Low Toxicity Imidazolium & Pyridinium Ionic Liquids: Synthesis, Antimicrobial Toxicity, Biodegradation Studies and Applications in Tsuji-Trost Reactions

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For the award of PhD

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Dedicated to Mother…

Declaration

I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of PhD is entirely my own work, and that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge breach any law of copyright, and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

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Abstract

A series of seventy achiral and chiral ionic liquids was designed, synthesized and characterized. Out of these seventy ILs, fifteen are achiral, twenty one lactic acid based and rest are mandelic acid based ILs. All compounds were characterized by a number of techniques including: ^{1}H, ^{13}C, ^{19}F NMR, IR, MS and specific rotation.

Antimicrobial and antifungal toxicity studies were carried out using the representative examples chosen from these ILs. Lactic and mandelic acid based ILs and ester based achiral ILs were found to be non toxic towards eight strains of bacteria and twelve strains of fungi. Antifungal toxicity was performed on two monoester and two diester CILs. Twenty one ILs were screened for biodegradation studies out of which the ILs with diester functionality were found to be readily biodegradable.

Six achiral ester and amide based ILs were chosen to employ in Tsuji-Trost reactions as reaction media. Reactions were performed using two methods consisting use of two different bases. Chiral catalysts (*S*,*S*)-iPr-phosferrox, mandyphos and *R*-BINAP were used for chiral induction. Excellent enantioselectivities with moderate yields were obtained in these reactions.

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- Ed. H. Xie and N. Gathergood, '*The Role of Green Chemistry in Biomass Processing and Conversion*', Wiley. Weilheim. J. Xu, W. Yu, H. Ma, F. Wang, F. Lu, M. Ghavre, N. Gathergood, '*Catalytic Conversion of Glycerol*', 2012, Chapter 12, in press.

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- N. Ferlin, M. Courty, S. Gatard, M. Spulak, B. Quilty, I. Beadham, M. Ghavre, N. Gathergood, S. Bouquillon, '*Biomass derived ionic liquids: synthesis, characterization, ecotoxicity and use as solvents for catalytic hydrogenation processes*', 2012, Submitted to ChemSusChem.

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- M. Ghavre, I. Beadham, N. Gathergood, '*Enantioselective Tsuji-Trost reactions in low toxicity and readily biodegradable ionic liquids*', in preparation.

Contents

Project Aim

- ✓ To synthesise and characterise a library of novel low toxicity and readily biodegradable achiral ionic liquids (ILs) containing ester and amide functionality in the side-chain of the cation moiety

- ✓ To investigate the antimicrobial toxicity and biodegradation properties of the achiral IL library

- ✓ To establish the effects of the ester moiety, oxygen-containing side-chain and anion on the toxicity and biodegradability

- ✓ To synthesise and characterise a library of novel mandelate and lactate based chiral ILs (CILs) containing the ester functionality

- ✓ To investigate the antimicrobial, antialgal toxicity and biodegradation properties of the CIL library

- ✓ To establish the effects of the ester moiety, side-chain and stereochemistry on the biodegradability of these novel compounds

- ✓ To evaluate the differences in both toxicity and biodegradability between the mandelate and lactate CILs

- ✓ To screen the novel achiral ILs as suitable reaction solvents for asymmetric Tsuji-Trost reactions

- ✓ To enable the identification of low toxicity and biodegradable ionic liquids through study of a suite of screening methods

List of Abbreviations

A

acac: acetylacetonate

ACN: acetonitrile

AP: aminopthalimide

ATCC: American type culture collection

B

BAC: benzalkonium chloride

BINAP: 2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl

[bmim]: 1-butyl-3-methylimidazolium

BSA: *bis*(trimethylsilyl)acetamide

[BuPy]: 1-butylpyridinium

C

CCM: Czech collection of micro-organisms

CIL: chiral ionic liquid

CFU: colony forming unit

COD: cyclooctadiene

COSY: correlation spectroscopy

Cp: cyclopentyl

CTAB: cetyltrimethylammonium bromide

D

DABCO: 1,4-diazabicyclo[2.2.2]octane

DAP: dialkylaminopthalimide

DAST: diethylaminosulfur trifluoride

dba: dibenzylideneacetone

DCM: dichloromethane

DCU: Dublin City University

DIPEA: *N,N*-di-*iso*propylethylamine

DMF: dimethylformamide

DMP: Dess-Martin periodinane

DMSO: dimethylsulfoxide

[dmim]: dimethylimidazolium

DSSC: dye-sensitized solar cell

E

EC: effective concentration

ee: enantiomeric excess

E factor: environmental factor

[emim]: 1-ethyl-3-methylimidazolium

E_N^T: normalised polarity parameter

EtOAc: ethyl acetate

ESBL: extended spectrum beta lactamase

H

HF: hydrofluoric acid

[hmim]: 1-hexyl-3-methylimidazolium

[hbim]: 1-hexyl-3-butylimidazolium

HPLC: high performance liquid chromatography

Hz: hertz

I

IBX: 2-iodoxybenzoic acid

IC: inhibitory concentration

IL: ionic liquid

IPA: isopropanol

IR: infrared

L

LC: lethal concentration

LCMS: liquid chromatography-mass spectrometry

M

MBC: minimum bactericidal concentration

MeOH: methanol

MFC: Minimum Fungicidal Concentrations

MIC: minimum inhibitory concentration

mim: methylimidazolium

mp/MP: melting point

MRSA: methicillin resistant *Staphylococcus aureus*

MS: mass spectrometry

N

nbd: norbornadiene

NBS: *N*-bromosuccinimide

NMO: *N*-methylmorpholine-*N*-oxide

NMR: nuclear magnetic resonance

O

[$OctOSO_3$]: octyl sulfate

OECD: organisation for economic cooperation and development

[omim]: 1-octyl-3-methylimidazolium

P

P_c: critical pressure

PEG: polyethylene glycol

[PF_6]: hexafluorophosphate

[pmim]: 1-propyl-3-methylimidazolium

PDA: potato dextrose agar

psi: pounds per square inch

PTSA: *para*-toluenesulfonic acid

ppm: parts per million

R

RT/rt: room temperature

RTIL: room temperature ionic liquid

S

$scCO_2$: supercritical carbon dioxide

SCF: supercritical fluid

S_N2: bimolecular nucleophilic

T

TBA: tetrabutylammonium

T_c: critical temperature

TEA: triethylamine

TGA: thermo-gravimetric analysis

THF: tetrahydrofuran

TLC: thin layer chromatography

TSIL: task specific ionic liquid

U

UCD: University College Dublin

UCC: University College Cork

V

VOC: volatile organic compound

Chapter 1

Introduction to Ionic Liquids

A vast number of chemical reactions both in research laboratories and in industry, are performed in the solution phase. Solvents are also applied in the later stage of reactions (work up), for example, the extraction and purification of the products and so chemistry is dominated by the study of the species in solution. Solvents play a vital role in chemical processes not only by bringing reactants into contact, but also affecting the rates, chemo-, regio- and stereoselectivities of the reactions. Many of the organic solvents used are volatile, highly flammable, toxic and hazardous making them high on the list of environment damaging chemicals as well as due to their employment as reaction media in large quantities. However, solvents still are an ubiquitous feature of modern industry. Every year millions of tons of solvent is discharged into the atmosphere by industries worldwide and as a result, deleterious effects of these materials are felt on human health, safety and the environment.

1.1 Need of Green Chemistry:

Such hazardous effects of solvents on the environment and human life compelled researchers to design products and processes in a way that minimises the usage and generation of hazardous substances. This was the birth of green chemistry as a subject. The term was coined by Paul Anastas in 1991 who later with John Warner developed twelve principles of 'Green Chemistry' in 1998 (Figure 1.1).[1] These principles are as follows,

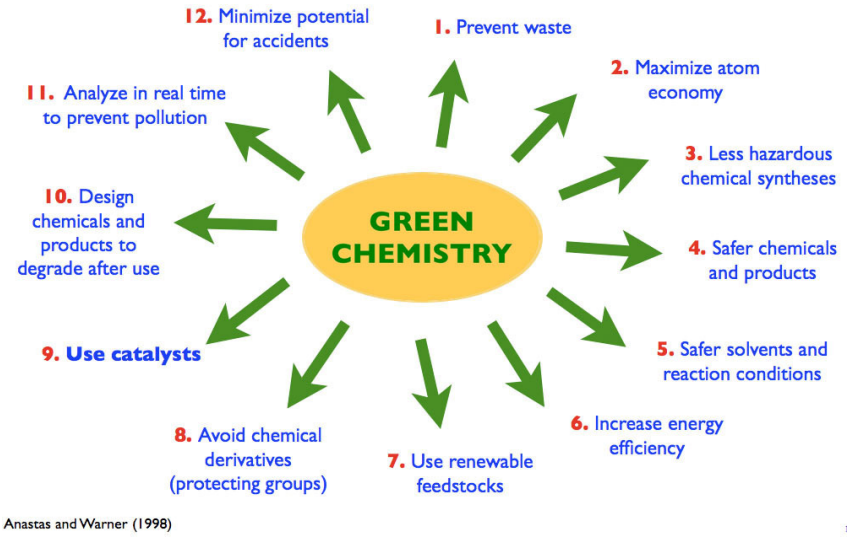


Figure 1.1: Green chemistry principles.[1]

01. Prevention of waste formation

It is better to avoid waste formation than to treat or clean up.

02. Atom Economy

Design synthetic methods which maximize the conversion of all raw materials used in the process into the final product.

03. Less Hazardous Chemical Syntheses

Design synthetic methods to utilise and generate substances that minimize toxic effects on human health and the environment.

04. Designing Safer Chemicals

Design chemical products which carry out their function while minimizing toxicity.

05. Safer Solvents and Auxiliaries

Minimize the use of auxiliary substances and promote use of safer solvents wherever possible.

06. Design for Energy Efficiency

Minimize the energy requirements of chemical processes and conducting them at ambient temperature and pressure wherever possible.

07. Use of Renewable Feedstocks

Use renewable raw materials or feedstock whenever possible.

08. Reduce Derivatives

Minimize or avoid unnecessary derivatization that requires additional reagents which also contributes in generation of waste.

09. Catalysis

Use of catalysts preferentially over stoichiometric reagents.

10. Design for Degradation

Design chemical products so they break down to form innocuous products that do not persist in the environment.

11. Real-time Analysis for Pollution Prevention

Develop analytical methodologies needed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. Inherently Safer Chemistry for Accident Prevention

Choice of raw materials that have least potential for chemical accidents, including explosions, and fires.

Many researchers have directed their research to make their target molecules and processes greener. Ryoji Noyori an eminent Nobel laureate (2001), has established methods of

asymmetric synthesis by asymmetric hydrogenation, 'greener' oxidations with aqueous H_2O_2, and use of supercritical CO_2 as solvent in hydrogenation reactions.[2]

1.1.1 Measure of Greenness-Green Chemistry Metrics:

The greenness of a chemical process can be measured using Green Chemistry Metrics. It is necessary to quantify the outcomes of chemical procedures in order to design green processes. Several metrics have been formulated which enable chemists to compare the difference between two chemical processes numerically.

1.1.1.1. Effective mass yield:

This can be defined as percentage of mass of desired product relative to the mass of all non-benign reagents used in synthesis.[3] It is mathematically represented as, Effective mass yield (%) = mass of products × 100 / mass of nonbenign reagents

According to Hudlicky, who formulated this equation, the benign substances are those by-products, reagents or solvents that have no environmental risk associated with them.

1.1.1.2. Environmental Factor (E-factor):

E-Factor is the ratio of mass of waste per unit mass of product formed.[4]

E-factor = total waste (kg) / product (kg)

This formula helps to those who try to fulfill first two principles of green chemistry.

Smaller the E-factor, greener is the process.

1.1.1.3. Atom Economy:

Atom economy is a measure of the conversion efficiency of reactant molecules to the product.[5]

For a general reaction: A + B → C

Atom economy = 100 × Mol. Wt. of C /(Mol. Wt. of A + Mol. Wt. of B)

This is an elementary calculation made to explore the green-ness of synthetic route. Essentially, such calculations can be done before finalising a synthetic route helping to formulate a cleaner synthetic strategy.

1.1.1.4. Carbon Efficiency:

Carbon efficiency is the ratio of carbon present in the product to carbon present in reactants.

Carbon efficiency (%) = amount of carbon in product × 100 / total carbon present in reactants

This calculation considers the stoichiometry of reactants and products and is more useful for pharmaceutical processes where bulky carbon skeletons are involved.

1.2 Development of Green solvents:

In past 20 years much attention has been devoted to the production of green and clean technologies, and to find ways of replacing conventional, volatile, hazardous and environmentally unfriendly organic solvents with alternative 'green solvents'. A green solvent must ideally have negligible vapour pressure, high boiling point, be non-toxic, and have the capacity to dissolve a wide range of organic/inorganic compounds. The solvent should also be chemically and physically stable, recyclable, inexpensive and easy to handle. In addition to these aspects, solvents that allow more selective and rapid chemical transformations will have a significant impact. Few chemical were considered as substitutes: supercritical fluids, low melting polymers, perfluorinated solvents, water and more particularly ionic liquids.

1.2.1. Alternative solvents in organic synthesis:

1.2.1.1. Supercritical fluids:

A supercritical fluid (SCF) is defined as substance above its critical temperature (T_c) and critical pressure (P_c),[6] and possesses properties of similar to its liquid and gaseous phases. These properties can be specifically tuned by varying the pressure and temperature in order to vary density. The most popular SCF is carbon dioxide ($scCO_2$) whose critical point is at 73 atm. and 31.1 $^{\circ}$C and can be readily achieved in the laboratory with the suitable apparatus (Fig 1.2).

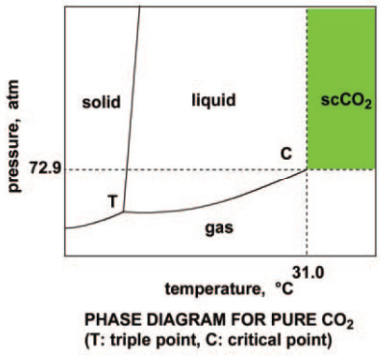
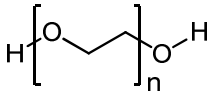


Figure 1.2: Graphical representation of the critical point of $scCO_2$.

There are numerous advantages related to the usage of $scCO_2$ and are clearly addressed in a recent article.[7] Supercritical CO_2 is non-flammable, less toxic than many organic solvents, has low viscosity and density compared to conventional solvents, is relatively inert towards reactive compounds and facile separation of the products can be achieved by depressurization of CO_2. Other advantages include high gas solubility, high diffusion rates and better mass transfer. Furthermore, the selectivity of a reaction can be dramatically changed when conducted in a supercritical fluid as compared to traditional organic solvents, hence they have been applied into several reactions[8-10] for instance hydrogenation,[11] enzymatic reactions,[12-18] metal catalysed coupling[17] etc.

1.2.1.2. Poly(ethylene glycol) – PEG(400-20000):

Poly(ethylene glycol) is the linear polymer formed from polymerization of ethylene oxide. PEG usually indicates the polyether of molecular weight less than 20000 and known to be inexpensive, thermally stable, recoverable, biologically compatible and non-toxic.[19] Furthermore, PEG and its monomethylethers have a low vapour pressure, are non-flammable, present easy workup procedures and can be recycled. For all these reasons PEG is considered to be an environmentally benign alternative for volatile solvents and a convenient media for organic reactions.



