]
Biofuels	Butyl alcohol (from fermentation broth)	$[C_4mim]PF_6$, $[C_8mim]PF_6$	Pervaporation was used	Meagher [40]
Antibiotic	Erythromycin-A	$[C_4mim]PF_6$	None	Holbrey [41]
Hydrocarbons	Olefins (such as ethylene, propylene, and butanes) from paraffins	$[C_nmim]X$, [HPy] X (*n* = 4, 6; X = BF_4^-, PF_6^-)	None	Boudreau [42,43]
	C_{4-8} diolefin (such as butadiene) from C_{1-18} paraffins	$[C_4mim]BF_4$	None	Herrera [44]

DC18C6: dicyclohexano-18-crown-6; TBP: tri-n-butyl phosphate; $[C_4mim]PF_6$: 1-butyl-3-methylimidazolium hexafluorophosphate; $[C_8mim]PF_6$1-octyl-3-methylimidazolium hexafluorophosphate; $[C_nmim]BF_4$: 1-alkyl-3-methylimidazolium tetrafluoroborate; $[C_2mim]$Beti: 1-ethyl-3-methylimidazolium bis(perfluoroethyl)sulfonylimide; $[C_4mim]N(CN)_2$: 1-ethyl-3-methylimidazolium dicyanamide

Table 3: Examples of some extractions with ionic liquids[45]

[32] Huddleston, J. G.; Rogers, R. D. *Chem. Commun.* **1998**, *16*, 1765.
[33] Vidal, S. T. M.; Correia, M. J. N.; Marques, M. M.; Ismael, M. R.; Reis, T. A. *Separ. Sci. Technol.* **2004**, *39*, 2155.
[34] ed. by Rogers, R.D.; Seddon, K. R., *Ionic Liquids as Green Solvents: Progress and Prospects. ACS,* Washington, DC, **2003**, p. 544.
[35] Smirnova, S.V.; Torocheshnikova, I. I.; Formanovsky, A. A.; Pletnev, I. V. *Anal. Bioanal. Chem.* **2004**, *378*, 1369.
[36] Visser, A. E.; Rogers, R.D.; Spear, S.K. *Proceedings of the Sugar Processing Research Conference*, New Orleans, LA, 14–15 March **2002**, 336.
[37] Liu, Q.; Janssen, M. H. A.; van Rantwijk, F.; Sheldon, R. A. *Green Chem.* **2005**, *7*, 39.
[38] Spear, S. K.; Holbrey, J. D.; Rogers, R. D.; Swatloski, R. P. *JACS* **2002**, *124*, 4974.
[39] Mochiduki, K.; Fukunishi, K.; Kondo, K.; Matsumoto, M. *Sep. Purif. Technol.* **2004**, *40*, 97.
[40] Meagher, M. M.; Fadeev, A. G. *Chem. Commun.* **2001**, *3*, 295.
[41] Holbrey, J. D.; Vargas-Mora, V.; Seddon, K. R.; Lye, G. J.; Cull, S.G. *Biotechnol. Bioeng.* **2000**, *69*, 227.
[42] Boudreau, L. C.; Driver, M. S.; Schinski, W. L.; Munson, C. L. US 6 339 182, **2002**.
[43] Boudreau, L. C., Driver, M. S., Schinski, W. L., Munson, C. L. US 6 623 659, **2003**.
[44] Herrera, P. S.; Reynolds, J. S.; Krzwicki, A.; Smith, R. S. US Pat Appl Publ US 2 004 106 838 5, **2004**.
[45] Xia, S., Ma, P., Zhao, H. *J. Chem. Technol. Biotechnol* **2005**, *80*, 1089.

The extraction of bioactive ingredients with conventional solvents provides several issues such as the use of large amounts of solvents causing environmental problems, the necessity of long extraction times as well as difficulties with the separations of the by-products, e.g. waxes or essential oil from the raw extract. These problems require the development of novel, more efficient and environmentally benign solvents as alterative extraction media. Ionic liquids could for instance be such solvents. Apart from their favorable properties such as lower vapor pressure and non-flammability as discussed above, ionic liquids assist the dissolution of biomass and could provide a better access to active compounds embedded in biopolymers.

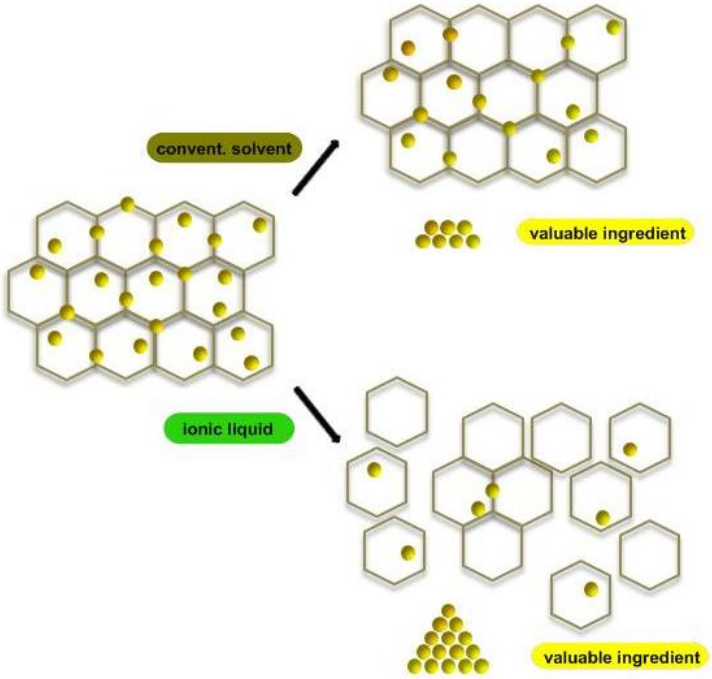


Figure 10: Strategy for active ingredients extraction from natural compounds with ionic liquids as solvents[46]

Recently, the application of ionic liquids for the extraction of bioactive compounds from plant materials on both analytical and preparative scale gained much interest. Some recent examples for the extraction of active ingredients on analytical or preparative scale with ionic liquids using different techniques, including extraction under heating, ultrasound-assisted extraction, microwave-assisted extraction are presented in Table 4.

[46] Zirbs, R.; Strassl, K.; Gaertner, P.; Schroeder, C.; Bica, K. *RSC Adv.* **2013**, *3*, 26010.

Plant	Compound	Extraction method	Ionic liquid	Reference
Acacia catechu and Terminalia chebuja	Hydrolysable tannins	LSE	DIMCARB, removable from extract by distillation	Chowdhury[47]
Apocynum venetum	Hyperoside, isoquercitin	MAE	$[C_4mim]BF_4$	Lin[48]
Artemisia annua	Artemisinin	LSE	DMEA oct; BMOEA bst	Lapkin[49,50,51]
Glaucium flavum	Alkaloids	LSE	$[C_nmim]X$, with X =Cl, Br, Sac, Ace	Bogdanov[52,53]
Nelumbo necifera	Phenolic alkaloids	MAE	$[C_nmim]X$, with X=Cl; Br; BF_4	Lu[54]
Ligusticum chuanxiong Hort.	Various lactones	MAE	Protic IL, DMCEAP, DMHEEAP	Yansheng[55]
White Pepper	Piperine	UAE	$[C_4mim]BF_4$	Cao[56]
Polygonum cuspidatum	*trans*-Resveratrol	MAE	$[C_4mim]Br$	Du[57]
Psidium guajava	Gallic acid, ellagic acid, quercetin	MAE	$[C_nmim]X$, with X=Cl; Br; a.o.	Du[58]
Rheum spp. (rhubarb)	Anthraquinones	UMAE	$[C_nmim]X$, with X=Cl; Br; BF_4	Lu[59]
Smilax china	*trans*-Resveratrol, quercetin	MAE	$[C_nmim]X$, with X=Cl; Br; a.o.	Du[57]
Sophora flavescens	Oxymatrine	1. LSE 2. SPE	1. Silica-confined IL; 2. MeOH	Bi[60]
Illicium verum, star anise	Shikimic acid	MAE	$[C_2mim]OAc$	Ressmann[61]
Guarana seeds	Caffeine	1. LSE 2. LLE	$[C_4mim]Cl$, aqueous solutions	Cláudio[62]

LSE: liquid-solid extraction; LLE: liquid-liquid extraction; MAE: microwave-assisted extraction; SPE: solid-phase extraction; UAE: ultrasound-assisted extraction; UMAE: ultrasound/microwave-assisted extraction. a.o.: and other anions; BMOEA bst: bis(2-methoxyethyl)ammonium bis(trifluoromethylsulfonyl)imide; $[C_nmim]Cl$; Br; Sac; Ace: 1-alkyl-3-methylimidazolium chloride, bromide, saccharinate, acesulfamate; DIMCARB: *N*,*N*-dimethylammonium *N*′,*N*′-dimethylcarbamate; DMEA oct: *N*,*N*-dimethylethanolammonium octanoate; $[C_8mim]Cl$ 1-octyl-3-methylimidazolium chloride; $[C_8mim]PF_6$: 1-octyl-3-methylimidazolium hexafluorophosphate

Table 4: Recent application in extraction of active ingredients [63]

[47] Chowdhury, S. A.; Vijayaraghavanb, R.; MacFarlane, D. R. *Green Chem.* **2010**, *12*, 1023.
[48] Lin, X.; Wang, Y.; Liu, X.; Huang, S.; Zeng, Q. *Analyst* **2012**, *137*, 4076.
[49] Lapkin, A. A.; Plucinski, P. K.; Cutler, M. *J. Nat. Prod.* **2006**, *69*, 1653.
[50] Extraction of Artemisinin using Ionic Liquids **2008**, Project Report 003-003/3, Bioniqs Ltd., York, UK.
[51] Lapkin, A. A.; Peters, M.; Greiner, L.; Chemat, S.; Leonhard, K.; Liauw, M. A.; Leitner, W. *Green Chem.*, **2010**, *12*, 241.
[52] Bogdanov, M. G.; Svinyarov, I.; Keremedchieva, R.; Sidjimov, A. *Sep. Purif. Technol.* **2012**, *97*, 221.
[53] Bogdanov, M. G.; Keremedchieva, R.; Sidjimov, A. *Sep. Purif. Technol.* **2015**, in press.
[54] Lu, Y.; Ma, W.; Hu, R.; Dai, X.; Pan, Y. *J. Chromatogr.* **2008**, *1208*, 42.
[55] Yansheng, C.; Zhida, Z.; Changping, L; Qingshan, L.; Peifang, Y.; Welz-Biermann, U. *Green Chem.* **2011**, *13*, 666.
[56] Cao, X.; Ye, X.; Lu, Y.; Yu, Y.; Mo, W. *Anal. Chim. Acta.* **2009**, *640*, 47.
[57] Du, F.-Y.; Xiao, X.-H.; Li, G.-K. *J. Chromatogr.* **2007**, *1140*, 56.
[58] Du, F.-Y.; Xiao, X.-H.; Luo, X.-J.; Li, G.-K. *Talanta* **2009**, *78*, 1177.
[59] Lu, C.; Wang, H.; Lv, W.; Ma, C.; Xu, P.; Zhu, J.; Xie, J.; Liu, B.; Zhou, Q. *Chromatographia* **2011**, *74*, 139.
[60] Bi, W.; Tian, M.; Row, K. H. *J. Chromatogr., B: Anal. Technol. Biomed. Life Sci.* **2012**, *880*, 108.
[61] Ressmann, A.; Gärtner, P.; Bica, K. *Green Chem.* **2011**, *13*, 1442.
[62] Cláudio, A. F. M.; Ferreira, A. M.; Freire, M. G.; Coutinho, J. A. P. *Green Chem.* **2013**, *15*, 2002.
[63] Bucar, F.; Wube, A.; Schmid, M. *Nat. Prod, Rep.* **2013**, *30*, 525.

The analysis for most active compounds was performed using either Ultra Performance Liquid Chromatography (UPLC) or High Performance Liquid Chromatography (HPLC).[64] While these examples often demonstrate the successful extraction of the value ingredient with ionic liquids in improved yields, less attention is spent on isolation of the active ingredient on preparative scale. Isolation processes for some of the active ingredients from the Table 4 with extraction under heating, ultrasound-assisted extraction, microwave-assisted extraction are described in detail below.

In 2008 Bioniqs Ltd investigated the extraction of artemisinin, the precursor for current antimalarial drugs. A strategy using the ionic liquids *N*,*N*-dimethylethanolammonium octanoate for the extraction of artemisinin was developed. After successful extraction, the active ingredient could be isolated *via* precipitation from the ionic liquids by addition of water. Later on, different conventional solvents, supercritical CO_2, fluorinated solvents were compared by *ab initio* quantum chemical calculations combined with statistical thermodynamics (COSMO-RS) and proved that ionic liquids are the most promising solvents for extraction of artemisinin from the herb *Artemesia annua*. [50,51]

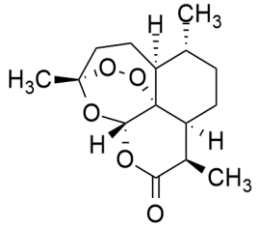


Figure 11: Structure of artemisinin

Another examples for actives ingredient isolation is the extraction of piperine from white pepper using an ionic liquid based, ultrasound assisted method. Piperine has many pharmacological applications as it possesses antifungal, antidiarrheal, anti-inflammatory and other activtities.

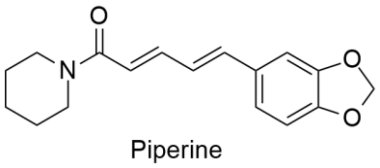


Figure 12: Structure of piperine

Various imidazolium based ionic liquids were tested and the best extraction efficiency was found 1-butyl-3-methylimidazolium tetrafluoroborate ($[C_4mim]BF_4$) under ultrasound assisted extraction conditions. The developed method was compared to the extraction with conventional solvents and it was shown that ionic liquid assisted extraction provides greater yields and reduced extraction time.[56] Later on, it was shown that aqueous- ionic liquid mixtures based on long-chain surface-active alkylmethylimdiazolium-based ionic liquids could also efficiently extract piperine from black pepper,

[64] Zeng, H.; Wang, Y.; Kong, J.; Nie, C.; Yuan, Y. *Talanta* **2010**, *83*, 582.

thereby considerably reducing the required amount of ionic liquid. In this case, piperine could be isolated from the ionic liquids after back-extraction with *n*-butyl acetate that allowed to separate piperine almost completely with only 0.2% loss.[65] Additionally, this strategy allowed to reuse the ionic liquid solution after extraction and isolation of piperine for five times without losses in performance.

An example of microwave-assisted extraction of lactones from *Ligusticum chuanxi*ong was investigated by Yansheng *et al.* Lactones as senkyunolide I, senkyunolide H and Z-ligustilide were extracted with *N,N*-dimethyl-*N*-(2-hydroxyethoxyethyl)ammonium propionate (DMHEEAP) and *N,N*-dimethyl(cyanoethyl)ammonium propionate (DMCEAP). Investigation also showed that the temperature was determinant factor for this microwave assisted extraction process. These lactones were isolated by back-extraction using n-hexane, achieving senkyunolide I, senkyunolide H in a good yields, while the concentration of Z-ligustilide decreased. [55]

One of the most recent examples of solid-liquid extraction of biologically active alkaloid *S*-(+)-glaucine from aerial parts of G. *flavum* Crantz with aqueous solution of [C_4mim]OAc was described by Bogdanov *et al.* The further isolation from aqueous solution of [C_4mim]OAc was achieved with back-extraction with chloroform, that allows to obtain the target compound in high-purity and recycle the ionic liquid.[53]

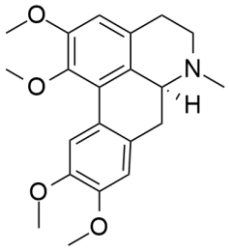
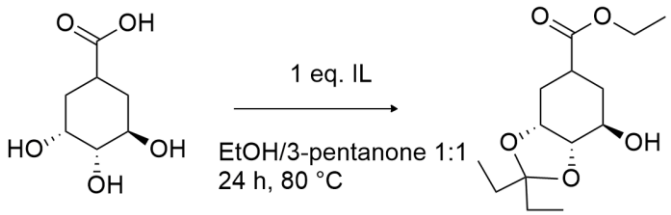


Figure 13: Structure of glaucine

The group of Dr. Katharina Bica and Prof. Gärtner from Vienna University of Technology has also experimented with active ingredients extraction using ionic liquids. One of the examples is isolation of shikimic acid from star anise. Extraction experiments showed that 1-ethyl-3-methylimidazolium acetate ([C_4mim]OAc) is the ionic liquid that provides the highest yields of shikimic acid from star anise pods.[46]Alternatively, ionic liquids were used not only as a solvent for active ingredient isolation, but also as a catalyst for further esterification to shikimic acid ethyl ester or formation of a ketal intermediate that are both used for further synthesis of anti-influenza drug Tamiflu™. Conversion in the presence of

[65] Ressmann, A.; Zirbs, R.; Pressler, M.; Gaertner, P.; Bica., K. *Z. Naturforsch. B* **2013**, *68(b)*, 1129.

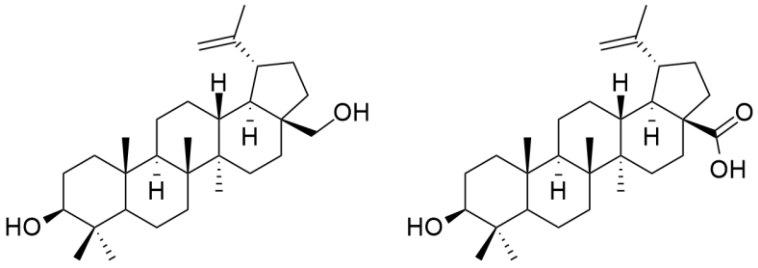
catalytically active ionic liquids and isolation by means of sequential extraction with ethyl acetate yielded the desired ketal intermediate.[61]



IL:$[HSO_3C_4mim]HSO_4$; $[C_2mim]HSO_4$;

Figure 14: Ionic liquid-catalyzed formation of ketal intermediate[66]

Another example performed by this group is isolation of pharmaceutically active betulin whose derivatives are currently in clinical trials for an anti-HIV drug.



Betulin Betulinic acid

Figure 15: Structure of betulin and betulinic acid

Conventional organic solvents and ionic liquids were applied and compared for the extraction of betulin from birch bark. Ionic liquids showed significantly higher extraction yields due to better access to the active ingredient with ionic liquids. A scalable procedure is shown in Figure 16. The best results were obtained with the ionic liquid 1-ethyl-3-methylimidazolium acetate ($[C_2mim]OAc$) that provided betulin in excellent purities of about 98% after precipitation with $EtOH/H_2O$ mixtures. Moreover $[C_2mim]OAc$ could be recovered after azeotropic distillation and re-used with only a slight decrease in performance.[67]

[66] Ressmann, A.; Gärtner, P.; Bica, K. *Green Chem.* **2011**, *13*, 1442.
[67] Ressmann, A.; Strassl, K.; Gärtner, P.; Zhao, B.; Greiner, L.; Bica, K. *Green Chem.* **2012**, *14*, 940.

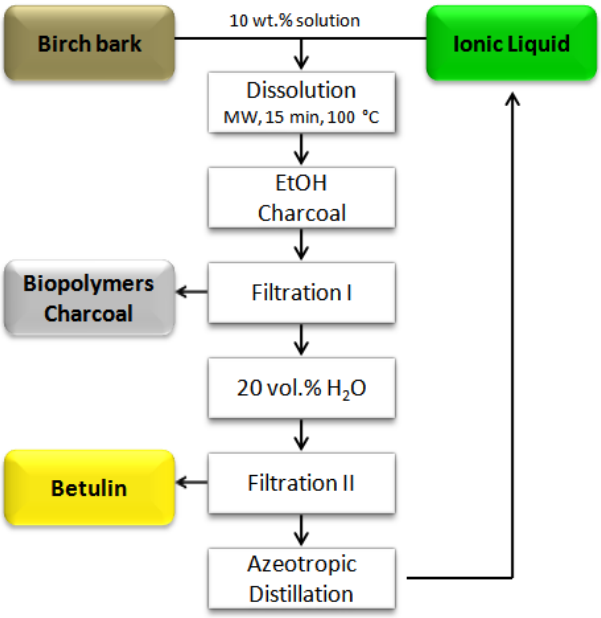
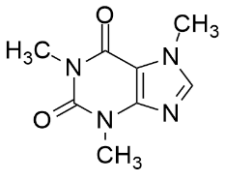


Figure 16: Work flow for the scaled isolation process of betulin (MW: microwave irradiation)[67]

One of the active compounds of interest in this master thesis is caffeine. In 2013, Claudio *et al.* applied an aqueous solution of [C_4mim]Cl for caffeine extraction from guaraná seeds. After biomass extraction, caffeine was isolated from the aqueous ionic liquid using liquid-liquid extraction with chloroform, methylene chloride or butanol which permitted the reuse of the ionic liquid/water mixture for further biomass extraction cycles.



Caffeine

Figure 17: Structure of caffeine

Different concentration ratios of [C_4mim]Cl/H_2O were screened and it was concluded that the best extraction yields are achieved with higher concentration of ionic liquid. Besides [C_4mim]Cl, five other ionic liquids were applied including [C_2mim]OAc, [C_2mim]Cl, 1-butyl-3-methylimidazolium tosylate ([C_4mim]Tos), *N*-butyl-3-methylpyridinium chloride ([C_4MePy]Cl) and 1-hydroxylethyl-3-methyl-imidazolium chloride ([(OH)C_2mim]Cl). All mentioned ionic liquids showed similar results of extracted caffeine. Up to 8 wt% of caffeine could be extracted from guaraná seeds with [C_4mim]Cl aqueous solution (3 M), which is higher than 3.86 wt% of extracted caffeine for water or 3.75 wt% for sodium chloride aqueous solution (1.5 M). The conditions applied were at temperature of 70 °C, S/L ratio = 0.10 and an extraction time of 30 min.[62]

As it was mentioned before, the extraction of active ingredients with ionic liquids is often highly efficient and results in improved yields. However, the separation of ionic liquid and active compounds is sometimes challenging. This problem could be circumvented by the use of novel ionic liquids strategies for active ingredients isolation. In 2009 Chowdhury *et al.* reported on the use of distillable ionic liquids for extraction of tannins from plant materials.[47] Vegetable tannins are water-soluble phenolic rich compounds that have molecular weight between 500 and 3000 g/mol and can bind water-soluble proteins. For the purpose of isolation of gallotannins a distillable protic ionic media was used. The formation of *N,N*-dimethylammonium *N',N'*-dimethylcarbamate (DIMCARB) takes place by addition of CO_2 to dimethyl amine in approximate ration of 1:2. DIMCARB can be removed *via* distillation at around 45 °C and the dynamic equilibria of the DIMCARB system is shown in the scheme in Figure 18.