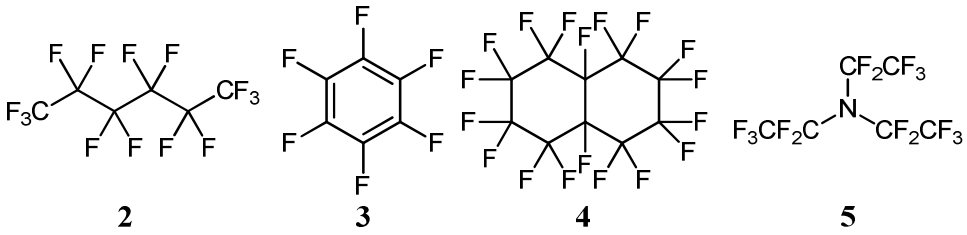
1

Figure 1.3: Polyethylene glycol.

Several examples show that PEG with low molecular weights (< 2000) were chosen as reaction media due to liquid nature at room temperature.[13-16,20-25] Although less popular, PEG is commercially available and is much cheaper than ionic liquids but unlike the latter, they have limited scope in tuning their properties only through the choice of end group selection. One of the major drawbacks is the low efficiency of product extraction by organic solvents.

1.2.1.3. Perfluorinated (fluorous) solvents:

Fluorous (perfluorinated) solvents (e.g. perfuoroalkenes, perfluoroalkyl ethers and perfluoroalkylamines, Fig. 1.4) are generally chemically benign and environmental friendly due to their non-flammable, thermally stable, recyclable properties. Some of these compounds were found to be less toxic, however, their chemical inertness results in low degradation rates and hence persist for a longer period in the environment.[26a] They also have been proved to possess global warming potential due to strong absorption of IR radiation.[26b]



2 **3** **4** **5**

Figure 1.4: Commonly used fluorous solvents.

Their ability to dissolve diatomic gases can assist mass transfer in gas-liquid reactions.[27] and although nonpolar, the polarity of these solvents is tunable and can be utilised in a wide range of reactions including Michael addition[28], oxidation,[29,30] Tsuji-Trost[31], Diels-Alder[32] etc. Some other examples have shown that reactions can be performed in biphasic systems,[33] or at supercritical conditions.[34]

1.2.1.4. Water:

Water is readily available, non-toxic, non-flammable and environmentally benign, providing opportunities for clean processing and pollution prevention. The application of water as solvent was limited to hydrolysis reactions due to the low solubility of many organic compounds and its high reactivity towards some organic compounds (e.g. organometallics). Breslow[35] and Grieco[36] in the early 1980s showed that water can be used as medium in several types of reactions.[37-39] Since then, a vast number of studies have been published[40-41]

showing that water has unique properties as a solvent that can sometimes lead to unexpected results. For instance, the rates and stereoselectivities of many types of organic reactions can be dramatically enhanced in water due to solvophobic effects. In many examples the addition of phase transfer catalysts or organic co-solvents facilitates the dissolution of non-polar reactants.[42] Besides the main drawback to water being that it can not be used in moisture sensitive reactions, the contaminated water after reaction requires treatment resulting in the need for a waste water treatment plant where the organic compounds can be converted into solid waste through oxidation (or in extreme cases disposal by incineration).

1.2.1.5. Ionic Liquids (ILs):

Ionic liquids are the next class of 'green' solvent, which can be considered as an alternative to conventional solvents and they have many advantages over the other green solvents discussed above.

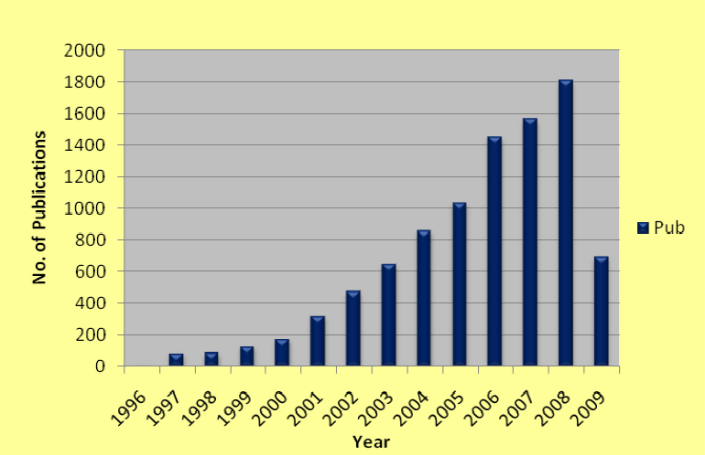


Figure 1.5: Number of publications on ionic liquids.[43]

A large number of publications have been published on ionic liquids and their applications. Fig. 1.5 shows tremendously increasing graph of publications on ionic liquids.[43] (data was determined between 1996-May 2009).

1.3 What is an Ionic Liquid?

An ionic liquid (IL) is a liquid containing ions i.e. cations and anions. Although in some papers, ionic liquids are referred as 'molten salts', there is an arbitrary distinction between molten salts and ionic liquids.[44,45] Ionic liquids are defined as pure compounds, consisting of cations (mostly organic moiety) and anions, which melts at or below 100 $^{\circ}$C [45,46] whereas,

salts which have high melting points, are highly viscous and corrosive are termed as 'molten salts' (liquid NaCl at 803 °C).

In some cases, ILs are liquid at room temperature, hence can be called 'room temperature ionic liquids' (RTILs).

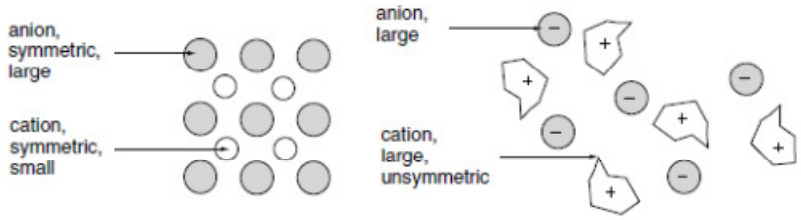


Figure 1.6: Comparison of cationic symmetry in NaCl (left) and ionic liquids (right).

The most characteristic feature, and which may be the reason why ionic liquids have low melting points, is that usually they are composed of a bulky organic cation with a low degree of symmetry and bulky inorganic/organic anion as shown in Fig. 1.6.[47] The huge interest in such compounds is based on the fact that they possess several attractive properties in particular negligible vapour pressure, high chemical and thermal stability, nonflammability, high ionic conductivity, wide electrochemical potential window and particularly their ability to act as catalysts.[45,48] In addition, many of their physico-chemical properties can be changed substantially by variation of the cation and the anion; thus, they are 'tunable' to desired reaction. For this reason, ILs have been referred to as "designer solvents'' in several publications.

1.4 Brief History of Ionic Liquids:

Although they have been of particular interest in the last 15 years, they have been known to exist for almost a century. The first ionic liquid was reported in 1914 by P. Walden,[49] when ethylamine was reacted with concentrated nitric acid to form $[EtNH_3][NO_3]$. The first application based synthesis of ILs was performed by Hurley and Weir[50] in 1948 where the final IL was synthesised from 1-ethylpyridinium chloride and aluminium chloride. This chloroaluminate IL was applied in the electrodeposition of aluminium, later on two other groups (Gale and Nardi) discovered that 1-butylpyridinium chloride-$AlCl_3$ gave better

results.[51] This class of ILs, with $[AlCl_4]^-$ as the anion, is called 'first generation ILs'. In 1967, Swain *et al*.[52], reported use of tetra-*n*-hexylammonium benzoate, as a solvent for their kinetic and electrochemical studies.

In late 70s, Dr. L. A. King, J. Wilkes and R. Carlin were working under a US Air Force Academy project aimed at finding a replacement for LiCl-KCl eutectic mixtures. As the melting temperature for LiCl-KCl mixture is 355 $^{\circ}$C, this causes problems with the materials inside the battery, as well as incompatibilities with any nearby devices.[53] With extensive research, they found that NaCl-$AlCl_3$ (which was remarkably close to be an IL by definition) has an eutectic composition possessing melting point of 107 $^{\circ}$C, and works well in batteries. The physico-chemical properties and electrochemical behaviour was determined for this class of salts to file a patent. In extensive research, Wilkes and Hussey were working on alkylpyridinium chloroaluminate salts with reference to Hurley and Weir's work[50a] reported in 1948, and found that the alkylpyridinium cation suffers from being easy to reduce chemically and electrochemically. They moved their attention on to 1-ethyl-3-methylimidazolium, (as it is resistant towards reduction) and prepared various compositions of [emim]Cl-$AlCl_3$ and discovered exceptionally well behaved new electrolyte for batteries.[54] As the anion contains Lewis acid, these ILs were applied as catalysts in Friedel-Craft reactions[55] and as solvent in polymerisation.[56,57]

Although ILs gave excellent results, their biggest disadvantage was their reactivity towards water. Hence efforts were taken to prepare water stable ILs, leading ultimately to Mike Zaworotko *et al*.[58] synthesizing a new series of [emim] based ILs, with iodide, tetrafluoroborate, hexafluorophosphate, nitrate, sulphate and acetate anions. These air and water stable ILs were referred to as 'second generation ILs'. Unlike the alkyl imidazolium chloroaluminate ILs, second generation ILs could be synthesized out of a glove box. These ionic liquids are largely water tolerant, however, prolonged exposure to moisture can cause some changes in their physical and chemical properties. It was found that the undried ionic liquid [bmim]PF_6 attacks gold substrate and its aggressiveness increases with the increase in water content. This is due to the formation of HF as a result of decomposition of the ionic liquid in the presence of water. Therefore, ionic liquids based on more hydrophobic anions such as tri-fluoromethanesulfonate ($CF_3SO_3^-$), *bis*- (trifluoromethanesulfonyl)imide $[(CF_3SO_2)_2N^-]$ and *tris*-(trifluoromethanesulfonyl)methide $[(CF_3SO_2)_3C^-]$ have been developed.[59-61]

The synthesis of 'second generation ILs' started a new era in ionic liquids research and since then numerous scientists (including J. Wilkes, Y. Chauvin, D. R. MacFarlane, K. Seddon, P. Wasserscheid, T. Welton, N. Gathergood, C. Chiappe to name just a few) have synthesized different classes of ionic liquids and utilized them in a number of applications. These details of the synthesis and application of ionic liquids over the past 15 years will be discussed later in this chapter.

1.5 Synthesis of Ionic Liquids:

The ionic liquid synthesis, consists of two steps, first is the formation of the cation followed by the second step of anion metathesis to obtain the IL containing the desired anion. In some cases, anion metathesis is not needed, as the first step serves the purpose of both. For example, quaternarization of ethyl amine with conc. HNO_3 would give the final IL. Figure 1.7 illustrates the reaction scheme for dialkylimidazolium IL synthesis.

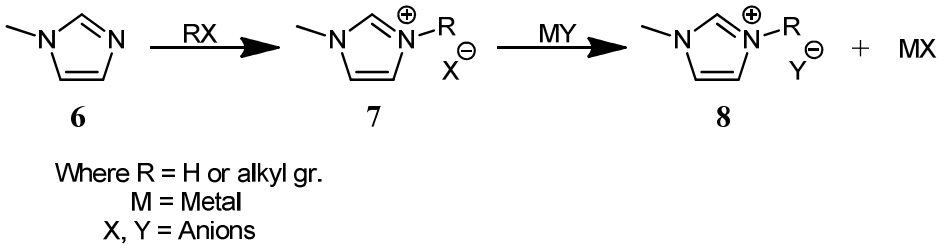


Figure 1.7: Synthetic route for imidazolium ILs.

The formation of the cation can be carried out either via protonation with protic acid[62] or via quaternization of the amine, phosphine or ternarization of the sulphide most commonly using alkyl halide or dialkylsulphates. The alkylation process to form the halide salt has the advantages of (i) a wide range of cheap alkyl halides are available, and (ii) the substitution reactions occur smoothly at reasonable temperatures. Several types of amines, phosphines, and sulphides were tried in the preparation of ILs, some of them are shown in Fig. 1.8.

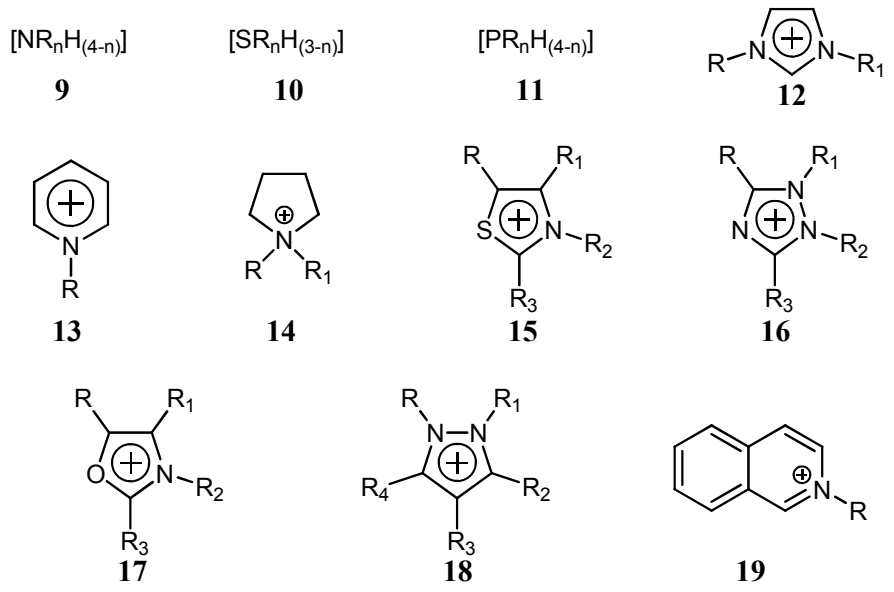


Figure 1.8: Cation diversity in the field of ILs.

Anion metathesis is needed as the halide anions obtained in the first step are often corrosive and the salts would be solid mostly. Hence metathesis is carried out to obtain an IL with an inert anion. The anion may affect the physicochemical properties of ionic liquid drastically. Different types of anions have been introduced and the combinations with several cations have been synthesized. K. Seddon predicted that there are a quintillion (10^{18}) number of compounds possible with the different combination of cations and anions.[63] Table 1.1 shows few papers which have been published over the years with different anions.

Table 1.1: Publications related to synthesis and applications of corresponding anions

Sr. No.	Anions	Sr. No.	Anions
1.	BF_4^-[58]	16.	$ZnCl_3^-$[72]
2.	PF_6^-[64]	17.	$CuCl_2^-$[72]
3.	SbF_6^-[65]	18.	$SnCl_3^-$[72]
4.	$CH_3CO_2^-$[58]	19.	$N(EtSO)_2^-$[72]
5.	HSO_4^-[66]	20.	$N(FSO_2)^-$[72]
6.	NO_3^-[58]	21.	$C(CF_3SO_2)_3^-$[73]
7.	NO_2^-[58]	22.	$CH_3SO_3^-$[72]
8.	$CF_3SO_3^-$[59]	23.	$N(CN)_2^-$[74]
9.	$(CF_3SO_2)_2N^-$[59]	24.	Halides[75]
10.	$CF_3CO_2^-$[59]	25.	$Al_2Cl_7^-$[72]
11.	$B(Et_3Hex)^-$[67]	26.	$Al_3Cl_{10}^-$[72]
12.	OTs^-[68]	27.	$Au_2Cl_7^-$[72]
13.	$AuCl_4^-$[69]	28.	$Fe_2C_{17}^-$[72]
14.	$AlCl_4^-$[70]	29.	SbF_6^-[72]
15.	Carborane[71] anions (as 1-R-$CB_{11}H_6Cl_6^-$)		

1.6 Purification of ILs:

Even small amounts of impurities can change the chemical and physical properties of ILs (usually originating from the starting materials being used in synthesis).[76] Major impurities found in ILs are halide anions that arise from the first step, either by incomplete reaction or incomplete removal of the resultant metal halide. Effects of halide impurities in several reactions are extensively studied and reported.[77] As ILs have negligible vapour pressure, purification by distillation is not so easy, in all cases. The easiest way to remove halide impurity is an extraction with deionised water in case of hydrophobic ILs.[78] Whereas in case of water-miscible ILs, Seddon *et al.*[76] used $AgBF_4$ to remove residual halide. When studied further, they found that if Na^+ salt is used for anion metathesis, reaction does not go to completion. In practical terms, it is suggested to ensure the purity of the ILs in any application where presence of halide may cause problems. This may be achieved by the use of an ion-sensitive electrode or by chemical means such as the Vollhard procedure for chloride ions.[76,79]

The second crucial impurity in ILs is trace amounts of water which can cause changes in the properties of ILs drastically.[78] Hence, it is recommended to dry ILs prior to use at (at least) 70 $^{\circ}C$ with stirring for several hours.[80] Here, stirring is crucial as ILs dilates at elevated temperatures and water desorption takes place at the superficial layer of the ionic liquid. Even water-immiscible ILs such as [bmim][PF_6] can absorb water when exposed to air, furthermore causing anion degradation to HF.[81] If necessary, the amount of water may be determined either by Karl-Fisher titration or IR spectroscopy.

A common problem encountered by all chemists working with ILs is synthesizing colourless IL. Alkylimidazolium based ILs tend to be pale yellow or brown in colour. Although the exact reason is yet unclear, it is believed that the colour originates from starting materials. i.e. either from 1-alkylimidazole or alkyl halide. Hence, it is advised to purify raw materials prior to use by the Amarego-Perrin method.[82] A colorimetric method has been developed to determine the level of unreacted alkylimidazole (< 0.2 mol%) in the ionic liquid.[83] A classical method of charcoalisation can be employed for removal of coloured impurities in ILs (Fig. 1.9).[81a]

Figure 1.9: Charcoalisation effect on colour; (right-after charcoalisation).

In order to obtain a colourless ionic liquid, the following general steps should be followed,

1. All starting materials should be purified by the Amarego-Perrin method.[82]

2. The presence of traces of acetone can sometimes result in discoloration during the quaternization step. Thus, all glassware used in this step should be kept free of this solvent.

3. The quaternization reaction should be carried out either in a system that has been degassed and sealed under nitrogen, or else under a flow of inert gas such as nitrogen. Furthermore, the reaction temperature should be kept as low as possible (no more than ca 80 $^{\circ}$C for Cl^- salts, and lower for Br^- and I^- salts).

1.7 Physicochemical and Biological Properties of ILs:

Ionic liquids are considered as green solvents and often are used as catalysts as well. Hence the determination of physical and chemical properties becomes extremely beneficial if ILs have to be incorporated in industrial applications. In order to encourage a widespread use of ILs, they should be cheaper to synthesize, recyclable, and robust to endure all types of processing conditions. Physical properties such as melting point, boiling point, solubility, refractive index, density, and viscosity, are related to the mechanics and engineering aspects associated with the process. For example, density, viscosity, and surface tension will determine critical parameters including rates of liquid–liquid phase separation, mass transfer and power requirements for stirring and mixing. Properties such as the structuredness, normalised polarity (E^N), polarizability (π^*), hydrogen bond donor acidity (α), and hydrogen

bond acceptor basicity (β) are more obviously related to the solubilities, partition coefficients, and reaction kinetics.[84,85] The physical and chemical properties of ionic liquids can be specifically varied over a wide range by the selection of suitable cations and anions. Toxicity and biodegradation are the properties which give information about ILs, such as their biological behaviour and environmental impact.

Knowledge of physico-chemical and biological properties enables chemists, to choose specific IL for a chemical process.

1.7.1. Melting Point:

By definition, the melting point is an evaluative property of ILs. The point of significance is the relationship between structural & chemical composition of an IL and melting point. The main reasons for ILs having low melting points, despite being a salt, are the low symmetry of the cation,[86] weak inter-molecular interactions,[59] and a diffuse distribution of charge in cation and/or anion.[87] Table 1.2[54,88] illustrates the effect of the cation clearly; high melting points are characteristics for alkali metal chlorides, whereas chlorides with organic cations melts at < 100 °C.

Table 1.2: Melting points of various chlorides.[54,88]

Salt	**Melting point** (°C)
NaCl	803
KCl	772
[dmim][Cl]	125
[emim][Cl]	87
[bmim][Cl]	65

Comparison of melting points of different salts of [emim] emphasises that, in most cases, the increasing size of an anion with the same charge leads to a further decrease in the melting point (Table 1.3).[78, 89]

Table 1.3: Influence of anions on melting point of ILs.[78,89]

Imidazolium salts	Melting points (°C)
[emim][Cl]	87
[emim][NO_2]	55
[emim][NO_3]	38
[emim][$AlCl_4$]	7
[emim][BF_4]	6[a]
[emim][PF_6]	62
[emim][CF_3SO_3]	- 9
[emim][CF_3SO_2]	-14
[emim][NTf_2]	- 3

[a] glass transition.

Along with an anion choice, variation in the alkyl chain length in the cation can achieve fine-tuning of the melting point.[80]

1.7.2. Vapour pressure and Thermal stability:

Ionic liquids have no measurable vapour pressure which is a significant advantage, since separation of a reaction mixture becomes more effective as a method of product isolation. The well-known problem of azeotrope formation between the solvent and the products does not arise.

Thermal stability of ionic liquids depends on the strength of carbon-heteroatom and heteroatom-hydrogen bond. For example, ionic liquids synthesised by the protonation of an amine or phosphine have low thermal stability.[45] Most of the ionic liquids are shown to be stable up to 400 °C, except some trialkylammonium salts which decompose at 80 °C *in vacuo* depending on the boiling point of the corresponding amine.[45,90]

Recent reports have described the TGA of imidazolium salts and noted that the thermal decomposition is heavily dependent on the salt structure.[91] These reports also indicate that experiments performed under N_2 or air produce the same results.

Table 1.4: Thermal decomposition temperature for ILs.

Ionic Liquid	Decomposition Temperature (°C)
[emim][Cl]	285
[pmim][Cl]	282
[emim][Cl]	254
[hmim][Cl]	253
[omim][Cl]	243
[bmim][I]	265
[bmim][BF_4]	403
[bmim][PF_6]	349
[bmim][NTf_2]	439

The onset of thermal decomposition is furthermore similar for the different alkyl chain lengths on imidazolium but appears to decrease as the anion hydrophilicity increases (Table 1.4). The general trend for the thermal stability has been [PF_6^-] > [NTf_2^-] ~ [BF_4^-] > halides.[92]

1.7.3. Viscosity:

One of the barriers in the application of ILs arises from their high viscosity. High viscosity may reduce the rate of organic reactions via reduction in the diffusion rate of the reacting species. Current research for new and more versatile ILs is driven, in part, by the need for materials with low viscosity.

The viscosity of ionic liquids is essentially determined by their tendency to form hydrogen bonding and the strength of their Van der Waals interactions. It is normally higher than that of water, ranging between 10-200 mPa.S, similar to those of vegetable and medium crude oils,

and decreases with increasing temperature.[93] Increasing the alkyl chain length or fluorination of the cation leads to an increase in viscosity.[91] This is due to stronger van der Waals forces between cations leading to an increase in the energy required for molecular motion. For example, an increase in viscosity was observed for the 1-butylmethylimidazolium IL when the $[CF_3SO_3]^-$ anion was replaced with the $[n\text{-}C_4F_9SO_3]^-$ ion and from the $[CF_3COO]^-$ ion to the $[n\text{-}C_3F_7COO]^-$ ions.

Table 1.5: Influence of alkyl chain in cation and fluorinated anions on viscosity of ILs[59] at 25 °C.

Ionic Liquid	**Viscosity** (mPa.s)
[emim][Cl]	43
[bmim][BF_4]	233
[hmim][BF_4][a]	314
[bmim][CF_3SO_3]	90
[bmim][n-$C_4H_9SO_3$]	373
[bmim][CF_3CO_2]	73
[bmim][n-$C_3F_7CO_2$]	182
[bmim][PF_6]	450
[bmim][NTf_2]	52

[a] measured at 20 °C

The ability of anions to form hydrogen bonds has a pronounced effect on viscosity. Fluorinated anions such as $[BF_4]^-$ and $[PF_6]^-$ form viscous ionic liquids due to hydrogen bonding. Table 1.5[59] shows the variation in viscosity with alkyl chain length and anion. The strength of hydrogen bonding decreases in the order $[PF_6]^- > [BF_4]^- > [NTf_2]^-$ which results in a decrease of viscosity.

1.7.4. Density:

The density of ILs is a property which affects the phase separation in biphasic media, diffusion coefficients and mass transfer of reactants when they are used as a reaction media In general, they are denser than water with values ranging from 1 to 1.6 g/mL.

Table 1.6: Densities of ILs at 25 °C.[91,94]

Ionic Liquid	**Density** (g/mL)
[bmim][Cl]	1.08
[hmim][Cl]	1.03
[omim][Cl]	1.00
[bmim][I]	1.44
[bmim][BF_4]	1.12
[bmim][PF_6]	1.36
[bmim][NTf_2]	1.43
[bmim][CF_3CO_2]	1.21
[bmim][CF_3SO_3]	1.29

Density of an ionic liquid depends on the length and type of substituent in the cation, and also on the kind of anion (Table 1.6). The molar mass of the anion,[91] alkyl chain length and bulkiness of the cation significantly affects the overall density of ILs. Density is also temperature dependent, as the temperature rises from 293 to 313 K, the density of [emim][BF_4] decreases linearly.[84]

1.7.5. Solvation ability and polarity:

The solvation ability of an IL determines the molecular dynamics of reactants and hence affects the rate of reaction. It is a well known fact that IL solubilises both polar and non-polar solutes depending on the substituents on the cation and anion. The more lipophilic substituents on the cation, the more it dissolves non-polar solutes. e.g. 1-octene was found to be 2500 times more soluble in methyl-tri-*n*-octylammonium tosylate than in methyl-tri-*n*-ethylammonium tosylate.[95] The influence of the anion on solvation characteristics of ILs can be demonstrated in an impressive fashion by the examples of water solubility of different salts of [bmim]. While [bmim]Br, [bmim][CF_3COO], and [bmim][CF_3SO_3] are highly water soluble, [bmim][PF_6] and [bmim][NTf_2] form biphasic mixtures. The water content of [bmim][NTf_2] after mixing and separating with water is only 1.4 w/w% at 20 $^{\circ}$C.[59]

During solvation by ILs, translational polarisation plays a key role (whereas in molecular solvents orientational polarisation occurs). Anions arrange themselves close to the positive head of solute and vice versa (Fig. 1.10).[96]

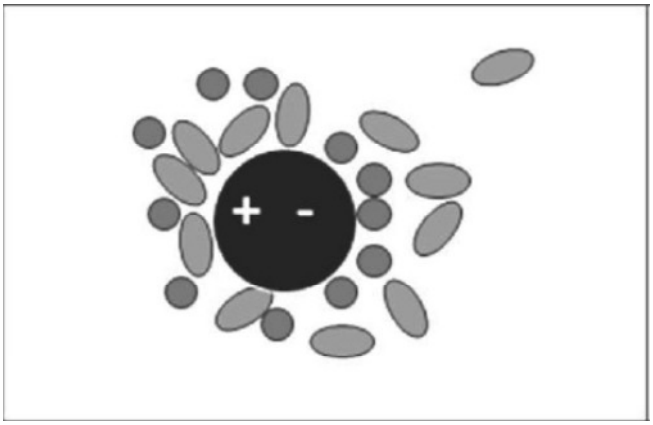


Figure 1.10: Solvation through translational polarization.[96]

As a consequence, the composition of ILs varies depending on the spatial position around the solute or, in other words, becomes inhomogeneous.

Now, polarisation of the solvent is dependent on solvent polarity, which is usually determined in a purely empirical fashion. Empirical solvent polarity parameters are derived from the measured absorption maxima of solvatochromic and fluorescent dyes (Fig. 1.11), which

reflects the solvating ability of a solvent comprehensively.[97]

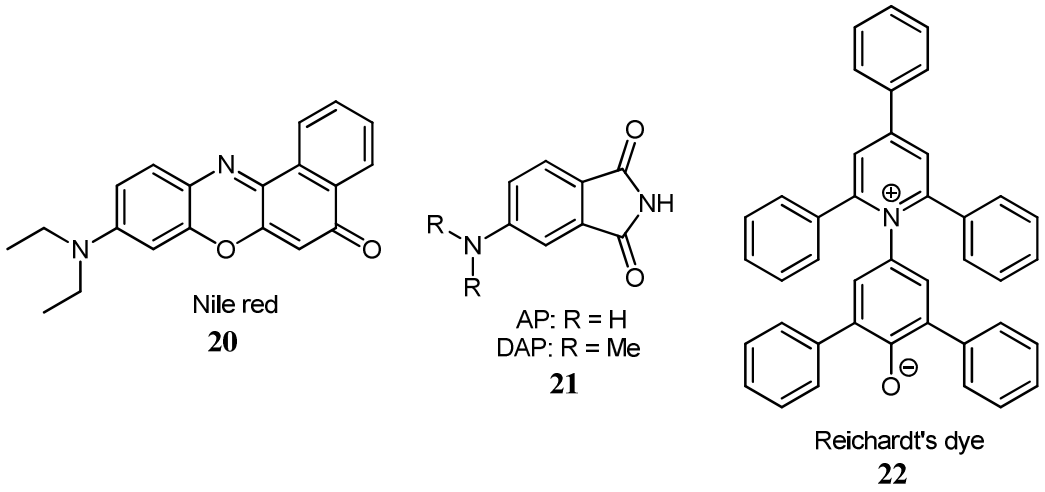


Figure 1.11: Solvatochromic and fluorescent dyes.