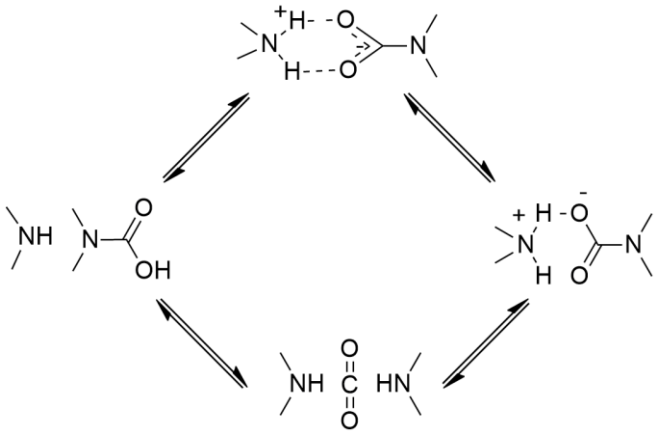


Figure 18: Dynamic equilibria in the DIMCARB system[47]

The extraction processes of tannins from plant sources can be described as follows: Initially the raw material was pretreated by grinding it to the powder. The pretreated plant was then dissolved in distillable ionic liquid at room temperature, followed by evaporation of DIMCARB. Hydrolysable tannins were dissolved in water and the desired condensed tannins were filtered. It was reported that the procedure of tannins extraction with distillable ionic liquid results in greater yields of the desired hydrolysable, that the products are more stable against bacterial molds, and that the quantities of water used in extraction procedure are much lower. [47]

2.3 Spent coffee grounds extraction

In past few years coffee beans production was growing. For instance in 2014 around 140 million bags of coffee beans were produced.[68]

Number of bags (mln)	2009	2010	2011	2012	2013	2014
World total	123.027	133.631	136.246	147.495	146.774	141.620

Table 5: Total coffee production statistics[68]

The use of coffee results in the generation of solid residues that are known as spent coffee grounds (SCG). So far spent coffee grounds are disposed as solid waste as they have no commercial value. However, it is known that a number of health-related compounds, such as phenolic compounds, melanoids, diterpenes, vitamin precursors and others are still present in these spent grounds. This suggests that several important antioxidants and bioactive compounds could be extracted from spent coffee grounds prior to the disposal, apart from several additional potential applications such as the use as animal feed, as adsorbent, or the valorization as biofuel, *e.g.* biodiesel or bioethanol.[69]

The main active component in coffee is caffeine which has many applications, among which a stimulation effect on the central nervous system, muscular and cardiovascular systems, antibacterial and antifungal properties. It was also discovered that caffeine can play a role of (bio-)pesticide.[62] Moreover, the presence of caffeine in spent coffee grounds is causing problems for the further use in agriculture due to the toxicity of caffeine, indicating the potential and importance of caffeine extraction from spent coffee grounds.[62]

However, caffeine is not the sole active ingredient with great importance that can be found in coffee. Coffee phenolics gained much interest lately due to their strong antioxidant activity and metal-chelating properties. Moreover, many phenols in coffee have considerable biological activity against chronic diseases such as cataracts, macular degeneration, as well as cancer and cardiovascular diseases. [62]

Generally, the main classes of phenolic compounds in coffee can be divided into two groups: Non-flavonoid compounds and flavonoid compounds as presented in Table 6.

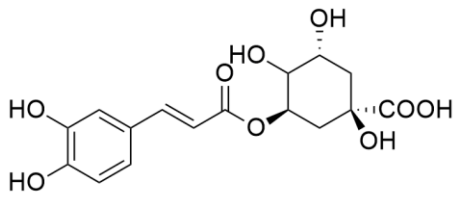
[68] http://www.ico.org/, last accessed 09-03-2015.
[69] Mussatto, S. I.; Ballesteros, L. F.; Martins, S.; Teixeira, J. A. *Sep. Purif. Technol.* **2011**, *83*, 173.

Classes and subclasses	Examples of specific compounds
Non-flavonoid compounds	
Phenolic acids	
Benzoic acids	Gallic acid; protocatechuic acid; *p*-hydroxybenzoic acid
Hydroxycinnamic acids	Coumaric acid; caffeic acids; ferulic acid; sinapic acid
Hydrolyzable tannins	Pentagalloylglucose
Stilbenes	Resveratrol
Lignans	Secoisolariciresinol, matairesinol, lariciresinol, pinoresinol
Flavonoid compounds	
Flavonols	Kaempferol; quercitin; myricetin
Flavones	Apigenin; luteolin
Flavanones	Naringenin; hesperetin
Flavanols	Catechins; gallocatechins
Anthocyanidins	Pelargonidin; cyanidin; malvidin
Condensed tannins or proathocyanidins	Trimeric procyanidin, prodelphinidins
Isoflavones	Daidzein; genistein; glycitein

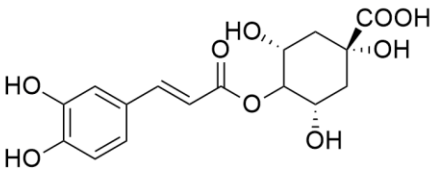
Table 6: Main classes of phenolics in coffee[70]

Among the phenols found in coffee, chlorogenic acids are the main compounds present in green coffee beans. They are formed by the esterification of one molecule of quinic acid and one to three molecules of *trans*-hydroxycinnamic acid. During the coffee processing, chlorogenic acids could chemically transform to compounds such as quinolactones, melanoidsins and other lower molecular weight compounds.[70]

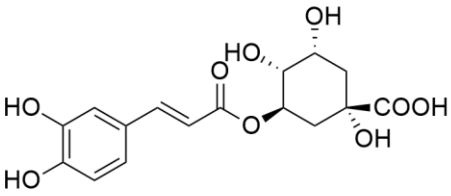
[70] Farah F.; Donangelo, C. M. *Braz. J. Plant. Physiol.* **2006**, *18*, 23.



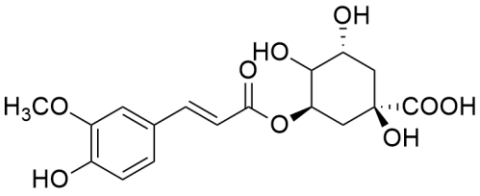
3-O-Caffeoylquinic acid



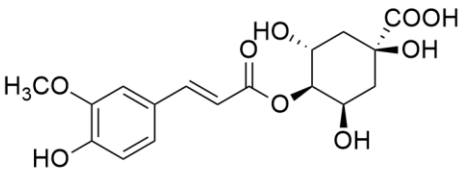
4-O-Caffeoylquinic acid



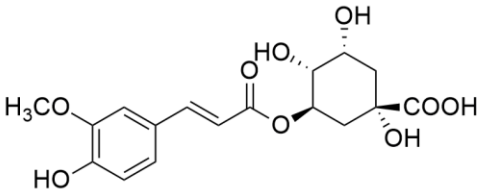
5-O-Caffeoylquinic acid



3-O-Feruloylquinic acid



4-O-Feruloylquinic acid



5-O-Feruloylquinic acid

Figure 19: Structure of major chlorogenic acids present in coffee

2.3.1 Analysis of spent coffee grounds

In a study carried out by Bravo *et al.,* caffeine in spent coffee obtained from the most common coffeemakers was quantified *via* HPLC. Before the extraction of caffeine, spent coffee grounds were defatted of with light petrol at 60 °C by Soxhlet extraction. Defatted coffee was further extracted with water for 6 minutes at 90 °C. The aqueous extract of spent coffee was and analysis showed that caffeine is in a range of 3.6 - 5.2 mg per gram of Arabica spent coffee and 5.73 mg - 8.09 mg per gram of Robusta spent coffee.[71]

[71] Bravo, J.; Juániz, I.; Monente, C.; Caemmerer, B.; Kroh, L.W.; De Peña, M.P.; Cid, C. *J. Agric. Food Chem.* **2012**, *60*, 12565.

In contrast to caffeine in waste coffee grounds that is directly quantified with chromatographic procedures, the determination of phenols and flavonoids typically relies on colorimetric assays. Folin-Ciocalteu's method is generally used for the quantification of the total phenolic content of a sample. This colorimetric method described by Singleton and Rossi uses the Folin-Ciocalteu reagent, a mixture of phosphomolybdate and phosphotungstate. For the sample preparation spent coffee ground extract, Folin-Ciocalteu reagent, sodium carbonate solution and water are reacted for five minutes at 60 °C and the light absorbance is measured at 700 nm using UV-Vis spectroscopy. The total content of phenolic compounds is expressed in gallic acid equivalents per dry weight of biomass, relying on a calibration curve prepared with gallic acid as standard.[72]

A similar method is used for the determination of flavonoids in spent coffee grounds as described by Chang *et al*. A mixture of spent coffee ground extract, aluminum chloride, potassium acetate, methanol and water is stored for half an hour in dark place prior to photometrical analysis at 415 nm. As for total phenols quantification, flavonoids determination relies on a calibration curve with quercetin and results are expressed as quercetin equivalent per dry material.[73]

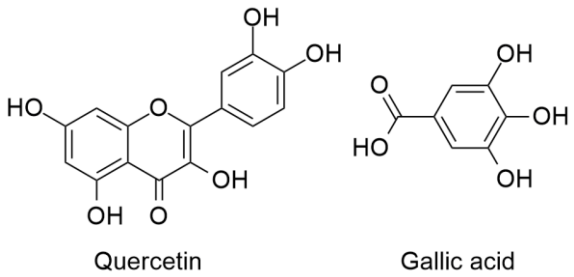


Figure 20: Structure of quercetin and gallic acid

Several studies were performed on extraction and quantification of phenolic compounds in spent coffee grounds. In 2011 Mussatto *et al*. investigated the extraction of active ingredients from spent coffee grounds with methanol as a solvent. Varying the concentration of methanol and the time of extraction, spent coffee grounds were extracted by a liquid-solid method. After separation of the remaining solids, total phenol content and total flavonoids in the extract were determined using the colorimetric assays as described above. Chlorogenic acid and protocatechuic acid were analyzed individually using HPLC, while the antioxidant activity of spent coffee grounds extracts was measured by the ferric reducing antioxidant power assays. A as a result the maximum value of phenols was extracted from spent coffee grounds with water/methanol solutions at 50% v/v after 90 min extraction time at 60 °C to 65 °C. More experimental results on different conditions are presented in a Table 7.[69]

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[72] Singleton V.L.; Rossi Jr. J.A. *Am. J. Enol. Vitic.* **1965**, *16*, 144.
[73] Chang C.-C.; Yang M.-H.; Wen H.-M.; Chern J.-C. *J. Food Drug Anal.* **2002**, *10*, 178.

Methanol conc.	Solvent/solid ratio	Total phenols	Flavonoids	Chlorogenic acid
(%)	(ml/g)	(mg GAE/SCG)	(mg QE/g SCG)	(mg/g SCG)
20	10	7.3	0.86	0.37
80	10	6.6	1.55	0.68
20	40	10.5	1.17	1.33
80	40	11.4	2.50	1.39
20	25	9.0	1.07	1.27
80	25	9.0	2.09	1.39
50	10	11.0	0.75	0.51
50	40	16.3	1.62	1.16
50	25	17.8	1.36	0.99
50	25	17.9	1.38	0.96
50	25	18.2	1.38	0.98
H_2O	10	6.0	0.51	0.58
H_2O	40	7.4	0.56	0.57

Table 7: Experimental conditions on spent coffee grounds extractions with MeOH/H_2O mixtures at 60-65 °C for 90 min.[69]

Despite the good extraction performance with methanol, large scale applications suffer from the inherent toxicity of this solvent. The application of non-toxic solvents, such as water or EtOH/H_2O 60:40 % v/v was investigated for spent coffee grounds extractions by Panusa *et al.* The extraction procedure took 30 minutes and the temperature applied was 60 °C. Various coffee types with different ratios of Robusta and Arabica were collected and analyzed. The yields of total phenols, flavonoids, caffeine and chlorogenic acid were analyzed by the methods described above as well as the antioxidant activity by DPPH (2,2-diphenyl-1-picrylhydrazyl) scavenging assay. In a different study, the same group was investigating the influence of extraction conditions on the recovery of phenolic compounds from spent coffee grounds. The variation of parameters such as temperature, solid-to-liquid ratio and extraction time had a substantial difference on the extraction yields of phenolic antioxidants. Different spent coffee ground waste (Robusta/Arabica; SCG collected from bars or from used capsules) were extracted either with pure ethanol or EtOH/H_2O mixture (60:40 %v/v) at 60 °C for 180 minutes at a solid-to-liquid ratio of 50 mL per g. The results for various extracted phenols are presented in a Table 8 [74]

[74] Panusa, A.; Zuorro, A.; Lavecchia, R.; Marrosu, G.; Petrucci, R. *J. Agric. Food Chem.* **2013**, *61*, 4162.

Waste material	Extraction solvent	Total phenolics	Flavonoids	Chlorogenic acid
	(EtOH/H_2O %v/v)	(mg GAE/g)	(mg QE/g)	(mg/g SCG)
SCG-b1	0:100	19.62	3.24	5.67
	60:40	28.26	5.63	5.97
SCG-b2	0:100	17.43	3.31	6.00
	60:40	23.9	8.03	6.09
SCG-c1	0:100	7.43	2.11	2.15
	60:40	12.58	5.21	2.26
SCG-c1	0:100	6.33	2.24	1.65
	60:40	11.83	5.01	1.81

SCG-b1: collected from bars in Rome, that are richer in Robusta; SCG-b2: collected from bars in Rome, that are richer in Arabica; SCG-c1: collected from used coffee capsules, that are richer in Robusta; SCG-c2: collected from used coffee capsules, that are richer in Arabica

Table 8: Total phenols, flavonoids, chlorogenic acid of extracts from spent coffee grounds

Another strategy for the extraction of spent coffee grounds was reported by Andrade *et al*. relying on supercritical fluid extraction. The supercritical fluid extraction with CO_2 and optional co-solvents was compared with low-pressure methods such as ultrasound and soxhlet extraction with different solvents. The highest yields of 587.7 (mg GAE/g) of total phenols were obtained by using ultrasound extraction techniques with ethanol as a solvent for spent coffee grounds. In case of supercritical fluid extraction the addition of 4 % of ethanol as co-solvent was essential and considerable increased the yield of total phenols to 57 (mg GAE/ g).[75]

[75] Andrade, K. S.; Gonçalvez, R.T.; Maraschin, M.; Ribeiro-do-Valle, R.M.; Martínez, J.; Ferreira, S.R. *Talanta* **2012**, *88*, 544.

3 Task

In this master thesis ionic liquids should be used for the extraction of several active ingredients from spent coffee grounds. In detail, the thesis comprises three parts as indicated in Figure 22:

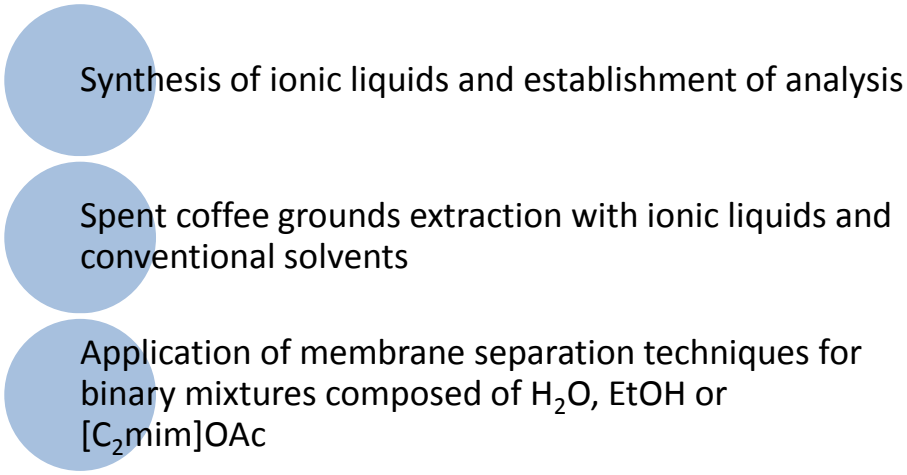


Figure 21: Task

The first part included the synthesis of ionic liquids of three different types:

- Conventional ionic liquids prepared *via* alkylation and/or ion exchange
- Distillable ionic liquids based on 1,1,3,3-tetramethylguanidine (TMG)
- Switchable guanidine based ionic liquids that change their polarity by addition or removal of CO_2

Furthermore, analytical methods for the quantification of active ingredients such as phenols, flavonoids and caffeine should be established.

In the second part, all previously synthesized ionic liquids should be applied for spent coffee grounds dissolution experiments to test active ingredients extraction and to compare the results to conventional solvents. Parameters such as time, temperature and application of microwave irradiation should be investigated to identify optimal solvent and extraction conditions.

In the last part, binary mixtures with different concentrations of ethanol, water or ionic liquid ($[C_2mim]OAc$) should be applied to a membrane separation set-up to recover the solvents after biomass treatment. Therefore, the analysis for the simultaneous determination of the components should be established.

4 Results and discussion

4.1 Synthesis of ionic liquids

Generally, the synthesis of conventional ionic liquids comprises one or two stages: alkylation of an amine or phosphine precursors that is sometimes followed by ion exchange with different strategies to modify the properties (see Figure 22). In some cases, ionic liquid can be obtained directly after alkylation without further ion exchange.

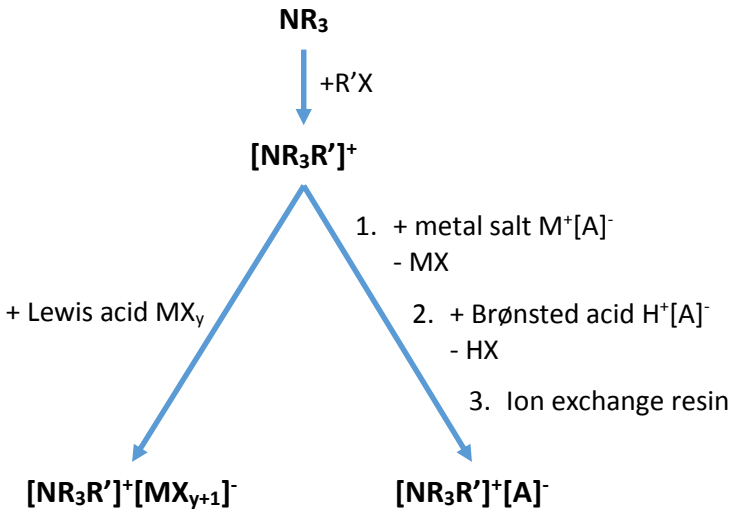


Figure 22 : General strategies of ionic liquids synthesis[1]

For this thesis, a set of 1-alkyl-3-methylimidazolium- or 1-alkyl-3-methylpyridinium-based ionic liquids have been selected due to their known ability to dissolve biomass.[15] In Figure 23, all ionic liquids that were used for the extraction of spent coffee grounds are shown.

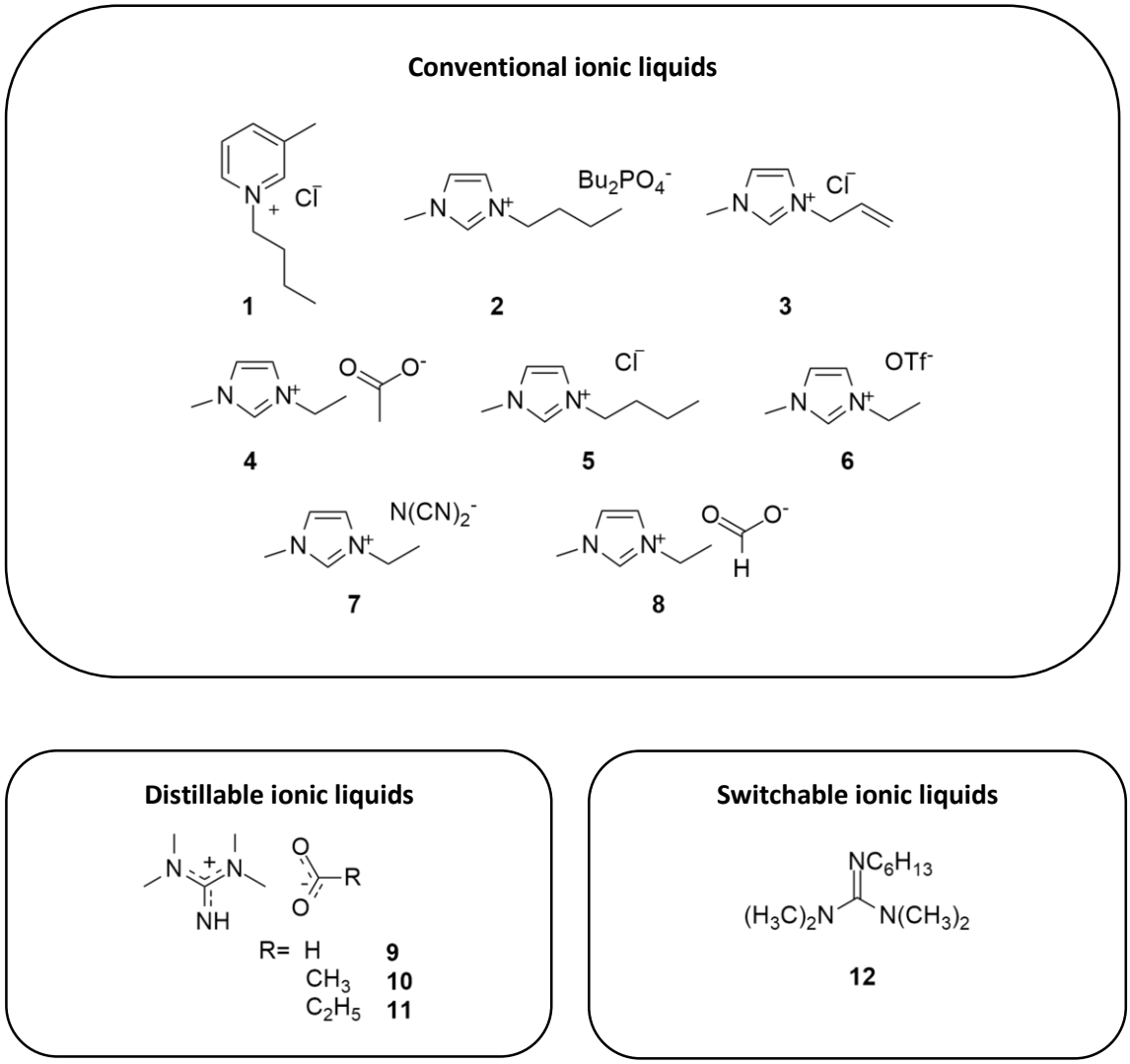


Figure 23: Ionic liquids used for extraction purposes

4.1.1 Synthesis of conventional ionic liquids

In the course of this thesis, ionic liquids **1,2,3,7** and **8** were synthesized either *via* alkylation and optional ion exchange as shown in the general scheme above. In contrast ionic liquids **4**, **5** and **6** were already available in the lab from previous experiments or from commercial suppliers.

The synthesis of ionic liquids **1**, **2** and **3** was performed with 1-methylimidazole or 3-methylpyridine as precursor with nucleophiles such as the corresponding alkyl halides or tributyl phosphate. Alkylation reactions were performed under inert atmosphere in solvent-free manner using a small excess of the alkylating agent. The reaction progress was followed by NMR spectroscopy for complete conversion of the starting material. In general, the synthesis of ionic liquids **1**, **2** and **3** *via* direct alkylation was found to be quite time consuming and required high temperatures. For example, the synthesis of ionic liquid **2** was initially run at 80 °C; however, after two days only a conversion of 30% was found according to NMR

spectroscopy. In order to increase the reaction speed the temperature was increased to 150 °C. This resulted in full conversion within 3 more days according to NMR spectroscopy.

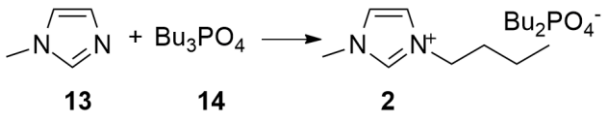


Figure 24: Synthesis of 1-butyl-3-methylimidazolium dibutylphosphate prepared by alkylation

In contrast ionic liquids**1**, **2** and **3** that were directly obtained in this single alkylation step, ionic liquids **7** and **8** were synthesized *via* an additional ion exchange reaction:

- In case of ionic liquid **1**, anion exchange was performed with the silver salt of the anion, as silver halide as a by-product could be easily precipitated (Figure 25). The reaction was performed in water, where an excess of silver salt **16** in water was dropwise added to ionic liquid **15** and left to be stirred for short time in a dark place. Disadvantage of this method is the usually high price of silver salts.

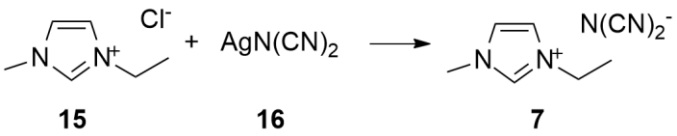


Figure 25: Anion exchange with silver salt

- In contrast, anion exchange with ion exchange resin was applied for the formation of 1-ethyl-3-methylimidazolium formate [C_2mim]Fmt **8**. First the chloride anion of [C_2mim]Cl **15** was exchanged *via* ion exchange resins to the intermediate hydroxide salt **17,** followed by addition of an equimolar amount of formic acid resulting in formation of [C_2mim]Fmt **8**. (Figure 26)[76]

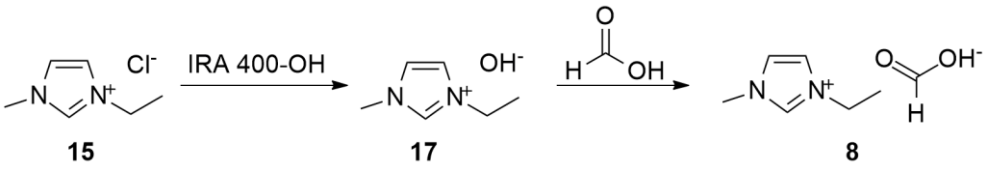


Figure 26: Anion exchange with ion exchange resin

4.1.2 Synthesis of distillable ionic liquids

In this thesis distillable ionic liquids based on the 1,1,3,3-tetramethylguanidinium cation were used. Protic ionic liquids were synthesized by addition of equimolar amount of carboxylic acids, such as formic, acetic and propionic acids (see Figure 27) to the precursor 1,1,3,3-tetramethylguanidine. The reaction was rather

[76] Wassell, D. F.; Ferguson, J. L.; Holbrey, J. D.; Ng, S.; Plechkova, N. V.; Seddon, K.R.; Tomaszowska, A. A. *Pure Appl. Chem.* **2013**, *84*, 723

fast and slightly exothermic. The purity of the formed ionic liquids was checked by NMR spectroscopy. In all cases, the yields of the formed ionic liquids were quantitative.

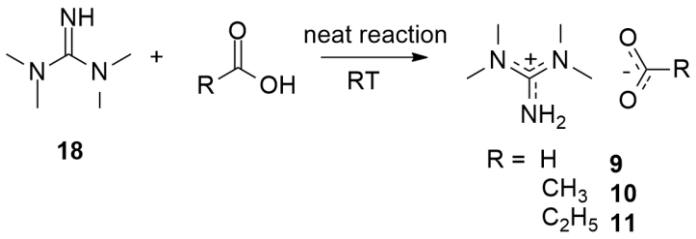


Figure 27: General scheme of distillable ionic liquids synthesis[31]

4.1.3 Synthesis of switchable ionic liquids

Apart from protic ionic liquids **7**-**9** that can be easily removed *via* distillation, switchable ionic liquids offer another strategy for removal after extraction. These neoteric solvents can be reversibly switched from a neutral and hydrophobic to an ionic and hydrophilic state. This switch from ionized to neutral form also offers the opportunity to remove the solvent *via* distillation or phase separation. The change in polarity is typically obtained *via* reaction with gases, e.g. CO_2 or SO_2.[30] Carbon dioxide is preferred for switching hydrophilicity as it has low cost, being environmentally benign and easily removable (Figure 28).

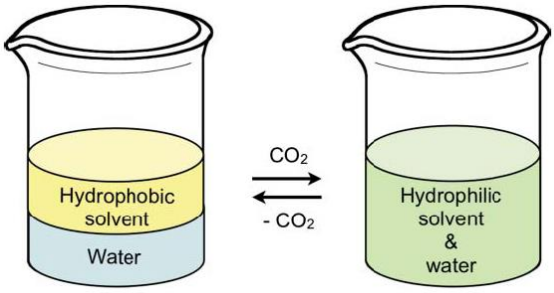


Figure 28: Phase behaviour of switchable ionic liquid[30]

The synthesis of switchable ionic liquid was performed in two steps. In the first part *N,N,N',N'*-tetramethylurea and oxalyl chloride reacted under inert atmosphere at 60 °C overnight according to the method of Fujisawa.[28]

The next step was the reaction of 1,1,3,3-tetramethylformamidinium chloride **21** with an amine. The exothermic reaction was performed in dry acetonitrile under cooling. The purification of the final product was accomplished by extraction followed by distillation. The reaction as given in Figure 29 was performed using the method of Wieland and Simchen.[28]

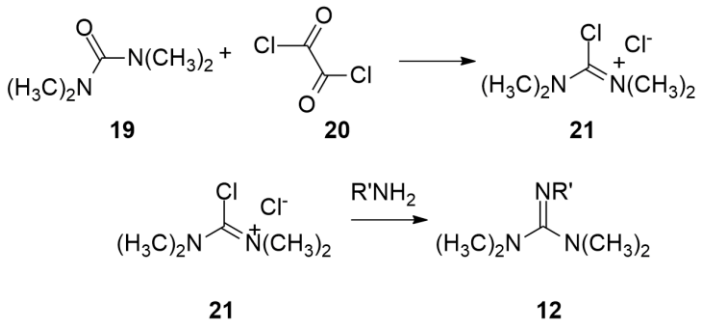


Figure 29: General scheme of switchable ionic liquids synthesis[28]

The switch reaction 2-hexyl-1,1,3,3-tetramethylguanidine **12** with CO_2 in presence of water or ethanol is presented in Figure 30. The amidine is converted in water-soluble bicarbonate salts.

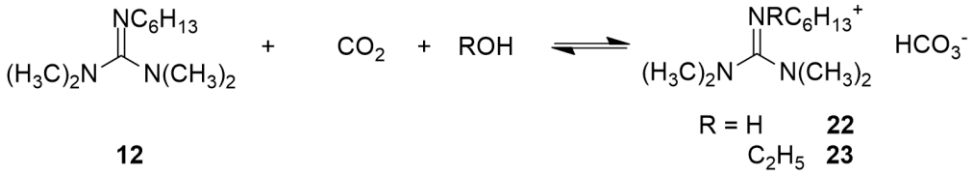


Figure 30: Switch reaction of amidine with carbonic acid

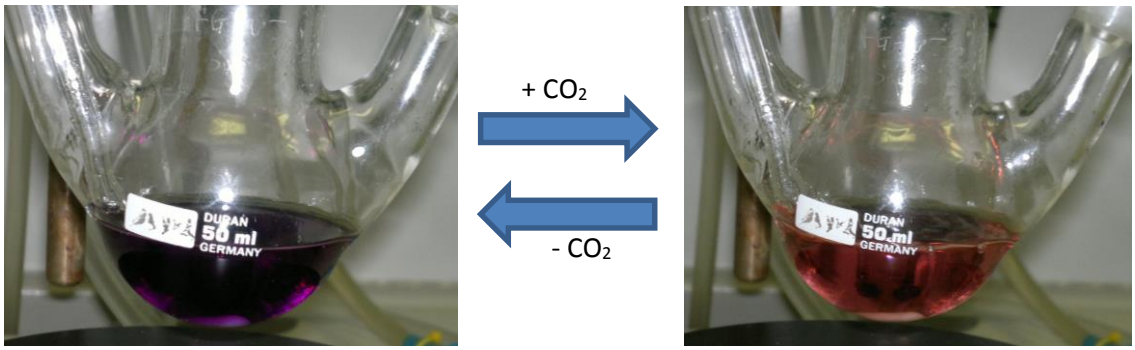


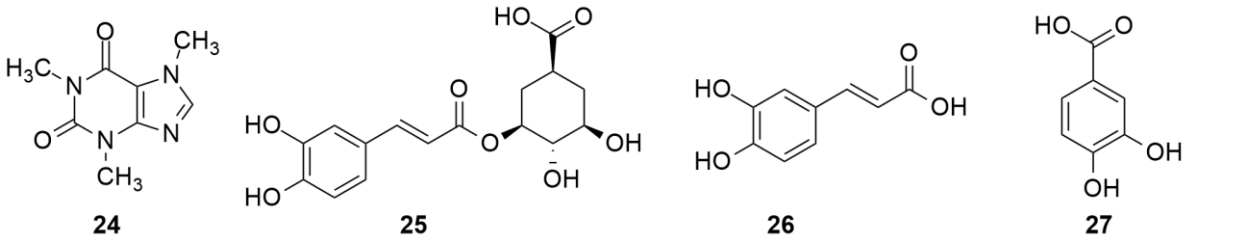
Figure 31: Switch reaction of 2-hexyl-1,1,3,3-tetramethylguanidine in ethanol

The change in polarity is visible from a preliminary experiment of the precursor molecule **12** in EtOH after reaction with CO_2. In order to visualize the switch between hydrophobic and hydrophilic form, a betaine dye was added as indicator to account for corresponding change in polarity. As can be seen from Figure 31 the solution changes its color from purple to red after short exposure to a stream of CO_2 gas.

4.2 Development of analytics for spent coffee grounds extraction

4.2.1 HPLC analysis of dissolved spent coffee grounds

For determination of active ingredients after the extraction of spent coffee grounds with various ionic liquids HPLC strategy was developed. A reversed phase column set-up with MeOH/H_2O and trifluoroacetic acid (TFA) as an eluent was used. As an internal standard phenol was chosen, since it does not overlap with any active ingredient or the ionic liquid. A chromatogram containing all four peaks of active ingredients of interest, such as: caffeine **24** chlorogenic acid **25**, caffeic acid **26** and 3,4-dihydroxybenzoic acid **27** is presented in a Figure 32.

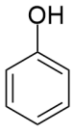


24 Caffeine

25 Chlorogenic acid

26 Caffeic acid

27 3,4-dihydroxybenzoic acid



28

Internal standard: Phenol

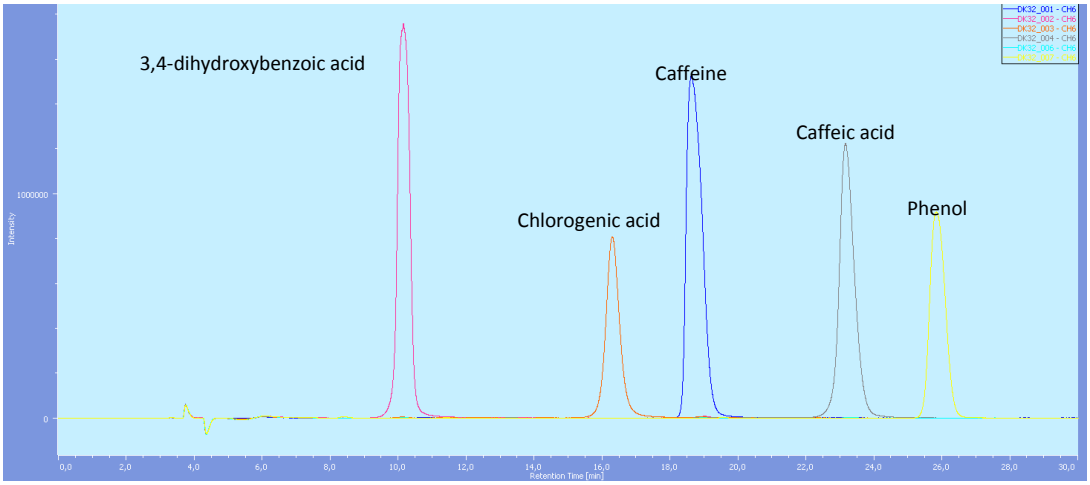


Figure 32: Compounds of interest and respective peaks in HPLC chromatogram

Figure 33 represents an example of a chromatogram of dissolved coffee grounds in [C_2mim]OAc/H_2O at room temperature for 24 hours sample after dilution with ethanol. Based on the high polarity of ionic liquids they were eluted in the beginning allowing rather apolar active ingredient such as caffeine and

chlorogenic acid to elute later on. After the initial peak from the ionic liquid, Chlorogenic acid is eluted at around 14.5 min, caffeine is eluted at around 16 min and internal standard phenol at 20 min.

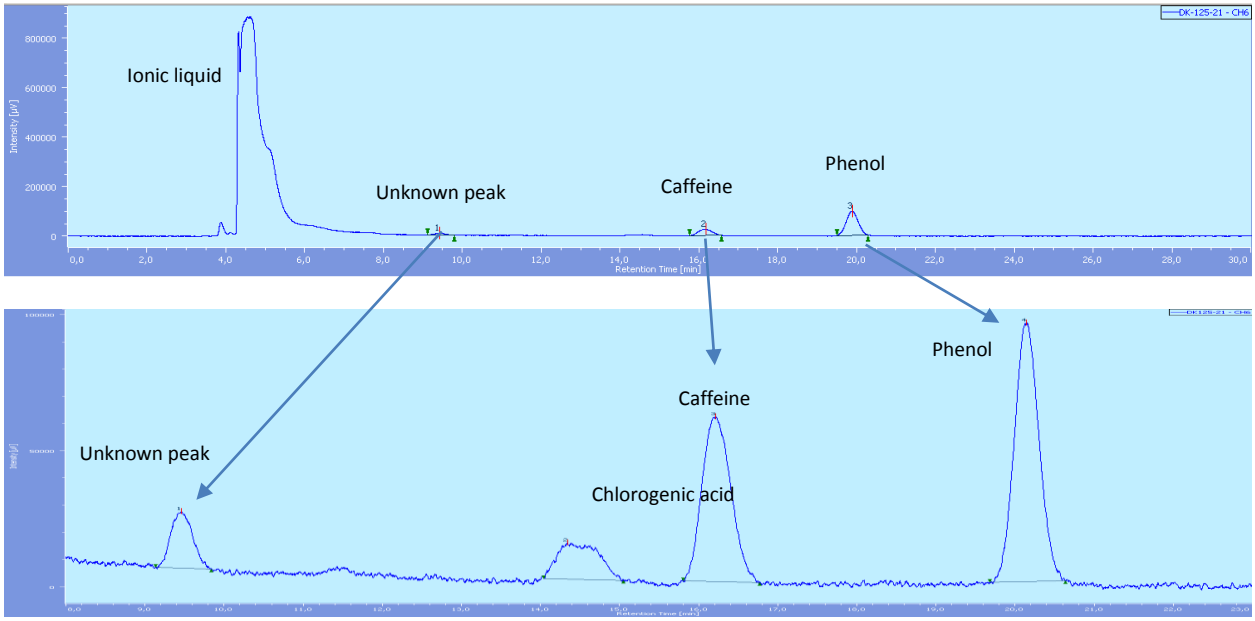


Figure 33: Example of chromatogram with dissolved coffee grounds in [C_2mim]OAc/H_2O (50 wt%) (top). The bottom chromatogram provides an enlarged view on the retention times of interest for the active ingredients.

The chromatogram also contains unknown peaks that could not be identified *via* HPLC. However 3,4-dihydroxybenzoic acid and caffeic acid were not identified or were below detection limit in most samples of extracted spent coffee grounds.

Calibration curves were prepared for known concentrations of active ingredients in methanol in a range of 0.005-0.1 mg/ml for caffeine and 0.005-2 mg/ml for chlorogenic acid with addition of a constant amount of internal standard of 0.1 mg by addition of 0.2 ml of stock solution.

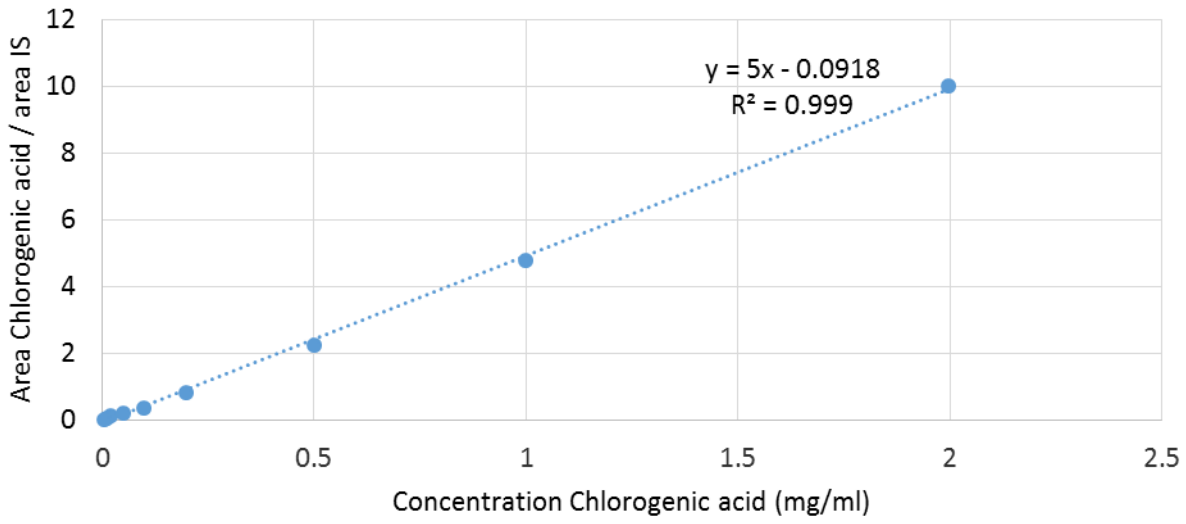


Figure 34: HPLC calibration curve for chlorogenic acid

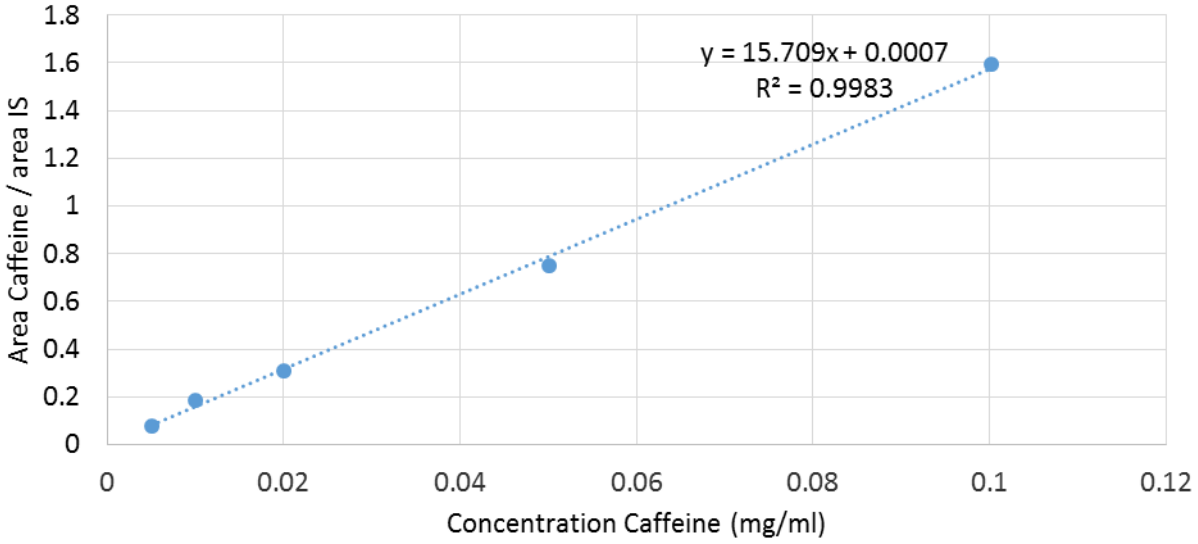


Figure 35: HPLC calibration curve for caffeine

As can be seen from Figure 34 and Figure 35 calibration curves for caffeine and chlorogenic acid are linear and show very good correlation coefficients $R^2 > 0.99$. Based on these calibration curves, the extraction yield of the active ingredient could be calculated based on the formula shown below and was be expressed as wt% based on the crude biomass

$$Yield[wt\%] = \frac{Active\ component\ calculated\ from\ HPLC\ [mg]}{Crude\ SCG[mg]} * 100$$

4.2.2 UV-Vis analysis of dissolved spent coffee grounds

4.2.2.1 Total phenol content determination

Total phenol content of extracted samples was analyzed by means of a colorimetric method using the Folin-Ciocalteu reagent, which is a mixture of polymeric ions formed from phosphomolybdic and phosphotungstic heteropoly acids. A sample of extracted spent coffee grounds, the Folin-Ciocalteu reagent, sodium carbonate solution and water were heated for five minutes and measured at 700 nm in an UV-Vis spectrometer. Folin-Ciocalteu reagent oxidizes phenolates, thereby reducing the heteropoly acids to a blue Mo-W complex.[72,73]

Calibration curves were prepared from a gallic acid standard solution with known concentrations of gallic acid in the range of 200-3000 mg/l. As the presence of ionic liquids might affect this calibration, the influence of [C_2mim]OAc on a calibration curve was investigated. Therefore, calibration curves for gallic acid standard solution in water and gallic acid standard solution in [C_2mim]OAc/H_2O were prepared (10:90 wt%) and compared.