For the evaluation of polarity parameters, partition coefficients and sometimes reaction rates are considered as an exact determination would not be possible using solvatochromatic dyes alone. Probably the most widely used empirical scale of polarity is the $E_{T(30)}$ scale.

$$E_{T(30)} \text{ (in kcal mol}^{-1}) = 28592/\lambda_{max}$$

Where λ_{max} (in nm) is the maximum absorbance by zwitterionic Reichardt's dye. Often a normalized scale of $E_{T(30)}$ polarity, E_N^T is used which is obtained by assigning water the value of 1.0 and tetramethylsilane zero. The solvatochromic shift of this probe is strongly affected by the hydrogen- bond donor ability of the IL, due to it's structure which stabilizes the ground state more than the excited state (Fig. 1.11). The $E_{T(30)}$ scale is therefore, largely but not exclusively, a measure of hydrogen-bonding acidity of the solvent system. The E_N^T values of several ILs are reported in Table 1.7.[98]

Table 1.7: E_N^T values for solvents

Solvents	E_N^T
Water	1.00
Methanol	0.762
Dichloromethane	0.309
Toluene	0.100
Acetone	0.350
[bmim][BF_4]	0.670
[bmim][PF_6]	0.669
[bmim][OTf]	0.656
[bmim][NTf_2]	0.644
[bmim][SbF_6]	0.673
[bm_2im][BF_4]	0.576
[bm_2im][NTf_2]	0.541

The alkyl chain length for the 1-alkyl-3-methylimidazolium ILs hardly affects E_N^T values which are similar to that for ethanol (E_N^T = 0:65), but the introduction of a methyl at C-2 reduces the solvent polarity.[98b]

1.7.6. Refractive index:

The refractive index of a medium is the ratio of the speed of light in a vacuum to its speed in the medium. It is also the square root of the relative permittivity of the medium at that frequency. This parameter is related to polarizability/dipolarity (π^*) of the medium and the excess molar refraction. The values found for [bmim] salts are comparable to those for organic solvents.[91]

Table 1.8: Refractive index[91]

Ionic liquid	Refractive index
[bmim][PF_6]	1.409
[bmim][I]	1.572
[bmim][NTf_2]	1.427
[hmim][Cl]	1.515
[omim][Cl]	1.505
[omim][PF_6]	1.423

Reported data suggests that increasing length and branching of alkyl chain on the cations increases the refractive index (Table 1.8). Changing the anion of the IL also affects the refractive index with less polarizable anions giving lower values.[76]

1.7.7. Surface tension:

Surface tension may be a key property in multiphase processes. ILs are widely employed in transition metal catalyzed reactions carried out under multiphase conditions. Especially, the extraction of products occurs at the interface between the IL and the overlying organic phase. These reactions should therefore be dependent on the access of the catalyst to the surface and the transfer of the products across the interface i.e. the rates of these processes depend on surface tension. In general, liquid/air surface tension values for ILs are somewhat higher than those for conventional solvents [$(3.3\text{-}5.7) \times 10^{-4}$ $N.cm^{-1}$], although not as high as for water.

Table 1.9: Surface tension for imidazolium ILs[91]

Ionic liquids	**Surface tension** (dyne/cm)
Water	71.9
[bmim][I]	54.7
[bmim][BF_4]	46.6
[bmim][PF_6]	48.8
[bmim][NTf_2]	37.5
[hmim][Cl]	42.5
[hbim][PF_6]	43.4
[omim][Cl]	33.8
[omim][PF_6]	36.5

Surface tension values vary with temperature and are affected by the alkyl chain length, decreasing with increasing chain length (Table 1.9).[91] For a fixed cation, ILs with a bulky anion have higher surface tension.[99]

1.7.8. Toxicity & biodegradation:

Volatile organic compounds (VOCs) in current industrial applications are causing concerns due to their toxicity, both towards process operators and the environment.[100] ILs being termed as 'green solvents', due to their properties, are considered as alternatives to traditional solvents. Despite the 'green' aspects of ILs, it is irresponsible to ignore the ultimate fate of ILs when released into the environment. Hence the evaluation of the toxicity of ILs becomes inevitable.

Biodegradation can be defined as a process "by which microbial organisms transform or alter (through metabolic or enzymatic action) the chemicals introduced into the environment."[101] There are two main types of biodegradation i.e. aerobic biodegradation and anaerobic

biodegradation. Aerobic biodegradation takes place in the presence of oxygen, whereas anaerobic biodegradation occurs in the lower stratum of soil or sediments, which lack molecular oxygen. Heterotrophic microorganisms utilize organic compounds as both carbon and energy sources for growth. The organic chemicals are transformed mainly by enzymes such as esterases, oxidases, etherases and sulphatases present in microorganisms.

In the early 90's, Boethling and co-workers[102,103] studied the structure-biodegradability relationship and suggested a number of factors that can increase the biodegradability of an organic compound, which are as follows;

(i) presence of phenyl rings, and unsubstituted linear alkyl chains (> 4 carbons in chain length), (ii) groups that provide possible sites for enzymatic hydrolysis (especially oxygen atoms in the form of hydroxyls, aldehydes, or carboxylic acids).

Furthermore, the authors also suggested that the presence of some functional groups will cause greater resistance of a compound to biodegradation, for instance halogens, nitro, nitroso, branched alkyl chains and fused ring systems all can result in decreased biodegradability. These observations enabled researchers to work towards the rational design and synthesis of biodegradable organic compounds.

Biodegradation studies are carried out to evaluate the environmental fate of the organic compounds. Due to the variety of biodegradation mechanisms in the natural environment, a number of methods are applied to test biodegradation of chemicals. The methods in common use are the Sturm test, Closed bottle test [approved by The Organisation for Economic Cooperation and Development (OECD 301B and D respectively)] and the BOD_5 test. As mentioned earlier in this chapter, the determination of toxicity and biodegradation of ionic liquids allows researchers to evaluate the 'greenness' of ILs, which consequently enables them to choose greener ILs for further applications. Several scientists around the globe, for instance, P. Scammells, N. Gathergood, S. Stolte etc, are already working in this area. Details on toxicities and biodegradation are discussed in a separate chapter. (see chapter 3.0)

Some more properties of ionic liquids are also studied in detail, in particular, conductivity,[80] electrochemical properties,[104] acidity and coordination ability.[105] All of these properties have persuaded chemists to utilise ILs in different fields of chemistry. Seddon and Plechkova put forward a pictorial representation for applications of ILs (Fig. 1.12).[106]

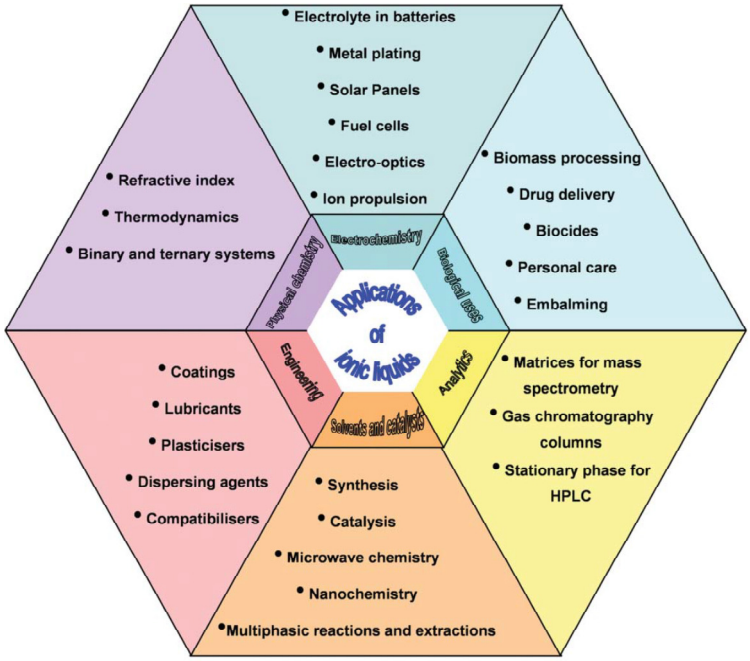


Figure 1.12: Pictorial representation for applications of ILs.[106]

Considering the scope of this thesis, some of the main synthetic applications are briefly discussed in Section 1.8 below.

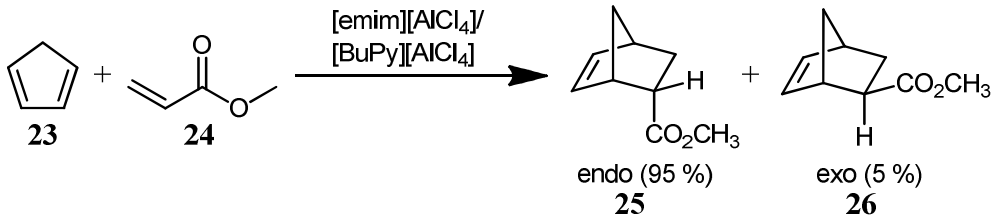
1.8 Applications of ionic liquids in organic synthesis:

1.8.1. Diels-Alder Reaction:

Diels-Alder reaction is a powerful tool in synthetic chemistry when building a molecule scaffold. The reaction was developed in 1928 by O. T. H. Diels and K. Alder and has been extensively studied in nonpolar solvents and water. Dramatically, reaction rates and stereoselectivities were found to be enhanced in water and the results were attributed to hydrogen bonding between transition states and aqueous media.[107] The reactions were also performed in other polar and environmentally friendly solvents (i.e. ionic liquids) to study their effects on stereoselectivities.

The first Diels-Alder reaction in IL was reported in 1989, which was performed in $[EtNH_3][NO_3]$ by Jaeger and Tucker.[108] Promising results were obtained when C. W. Lee carried out cycloaddition of cyclopentadiene (**23**) and methyl acrylate (**24**) (Scheme 1.1).

Improved reaction rates, and selectivities were obtained in [emim][Cl] and [BuPyr][Cl] compared to traditional solvents .[109]



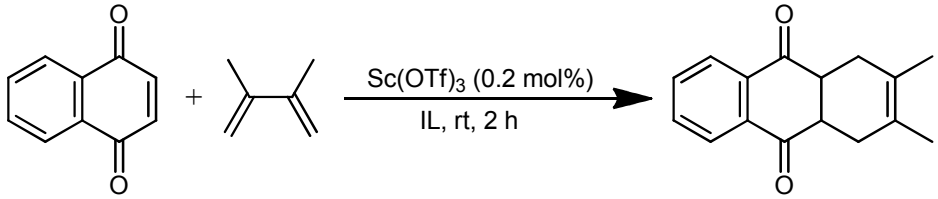
23 **24** **25** **26**

Scheme 1.1: Diels-Alder reaction of cyclopentadiene and methyl acrylate.

Furthermore, the authors studied chloroaluminate derivatives of the same ILs as reaction media and obtained even higher reaction rates and with *endo:exo* (19:1) selectivity. In some cases, ILs can reverse the selectivity obtained in traditional solvents.[110]

Welton *et al.*[111] investigated the effect of the anion on the selectivity of *endo:exo* products and found a clear trend for [bmim] salts. The selectivity decreased in the order $[CF_3CO_2]^-$ >$[NTf_2]^-$ >$[OTf]^-$ >$[BF_4]^-$ >$[PF_6]^-$ which is in agreement with the E_T^N values evaluated for these salts.

Studies have already revealed that when Lewis acids are being used as catalyst, Diels-Alder reactions produce enhanced yields and selectivities. Hence chloroaluminate,[110] chlorozincate[112] and chloroferrate salts of ILs were also studied. The most common Lewis acid is $Sc(OTf)_3$, being a highly active catalyst for these reactions. In 2001, Song *et al.*[113] reported cycloaddition of a variety of substrates in [bmim] ILs using 0.2 mol% $Sc(OTf)_3$ at 20 °C (Scheme 1.2). They achieved quantitative yields (>99 %) with almost complete stereoselectivity for the *endo* product (Table 10).



27 **28** **29**

Scheme 1.2: Cycloaddition of 1,4-naphthoquinone and 2,3-dimethylbuta-1,3-diene.

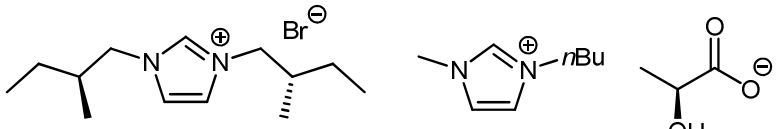
Table 1.10 shows the results of cycloaddition between 1,4-naphthoquinone (**27**) and 2,3-dimethylbuta-1,3-diene (**28**).

Table 1.10: Results for Diels-Alder reaction[113]

Entry	Solvent	Yield **29** (%)
1	CD_2Cl_2	22
2	[bmim][PF_6](0.1 eq.) + CD_2Cl_2	46
3	[bmim][PF_6](0.5 eq.) + CD_2Cl_2	85
4	[bmim][PF_6](1.0 eq.) + CD_2Cl_2	>99
5	[bmim][PF_6]	>99
6	[bmim][SbF_6]	>99
7	[bmim][OTf]	>99

Reaction conditions: 3 mmol 2,3-dimethylbuta-1,3-diene (**28**), 1 mmol 1,4-naphthoquinone (**27**), 0.2 mol% $Sc(OTf)_3$, 1 mL solvent, 20 °C, 2 h

Chiral induction was investigated using chiral ionic liquids (CILs) (**30**) and (**31**) as solvents (Fig. 1.13).

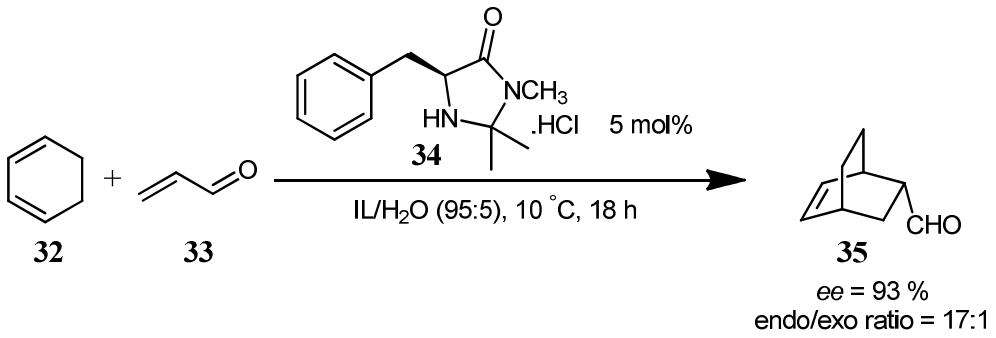


30 **31**

Figure 1.13: Chiral ionic liquids.

When (**30**) was employed in the reaction, < 5 % *ee* was achieved[114] whereas (**31**) gave 4.4:1 diastereoselectivity with no significant enantioselectivity.[115] Although not with CIL, notable chiral induction was observed, in the cycloaddition of cyclohexadiene (**32**) and acrolein (**33**)

using a chiral catalyst (**34**) immobilised in [bmim][PF_6] or [bmim][SbF_6] with 5 v/v% water (Scheme 1.3).[116]



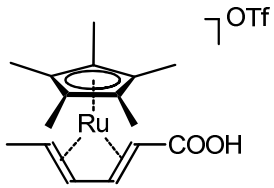
Scheme 1.3: Cycloaddition using chiral catalyst in IL.

Moderate yields (70-80 %) and selective *endo:exo* ratio (17:1) with 93 % of *ee* was obtained. Authors attribute improved results to critical role of water in iminium ion hydrolysis during catalytic cycle.[116]

1.8.2. Hydrogenation:

Hydrogenation is often referred to as a 'green' reaction in present day chemistry. A number of solvents including ILs have been employed in hydrogenations with the first publication of a hydrogenation in ILs reported by Chauvin *et al.*[117] in 1995. 'Osborn complex' [Rh(nbd)(PPh_3)$_2$][PF_6] (nbd=norbornadiene) (**36**) was dissolved in [bmim] ILs with weakly coordinating anions (e.g. PF_6^-, BF_4^-, SbF_6^-) for the hydrogenation of 1-pentene at 30 °C. Independent of the limited solubility of the reactants, the reaction rates in [bmim][SbF_6] were five times faster than in acetone, with improved product selectivity.[117b] The Rh-catalyst was immobilised in the IL without any structural modification, which is generally required in the case of other polar solvents. Secondly, only 0.02 % leaching of catalyst was observed in the organic phase. Furthermore authors investigated the hydrogenation of cyclohexadiene (**32**) with the same conditions and observed 96 % conversion with 98 % product selectivity to cyclohexene. Product selectivity was attributed to low solubility of cyclohexene in [bmim][SbF_6], so that further reduction is restricted. Many other researchers obtained similar results on several substrates including 1,3-butadiene, 1,4-cyclooctadiene and benzene.[118] Different metal catalysts have been reported to be successful for hydrogenation in ILs, for instance, Rh and Co-catalysts for olefins,[119] Ru-catalysts for aromatic compounds.[120]

Stereoselective hydrogenation of sorbic acid was successfully carried out by Steines *et al.*[121] in [bmim][PF_6] at 40 °C with [RuCp*(η^4-sorbic acid)][OTf] (**36**) (Fig. 1.14) as a catalyst.

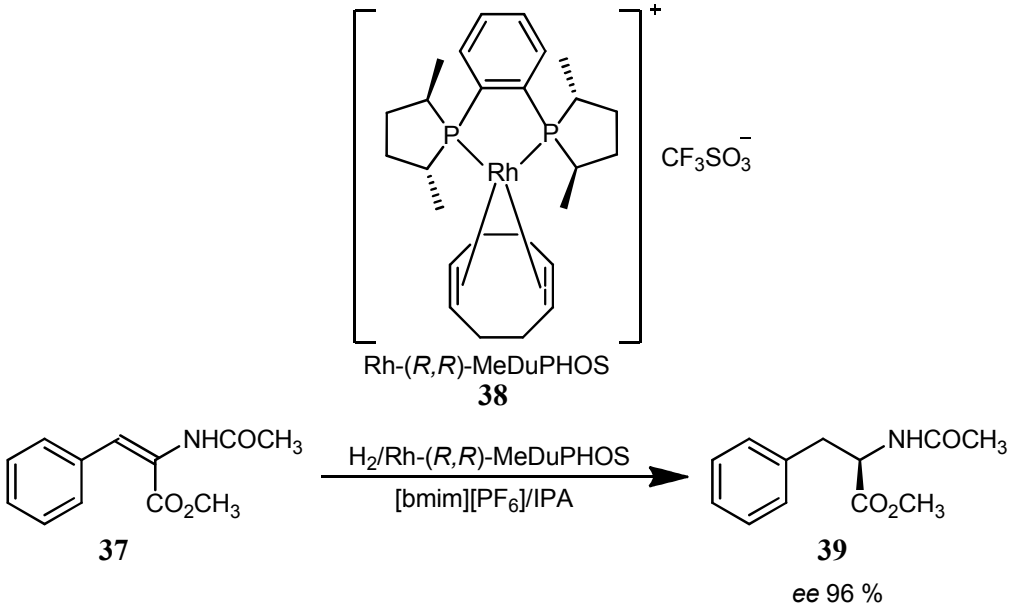


36

Figure 1.14: [RuCp*(η^4-sorbic acid)][OTf].

The product, *cis*-3-hexanoic acid was obtained with up to 93 % selectivity with moderate conversion (52 %). Increased H_2 pressure lead to reduced selectivity (*cis/trans*) whereas the effect of temperature was found to be less pronounced.

Asymmetric hydrogenation is an important reaction in organic synthesis which is used to synthesize chiral molecules. The application of ILs as reaction media in hydrogenation provides the advantage of a recyclable catalytic system. Reduction of α-acetamidocinnamic acid (**37**) was carried out in [bmim][PF_6]/IPA mixture using Rh-DuPHOS (**38**) at 25 °C and 2 bar of H_2 (Scheme 1.4).[122]



Scheme 1.4: Asymmetric hydrogenation in [bmim][PF_6]/IPA.

Moderate to good yields (83-60 %) and 96 % enantioselectivity was achieved. Although these results are slightly lower than obtained in 2-propanol, the immobilised catalyst is far more stable towards oxidation in IL.

Table 1.11: Results for asymmetric hydrogenation of **37** to **39**

Entry	**Conversion** (%)	***ee*** (%) (***R***-isomer)
1	83	96
2 (1st recycle)	64	96
3 (2nd recycle)	62	95
4 (3rd recycle)	60	94
5 (4th recycle)	58	94

Reaction conditions: 7 g IPA + 5 g [bmim][PF_6], 25 °C, 2 bar of H_2, 20 min.

No significant drop in enantioselectivity was observed until the fourth recycle whereas conversion showed a considerable decrease (Table 1.11).

The major problem encountered in hydrogenations using ionic liquids is low H_2 solubilities compared to traditional solvents.[123,124] Table 1.12 shows the H_2 gas solubility in several solvents.

Table 1.12: Hydrogen concentration in common solvents and selected ILs[a] at 298 K and atmospheric pressure.[123]

Solvent	H_2 [mM]	Solvent	H_2 [mM]
Water	0.81	[bmim][BF_4]	0.86
Methanol	3.75	[bmim][PF_6]	0.73
Ethanol	2.98	[bmim][SbF_6]	0.93
Benzene	4.47	[bmim][OTf]	0.97
Toluene	3.50	[bmim][NTf_2]	0.77
Cyclohexane	3.63	[bmim][CF_3CO_2]	0.98
		[hmim][BF_4]	0.79
		[omim][BF_4]	0.62

The problem can be solved by carrying out reactions at elevated temperatures as at higher temperature the viscosity of the IL decreases, and mass transfer effects become less significant.[125] A similar technique was applied by Dyson *et al.*[126] where they demonstrated a biphasic hydrogenation system consisting of catalyst immobilised in [omim][BF_4] and substrate, 2-butyne-1,4-diol dissolved in water (Fig. 1.15).

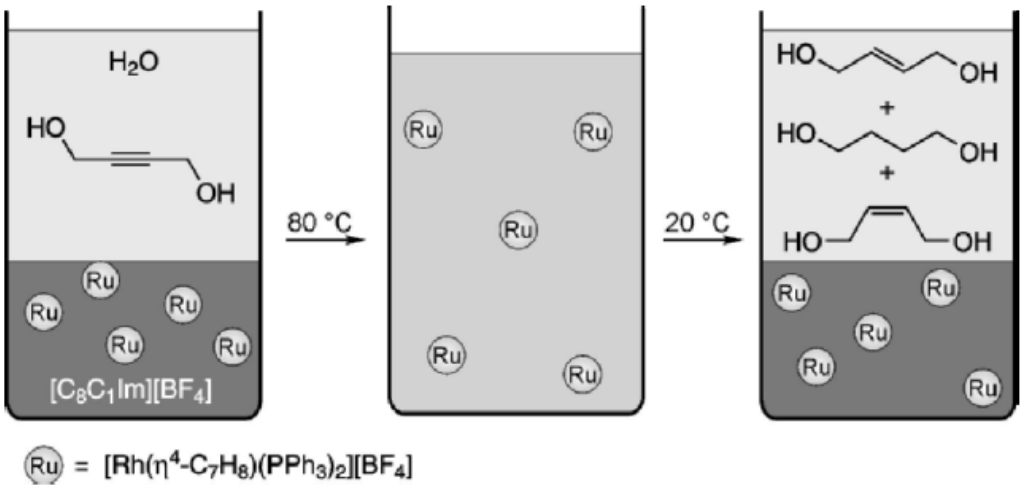


Figure 1.15: Hydrogenation under reversible dual-single phase solvent system.[126]

At room temperature, the phases were immiscible; however at the reaction temperature of 80 °C homogeneity was attained. The reaction was carried out under 60 atm. of the H_2 gas with facile separation of the reduced products from the catalyst/IL phase being achieved simply by cooling the reaction (Fig. 1.15). Products dissolved in the aqueous layer were isolated and reuse of the IL/catalyst system demonstrated.

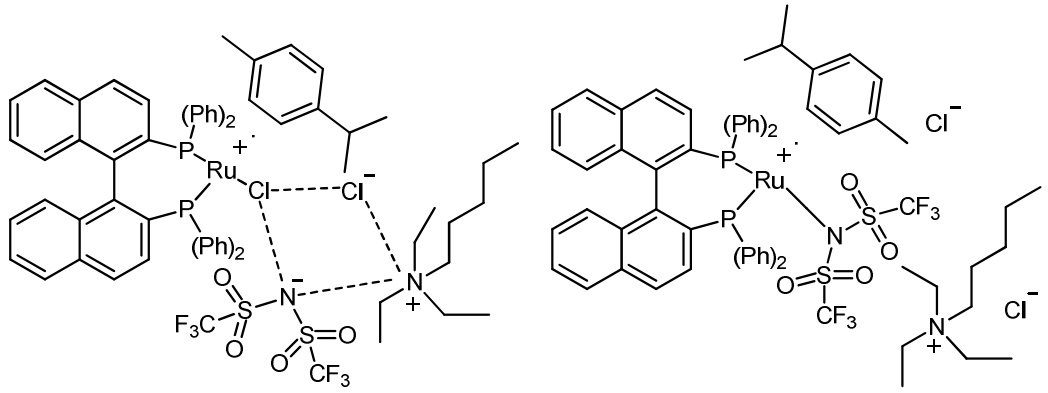


Figure 1.16: Proposed ‘‘weak’’ catalyst-IL ionic pairs interaction.[127]

Anions are believed to have a considerable effect on the reaction rates by defining the physical properties of IL, and also via stabilisation of the catalyst.[127,128] T. Floris proposed that stabilisation occurs through structural modification of the active catalytic centre with the anionic pair as shown in Fig. 1.16. Similar stabilisation was observed for Wilkinson's catalyst by chloroaluminate anion, but these ILs are rarely used for hydrogenations due to their tendency to polymerise olefins.[128]

1.8.3. Oxidation:

Ionic liquids were initially developed for applications in electroplating and batteries due to their wide electrochemical window allowing their usage in redox reactions.[129] The first metal catalysed oxidation in an IL was reported in 2000,[130] where *p*-substituted benzaldehydes were oxidised to corresponding carboxylic acids using nickel(II)acetylacetonate [$Ni(acac)_2$] and molecular oxygen in [bmim][PF_6] at 60 °C. Common oxidants utilised in ILs are tabulated below (Table 1.13).

Table 1.13: Oxidants currently used in ILs[123]

Oxidants	Comment
O_2	Cheap and environment friendly, low solubility in ILs
aq. H_2O_2	Cheap and environment friendly, water may be unwanted in some cases
aq. NaOCl	Cheap and environment friendly, water may be unwanted in some cases
^{t}BuOOH	Relatively cheap, available as both aq. and anhydrous solutions
$PhI(OAc)_2$	Relatively expensive but easy to handle
$H_2NCONH_2.H_2O_2$	Water free peroxide source, readily soluble in many ILs
N-morpholine-*N*-oxide	Expensive, residual morpholine may be a problem

For a clean and green synthesis, oxidants should produce non-toxic by-products, or ideally water. Earle *et al.*[131] developed an oxidation method for alkylaromatic compounds using nitrate based ILs. Such ILs are termed as 'task specific ionic liquids' (TSILs) where IL is employed as media and reagent. 70-90 % yields were obtained in these reactions. Substituted benzyl alcohols were oxidised to their corresponding carbonyl compounds, using NaOCl and guanidium IL (**41**) (Fig. 1.17), at pH~8-9.[132]

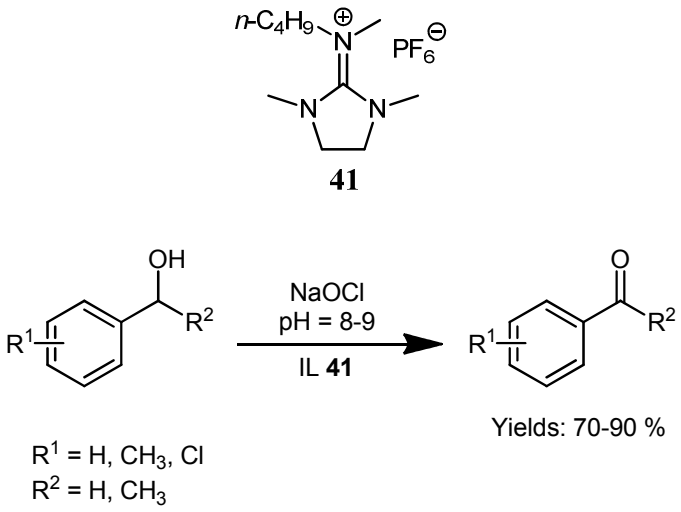
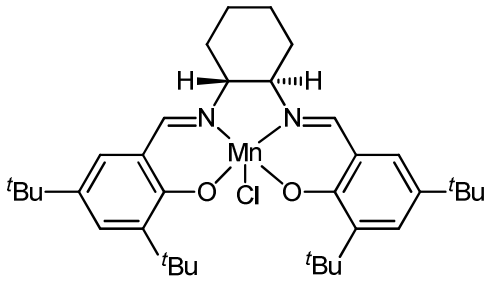


Figure 1.17: Guanidium IL for oxidation.[132]

A guanidium based IL was chosen for this reaction due to its greater stability under basic conditions. In this case, the IL also works as a phase transfer catalyst with 65-99 % reaction yields obtained. Similar oxidations were attempted with IBX and DMP using [bmim][BF_4] as a solvent to achieve > 90 % yields.[133]

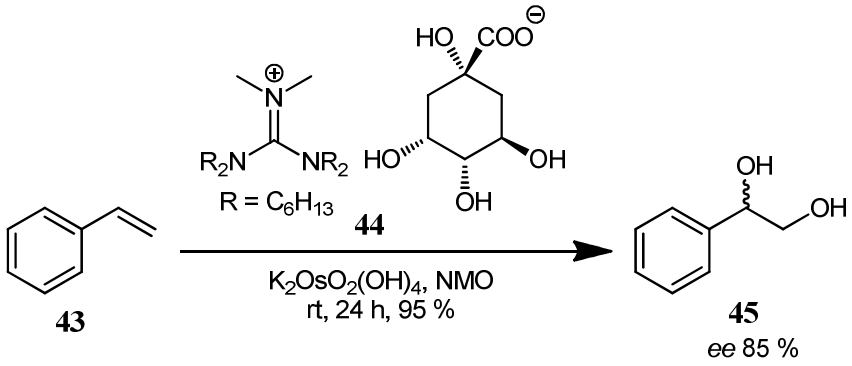
K. Tong *et al.*,[134] carried out epoxidation reactions using styrenes, pinene, norbornene in [bmim][BF_4] with tetramethylammonium bicarbonate and manganese (II) sulphate as a catalyst at rt. The reaction worked successfully, affording 98-99 % yields and the catalytic system could be recycled without loss in activity up to 5 times. Asymmetric epoxidations are extensively studied with ILs. As the Jacobsen epoxidation can occur even in unfunctionalised olefins, this is one of the popular methods of epoxidation. Song *et al.*[135] investigated the biphasic epoxidation of chromenes with chiral Mn^{III} (salen) (**42**) (Fig. 1.18) and NaOCl in mixture of [bmim][PF_6] and CH_2Cl_2 (1:4 ratio).