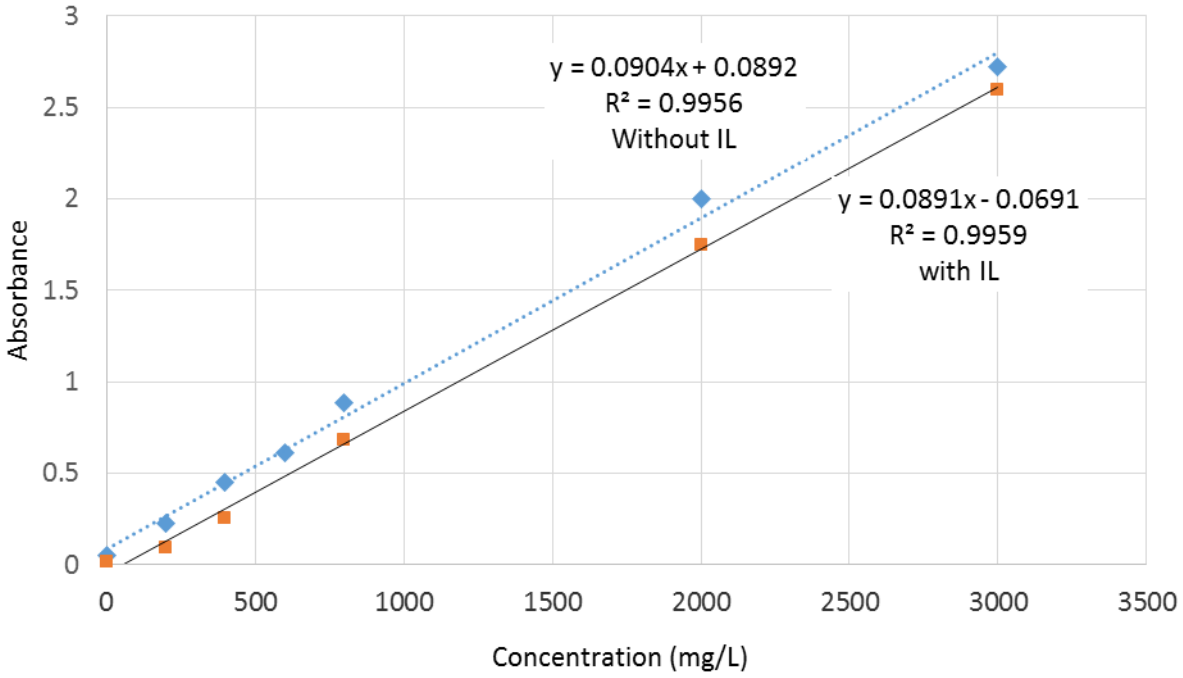


Figure 36: UV-Vis spectroscopic calibration curve for total phenol content determination

As can be seen from Figure 36 the calibration curves for gallic acid standard solution in water and gallic acid standard solution in [C_2mim]OAc /H_2O (10:90 wt%) do slightly differ so that the second calibration with ionic liquid curve was used for the determination of total phenol content in the presence of ionic liquid. However, both are linear and show very good correlation coefficients $R^2 > 0.99$. Again, the total phenol content in the sample could be calculated according to the formula below. Results in extraction sample are then expressed as gallic acid equivalents per dry material.

$$Yield[wt\%] = \frac{Active\ component\ calculated\ from\ UV-Vis\ [mg]}{Crude\ SCG[mg]} * 100$$

4.2.2.2 Flavonoids determination

As for the determination of total phenol content, flavonoids were also analyzed using a colorimetric method. A sample of extracted spent coffee grounds, aluminum chloride solution, potassium acetate solution, methanol and water were stored in dark place for half an hour and measured at 415 nm in an UV-Vis spectrometer.

Calibration curves were prepared from a quercetin standard solution with known concentrations of quercetin in the range of 25-200 mg/l. Again, the influence of [C_2mim]OAc on the absorbance was investigated. Both calibration curves for quercetin standard solution in water and quercetin standard solution in [C_2mim]OAc/H_2O (10:90 wt%) were prepared and show very good correlation coefficients $R^2 > 0.99$ (Figure 37).

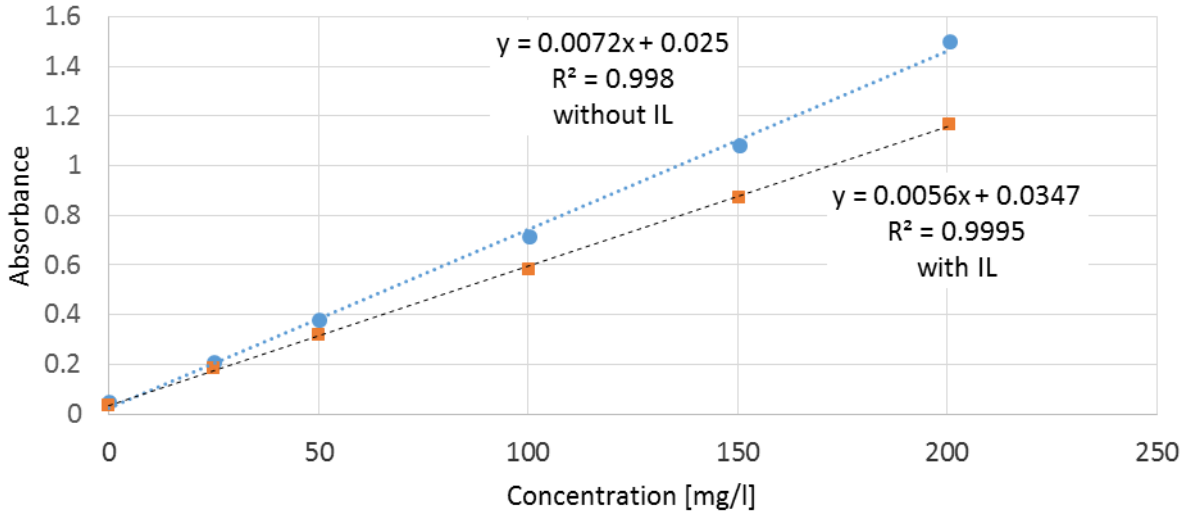


Figure 37: UV-Vis spectroscopic calibration curve for flavonoids determination

Results are expressed as quercetin equivalents per dry material.

$$Yield[wt\%] = \frac{Active\ component\ calculated\ from\ UV - Vis\ [mg]}{Crude\ SCG[mg]} * 100$$

4.4 Spent coffee grounds extraction

Currently spent coffee grounds do not have any commercial application, although they contain a number of health-related chemicals that could find application in many fields. In order to investigate if ionic liquids increase the extraction yields of valuable components from spent coffee grounds, [C_2mim]OAc was compared with conventional solvents, such as water or ethanol.

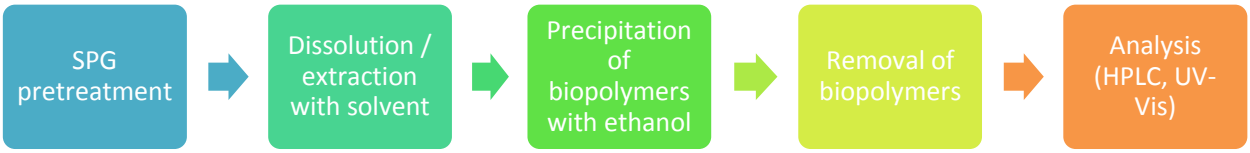


Figure 38: General strategy for spent coffee grounds (SPG) extraction

The first step in the general strategy of biomass dissolution is spent coffee grounds pretreatment that included collection of spent coffee grounds from 100% Arabica coffee (Illy espresso) and drying in a vacuum drying oven at 60 °C/ 20 mbar for 20 days (see Figure 38). After that, 10 wt% of spent coffee grounds were treated with a solvent at certain temperature (room temperature or 100 °C) for a certain period of time (1 h, 3 h, 6 h, 24 h). The influence of microwave irradiation was investigated as well (15 min, 100 °C). Extraction of biomass was followed by precipitation of biopolymers, depending on consistency of biopolymers with 5 or 10 ml of ethanol. Biopolymers were removed *via* centrifugation and the supernatant was analysed *via* HPLC and UV-Vis as described above. All experiments were repeated five times to deplete inconsistencies in the crude biomass and results were reported as average values.

4.4.1 Influence of [C_2mim]OAc and conventional solvents on SCG extraction at ambient conditions

Initially the extraction performance of the ionic liquid ([C_2mim]OAc) was compared with conventional solvents such as water and ethanol under ambient conditions at room temperature for 24 hrs using a biomass loading of 10 wt%.

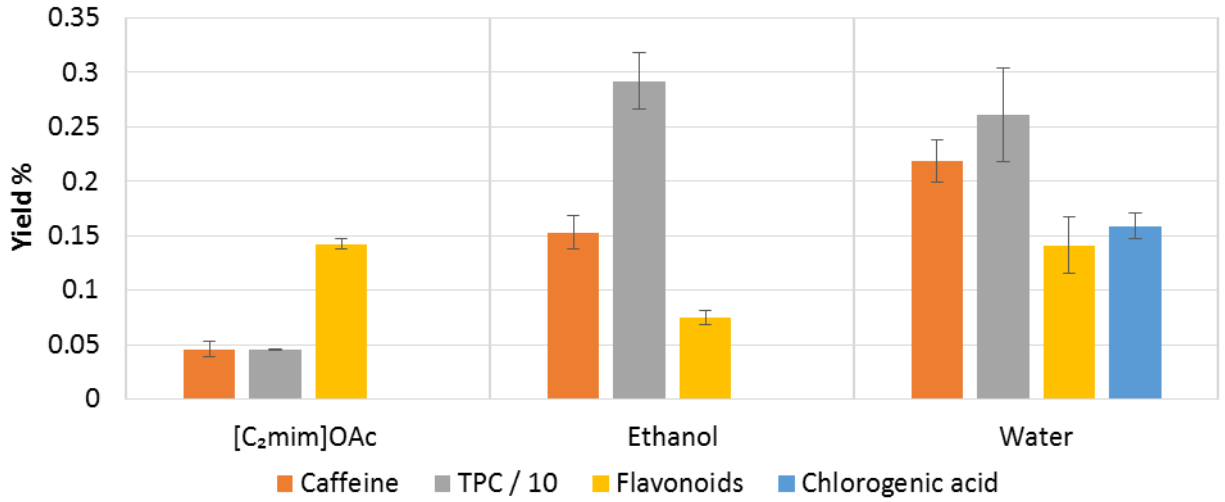


Figure 39: Comparison of conventional solvents and [C_2mim]OAc for spent coffee grounds extraction at room temperature for 24 hours, where TPC/10 is 1/10 of total phenol content as gallic acid equivalent.

Figure 39 represents the results obtained under these conditions. The values of total phenol content expressed as gallic acid equivalents were divided by 10, in order to make the diagram comparable to other extracted active ingredients. The best extraction yield for caffeine and total phenols was obtained in case of water and ethanol as a solvents. On the other hand flavonoids were extracted preferentially with the ionic liquid [C_2mim]OAc. In contrast, chlorogenic acid could be only extracted with water.

4.4.2 Influence of different extraction conditions on SCG dissolution with water and [C_2mim]OAc

In order to investigate the influence of different extraction conditions on the yields of active ingredients from spent coffee grounds, the extraction process was also performed at 100 °C for 1, 3 and 6 hours and at 100 °C for 15 minutes under microwave irradiation and compared to ambient conditions. This experiments were performed with water or the ionic liquid [C_2mim]OAc as solvent and are summarized in Figure 40 and Figure 41.

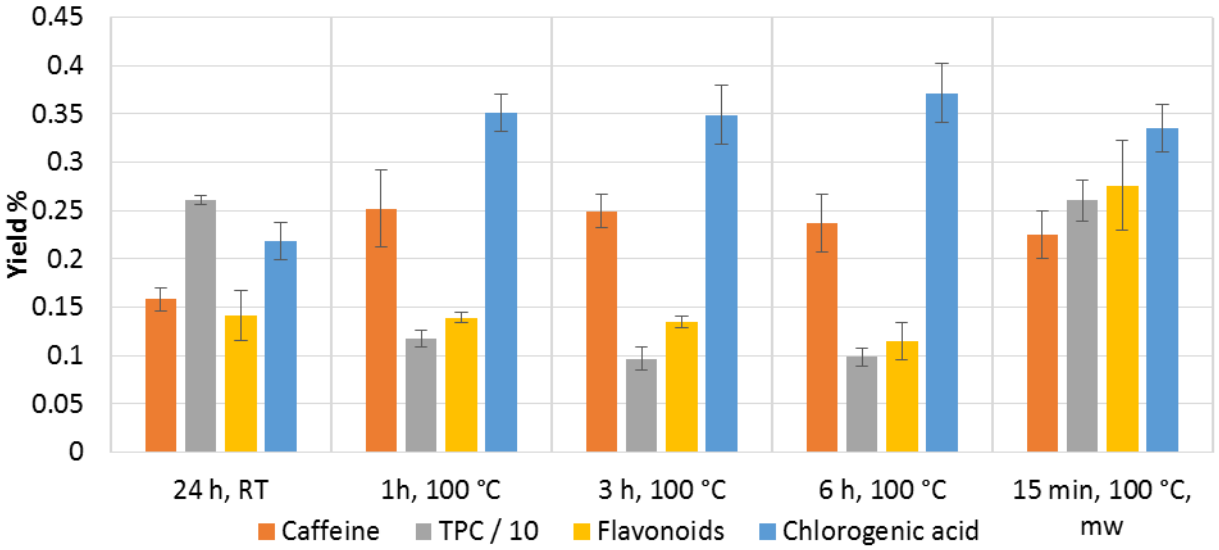


Figure 40: Comparison of different conditions for spent coffee grounds extraction with water as a solvent (RT: Room temperature, mw: microwave extraction, TPC/10 is 1/10 of total phenol content as gallic acid equivalent)

In case of water as a solvent an increased extraction temperature helps to increase the yield of chlorogenic acid, whereas the yields of total phenols decreases with prolonged heating – probably due to thermal decomposition. However applying microwave irradiation increases the total amount of phenols and flavonoids. In case of caffeine, little influence was observed concerning heating time or methods, as extraction yields at prolonged heating for 1, 3 or 6 hours at 100 °C and under microwave irradiation for 15 min at 100°C are similar.

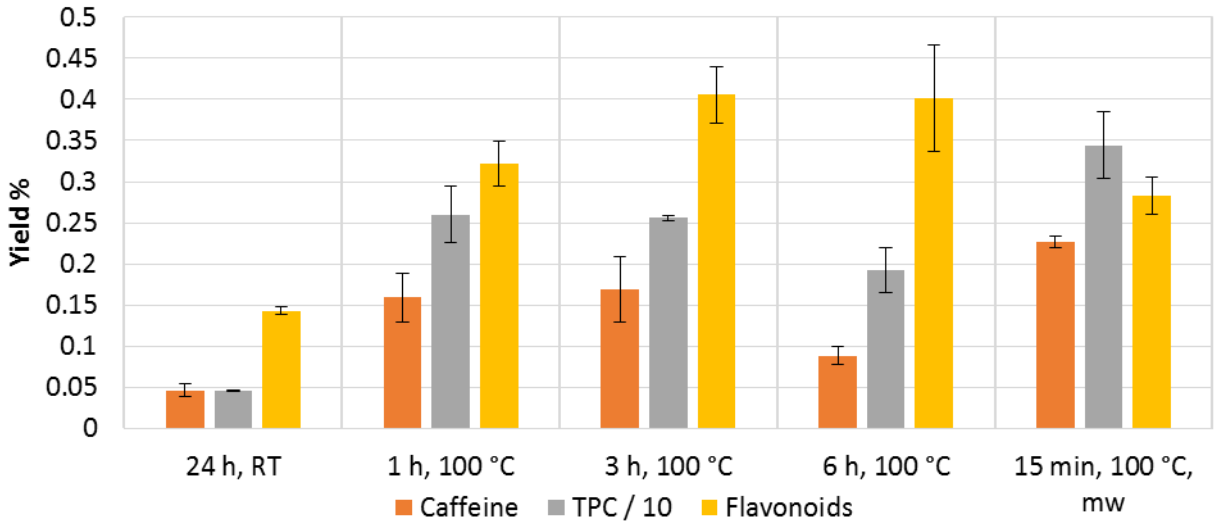


Figure 41: Comparison of different conditions for spent coffee grounds extraction with [C_2mim]OAc as a solvent (RT: Room temperature, mw: microwave extraction, TPC/10 is 1/10 of total phenol content as gallic acid equivalent)

In contrast to the extraction with water, an increase in reaction time and temperature could significantly improve the yields of extraction yields of caffeine, phenols and flavonoids. This is probably caused by the disruption of the biopolymer matrix by the ionic liquid, as the dissolution of biomass with the ionic liquid [C_2mim]OAc was greatly increased at higher temperatures. The best results for extraction of caffeine as

well as for phenols were achieved when dissolving spent coffee grounds in [C_2mim]OAc under microwave irradiation. Flavonoids could be extracted best with [C_2mim]OAc under heating to 100 °C for longer time (3 or 6 hours). Comparing results for spent coffee grounds dissolution for 1, 3 and 6 hours showed again that the amount of extracted caffeine and phenols is decreasing with a longer heating probably due to degradation or reaction of the actives with the ionic liquid in the solution. The flavonoid content, in contrast, is increasing.

4.4.3 Spent coffee grounds extraction with different conventional ionic liquids

Based on the results obtained with [C_2mim]OAc extraction, the most favorable condition for spent coffee grounds dissolution for various conventional ionic liquids were identified as 100 °C extraction temperature for 1 h, as this provides a compromise between time and energy consumption and high extraction yields. These conditions were further applied to investigate the influence of different ionic liquids that have been previously synthesized. Figure 42 shows a comparision of the extraction performance with the ionic liquids 1-allyl-3-methylimidazolium chloride ([amim]Cl) **3**, 1-butyl-3-methylimidazolium dibutyl-phosphate ([C_4mim]Bu_2PO_4) **2**, 1-butyl-3-methylimidazolium chloride ([C_4mim]Cl) **4**, *N*-butyl-3-methylpyridinium chloride ([C_4MePy]Cl) **1**, 1-ethyl-3-methylimidazolium formate ([C_2mim]Fmt) **8**, 1-ethyl-3-methylimidazolium triflate ([C_2mim]OTf) **6**, 1-ethyl-3-methylimidazolium dicyanamide ([C_2mim]$N(CN)_2$) **7** and 1-ethyl-3-methylimidazolium acetate([C_2mim]OAc) **4**.

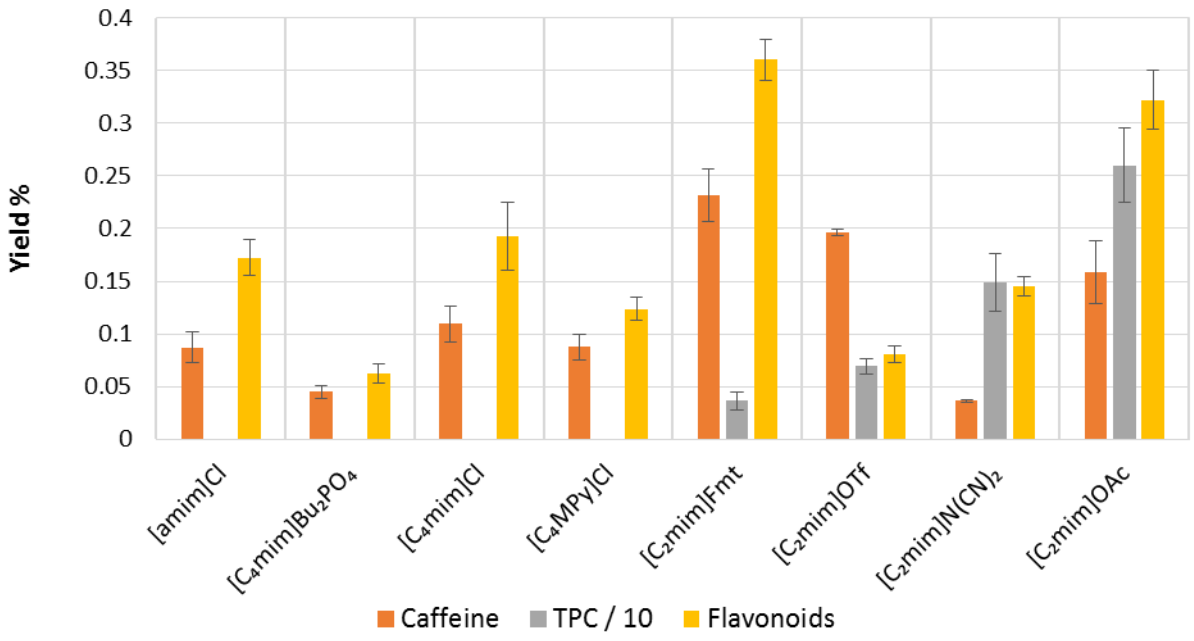


Figure 42: Comparison of different conventional ionic liquids for spent coffee grounds extraction at 100 °C for 1 hour (TPC/10 is 1/10 of total phenol content as gallic acid equivalent)

The comparison of various conventional ionic liquids for spent coffee grounds dissolution in Figure 42 indicates that the highest yields for caffeine and flavonoids were achieved with [C_2mim]OAc, [C_2mim]Fmt

and [C_2mim]OTf. Total phenols are preferentially extracted with [C_2mim]OAc, whereas the highest yield of caffeine and flavonoids was found with [C_2mim]Fmt.