42

Figure 1.18: Mn^{III}-salen complex.[135]

The authors found an enhancement in catalytic activity upon addition of IL to DCM. With the IL, 86 % conversion was observed in 2 h, whereas it took 6 h for same conversion without the IL. In both cases 96 % enantiomeric excess was observed which reduced by only 6 % after the 5th cycle. Recently, asymmetric epoxidation of styrene derivatives was studied using 10 mol% silica supported Mn^{III}(salen) complex and NaOCl in [bmim][X]-DCM (X=PF_6, BF_4) mixtures with NH_4OAc as a co-catalyst.[136] After 2 h, 45-82 % yields with 65-95 % *ee* were obtained. The outcome of the process was the catalytic system could be re-used up to 4 times without any leaching of the catalyst. Chiral building blocks available from Nature are often applied for chiral induction. Interestingly, guanidium quinate (**44**), was synthesized and employed as a solvent in the asymmetric dihydroxylation of styrene (**43**) (Scheme 1.5) and 1-hexene.[137]



Scheme 1.5: Chiral induction by IL in asymmetric dihydroxylation.[137]

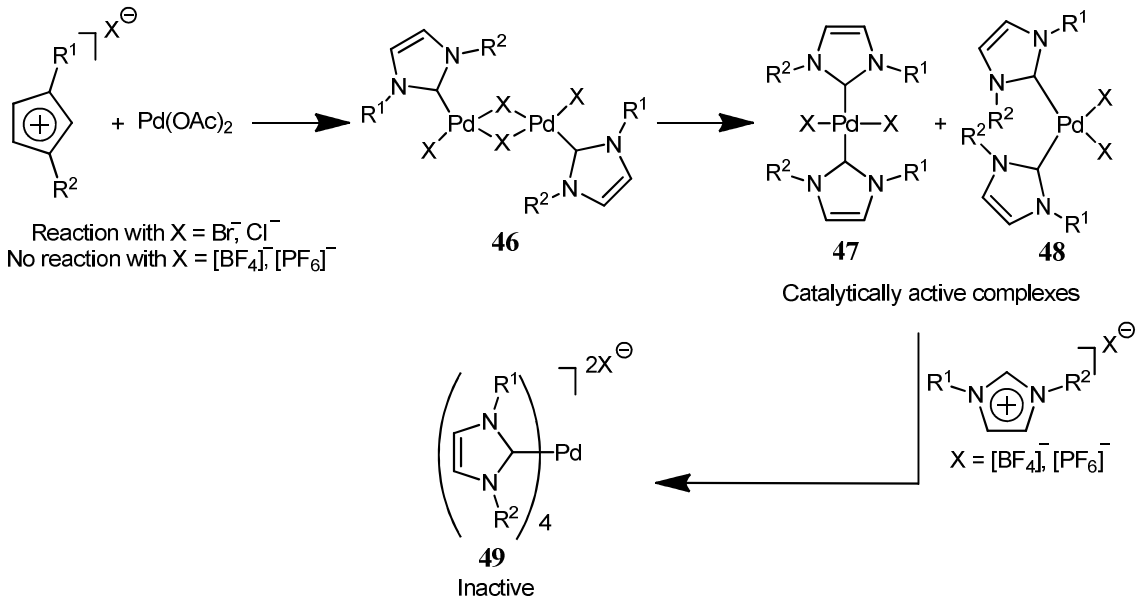
The catalytic system utilised was $K_2OsO_2(OH)_4$/NMO and reactions were performed at rt. Remarkably, 85 % enantiomeric excess and 95, yield was obtained when styrene was the substrate. A similar yield (92%) was found using 1-hexene, although the *ee* decreased to 72%.

1.8.4. Carbon-carbon coupling reactions:

Coupling reactions have had a huge impact on synthetic chemistry over the last thirty years. Large carbon scaffolds can be built using metal catalysed C-C coupling reactions, generally in excellent yields. Hence, by appreciation of the usefulness of the three main Pd-catalysed coupling reactions, a Nobel prize (chemistry) was awarded to their inventors in 2010. Heck, Suzuki, Negishi, Stille and Sonogashira couplings present easy procedures to serve the purpose of C-C linkage, usually with low catalyst loading (2-5 mol%). The ionic liquids possessing high polarity, density and viscosity interact with metal catalysts in a different way to conventional solvents. The hydrogenation section 1.8.2 (*vide supra*) shows that ionic liquids can be employed in metal catalysed reactions with successful recycling. C-C coupling reactions in ILs were studied by many researchers to investigate the effect of the IL-catalytic system on the yield, enantioselectivity and stability of the catalytic system.

1.8.4.1 Heck coupling.

Imidazolium based ILs have been studied in detail for past two decades. Their utility in Pd-catalysed reactions, whether hydrogenation or C-C coupling reactions, was investigated revealing that at high temperatures under basic condition imidazolium moieties form carbene complexes with palladium.[138] Mostly this reduces the yield of the reactions but in some cases better results were observed. The carbene complexes (**47**, **48**) were formed and found to give better results than the original palladium catalyst during the coupling of various aryl halides and acrylates (Scheme 1.6).[139]



Scheme 1.6: Formation of Pd-carbene complex.[139]

Reactions in [bmim]Br gave quantitative conversions (100 %) with ~ 99 % selectivity to the *trans* product. Investigation revealed that complex formation takes place only in the presence of halides and when [bmim][BF_4] was employed in the reaction, no carbene complex was formed giving poor conversions. A range of Pd catalysts were tested for their catalytic activity in the coupling of styrene (**43**) and chlorobenzene.[140]

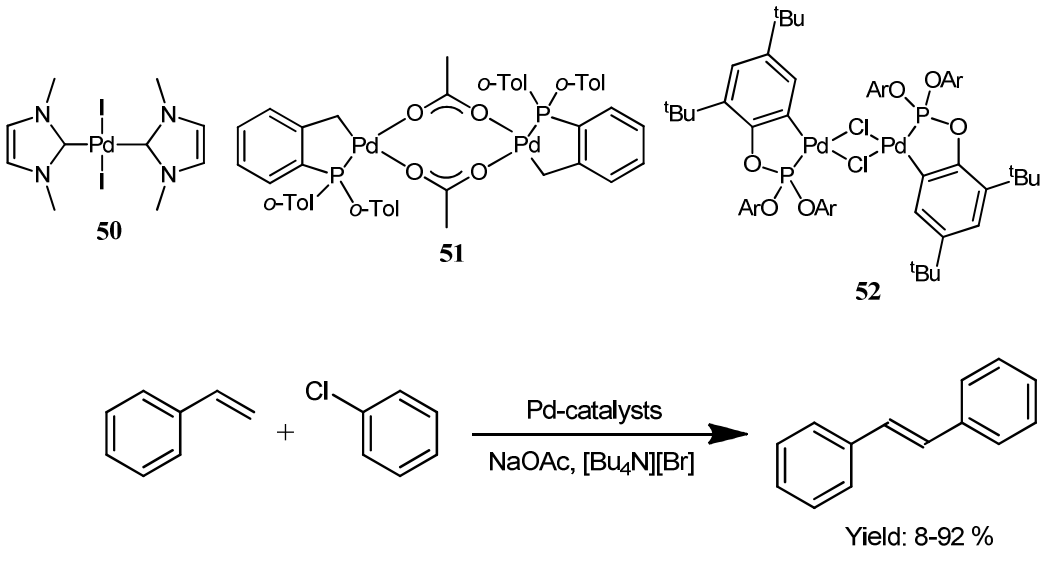


Figure 1.19: Pd-carbene complexes for Heck coupling.[140]

Pd-carbene complexes that were used are shown in Fig. 1.19. The results for these reactions are shown in Table 1.14. Provided that the chlorobenzene possesses low reactivity towards Heck coupling, even in conventional solvents (especially when $PdCl_2$ and $Pd(OAc)_2$ used as catalysts) tetrabutylammonium bromide (TBAB) has yielded satisfying results.

Table 1.14: Heck coupling of chlorobenzene and styrene in $[Bu_4N][Br]$.[140]

Catalyst	**Yield** (%)	
	DMF	**$[Bu_4N][Br]$**
$PdCl_2$	0	50
$Pd_2(dba)_3$	2	8
$Pd_2(dba)_3$ + 2 eq. $P(^tBu)_3$	72	92
$Pd(OAc)_2$ + 3 eq. $P(o\text{-Tol})_3$	29	46
$Pd(PPh_3)_4$	17	65
(**51**) + 5 eq. $[AsPh_4][Cl]$	41	84
(**50**)	3	51
(**52**)	5	49

Reaction conditions: Styrene (1.5 eq.), NaOAc (1.2 eq.), Pd (2 mol%), 150 °C, 18 h

Recently, ligand free Heck arylation was successfully demonstrated by Petrvic *et al.*[141] They synthesized triethanolammonium acetate to employ ligand-free Heck coupling. The reaction was carried out with iodo/bromobenzene and alkylacrylates using 2 mol% $PdCl_2$ and [TEA][OAc] at 110 °C with quantitative yields (>90 %). The authors concluded that the IL in this case acted more than a medium and worked as a base, precatalyst, and mobile support for the active Pd species. Further studies revealed that cations and anions were not distinctive as such still molecule showing high dipole moment and also behaved like a molecular solvent due to strong hydrogen bonding (Fig. 1.20).

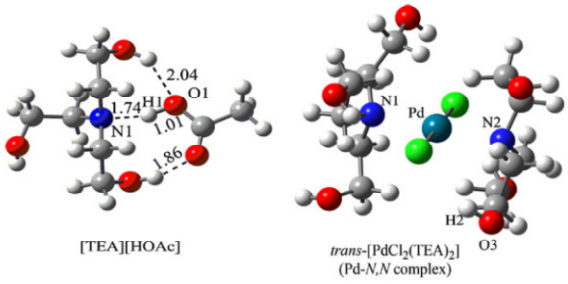
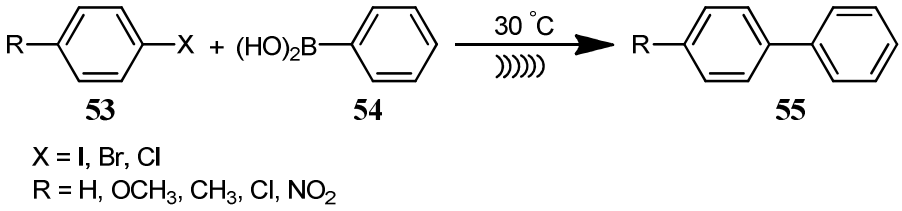


Figure 1.20: X-ray models of triethanolammonium acetate and its Pd-complex; (left-intramolecular H-bonding, right-precatalyst)

1.8.4.2 Suzuki coupling.

Coupling of aryl/vinyl boronic acid with aryl/vinyl halide catalyzed by a palladium complex is known as Suzuki coupling.[142] This reaction enables the linkage of aryl, vinyl, benzyl, allyl and alkyl groups (cf Heck coupling). Several papers have described the Suzuki reaction using [bmim] ILs and Pd catalysts bearing phosphanes,[143] nitrogen compounds[144] and carbenes.[145]

The reaction of bromobenzene with phenylboronic acid in benzene, catalysed with $Pd(PPh_3)_4$ and K_2CO_3, gave a 88% yield in 6 h, while the same reaction in [bmim][BF_4] gave a 93% yield of the desired product in 10 minutes with a high turn over number.[146] Microwave/ultrasound assisted reactions are generally clean and can be put forward under 'green' chemistry due to their environment friendly energy efficiency. Shrinivasan *et al.*[144a] performed coupling of a range of halobenzenes (**53a-k**) with phenylboronic acid (**54**) in [bbim][BF_4]/MeOH mixture under ultrasonic irradiation at 30 °C (Scheme 1.7).



Scheme 1.7: Sono-chemical Suzuki reaction in [bbim][BF_4]/MeOH.[144a]

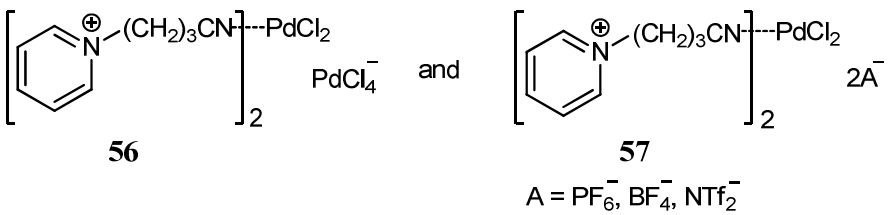
Palladium acetate was employed as a catalyst and 40-93 % yields were obtained as shown in Table 1.15.

Table 1.15: Ultrasonic Suzuki cross-coupling of halobenzenes with phenyl boronic acid in [bbim][BF_4]/MeOH.[144a]

No.	Substrate	**Time** (min)	**Yield** (%)
1	Iodobenzene (**53a**)	20	92 (**55a**)
2	4-Methoxyiodobenzene (**53b**)	20	93 (**55b**)
3	4-Chloroiodobenzene (**53c**)	30	85 (**55c**)
4	4-Nitroiodobenzene (**53d**)	30	82 (**55d**)
5	Bromobenzene (**53e**)	45	82 (**55e**)
6	4-Methoxybronobenzene (**53f**)	10	85 (**55f**)
7	4-Nitrobromobenzene (**53g**)	20	90 (**55g**)
8	Chlorobenzene (**53h**)	60	42 (**55h**)
9	4-Nitrochlorobenzene (**53i**)	30	65 (**55i**)
10	4-Chlorotoluene (**53j**)	60	52 (**55j**)
11	2,4-Dinitrochlorobenzene (**53k**)	90	42 (**55k**)

Reaction conditions: 0.5 g [bbim][BF_4], 1 mL MeOH, 0.001 g $Pd(OAc)_2$

To achieve better immobilisation of Pd complex in ionic liquid, Dyson *et al.*[147] synthesized pyridinium based ILs containing the coordinating nitrile functional group.



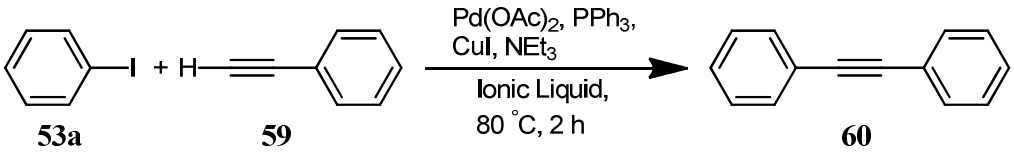
56 **57**

Figure 1.21: Interaction between nitrile functionalised IL and $PdCl_2$.[147]

Coupling of iodobenzene (**53a**) and phenylboronic acid (**54**) was carried out in these ILs. The nitrile groups coordinate with $PdCl_2$ forming a pre-catalyst (Fig. 1.21) and good yields (81-88 %) were achieved with the catalyst found to be air stable. Leaching of the catalyst during work-up was reduced compared to $[BuPy][NTf_2]$.

1.8.4.3 Sonogashira Coupling.

Sonogashira coupling is recognized as a powerful synthetic tool for the formation of asymmetrically substituted acetylenes.[148]The reported publications using ILs show improved results compared to traditional solvents.[149-151] Kmentova *et al.*[149] performed coupling of iodobenzene (**53a**) and phenylacetylene (**59**) in various imidazolium based ILs with $Pd(OAc)_2/PPh_3$ as a catalyst, CuI as a co-catalyst and NEt_3 (TEA) as a base (Scheme 1.8).



Scheme 1.8: Sonogashira coupling of iodobenzene and phenylacetylene[149]

The results obtained are tabulated below (Table 1.16).

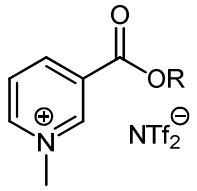
Table 1.16: Yields of Sonogashira coupling in different ILs.[149]

Entry	Ionic liquid	Yield (%) (60)
1	[bmim][PF_6]	97
2	1st recycle	93
3	2nd recycle	67
4	3rd recycle	58
5	4th recycle	52
6	[bmim][BF_4]	99
7	[hmim][PF_6]	95
8	[hmim][BF_4]	96
9	[bbim][BF_4]	97

Reaction conditions: 4 mol % $Pd(OAc)_2$, 4 mol% CuI, 0.4 mL TEA, 80 °C, 2 h

Excellent yields (>90 %) were obtained for imidazolium ILs and experiments with recycled catalyst showed a gradual decrease in yield which was due to catalyst leaching during work-up.