Obtained results are in accordance with previous data on biomass dissolution. For example Brandt *et al.* used the β Kamlet-Taft parameter as a useful tool for measuring the pretreatment efficiency of certain ionic liquids in disrupting lignocellulose networks. It was shown that ionic liquids with acetate anions (β =1.2) are more efficient than chloride ionic liquids (β =0.83) in dissolution of pine wood chips. Generally ionic liquids with β ≥1.0 support higher yields of fermentable sugars following pretreatment.[77] Furthermore, it was found that increased hydrogen bond basicity of anion reduces the dissolution ability of biomass with ionic liquids. This was also found in the results obtained in this work, which show the highest yields of caffeine for ionic liquids with such basic anions as acetate and formate.

4.4.4 Influence of ionic liquid/H_2O mixtures on SCG dissolution

Since water showed competitively good results, more detailed investigations on the extraction of active ingredients from spent coffee grounds with mixtures of different concentrations of [C_2mim]OAc with water were made, thereby combining the benefits of both solvents of extraction while equally considering economic criteria for the extraction media. Table 9 represents the chosen concentrations of [C_2mim]OAc/H_2O that were examined.

Number of the mixture	[C_2mim]OAc (wt%)	Water (wt%)	[C_2mim]OAc (mol%)	Water (mol%)
1	100	0	100	0
2	90	10	48.8	51.2
3	75	25	24.1	75.9
4	60	40	13.7	86.3
5	50	50	9.6	90.4
6	40	60	6.6	93.4
7	25	75	3.4	96.6
8	10	90	1.2	98.8
9	0	100	0	100

Table 9: Concentrations of [C_2mim]OAc /H_2O mixtures

The results presented in Figure 43, show that the amount of extracted flavonoids is almost independent of the ionic liquid concentration with only small fluctuations. In contrast, total phenols and caffeine content are strongly dependent on the composition of the extraction media. As can be seen from Figure 43, both values are steadily increasing and reach a maximum at approximately 50 wt% mixtures [C_2mim]OAc /H_2O and then again slightly decrease. Surprisingly, the extraction efficiency of pure water still shown rather good results for all caffeine and total phenols.

[77] Brandt, A.; Hallett, J.P.; Leak, D.J.; Murphy, R. J.; Welton, T. *Green Chem.* **2010**, *12*, 672.

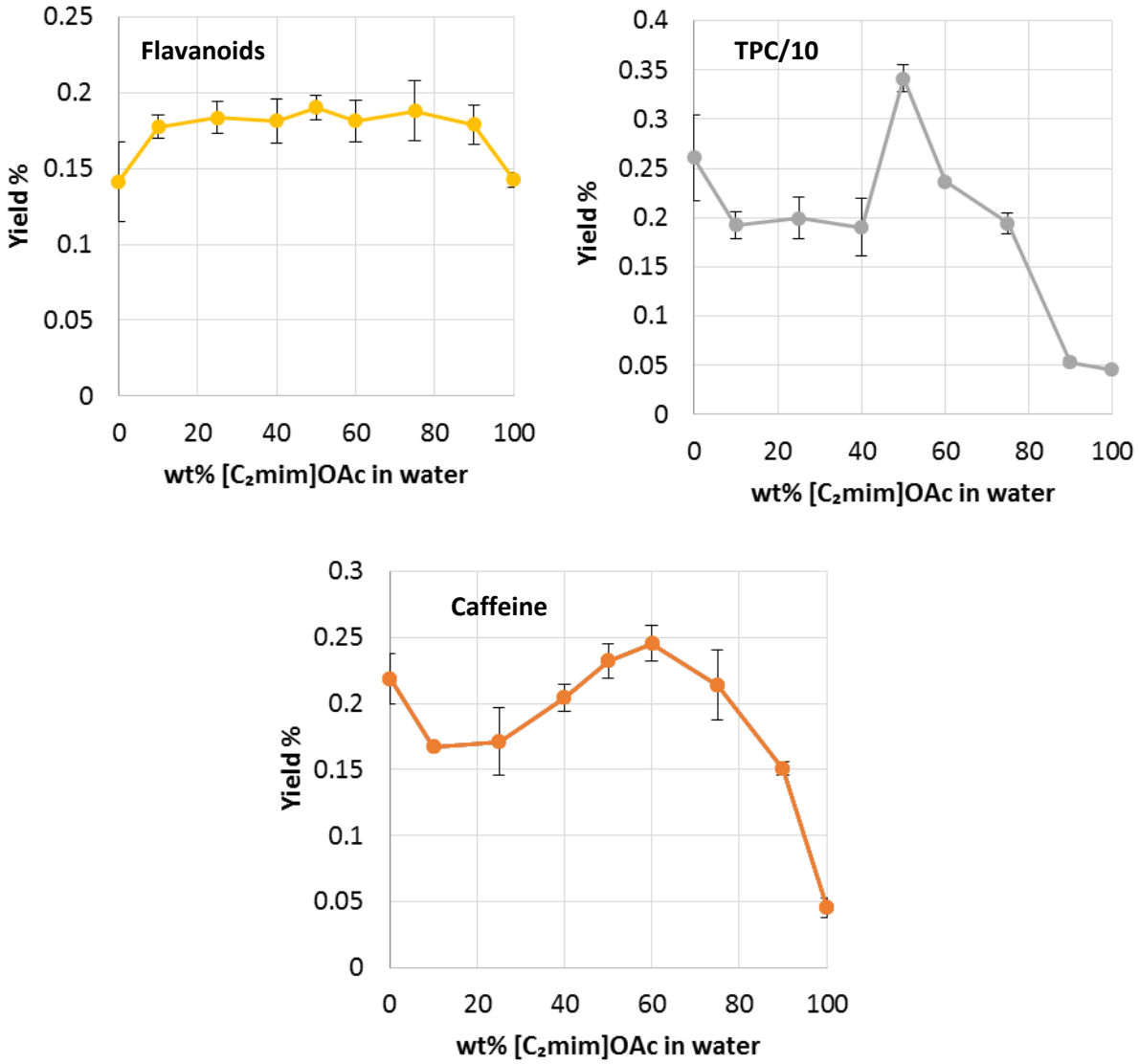


Figure 43: The extraction yields for flavonoids (top left), TPC/10 (top right) and caffeine (bottom) dependent on a different ratios [C_2mim]OAc/H_2O (TPC/10 is 1/10 of total phenol content as gallic acid equivalent)

4.4.5 Influence of extraction conditions with 50 wt% [C_2mim]OAc/H_2O as a solvent

To further improve the best yielding results obtained with [C_2mim]OAc/H_2O mixture, different extraction conditions were applied for spent coffee grounds extraction. Spent coffee grounds were extracted with 50 wt% [C_2mim]OAc/H_2O at room temperature for 24 hours but also at 100 °C for 1, 3 and 6 hours as well as at 100 °C for 15 minutes under microwave irradiation.

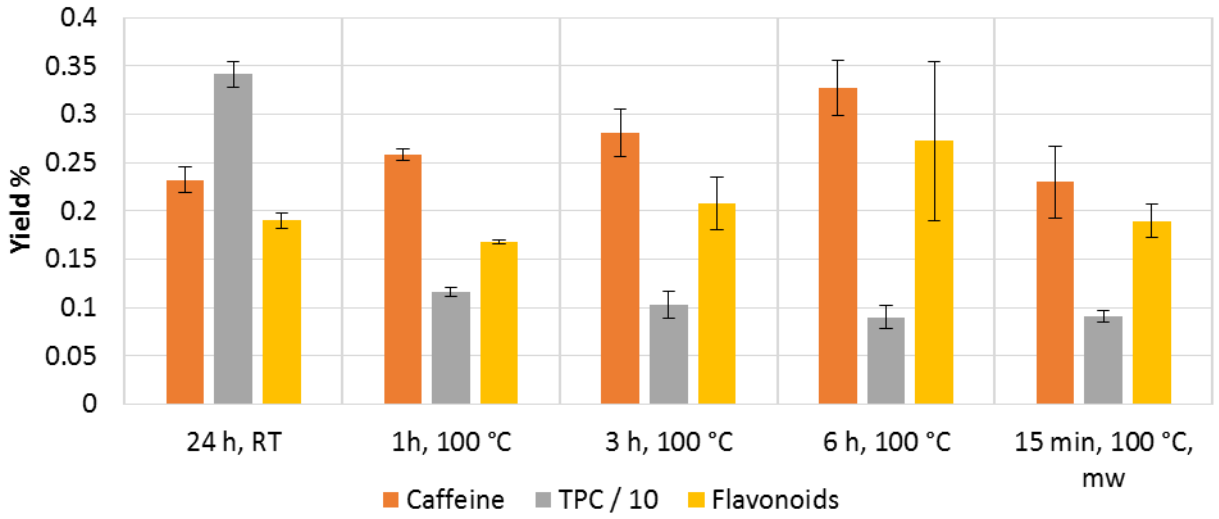


Figure 44: Comparison of different conditions for spent coffee grounds extraction with 50 wt% [C_2mim]OAc/H_2O as a solvent, (RT: Room temperature, mw: microwave extraction, TPC/10 is 1/10 of total phenol content as gallic acid equivalent)

The trend shows that applying a temperature of 100 °C increases the yield of active ingredients in case of caffeine but decreases the extraction of total phenols. The yield of flavonoids remains approximately the same under all extraction conditions.

4.5 Separation of [C_2mim]OAc, water or ethanol binary mixtures

4.5.1 Establishing analytics

While the extraction of active ingredients from biomass with ionic liquids or their mixtures with solvents can and has been successfully established, the separation of the active ingredient as well as the recovery and recycling of the ionic liquids remains a challenge until today. A number of strategies for the separation of ionic liquid and anti-solvent for the precipitation of biopolymers as discussed in chapter 2.1 and 2.2 has been used. Among these technologies, membrane separation has received little attention despite its promising application in environmental applications, as for example the generation of high purity water due to the removal capacity of contaminants with lower energy consumption. Nanofiltration assisted by of membranes is widely used for desalination. Another important application of membrane separation technique is purification of active pharmaceutical ingredients from genotoxic impurities.[78] For example, Szekely *et al.* proved an adequacy of different approaches for the removal of 1,3-diisopropylurea, that is potentially genotoxic impurity in active pharmaceutical ingredients.[79]

Consequently, after finding the solvent that extracts the most of active ingredients from spent coffee grounds we focused on the development of membrane separation technique for the separation and recovery of active ingredients and/or solvents used in the process. Initially it was important to establish analytics for concentration determination of binary mixtures of ionic liquid with water or with ethanol. The ionic liquid of choice was [C_2mim]OAc, due to its previous good results for biomass dissolution, particularly with respect to spent coffee grounds dissolution. Two analytical techniques relying on NMR spectroscopy or HPLC were developed in order to determine the composition of binary mixtures before and after membrane separation. Mixtures of EtOH/[C_2mim]OAc, [C_2mim]OAc/H_2O and EtOH/H_2O with different concentrations of the components were prepared. Before each experiment [C_2mim]OAc was checked by Karl-Fischer titration for water content determination that was always less than 0.7%. For determining concentrations *via* NMR, the NMR tubes were charged with approximately 10.0 mg of internal standard maleic acid, 20.0 mg of mixture sample and 0.5 ml of d_6-acetone. Ethanol and [C_2mim]OAc were directly determined *via* integration and comparison with the known amount of internal standard. An example NMR spectrum for the mixture [C_2mim]OAc/EtOH 75:25 (wt%) is given in Figure 45.

[78] Mohammad, A.W.; Teow, Y.H.; Ang, W.L.; Chung, Y.T.; Oatley-Radcliffe, D.L.; Hilal, N. *Desalination* **2015**, *356*, 226.

[79] Szekely, G.; Bandarra, J.; Heggie, W.; Sellergren, B.; Ferreire, F. C. *Sep. Purif. Technol.* **2012**, *86*, 79.

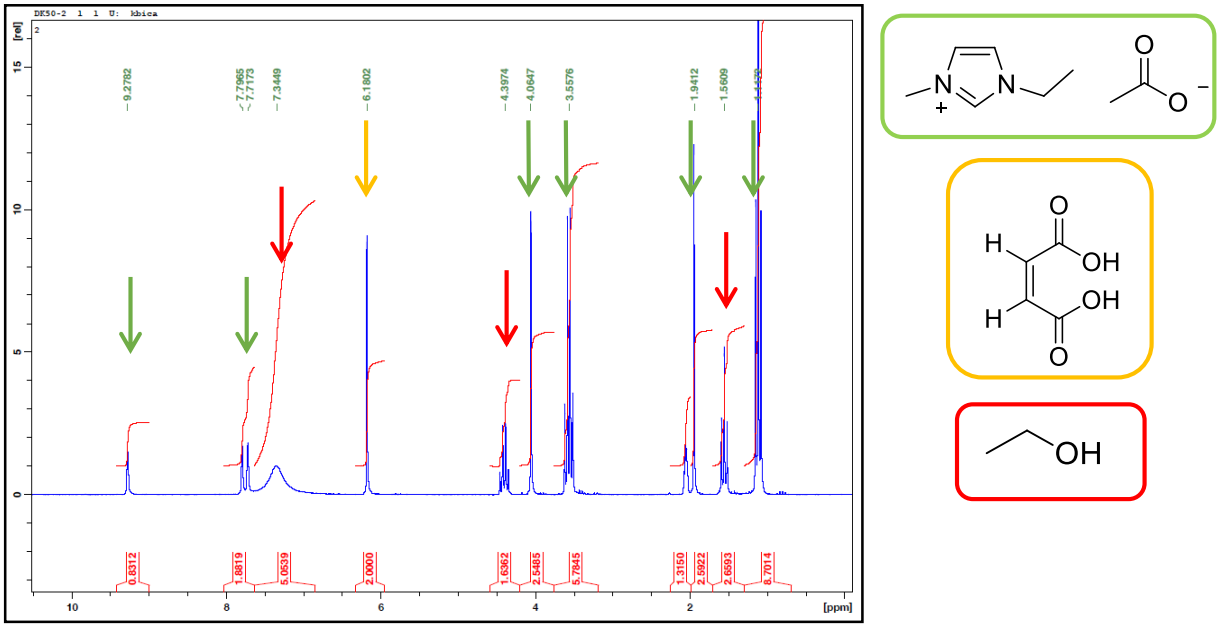


Figure 45: NMR spectrum of mixture [C_2mim]OAc/ethanol 75:25 (wt%)

Based on the chemical shift of the two hydrogens of maleic acid are near 6.25 ppm, the concentration of [C_2mim]OAc and ethanol could be calculated depending on the integral ratios of these compounds. In Figure 45 the peaks of maleic acid are marked with yellow arrow, peaks of ethanol with red arrow and peaks of [C_2mim]OAc with green arrow. The advantage of this NMR based method for concentration determination is its simplicity and relatively low time consumption without requiring calibration curves. However the rather big deviation is a clear disadvantage (see Table 10).

As alternative, the composition can also be determined *via* HPLC. Calibration curves were prepared for ethanol and [C_2mim]OAc for known concentrations of ionic liquid and ethanol in water (HPLC grade) in a range of 0.005 - 2 mg/ml with addition of constant amount of internal standard (3-hydroxybenzyl alcohol) of 0.1 ml.

Figure 46 shows a chromatogram of a [C_2mim]OAc/EtOH sample. A good separation of ethanol with retention time 11 min, [C_2mim]OAc with retention time 7.5 min and internal standard with retention time 14.5 min was obtained using water/5% trifluoroacetic acid as eluent on a Resex RHM-monosaccharide H^+ column.

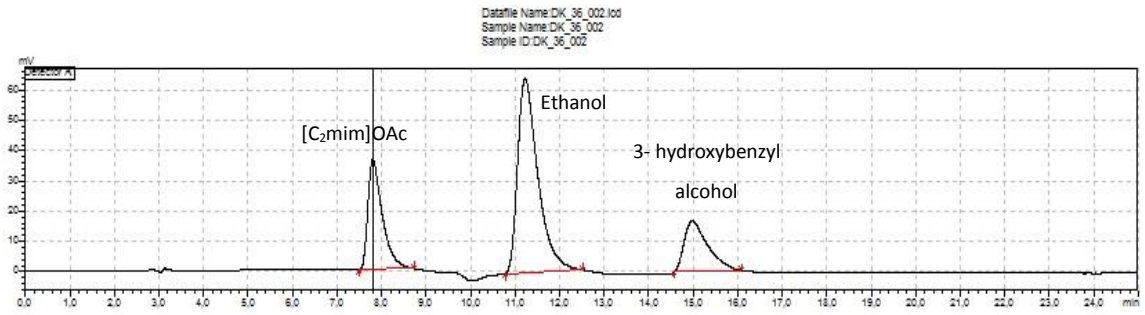


Figure 46: Example of chromatogram of with [C₂mim]OAc, ethanol and 3-hydroxybenzyl alcohol.

Calibration curves for [C₂mim]OAc in Figure 47 and ethanol are displayed in Figure 48 and show very good correlation coefficients R^2>0.999.

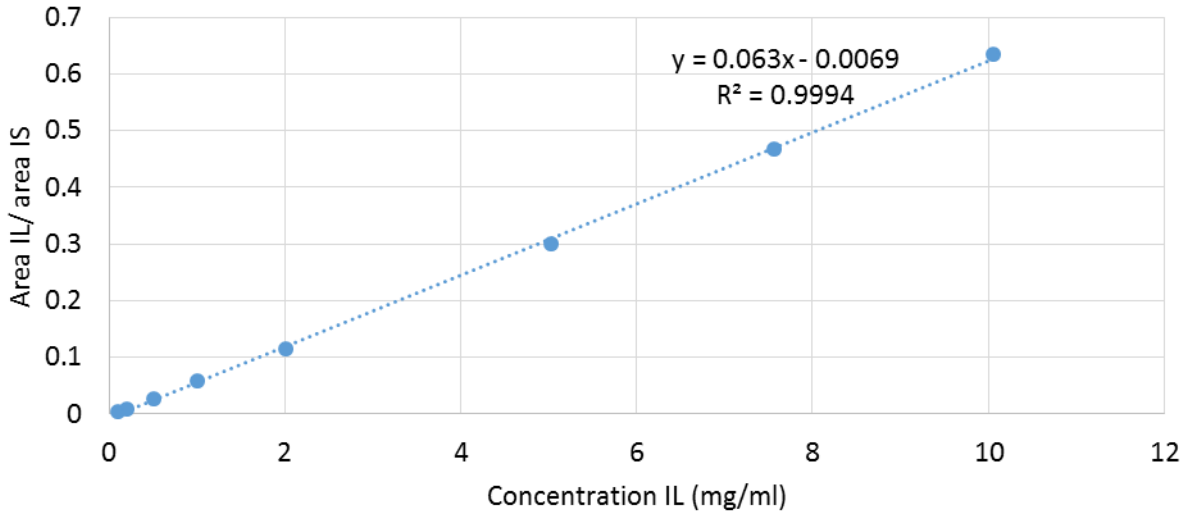


Figure 47: HPLC calibration curve for [C₂mim]OAc

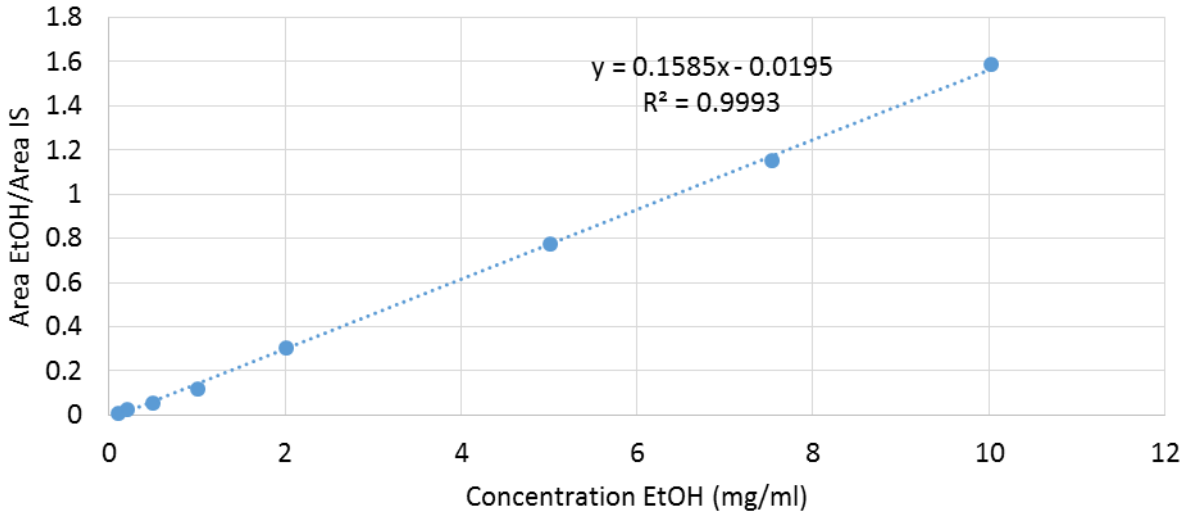


Figure 48: HPLC calibration curve for ethanol

Table 10 represents analytical data for the composition determination with NMR and HPLC of binary samples of [C_2mim]OAc/EtOH with known concentration. Mixtures of [C_2mim]OAc/EtOH with different percentage of the components were prepared and tested for concentration determination. Similarly binary mixtures of [C_2mim]OAc/H_2O and EtOH/H_2O were prepared and analyzed *via* HLPC and NMR. The deviation between experimental and actual values was considerably lower in case of HPLC. Consequently this technique was chosen as the analytical method for further investigations of binary mixtures of [C_2mim]OAc/H_2O, [C_2mim]OAc/EtOH, EtOH/H_2O mixtures after membrane separation.

Actual	Calculated from NMR		Calculated from HPLC	
%wt [C_2mim]OAc in ethanol	%wt [C_2mim]OAc in ethanol	Deviation %	%wt [C_2mim]OAc in ethanol	Deviation %
5.00	4.47	10.6	5.18	3.60
25.0	9.95	60.2	24.8	1.00
50.0	48.3	3.44	49.3	1.50
75.0	85.5	14.0	74.7	0.36

Table 10: Deviation comparison for concentration determination by NMR and HPLC methods

4.5.2 Separation of binary mixtures by membrane techniques

In total, four different membranes were selected for the separation of binary mixtures. A standard nanofiltration polyamide membrane Dow Filmtec “NF90”, two “solvent stable”-designated polyimide membranes from the Evonik “Duramem” series with different molecular weight cut-offs (150 and 900 Dalton), “DM150” and “DM900”, and one “solvent stable” membrane of proprietary material SolSep “NF080105” were chosen. Table 11 summarizes properties of chosen membranes.