Many attempts have been made to carry out coupling without Cu catalyst because in some of the cases Glaser-Hay coupling can occur under Sonogashira conditions giving rise to unwanted homocoupling products.[152] In 2002, Fukuyama *et al.*[153] carried out coupling of several aryl iodides and substituted acetylenes in [bmim][PF_6] with 5 mol% $PdCl_2(PPh_3)_2$ and Hünig's base. The authors obtained 85-97 % yields despite the absence of Cu catalyst. Often coupling reactions are carried out at higher temp. in the presence of base which can cause degradation or hydrolysis of the ionic liquid. Hence in such cases, reaction conditions demand robust ILs that can facilitate the reaction. Recently, Harjani and co-workers[154] synthesized nicotinate ester based ILs with the purpose to achieve stability for hydrolysis.



61a-d

R = *n*-Bu (**a**), *iso*Bu (**b**), *sec*-Bu (**c**), ^{t}Bu (**d**)

Figure 1.22: Nicotinate based ILs.[154]

Coupling was carried out with phenyl acetylene (**59**) and different aryl iodides (including **53a-b** and **53d**) in ionic liquids (**61a-d**) (Fig. 1.22) using $PdCl_2$ and TEA under ultra-sound irradiation. 78-93 % yields were obtained in these reactions in accordance with expected reactivities of electron donating/withdrawing substituents on phenyl iodide.

1.9 Introduction to the work in thesis:

Apart from synthetic usage, ionic liquids have a very widespread application window in nuclear fuel reprocessing,[155] solar thermal energy, electro-chemical devices,[156] cellulose processing,[157] etc. Along with physiochemical properties, the low toxicity and high biodegradability of ILs have created a keen interest in researcher's minds to test their 'green' applications in various fields.

Considering toxicity and biodegradability of our first generation ILs and for the preparation of extensive library of ILs, we planned to synthesize less toxic and readily biodegradable second generation ionic liquids. These ionic liquids were screened for antimicrobial toxicity and biodegradability. Their applications in dye sensitised solar cells (DSSCs), Tsuji-Trost reactions and hydrogenations were investigated, depending on the results of toxicity and biodegradation studies. The forthcoming chapters include results and discussions of synthetic methods, toxicological and biodegradation studies, applications in Tsuji-Trost, hydrogenation, Baylis-Hillman reactions, followed by an experimental section. The outcome of the project is concluded with the scope for future work presented at the end.

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Chapter 2

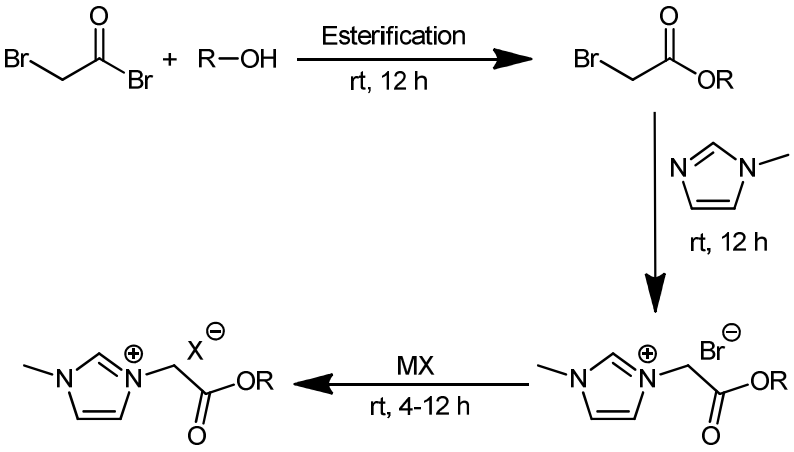
Synthesis and Characterisation of Ionic Liquids

2.1 Introduction:

With respect to the results obtained previously in our group, and following the Boethling's 'rules of thumb',[1] we planned the synthesis of achiral and chiral ILs which would exhibit low toxicity and be readily biodegradable. This structural design was based on the guidelines that ester and ether functionalities facilitate biodegradation.[2] (see section 1.7.8 for guidelines) Achiral ester and amide ILs and chiral monoester and diester ILs were synthesized. All of these compounds were either 1-methylimidazol-3-ium or 1-pyridinium based ILs with the synthetic route following a regular trend consisting of quaternarization of the nitrogen in an aromatic base followed by anion metathesis.

2.2 Synthesis of Achiral ester and amide based ionic liquids:

The synthetic route for achiral ILs involved three steps (Scheme 2.1). In the first step ester/amide functionality was generated by the acylation of alcohol/amine. The quaternarization of tertiary nitrogen from 1-methylimidazole/pyridine yields the halide IL in the second step. Finally, anion metathesis was carried out producing an IL with the desired counter anion. Scheme 2.1 depicts the synthetic route for achiral ester and imidazolium based ILs.[2d]



Scheme 2.1: General synthetic route for ester based ILs.

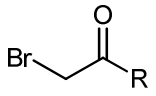
Once the alkylating agent is obtained, this can be reacted with a number of aromatic bases containing tertiary nitrogen atoms to prepare different ILs. The 1-methylimidazolium was

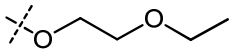
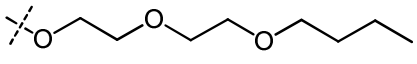
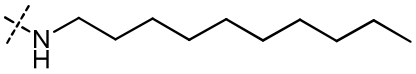
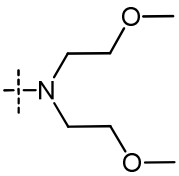
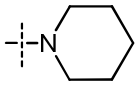
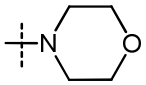
chosen as a target cation because of its robustness to many reaction conditions allowing for its usage in a wide range of applications. Although pyridine has been reported as susceptible to reduction,[3] the pyridinium based ILs were reported to be readily biodegradable[4] hence it was also chosen as a cation for study.

2.2.1. Preparation of the Alkylating Agent:

The first step i.e. ester/amide formation was achieved by acylation of the alcohol or amine. The reaction was carried out using DCM as solvent, TEA or Na_2CO_3 as base, and bromoacetyl bromide as the acylating reagent. Bromoacetyl bromide was added dropwise to the mixture of alcohol/amine and base in DCM at 0 to -5 $^{\circ}$C. There were two reasons to lower the temperature; (i) to quench the exotherm (ii) due to the two potential electrophilic sites in bromoacetyl bromide, unwanted by-products may be formed, especially in the case of the more nucleophilic amines. Acylation reactions are believed to occur through a addition-elimination mechanism.[5] During the reaction HBr is released and hence an acid binder was used, either TEA or Na_2CO_3. When TEA was used as the base, coloured final products were obtained whereas use of Na_2CO_3 produced colourless products. This may be explained by triethylammonium bromide having partial solubility in the organic layer leaving behind traces of bromide which could impart colour to the final compound, whereas NaBr does not dissolve in DCM and results in colourless products. The hydrolysis of bromoacetyl bromide was observed when the Schotten-Baumann procedure was applied to the reaction, hence Na_2CO_3 was used as a solid in these reactions. Moderate to high (67-98 %) yields were obtained for the acylation of both alcohols and amines giving products in liquid form at room temperature (Table 2.1).

Table 2.1: List of achiral bromoester/amides.



Compound	R =	Yield (%)
62		97
63		98
64		67
65		76
66		78
67		85

The reaction using triethylamine as a base was performed only in the case of **65** according to the literature method.[2d,6] All other alkylating agents were synthesized using Na_2CO_3 as a base.

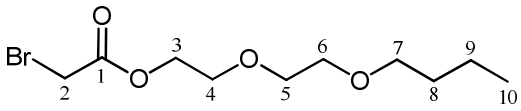


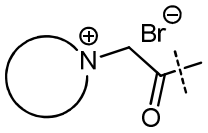
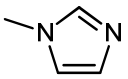
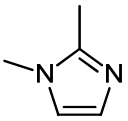
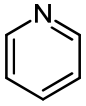
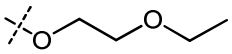
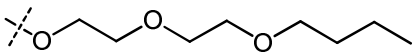
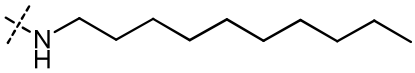
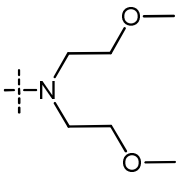
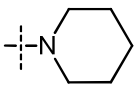
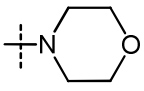
Figure 2.1: 2-(2-butoxyethoxy)ethyl-2-bromoacetate **63**.

The ^{1}H NMR for compound **63** shows a singlet at 3.82 ppm for the H2 protons (Fig 2.1). The peak for -CH_2 shows downfield shift due to the presence of two electron withdrawing neighbouring groups i.e. the bromide and carbonyl group which possess an electron withdrawing (-I) effect through σ bonds.[7]

2.2.2. Preparation of Bromide Ionic Liquids:

The synthesis of bromide ionic liquids was performed according to the literature method[2d,6] and involves the addition of 1-methylimidazole/1,2-dimethylimidazole or pyridine to a solution of alkylating agent in diethyl ether.

Table 2.2: Bromide ILs with different heterocycles; compound numbers in bold, and melting points are denoted in parentheses.

			
Side chain			
	91% (24-26°C)	-	-
	68a		
	90% (78-80°C)	-	-
	69a		
	90% (94-96°C)	91% (120-122°C)	97% (168-169°C)
	70a	**71a**	**72a**
	83% (68-70°C)	-	-
	73a		
	89% (96-98°C)	87% (135-137°C)	-
	74a	**75a**	
	85% (170-172°C)	95% (224-226°C)	94% (95-97°C)
	76a	**77a**	**78a**

Reactions were carried out at RT under nitrogen atmosphere producing the ILs in good yields (83-97 %) (Table 2.2). All ionic liquids were obtained as white or off white solids. Table 2 shows a wide range of melting points. All 1-methylimidazolium based ILs melt below 100°C except for **76a** compared to ILs possessing other heterocycles (pyridinium and 1,2-dimethylimidazolium) melt above 100°C except for **78a**. The range of high yields achieved with the reactions demonstrates the efficiency of the process. In this reaction heterocycles containing 3° nitrogen atoms displace the bromide from the alkylating agent and hence can be termed as a bimolecular substitution (S_N2) reaction. The reaction largely produces pure product, but, if required purification can be carried out simply by washing the product with dry diethyl ether. The reactions were also carried out using dry solvent under nitrogen atmosphere to minimize the contamination by moisture.

The ^{1}H NMR for compound **69a** shows (Fig. 2.2) the -CH_2 singlet for the H2 protons at 5.50 ppm. In the alkylating agent the peak appeared at 3.82 ppm indicating the stronger electron withdrawing effect by the imidazolium core. This fact is supported by the ^{13}C NMR showing significant shift of the C2 carbon signal from 25.85 ppm (alkylating agent **63**) to 50.14 ppm.

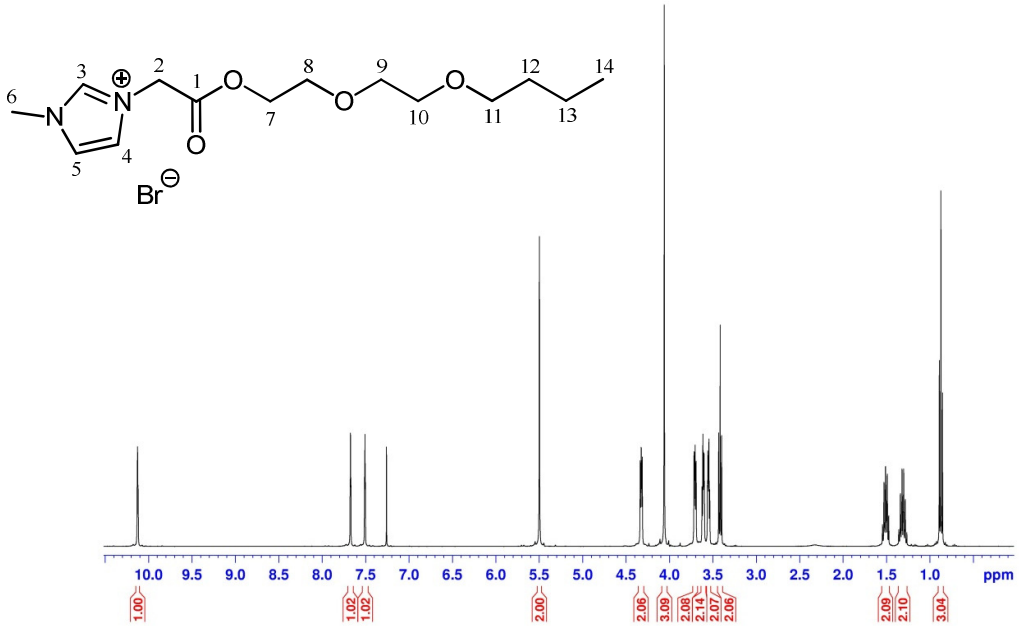


Figure 2.2: ^{1}H NMR of compound **69a**.

The imidazolium proton H3 (Fig. 2.2) appears as a singlet at 10.13 ppm, whereas H4 and H5 appears as triplets at 7.68 and 7.51 ppm both with J = 1.8 Hz. It was confirmed from the COSY spectrum that H3 couples with H4 and H5 but a singlet was observed due to a very low

coupling constant.[8] The methylene protons H7 and H8 shows triplets at 4.33 and 3.71 ppm respectively. They couple with a coupling constant of 4.8 Hz. The IR spectrum shows a peak at 1752 cm^{-1} indicating an ester group.

The amide side chain in the ILs **73a**-**78a** is not symmetrical, the methylene groups shows distinctive peaks in the ^{1}H NMR spectrum due to restricted rotation around C-N bond (Fig. 2.3).

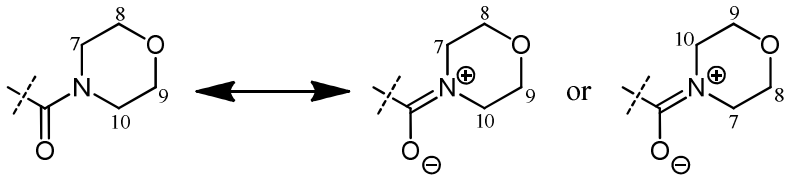


Figure 2.3: Isomers formed due to restricted rotation.

2.2.3. Anion Metathesis:

Anion metathesis alters the properties of bromide ionic liquids and thus enables their utility in different applications.

(1) [NTf_2] ILs:

The [NTf_2] ILs were synthesized according to the literature procedure[2d,6] involving addition of solid $LiNTf_2$ to a solution of bromide IL in distilled water. The reactions were maintained at room temperature for 4 h and the $[NTf_2]^-$ ILs were washed with distilled water 3-4 times to remove any unreacted starting materials. However, in the case of **69b** and **73b** the reaction time was increased (12 h) to ensure completion. The ILs **68b**, **69b**, **71b**-**73b**, **75b**-**78b** were synthesized in moderate to good yields (62-97 %). Compounds **71b**, **72b** and **76b** were found to be white solids with melting points 53-55°C, 70-72°C and 63-65°C respectively. The success of the anion metathesis can be confirmed by NMR. In the ^{1}H NMR spectrum, the H3 proton shifts upfield due to slight shielding by $[NTf_2]^-$ counter ion and in the ^{13}C NMR spectrum, two carbon atoms from the anion couple with neighbouring -F atoms leading to a quartet with a coupling constant of J = 319 Hz (Fig. 2.4).