Membrane	**Manufacturer**	**MWCO**	**Material**
NF90	Dow Filmtec	100-200 Da	Thin film polyamide on polysulfone/polyester support
NF080105	Solsep	n.a.	Proprietary
Duramem 150	Evonik	150 Da	Modified polyimide
Duramem 900	Evonik	900 Da	Modified polyimide
n.a.: not available			

Table 11: Membrane properties

Before applying membrane separation techniques, the influence of ionic liquids or their mixtures on the chosen membranes was investigated *via* scanning electron microscopy (SEM). Square samples with approximately 1 cm edge length of each membrane were taken from a dry sample sheet. One sample of each membrane was left untreated, one was submerged in pure ethanol, one in pure [C_2mim]OAc, and one in a 50 wt % mixture of [C_2mim]OAc/EtOH. After a period of 24 hours, the treated membranes were rinsed with water and left in the open to dry at room temperature.

After the membranes were pretreated, scanning electron microscopy was performed. Images of the surface of the selective layer of the membrane samples were taken at 10k, 25k and 50k magnification.

The untreated samples of NF90 appear to have a fine-pored structure. Treatment with ethanol did not seem to alter the structure of the membrane significantly. However, after treatment with [C_2mim]OAc though, the membrane seems to have more and larger pores. Treatment with the mixture seems to have an even more severe effect on the membrane as can be seen from Figure 49.

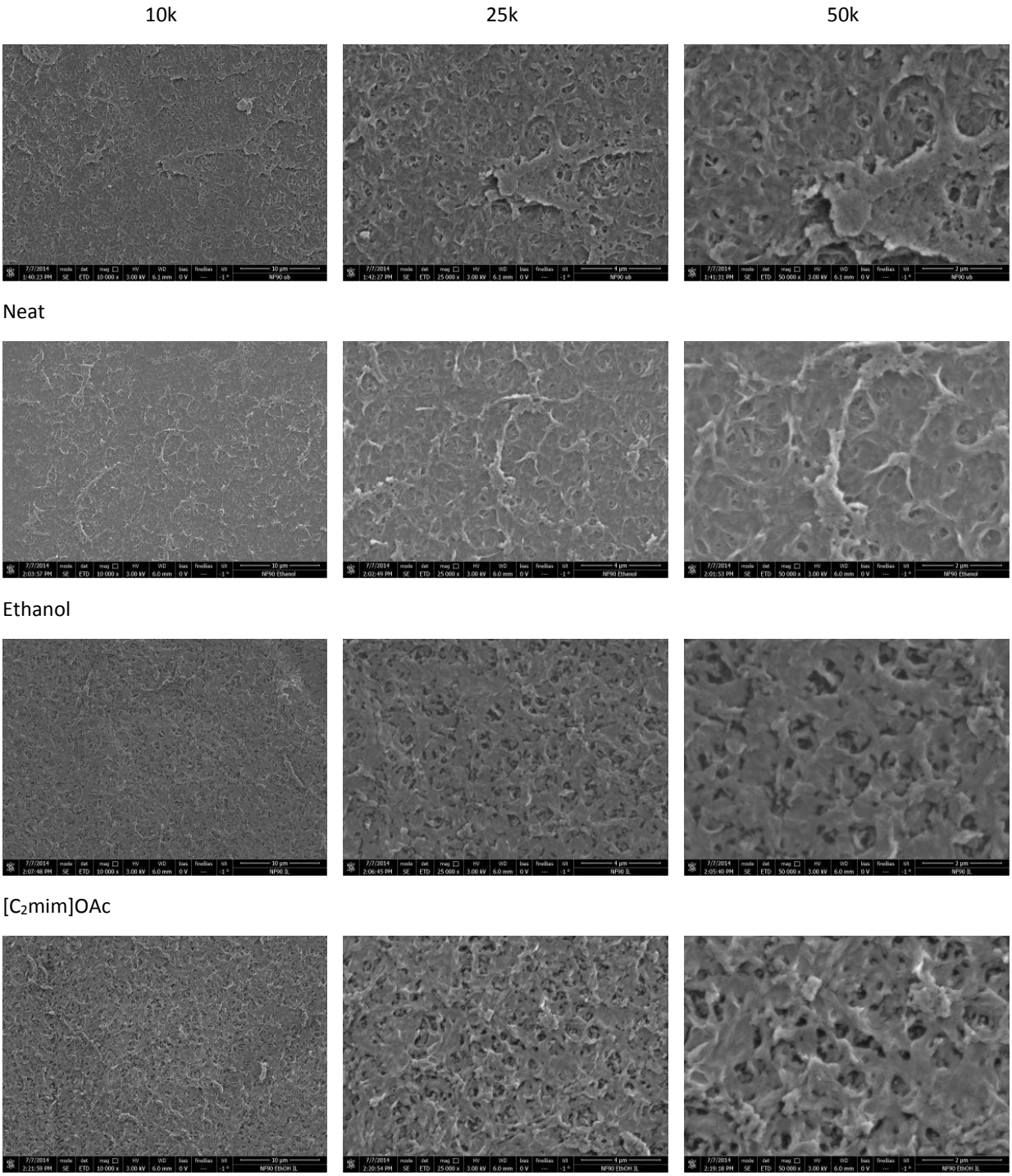


Figure 49: SEM results on NF90

The untreated Duramem 150 seems to have a very smooth and non-porous surface, although the manufacturer specified the molecular weigth cut-off is roughly the same as the one for NF90. No changes of the surface by treatment with ethanol could be observed. Pure [C_2mim]OAc though apparently causes cracks in the membrane surface. In a 50 wt% [C_2mim]OAc /EtOH mixture, this effect was not observed (see Figure 50).

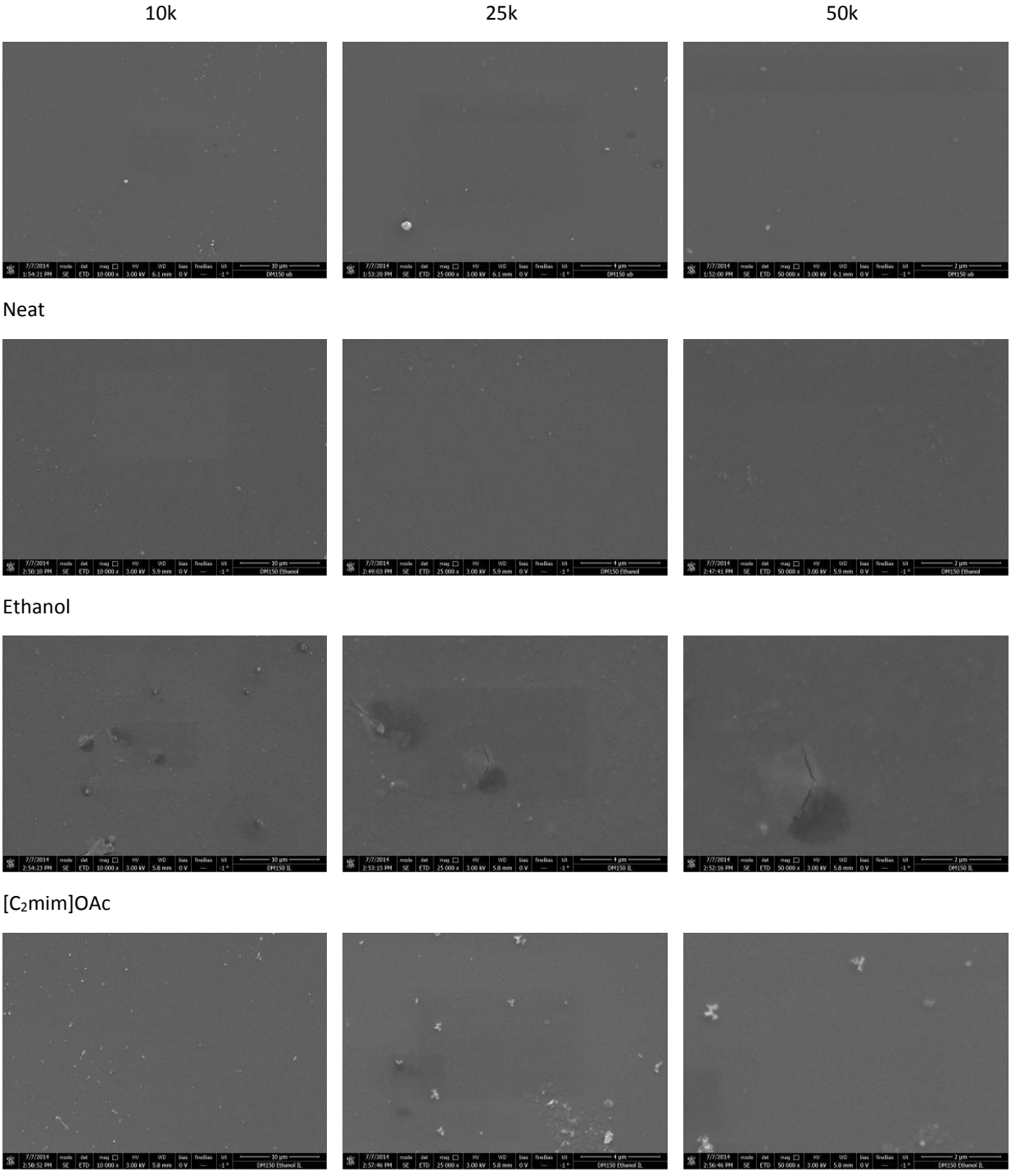


Figure 50: SEM results on DM150

Although the molecular weight cut-off of the Duramem 900 membrane is roughly 10 times higher than the NF90s, the surface is as smooth and non-porous as the DM150s. Since DM150 and DM900 are made of the same material, pure ethanol and the mixture 50 wt% [C_2mim]OAc/EtOH mixture did not have an effect on the structure. When treated with pure [C_2mim]OAc, numerous small pores formed in the membrane material, but no cracks were found.

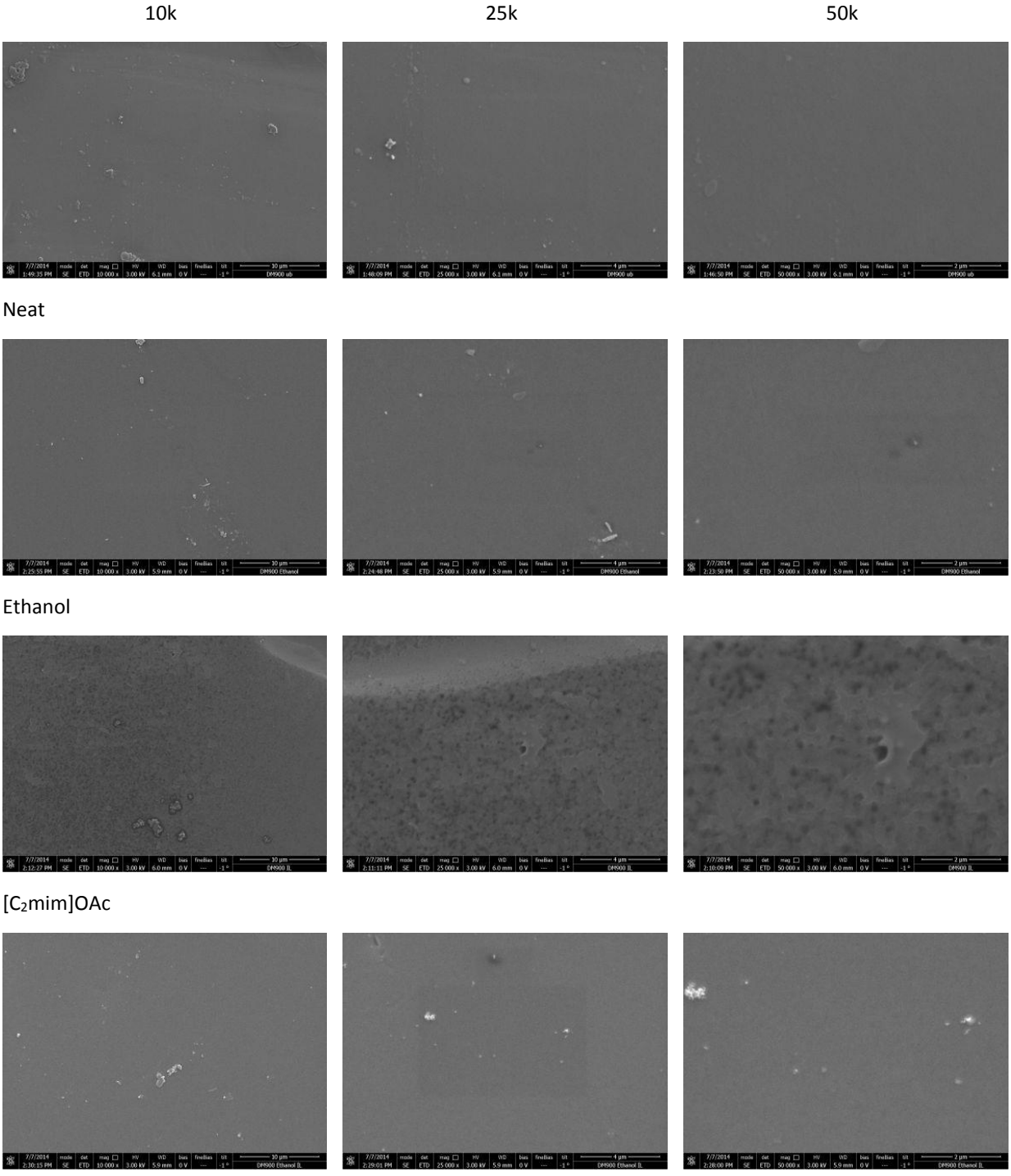


Figure 51: SEM results on DM900

The NF080105 membrane also exhibits a smooth and non-porous surface. Compared to the Duramem membranes, the effect of the solvents was different. While the pure [C_2mim]OAc did not change the membrane surface, pure ethanol and the mixture caused severe cracks in the membrane.

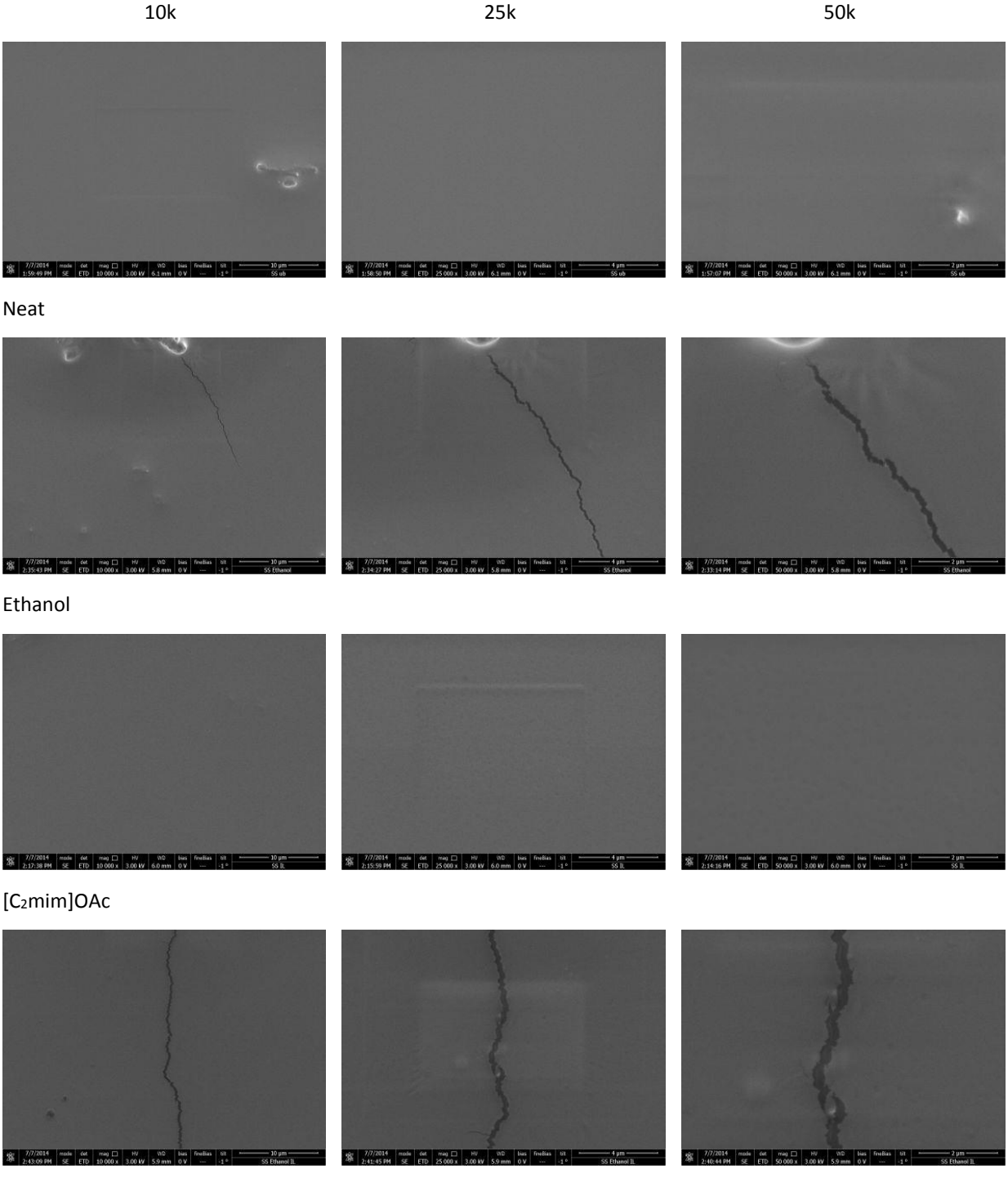


Figure 52: SEM results on NF080105

After the scanning electron microscopy was performed and the influence of the solvents on the membranes was investigated, membranes were tested at the stirred cell test unit.

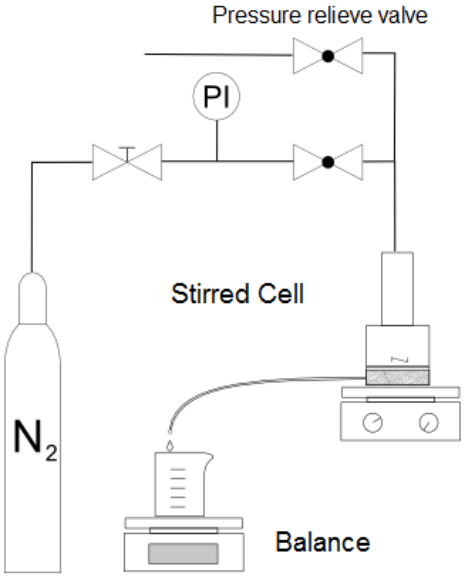


Figure 53: Stirred cell membrane setup[80]

The membrane filtration experiments were performed using a dead-end filtration stirred cell setup according to Figure 53. It consists of a cylindrical stainless steel pressure chamber and bottom cap with a porous center, where the membrane samples are placed with the selective layer facing up. The active membrane area is 3.8 cm^2. The pressure chamber and cap are secured by a clamp. Pressure is applied through a N_2 gas cylinder. The pressure chamber was agitated by a magnetic stirrer located approximately 1 mm above the membrane surface.[80]

All four chosen membranes were applied to the stirred cell membrane setup with binary mixtures of [C_2mim]OAc/H_2O, [C_2mim]OAc /EtOH, EtOH/H_2O in different ratios. However, after analyzing the retentate and permeate *via* HPLC no separation was observed as shown for the mixture of 25 wt% of [C_2mim]OAc in ethanol in Figure 54.

[80] Figure on stirred cell membrane set-up was kindly provided by Univ. Ass. Dipl.-Ing. Felix Weinwurm.

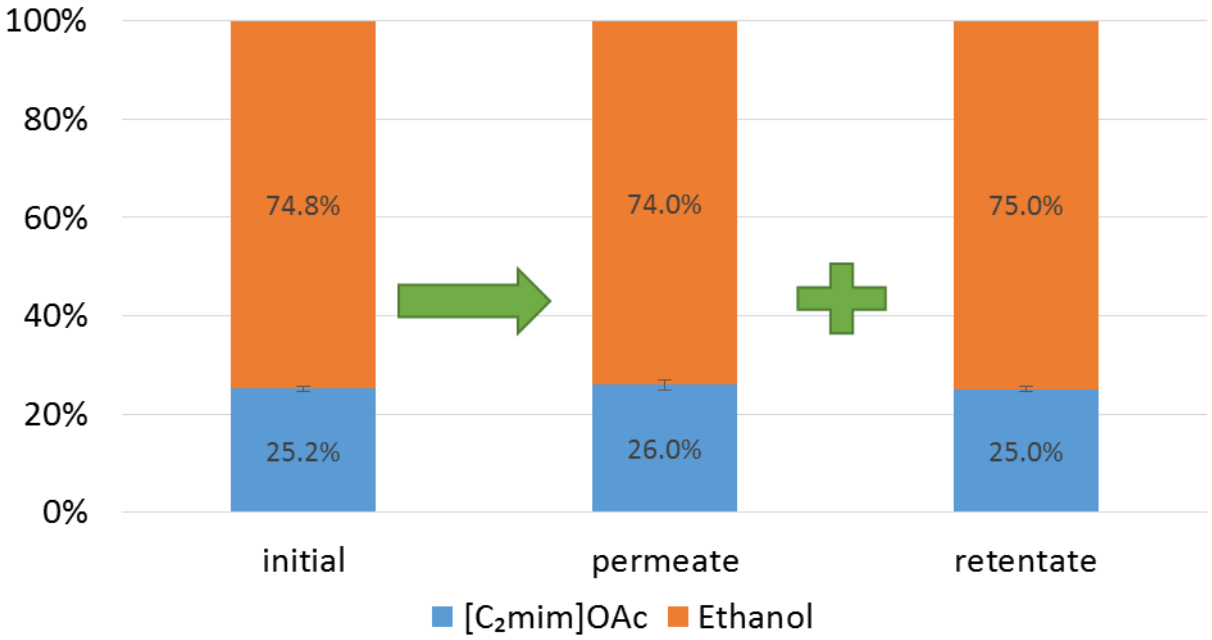


Figure 54: Example of separation results on a membrane NF 90

6 Conclusion

In the first part of this thesis three different types of ionic liquids were synthesized in good yields. Conventional ionic liquids were prepared by the process of alkylation of an amine precursor with an optional further ion exchange step. As an alternative, distillable ionic liquids that are based on 1,1,3,3 tetramethylguanidine (TMG) and switchable ionic liquids relying on a guanidine core were synthesized according to literature procedures.

All synthesized ionic liquids and their mixtures with conventional solvents were further applied for the extraction of active ingredients such as caffeine, chlorogenic acid as well as phenols and flavonoids from spent coffee grounds. The extraction yield of different valuable ingredients was strongly dependent on extraction solvent and condition. The best two solvents and conditions for extraction of each component were selected and are shown in a Table 12 below.

Caffeine	**Total phenols**	**Flavonoids**	**Chlorogenic acid**
• 50% [C_2mim]OAc/H_2O 6 h, 100 °C (0.33%)	• [C_2mim]OAc 15 min, 100 °C, mw (3.45%)	• [C_2mim]OAc 6 h, 100 °C (0.41%)	• Water 6 h, 100 °C (0.37%)
• 50% [C_2mim]OAc/H_2O 3 h, 100 °C (0.28%)	• 50% [C_2mim]OAc/H_2O 24 h, RT (3.41%)	• [C_2mim]OAc 1 h, 100 °C (0.40%)	• Water 1 h, 100 °C (0.35 %)

Table 12: Selection of solvents that extract the highest yields of individual active ingredient in spent coffee grounds. Percentages refer to wt%.

The final part of the thesis focused on the development of membrane separation techniques for the separation of active ingredients and the recovery of solvents. Therefore analytical procedures for the simulation quantification of [C_2mim]OAc, water or ethanol) in binary mixtures were developed. Further experiments on the membrane separation of binary mixtures of [C_2mim]OAc/H_2O or [C_2mim]OAc/ EtOH were conducted. However, no separation of the prepared mixtures was observed with the tested membranes.

7 Outlook

Due to the limited time available for this thesis, only preliminary experiments could be conducted with distillable and switchable ionic liquids. The first results on these two extraction media are thus provided in the form of an outlook on future investigations.

7.1 Distillable ionic liquids

The pretreatment and extraction of spent coffee grounds was investigated in three different distillable ionic liquids based on 1,1,3,3-tetramethylguanidine(TMG), namely 1,1,3,3-tetramethylguanidine formate [TMGH][CO_2H] **9**, 1,1,3,3-tetramethylguanidine acetate [TMGH][OAc] **10** and 1,1,3,3-tetramethylguanidine propionate [TMGH][CO_2Et] **11.** After pretreatment of biomass and removal of the distillable ionic liquids, the pretreated biomass was extracted with conventional solvents such as water and ethanol and compared to untreated extraction samples.

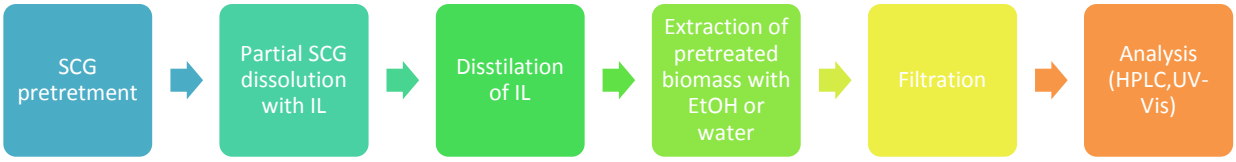


Figure 55: General strategy for spent coffee grounds dissolution with distillable ionic liquids

The general procedure of spent coffee grounds dissolution in distillable ionic liquids is represented in Figure 55 and described detailed in the experimental part section of this thesis.

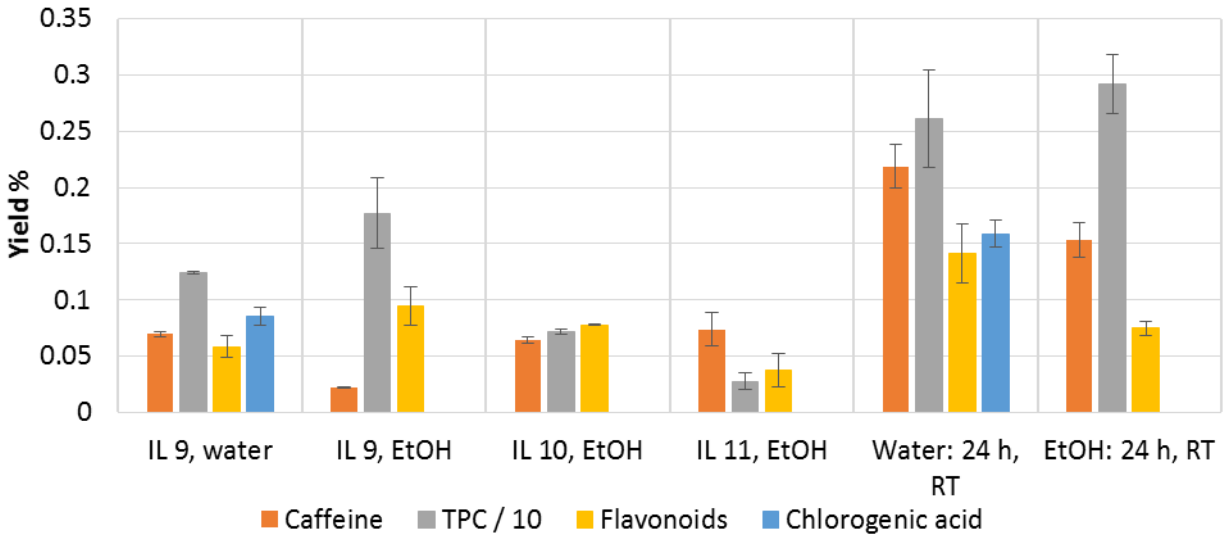


*Figure 56: Comparison of different distillable ionic liquids and conventional solvents for spent coffee grounds (IL **9**: [TMGH] [CO_2H]; IL **10**: [TMGH] [OAc]; IL **11**: [TMGH] [CO_2Et], RT: Room temperature, TPC/10 is 1/10 of total phenol content as gallic acid equivalent)*

The first results for biomass pretreatment in distillable ionic liquids showed that extraction yields are lower than with established extraction with conventional solvents or with [C_2mim]OAc/H_2O mixtures.

However, the results could be still modified with variation of temperature of extraction and distillation conditions in the pretreatment process.

7.2 Switchable ionic liquids

Additionally to distillable ionic liquids, a switchable ionic liquid based on 2-hexyl-1,1,3,3-tetramethylguanidine was investigated. The switch reaction was carried out in water **22** or ethanol **23**, providing two different possible strategies for spent coffee extraction as outlined in the flow scheme below (Figure 57). In case of switchable ionic liquid together with ethanol, the extraction was run with both hydrophobic and hydrophilic form in order to investigate the influence of the ionic structure.

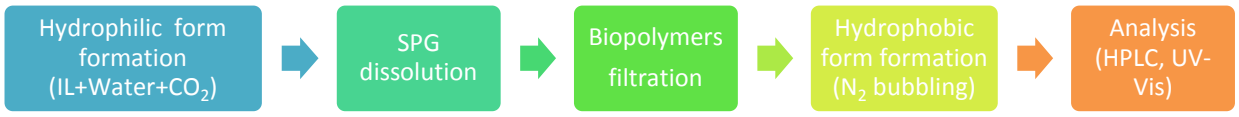


Figure 57: General strategy for spent coffee grounds dissolution with switchable ionic liquids in water.

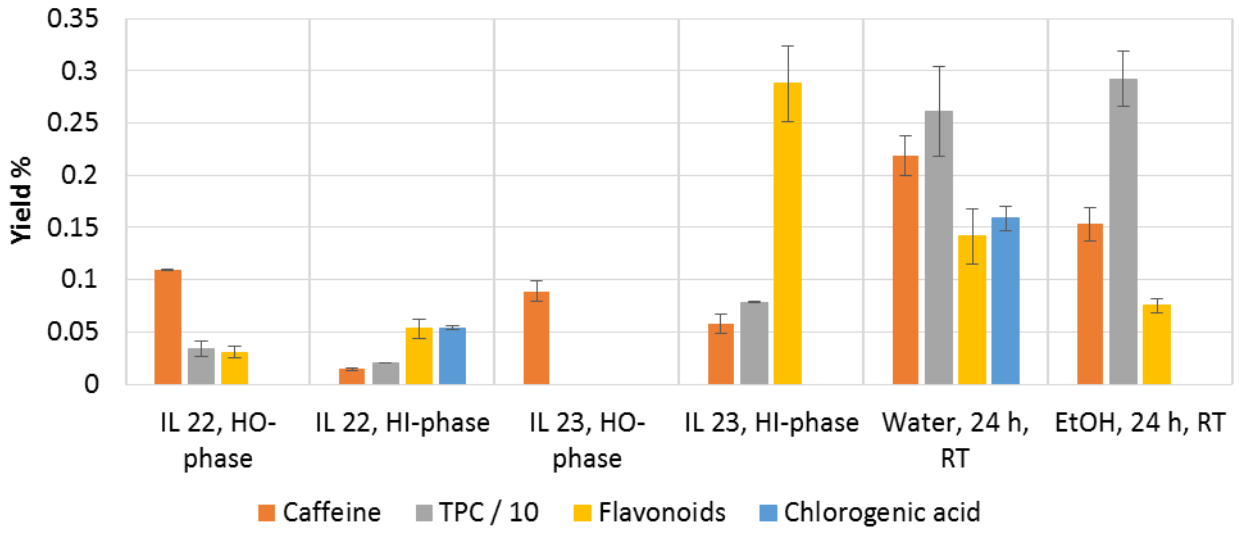


Figure 58: Comparison of switchable ionic liquids and conventional solvents for spent coffee grounds (IL 22/23: 2-hexyl-1,1,3,3-tetramethylguanidine switched with EtOH/H_2O, HO: hydrophobic phase, HI: hydrophilic phase, RT: Room temperature, TPC/10 is 1/10 of total phenol content as gallic acid equivalent)

As can be seen from the preliminary results presented in Figure 58, switchable ionic liquids did not result in higher extraction yields when compared to conventional solvents. However, the flavonoid content could be significantly increased in the ionic liquid switched in its hydrophilic form in ethanol, indicating the potential of this strategy that will be further investigated in future.

8 Experimental part

8.1 Materials and methods

Commercially available reagents and solvents were purchased from Sigma Aldrich unless otherwise specified. [C_2mim]OAc was purchased from BASF (Germany). Dichloromethane, ethyl acetate, light petrol and diethyl ether were distilled before use.

^{1}H NMR spectra were recorded on a Bruker AC 200 at 200 and 50 MHz or on a Bruker AC 400 at 200 and 50 MHz, resp., using the solvent peak or TMS as reference. Multiplicities from DEPT were referred to as s (singlet), d(doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), sept (septet) and m (multiplet).

High performance liquid chromatography (HPLC): HPLC analysis was performed on Jasco HPLC unit equipped equipped with a PDA detector (*Method A*) or on a a Nexera LC-30AD UPLC system equipped with a SPD-M20A diode array detector (*Method B*).

For the determination of caffeine and chlorogenic acid a equipped with a Maisch Reprosil 5 μm C18 column (250 × 4.60 mm) was used with Methanol/ H_2O/5% trifluoroacetic acid 25/75 as solvent and a flow of 1 ml/min; detection was done at 210 nm. (*Method A*)

For simultaneous determination of ethanol and [C_2mim]OAc Phenomenex Resex RHM-monosaccharide H^+ column (150 x 7.80 mm) was used with H_2O/5% trifluoroacetic acid as solvent and a flow of 0.6 ml/min; detection was done *via* refractive index. (*Method B*)

Ultraviolet-visible light spectroscopy (UV-Vis) was performed on a Shimadzu UV/Vis 1800, with wavelength range of 190 to 1100 nm, and spectral bandwidth of 1 nm.

Microwave reactions were performed on a BIOTAGE Initiator^{TM} sixty microwave unit. The reported times are hold times.

Thin layer chromatography (TLC): TLC analysis was done with precoated, aluminium-backed plates (Silica gel 60 F254, Merck). Compounds were visualized by spraying with 5% phosphomolybdic acid hydrate in ethanol and heating.

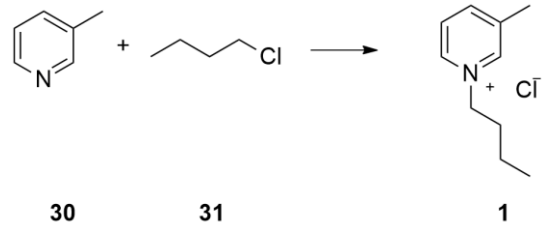
Karl Fischer Titration to determine the water content of ionic liquids was performed on Mitsubishi CA-21 Moisture Meter.

Biomass pretreatment: 1 kg of spent coffee grounds was collected from 100% Arabica (Illy espresso) and dried in a vacuum drying oven at 60 °C/20 mbar for 20 days, until there was no change of mass.

8.2 Synthesis of ionic liquids

8.2.1 Synthesis of conventional ionic liquids

1-Butyl-3-methylpyridinium chloride 1



30 **31** **1**

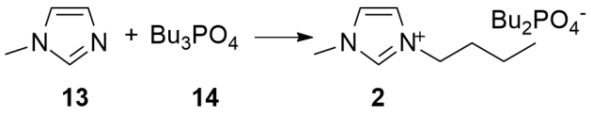
Picoline **30**	43.60g	4.620 mmol	1 eq.
1-Chlorobutane **31**	64.19 g	6.935 mmol	1.5 eq.

1-Chlorobutane **31** was added dropwise to freshly distilled 3-methylpyridine **30**. The reaction mixture was left to reflux for 72 hours under an Argon atmosphere. The reaction completion was monitored *via* NMR spectroscopy. The dark crystalline product obtained was recrystallized twice from ethyl acetate: acetonitrile 3:1.The product was dried *in vacuo* ($1 \cdot 10^{-2}$ mbar) for 24 h to yield colourless crystals in 91% yield.

^{1}H-NMR (200 MHz, $CDCl_3$, [ppm]): δ_H = 0.870 (t, 3H, N-CH_2-CH_2-CH_2-$\underline{CH_3}$, J = 11,8 Hz), 1.23–1.49 (m, 2H, N-CH_2-CH_2-$\underline{CH_2}$-CH_3), 1.83–2.08 (m, 2H, N-CH_2-$\underline{CH_2}$-CH_2-CH_3), 2.54 (s, 3H, -$\underline{CH_3}$), 4.87–5.08 (t, 2H, N-$\underline{CH_2}$-CH_2-CH_2-CH_3, J = 11 Hz), 7.85–8.07 (m, 1H, H-4), 8.09–8.03 (m, 1H, H-5), 9.40–9.48 (m, 1H, H-6), 9.55 (s, 1H, H-2).

Analytical data is in accordance to literature values.[81]

1-Butyl-3-methylimidazolium dibutyl phosphate 2



13 **14** **2**

1-Methylimidazole **13**	10.00g	121.8 mmol	1 eq.
Tributylphosphate **14**	34.05 g	127.9 mmol	1.05 eq.

Tributylphosphate **14** was added dropwise to freshly distilled 1-methylimidazol **13** under Argon atmosphere. The mixture was heated up to 80 °C and stirred for 48 h. Since NMR spectroscopy did not show completion of the reaction, the temperature was raised to 150 °C for additional 72 hours. After complete conversion, the mixture was washed with ethyl acetate (3 × 30 ml). Remaining solvent traces were removed *in vacuo*. To the resulting dark brown oil 100 ml of ethanol and 50 g of charcoal were added and refluxed for 2 hours. The charcoal was filtered off and the solvent was removed *in vacuo*. Solvent

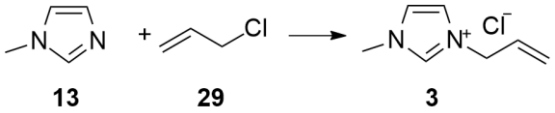
[81] Harjani, J. R.; Singer, R. D.; Garciac, M. T.; Scammells, P. J. *Green Chem.* **2009**, *11*, 83.

traces were removed under vacuum with stirring at 80°C and *vacuo* ($1 \cdot 10^{-2}$ mbar) for 24 h to obtain an orange oil in 75% yield.

^{1}H-NMR (200 MHz, $CDCl_3$, [ppm]): δ_H = 0.89-0.78 (9H, m, N-CH_2-CH_2-CH_2-$\underline{CH_3}$, P(OCH_2-CH_2-CH_2-$\underline{CH_3}$)$_2$), 1.19-1.38 (6H, m, P(O-CH_2-$\underline{CH_2}$-$\underline{CH_2}$-CH_3)$_2$), 1.50 (4H, m, P(O-$\underline{CH_2}$-CH_2-CH_2-CH_3)$_2$), 1.68-1.72 (2H, m, P(O-CH_2-CH_2-$\underline{CH_2}$-CH_3)$_2$), 3.70-3.89 (4H,q, N-CH_2-$\underline{CH_2}$-$\underline{CH_2}$-CH_3, J = 11.47 Hz), 4.00 (3H, s, N-$\underline{CH_3}$), 4.23 (2H, t,N-$\underline{CH_2}$-CH_2-CH_2-CH_3, J = 10.45 Hz), 7.3 (1H, s, H-5), 7.5 (1H, s, H-4), 10.69 (1H, s,H-2).

Analytical data is in accordance with literature values.[82]

1-Allyl-3-methylimidazolium chloride 3



13 **29** **3**

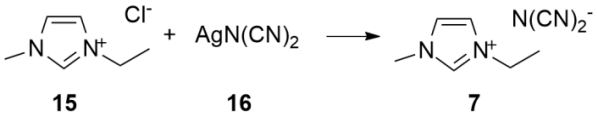
1-Methylimidazole **13**	10.10 g	121.8 mmol	1 eq.
3-Chloro-1-propene **29**	13.79 g	182.7 mmol	1.5 eq.

3-Chloro-1-propene **29** was added dropwise to freshly distilled 1-methylimidazole **13**. The resulting mixture was refluxed for 20 hours. After cooling to RT the solution was washed with ethyl acetate (3 × 10 ml) and dried *in vacuo* ($1 \cdot 10^{-2}$ mbar) for 24 h. A light yellowish oil was obtained in 88% yield.

^{1}H-NMR (200 MHz, $CDCl_3$, [ppm]): δ_H = 4.34 (d, 2H, J= 8.59 Hz, N-CH_2-CH=$\underline{CH_2}$), 4.72 (m, 2H, N-$\underline{CH_2}$-CH=CH_2), 5.29 (m, 1H, N-CH_2-$\underline{CH}$=CH_2), 6.99 (s, 1H, H-5), 3.41 (s, 3H, N-$\underline{CH_3}$), 7.22 (s, 1H, H-4), 9.67 (s, 1H, H-2).

Analytical data is in accordance with literature values.[83]

1-Ethyl-3-methylimidazolium dicyanamide [C_2mim]N(CN)$_2$ 7



15 **16** **7**

1-Ethyl-3-methylimidazole chloride **15**	5.00 g	34.1 mmol	1 eq.
Silver dicyanamide **16**	6.19 g	35.8 mmol	1.05 eq.

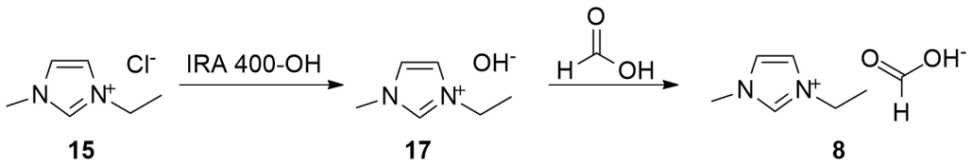
1-Ethyl-3-methylimidazole chloride **15** was dissolved in 40 ml of water in a conical flask covered with aluminum foil. Silver dicyanamide **16** was dissolved in separate beaker in 20 ml of water and added dropwise to the solution of 1-ethyl-3-methylimidazolium chloride in water. The mixture was stirred for an hour. The precipitated silver chloride was filtered off and water was removed in vacuo. The resulting yellow oil was dried *in vacuo* ($1 \cdot 10^{-2}$ mbar) for 24 h to yield 98%.

[82] Palgunadi, J.; Kang, J. E.; Chung, S. Y.; Lee, K. C.; Lee, H.; Kim, H.; Kim, H. S.; Cheong, M. *Bull. Korean Chem. Soc.* **2009**, 30, 1749.
[83] Holma, J.; Lassi, U.; Romara, H.; Lahtia, R.; Kärkkäinen, J.; Lajunen, M. *Catal. Today* **2012**, *196*, 11.

^{1}H-NMR (200 MHz, $CDCl_3$, [ppm]): δ_H = 1.50 (t, 3H, N-CH_2-$\underline{CH_3}$, , J=10.9 Hz), 3.90 (s, 3H, N- $\underline{CH_3}$), 4.29 (q, 2H, N-$\underline{CH_2}$-CH_3, , J=13,1 Hz), 7.24 (s, 1H, H-5), 7.36 (s, 1H, H-4), 9.12 (s, 1H, H-2).

Analytical data is in accordance with literature values.[84]

1-Ethyl-3-methylimidazolium formate 8



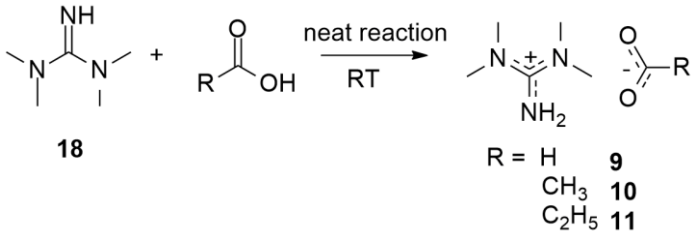
A glass chromatography column (l = 80 cm, d = 32 mm), fitted with glass wool at the end of the column, was used. The slurry of Amberlite IRA 400-OH ion-exchange resin in deionized water was filled into the colomn until the resin filled two thirds of the colomn height. The column was pretreated by flushing with 1000 ml of water. The halide content was tested by addition of 1 drop aqueous Silver (I) nitrate to verify that the eluent was free of halides. 1-Ethyl-3-methylimidazolium chloride **15** (5.00g, 34.1 mmol) was dissolved in 200 ml of deionized water and carefully filled into the column. The stopcock of the column was adjusted to a rate of elution of 1 drop per 10-20 seconds. The column was eluted for 12 hours. Than the column was flushed with deionized water (300 ml), using the same elution rate. A sample of 5 ml of the eluent was titrated with 1M hydrochloric acid to determine the concentration of ionic liquid **17** to be 0.048 N. This solution was neutralized with an equivalent amount (0.45 ml) of formic acid. Water was removed by a rotary evaporator and the resulting colorless oil was was dried *in vacuo* ($1 \cdot 10^{-2}$ mbar) for 24 h. The obtained yield was 72%.

^{1}H-NMR (200 MHz, $CDCl_3$, [ppm]): δ_H = 1.50 (t, 3H, N-CH_2-$\underline{CH_3}$, , J=11.09 Hz), 4.01 (s, 3H, N- $\underline{CH_3}$), 4.29 (q, 2H, N-$\underline{CH_2}$-CH_3, , J=15.55 Hz), 7.26 (s, 1H, H-5), 7.41 (s, 1H, H-4), 8.86 (s, 1H, H-2).

Analytical data is in accordance with literature values.[76]

[84] Ding, Z.-D.; Chi, Z.; Gu, X.-W.; Gu, S.-M.; Wang, H.-J. *J. Mol. Struct.* **2012**, *1015*, 147.

8.2.2 Synthesis of distillable ionic liquids



The corresponding carboxylic acid was added dropwise to 1,1,3,3-tetramethylguanidine(TMG) **18** under cooling in an ice bath. The mixture was stirred overnight and waxy crystals were obtained that were used as received.

1,1,3,3- Tetramethylguanidine formate 9:

1,1,3,3-Tetramethylguanidine **18**	20.0 g	1.74 mmol	1 eq.
Formic acid	7.99 g	1.74 mmol	1 eq.

^{1}H-NMR (200 MHz, $CDCl_3$, [ppm]): δ_H = 2.91 (s, 12H, -(CH_3)$_2$, -(CH_3)$_2$), 8.69 (s, 1H, CO_2H), 9.12 (br s, 2H, -NH_2).

Analytical data are in accordance with literature values.[31]

1,1,3,3- Tetramethylguanidine acetate 10:

1,1,3,3-Tetramethylguanidine **18**	20.0 g	1.74 mmol	1 eq.
Acetic acid	10.43 g	1.74 mmol	1 eq.

^{1}H-NMR (200 MHz, $CDCl_3$, [ppm]): δ_H = 1.86 (s, 3H,-OCH_3), 2.89 (s, 12H, -(CH_3)$_2$, -(CH_3)$_2$), 8.39 (br s, 2H, NH_2).

Analytical data are in accordance with literature values.[31]

1,1,3,3- Tetramethylguanidine propiate 11:

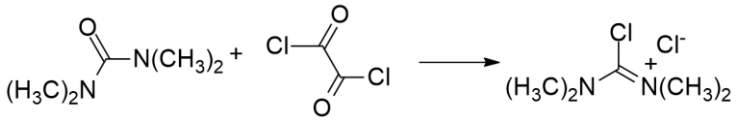
1,1,3,3-Tetramethylguanidine **18**	15.0 g	1.30 mmol	1 eq.
Propionic acid	9.65 g	1.30 mmol	1 eq.

^{1}H-NMR (200 MHz, $CDCl_3$, [ppm]): δ_H = 1.03 (t, 3H,-C(=O)-CH_2-CH_3, J=12.19 Hz), 2.29 (q, 2H, -C(=O)-CH_2-CH_3, J=12.7 Hz), 2.71 (s, 12H, -(CH_3)$_2$, -(CH_3)$_2$), 9.86 (br s, 2H, NH_2).

Analytical data are in accordance with literature values.[31]

8.2.3 Synthesis of a switchable ionic liquid

Chloro-1,1,3,3-tetramethylformamidinium chloride



19 **20** **21**

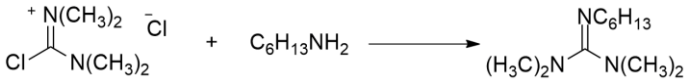
Oxalyl chloride **20**	2.50g	21.5 mmol	1.7 eq.
1,1,3,3-Tetraalkylurea **19**	4.64 g	36.0 mmol	1 eq.

A flame-dried 3-necked round-bottom flask was charged with anhydrous dichloromethane under an Argon atmosphere. Oxalyl chloride **20** and 1,1,3,3-tetramethylurea **19** were added dropwise *via* syringe. The reaction mixture turned yellow and was left under Argon atmosphere to reflux for 24 hours. The completion of reaction was monitored with TLC (dichloromethane:methanol 20:1). The solvent was removed *in vacuo* to obtain a yellow oil in 98% yield that was used without further purification

^{1}H-NMR (200 MHz, $CDCl_3$, [ppm]): δ_H = 3.50 (s, 12H).

Analytical data is in accordance with literature values.[28]

2-Hexyl-1,1,3,3-tetramethylguanidine



21 **32** **12**

Chloro-1,1,3,3-tetramethylformamidinium chloride **21**	5.60 g	32.8 mmol	1 eq.
Hexylamine **32**	9.95 g	98.4 mmol	3 eq.

Hexylamine **32** in freshly distilled acetonitrile (18 ml) was dropwise added at room temperature to chloro-1,1,3,3-tetramethylformamidinium chloride **21** in dry acetonitrile. During the exothermic reaction gas development was observed. The resulting dark brown mixture was stirred for 4 hours at 60 °C under Argon atmosphere. After reaction completion, the solvent was removed *in vacuo*. Diethyl ether (75 ml) was added to the brown oil. A solution of sodium hydroxide (4.3 g) in water (30 ml) was added to the mixture at 0 °C under stirring. The resulting two phases were separated and the aqueous layer was extracted three times with diethyl ether. The organic layers were combined and the solvent was removed *in vacuo*. The crude product was distilled under reduced pressure (130 °C, 30 mbar). A colorless liquid was obtained in 77% yield.

^{1}H-NMR (200 MHz, $CDCl_3$, [ppm]): δ_H = 0.78 (t, 3H, N-CH_2-CH_2-CH_2-CH_2-CH_2-CH_3, J=13.1 Hz), 1.17 (s, 1H, N-CH_2-CH_2-CH_2-CH_2-CH_2-CH_3), 1.40 (m, 2H, N-CH_2-CH_2-CH_2-CH_2-CH_2-CH_3), 2.55 (m, 6H, N-(CH_3)-CH_3, J=15.55 Hz), 2.63 (s, 6H, , N-(CH_3)-CH_3), 3.01 (t, 2H, N-CH_2-CH_2-CH_2-CH_2-CH_2-CH_3, J=10.11 Hz).

Analytical data is in accordance with literature values.[28]

8.3 Analytics development

8.3.1 Preparation of calibration curves for caffeine 23, caffeic acid 25, dihydroxybenzoic acid 26 and chlorogenic acid 24

A stock solution of 100 mg of each component was dissolved in 10 ml of methanol. Solutions (A-H) were prepared by diluting stock solution with methanol as given in Table 13.

Solution	ml	Diluted solution	Diluted to ml	Substance mg/ml
A	2	Stock	10	2
B	1	Stock	10	1
C	0.5	Stock	10	0.5
D	1	A	10	0.2
E	1	B	10	0.1
F	1	C	10	0.05
G	1	D	10	0.02
H	1	E	10	0.01
I	1	F	10	0.005

Table 13: Solutions for standard calibration curves for HPLC

Phenol internal standard stock solution (0.2 ml solution; 50 mg in 100 ml of methanol) were added to 1 ml of the sample solutions (A-I). The samples were analyzed by HPLC according Method A.

8.3.2 Calibration curves for flavanoid and total phenol content analysis

The preparation of gallic acid standards for the calibration of total phenol content analysis *via* UV-Vis spectroscopic analysis was carried out as following:

A stock solution of 1000 mg of gallic acid was dissolved in 100 ml of water (HPLC grade). Solutions (A-G) were prepared by diluting the stock solution with water according to Table 14.

Solution	ml	Diluted solution	Diluted to ml	Substance mg/ml
A	3	Stock	10	3000
B	2	Stock	10	2000
C	1	Stock	10	1000
D	0.8	Stock	10	800
E	2	A	10	600
F	2	B	10	400
G	1	B	10	200

Table 14: Solutions for standard calibration curves for UV-Vis (total phenols determination)

A sample of 50 µl of the prepared solutions, 600 µl of sodium carbonate solution (7.5 % w/v), 150 µl of Folin-Ciocalteu reagent and 2000 µl of water were mixed and heated to 60 °C for 5 minutes. Additionally, a blank sample was prepared. The samples were analyzed by UV-Vis spectroscopy at a wavelength of 700 nm.

To determine the influence of [C_2mim]OAc on a calibration curve, standard solution of gallic acid in [C_2mim]OAc /H_2O (10:90 wt%) were prepared. A sample of 50 µl from the solutions, 600 µl of sodium carbonate solution (7.5 % w/v), 150 µl of Folin-Ciocalteu reagent and 2000 µl of water were mixed and heated to 60 °C for 5 minutes. Additionally, a blank sample was prepared. The samples were analyzed by UV-Vis spectroscopy at a wavelength of 700 nm.

The preparation of quercetin standards for the calibration of flavonoid analysis by UV-Vis spectroscopy was carried out as following:

A stock solution (A), containing 20 mg of quercetin dissolved in 100 ml of water (HPLC grade) was prepared. Solutions (B-E) were prepared by diluting the stock solution with water according to Table 15.

Solution	ml	Diluted solution	Diluted to ml	Substance mg/ml
A	-	-	-	200
B	7.5	Stock	10	150
C	5	Stock	10	100
D	2.5	Stock	10	50
E	1.25	A	10	25

Table 15: Solutions for standard calibration curves for UV-Vis (flavonoids determination)

A sample of 300 µl from the prepared solutions, 900 µl of methanol, 60 µl of aluminum chloride (10% w/v), 60 µl of potassium acetate (1 mol/L) and 1700 µl of water were mixed and stored for 30 minutes at room temperature in a dark place. Additionally, a blank sample was prepared. The samples were analyzed by UV-Vis spectroscopy at a wavelength of 415 nm.

To determine the influence of [C_2mim]OAc on the calibration curve, a standard solution of quercetin in [C_2mim]OAc /H_2O (10:90 wt%) was prepared. The prepared solutions (300 µl), 900 µl of methanol, 60 µl of aluminum chloride(10% w/v), 60 µl of potassium acetate (1 mol/L) and 1700 µl of water were mixed and stored for 30 minutes at room temperature in dark place. Additionally, a blank sample was prepared. The samples were analyzed by UV-Vis spectroscopy at a wavelength of 415 nm.

8.4 Extraction of spent coffee grounds using conventional solvents and conventional ionic liquids

8.4.1 General extraction procedure using conventional solvents and ionic liquids

A 5 ml screw-cap vial was charged with a 10 wt% of spent coffee grounds (0.100 ± 0.010 g) in the respective solvent (0.900 ± 0.150 g) and stirred at room temperature for 24 h or stirred at 100°C for 1 h, 3 h and 6 h. The solution prepared at RT were diluted to 5 ml using ethanol while the solutions prepared at 100° C were diluted to 10 ml using ethanol.

A sample of 1 ml was taken from the solution and 0.2 ml of internal standard (50 mg of phenol in 100 ml of methanol) were added. The samples were centrifuged for 5 min at 13000 min^{-1} and the supernatant solution was directly analyzed *via* HPLC according to Method A.

A sample of 300 µl from solution of spent coffee grounds in ethanol, 900 µl of methanol, 60 µl of aluminum chloride (10% w/v), 60 µl of potassium acetate (1 mol/L) and 1700 µl of water were added, mixed and stored for 30 minutes at room temperature in a dark place. The samples were analyzed for their content of flavonoids by UV-Vis spectroscopy at a wavelength of 415 nm.

Additionally, a sample of 50 µl from the solution of spent coffee grounds in ethanol, 600 µl of sodium carbonate solution (7.5 % w/v), 150 µl of Folin-Ciocalteu reagent and 2000 µl of water were mixed and heated to 60 °C for 5 minutes. The samples were analyzed for determination of total phenol content by UV-Vis spectroscopy at a wavelength of 700 nm.

8.4.2 Screening of different conventional ionic liquids

A 5 ml screw-cap vial was charged with a 10 wt% solution of spent coffee grounds(0.100 ± 0.100 g) in ionic liquid (0.900 ± 0.150 g) and stirred at 100 °C for 1 h, 3 h and 6 h. The solution was diluted to 10 ml with ehtanol. Analysis of the resulting solutions was performed as given in Chapter 8.4.1.

Ionic liquids that were used for dissolution under conventional heating: $[C_4MePy]Cl$ **1** , $[C_4mim]Bu_2PO_4$ **2**, [amim]Cl **3**, $[C_2mim]OAc$ **4**, $[C_4mim]Cl$ **5**, $[C_2mim]OTf$ **6**, $[C_2mim]N(CN)_2$ **7** and $[C_2mim]Fmt$ **8**.

8.4.3 General extraction procedure under microwave irradiation

A 5 ml microwave vial was charged with a 10 wt% solution of spent coffee grounds (0.100 ± 0.100 g) in solvent (0.9000 ± 0.150 g) and sealed with a Teflon septum and heated for 15 min at 100 °C under microwave irradiation (high absorption level). The solution was diluted to 5 or 10 ml with EtOH depending on dissolved spent coffee grounds consistency. Analysis of the resulting solutions was performed as given in Chapter 8.4.1.

Solvents that were used for dissolution under microwave irradiation: $[C_2mim]OAc$ **4**, $[C_2mim]OAc/H_2O$ (50 wt%), water.

8.4.4 Screening of different concentrations $[C_2mim]OAc/H_2O$

A 5 ml screw-cap vial was charged with a 10 wt% of spent coffee grounds (0.100 ± 0.100 g) in $[C_2mim]OAc/H_2O$ mixture (see Table 16) and stirred at room temperature for 24 h. The solution was diluted to 5 ml with the ethanol used in the extraction process. Analysis of the resulting solutions was performed as given in Chapter 8.4.1.

C(wt% water)	C(wt% [C2mim]OAc)	m (water g)	m ([C2mim]OAc g)
10 %	90%	90 mg	810 mg
25 %	75%	225 mg	675 mg
40 %	60 %	360 mg	540 mg
50 %	50 %	450 mg	450 mg
60 %	40 %	540 mg	360 mg
75 %	25 %	675 mg	225 mg
90 %	10 %	810 mg	90 mg

Table 16: Different concentration [C_2mim]OAc/H_2O

8.4.5 General extraction procedure using distillable ionic liquids

A previously weighed 25 ml round-bottom flask with a glass stopper was charged with a 10 wt% solution of spent coffee grounds (0.500 ± 0.100 g) in distillable ionic liquid (4.5000 ± 0.250 g) and heated for 1 h to 100 °C. Afterwards, the ionic liquid was distilled off using a Kugelrohr distillation apparatus and the flask was weighed again. To a known amount of extracted spent coffee grounds, 90 wt% of solvent (water or ethanol were added) and stirred for 24 h at room temperature. Analysis of the resulting solutions was performed as given in Chapter 8.4.1.

Ionic Liquid	Solvent for dilution
[TMGH][CO_2H]	Water
[TMGH][CO_2H]	Ethanol
[TMGH][OAc]	Ethanol
[TMGH][CO_2Et]	Ethanol

Table 17: Different distillable ionic liquids and solvents used for dilution

8.4.6 Extraction procedure using switchable ionic liquids with water

Water or ethanol (15 g) and 2-hexyl-1,1,3,3-tetramethylguanidine (1.5 g) were charged in a 3-necked round bottom flask equipped with a cooler, gas inlet and a gas outlet. While bubbling CO_2 the solution was stirred for 2.5 h, until a single phase was formed. Than 1.83 g (10 wt%) of spent coffee grounds were added and stirred at room temperature for 24 h. After that, undissolved spent coffee grounds were filtered off. Nitrogen was bubbled through the remaining solution for 2.5 h until phase separation occurred. The hydrophobic layer was diluted to 10 ml with ethanol. Analysis of the resulting hydrophilic as well as hydrophobic solutions was performed as given in Chapter 8.4.1.

8.6 Separation of binary mixtures of [C_2mim]OAc, water or ethanol using membrane separation techniques

8.6.1 Establishing analytics

The preparation of the standard calibration of [C_2mim]OAc **4** and ethanol for HPLC analysis was performed as following.

A stock solution of 1 g of [C_2mim]OAc and 1 g of ethanol were dissolved in 100 ml of water (HPLC grade). Solutions (A-H) were prepared by diluting the stock solution with water (HPLC grade) according to Table 18.

Solution	ml	Diluted solution	Diluted to ml	Substance mg/ml
A	-	-	-	10
B	7.5	Stock	10	7.5
C	5	Stock	10	5
D	2	Stock	10	2
E	1	Stock	10	1
F	1	C	10	0.5
G	1	D	10	0.2
H	1	E	10	0.1

Table 18: Solutions for standard calibration curves for HPLC

3-Hydroxybenzyl alcohol internal standard stock solution (0.1 ml, 2 g in 100 ml of water) were added to a 1 ml sample taken from the prepared A – H solutions. The samples were analyzed by HPLC according *Method B.*

Binary mixtures of [C_2mim]OAc, ethanol or water (5 g) with known concentrations (see Table 19) were prepared and analyzed *via* HPLC and NMR spectroscopy.

	C([C_2mim]OAc wt%)	C(ethanol wt%)	C(water wt%)
1	25 %	75 %	-
2	50 %	50 %	-
3	75 %	25 %	-
4	5 %	95 %	-
5	25%	-	75 %
6	50 %	-	50 %
7	75 %	-	25 %
8	5 %	-	95 %
9	-	25%	75 %
10	-	50 %	50 %
11	-	75 %	25 %

Table 19: Concentrations of binary mixtures [C_2mim]OAc, ethanol or water

100 mg of each sample were diluted to 10 ml with water (HPLC grade). A sample of 1 ml was taken from the solution and 0.1 ml of internal standard solution (3-hydroxybenzyl alcohol) was added. The samples were analyzed *via* HPLC according to *Method B.*

The NMR spectroscopy was performed by charging NMR tubes with 10 mg of internal standard (maleic acid), 20 mg of binary mixtures of [C_2mim]OAc, ethanol or water with known concentration and 0.5 ml of acetone-d_6. The concentrations of binary mixtures are indicated in Table 19.

8.6.2 Membrane separation of binary mixtures of [C_2mim]OAc, ethanol or water

The mixture of [C_2mim]OAc/EtOH in a concentration of 25:75 wt% was prepared in quantity of 50 g. Prepared mixtures were applied on stirred cell membrane setup with four different membranes: NF90, NF080105, Duramem 150, Duramem 900. A pressure of 10 bar or 25 bar was applied. Subsequent retentate and permeate samples were collected, their volume was measured and samples were further analyzed.

100 mg of the starting mixtures were diluted to 10 ml with water (HPLC grade). A sample of 1 ml was taken from the solution, 0.1 ml of internal standard (3-hydroxybenzyl alcohol) were added. The samples were analyzed *via* HPLC according to *Method B*. HPLC of the initial mixture was performed three times.

Around 30 ml of the prepared mixture were used for membrane separation. Permeate and retentate were analyzed *via* HPLC if possible in triplicate as well. 100 mg of the mixture were diluted to 10 ml with water (HPLC grade). A sample of 1 ml was taken from the solution, 0.1 ml of internal standard (3-hydroxybenzyl alcohol) was added. The samples were analyzed *via* HPLC according to Method B.

The same procedure was applied to 25:75 wt% [C_2mim]OAc/H_2O mixtures.

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10 Appendix

10.1 Abbreviations

[amim]Cl	1-allyl-3-methyl-imidazolium chloride
[C_4mim]dca	1-butyl-3-methylimidazolium dicyanamide
[C_4mim]PF_6	1-butyl-3-methylimidazolium hexafluorophosphate
[C_2mim]Cl	1-ethyl-3-methylimidazolium chloride
[C_2mim]OTf	1-ethyl-3-methylimidazolium triflate
[C_2mim]Fmt	1-ethyl-3-methyl-imidazolium formate
[C_2mim]$N(CN)_2$	1-ethyl-3-methylimidazolium dicyanamide
[C_2mim]OAc	1-ethyl-3-methylimidazolium acetate
[C_4mim]BF_4	1-butyl-3-methylimidazolium tetrafluoroborate
[C_4mim]Bu_2PO_4	1-butyl-3-methylimidazolium dibutyl-phosphate
[C_4mim]Cl	1-butyl-3-methylimidazolium chloride
[C_4MPy]Cl	*N*-butyl-3-methylpyridinium chloride
[C_6mim]BF_4	1-hexyl-3-methylimidazolium tetrafluoroborate
[C_2mim]Beti	1-ethyl-3-methylimidazolium bis(perfluoroethyl)sulfonylimide
[TMGH][CO_2Et]	1,1,3,3- tetramethylguanidine propiate
[TMGH][CO_2H]	1,1,3,3- tetramethylguanidine formate
[TMGH][OAc]	1,1,3,3- tetramethylguanidine acetate
BASIL^{TM}	Biphasic Acid Scavenging utilizing Ionic Liquids
BMOEA	bis(2-methoxyethyl)ammonium bis(trifluoromethylsulfonyl)imide
$CDCl_3$	Deuterated chloroform
[$C_n$mim]Cl; Br; Sac; Ace	1-alkyl-3-methylimidazolium chloride, bromide,saccharinate, acesulfamate
COSMO-RS	COnductor like Screening MOdel for Real Solvents
d	doublet
DBU	1,8- diazabicyclo[5.4.0]undec-7-ene
DC18C6	dicyclohexano-18-crown-6

DIMCARB	*N*,*N*-dimethylammonium *N'*,*N'*-dimethylcarbamate
DMCEAP	*N,N*-dimethyl(cyanoethyl)ammonium propionate
DMEA oct	*N*,*N*-dimethylethanolammonium octanoate
DMHEEAP	*N,N*-dimethyl-*N*-(2-hydroxyethoxyethyl)ammonium propionate
DMSO	dimethylsulfoxide
EtOH	ethanol
HIV	Human Immunodeficiency Virus
HPLC	high performance liquid chromatography
IL	ionic liquid
LSE	liquid-solid extraction
m	multiplet
MAE	microwave-assisted extraction
NMR	nuclear magnetic resonance
$[C_8mim]Cl$	1-octyl-3-methylimidazolium chloride
$[C_8mim]PF_6$	1-octyl-3-methylimidazolium hexafluorophosphate
q	quartet
q	quadruplet
quin	quintet
s	singlet
SEM	scanning electron microscopy
sept	septet
sext	sextet
SPE	solid-phase extraction
t	triplet
TBP	tri-*n*-butylphosphate
TFA	trifluoroacetic acid
TLC	thin layer chormatography

TMG	1,1,3,3-tetramethylguanidine
UAE	ultrasound-assisted extraction
UMAE	ultrasound/microwave-assisted extraction
UPLC	Ultra Performance Liquid Chromatography
UV-Vis	Ultraviolet–visible light spectroscopy