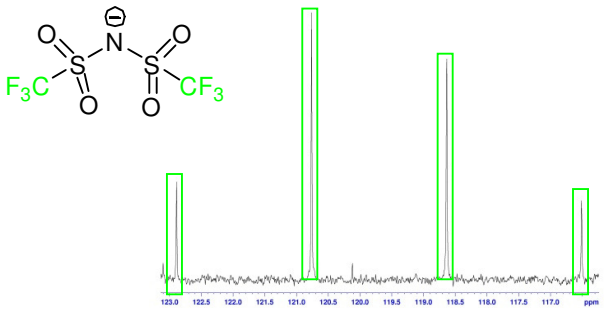


Figure 2.4: A quartet shown by -CF_3 in ^{13}C NMR spectrum.

The IR spectra also confirm the metathesis by showing a strong absorption for -NSO_2 group in 1370-1335 and 1170-1155 cm^{-1} region.

(2) [$OctOSO_3$] ILs:

Octylsulfate ILs were prepared with little modification to literature procedure[2d,6] which states the reaction mixture should be heated at 60°C for 2 h. However, heating was determined as not necessary for the completion of reaction. Hence after the addition of solid sodium octylsulfate to the solution of bromide IL in distilled water, the reaction was stirred at RT for 12 h. The ILs **71c**-**73c**, **77c** and **78c** were prepared by this method in moderate yields (54-79 %). The [$OctOSO_3$] salts are known to increase the biodegradability of ILs as demonstrated by N. Gathergood *et al*.[9-12] However, a major drawback of synthesising the [$OctOSO_3$] ILs is the cost of the sodium octylsulfate. Hence a cheaper method for its synthesis was adopted and developed.[13] 1-Octanol was dissolved in dichloromethane, followed by addition of chlorosulfonic acid at 0 to -5°C. A subsequent neutralization of the mixture with $NaHCO_3$ and filtration with methanol resulted in the synthesis of sodium octylsulfate on a relatively large scale (65 mmol) in excellent yield (95 %).

(3) Iodide ILs:

Usually, the synthesis of iodide ILs involve the alkylation of 1-alkylimidazole with alkyl iodide.[14] In our case, the iodide ILs were prepared by a step down synthesis using [NTf_2] salts. The method was developed in our laboratory which includes the addition of tetrabutylammonium iodide (TBAI) to the solution of [NTf_2] IL in DCM. The reaction mixture was stirred at RT for 3 h. The volatiles were removed by means of rotary evaporation, with the residue dissolved in distilled water then backwashed with DCM to remove the tetrabutylammonium *bis*(trifluoromethylsulfonyl)imide ($TBANTf_2$) salt. Removal of water by

rotary evaporation permits the synthesis of iodide IL. The compounds **69d** and **73d** were prepared by this procedure to obtain yellow and brown solid products in 66 and 74 % yields possessing melting points of 52-54°C and 48-50°C respectively. The ^{1}H NMR in both cases shows the H3 protons shift slightly downfield indicating deshielding by the iodide anion. The metathesis also can be confirmed with the absence of -CF_3 quartet in the ^{13}C NMR spectrum.

(4) [$N(CN)_2$] IL:

The dicyanamide IL **69e** was synthesized according to the literature procedure.[2d] This method involves the addition of solid sodium dicyanamide [$NaN(CN)_2$] to a solution of bromide IL in acetonitrile at RT under nitrogen. The reaction was stirred at RT for 4 days to obtain an off white solid in 97 % yield with a melting point of 58-60°C. Signals corresponding to the C15 and C16 carbons (Fig. 2.5) do not show up in the ^{13}C NMR spectrum however the anion metathesis can be confirmed by the significant absorption band present at 2231 cm^{-1} in the IR spectrum.

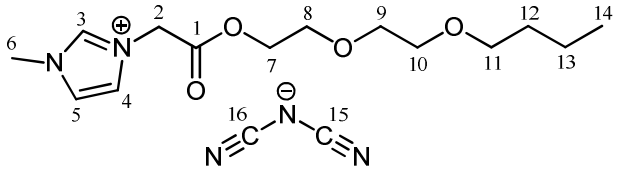


Figure 2.5: 3-{2-[2-(2-butoxyethoxy)ethoxy]-2-oxoethyl}-1-methyl-1H-imidazol-3-ium dicyanamide (**69e**).

(5) [OAc] IL:

Acetate IL **73f** was synthesized according to the literature procedure.[15a] A solution of AgOAc in water was added slowly to a solution of bromide IL **73a** in water at RT with the reaction flask covered with aluminium foil to avoid photodegradation of the silver acetate. The reaction was stirred for 2 h, filtered to remove the AgBr precipitate and the resultant aq. solution was treated with charcoal to remove any coloured impurities. A colourless oil was obtained in 65 % yield. ^{1}H NMR shows a H3 peak giving a broad singlet at 11.17 ppm but with integration 0.59 in comparison to H4 and H5. This observation was surprising as H3 proton has shown extreme downfield shift. In [emim][OAc], the proton at same position shows a singlet at 10.36 ppm.[15b] The H2 protons integrate to 1.59 (should be 2) which indicates that these protons are partially bonded to acetate anion (Fig. 2.6).

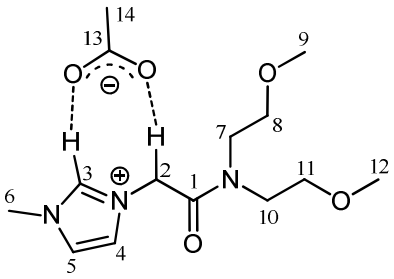


Figure 2.6: Plausible partial bonding between $[OAc]^-$ and cation.

2.2.4 Effect of anion on chemical shift:

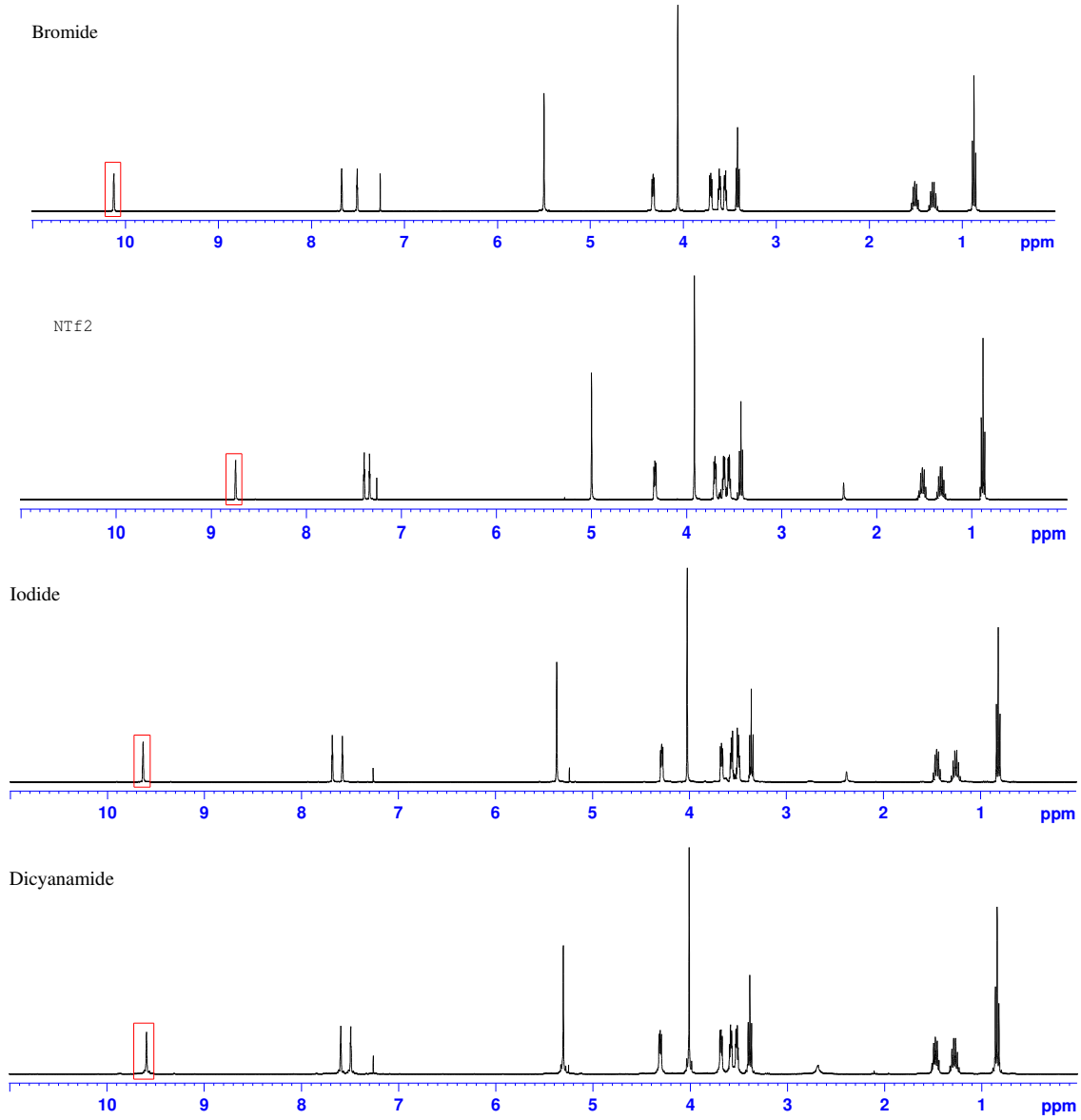


Figure 2.7: H3 proton shift in **69a-b** and **69d-e.**

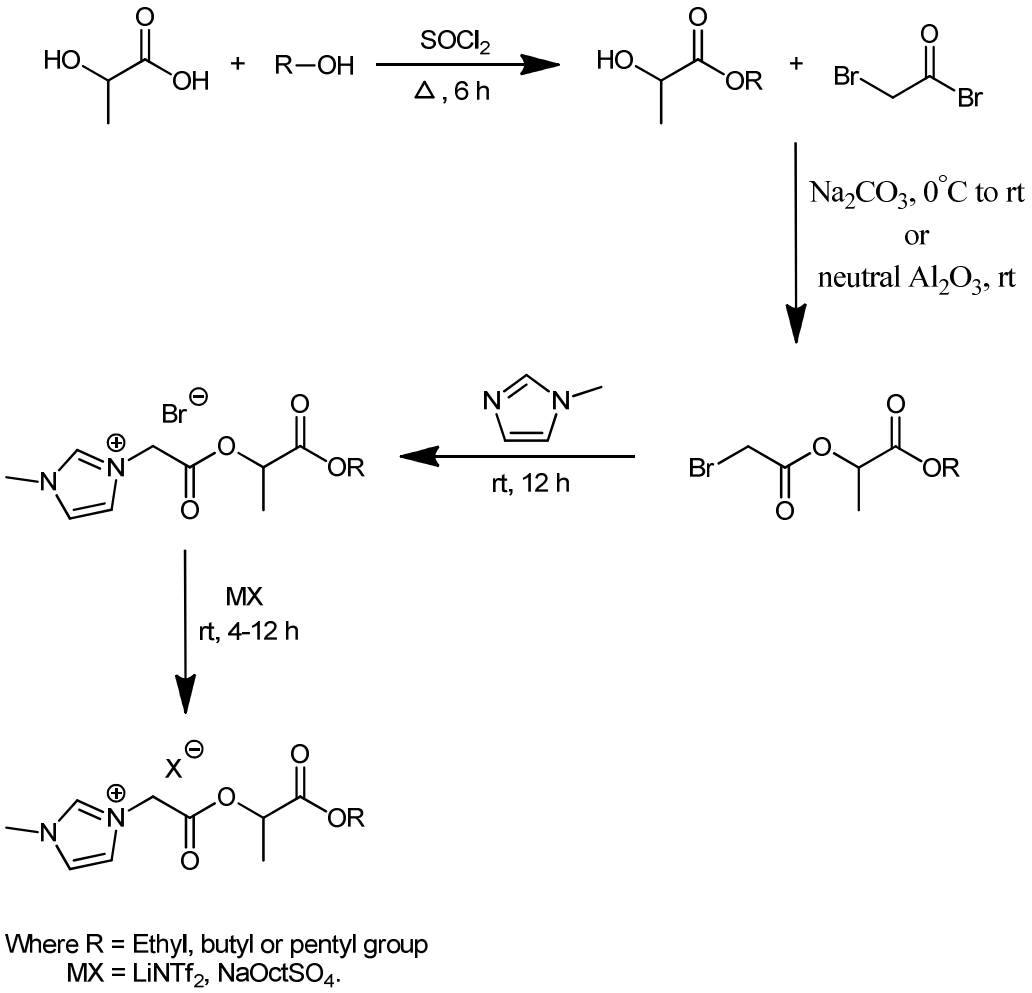
Fig. 2.7 illustrates the acidic proton shift in imidazolium moiety by different anions due to shielding or deshielding effects. From the spectra one can conclude that bromide has a significant deshielding effect on proton whereas [NTf_2] seems to have a shielding effect. This is due to the localised charged on bromide showing better charge separation whilst the negative charge in bulky [NTf_2] is delocalised which causes shielding of proton. Less deshielding is observed in the case of iodide due to large size of the anion. This feature may also be used as a rough estimation of the varying degree of charge separation in the anions.

2.3 Synthesis of Chiral Lactate and Mandelate based ionic liquids:

Lactic and mandelic acids are both bio-renewable resources with lactic acid found in sour milk products such as yogurt, koumiss, laban etc. while industrially produced by the fermentation of carbohydrates,[16a] and mandelic acid derivatives found naturally in almonds, peaches, wheat leaves, grapes etc[16b] and industrially, through the hydrolysis of mandelonitrile by acid catalyst or enzymes.[16c] Although the derivatives of these feedstocks are released into the environment from a number of sources, no significant concentrations in the soil or water are found thus suggesting rapid metabolism with the metabolic pathways of mandelates discussed in a review by C. Fewson.[16b] Hence usage of such renewable feedstocks in the synthesis of ILs satisfy 3rd, 7th and 10th principles of green chemistry.

2.3.1 Lactate based ILs:

Lactate based ILs were synthesized according to the synthetic route depicted in Scheme 2.2 comprising of four steps.

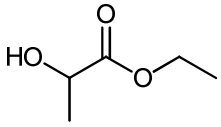
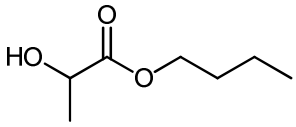
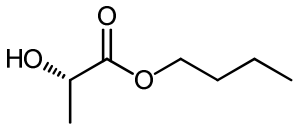
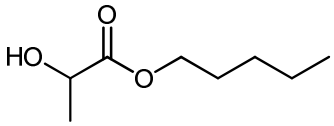


Scheme 2.2: Synthetic route for Lactate based ionic liquids.

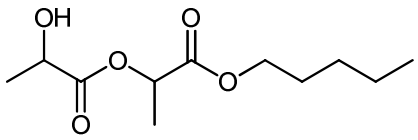
2.3.1.1 Fischer-Speier esterification:

In this step the lactic acid was converted into an alkyl ester by Fischer-Speier esterification.[17] The substrate was dissolved into excess alcohol followed by a slow addition of thionyl chloride to the reaction mixture which was heated to reflux for 6 h.[18] As an equilibrium reaction, analysis by TLC showed unreacted lactic acid. The reaction was then quenched with water followed by repetitive extraction with ethyl acetate however, in the case of ethyl esters, ethanol was removed by rotary evaporation prior to extractions. Table 2.3 shows the esters synthesized with this method.

Table 2.3: Yields for lactate esters.

Compound	Structure	Yield (%)
79		56
80		66
81		71
82		76

As butanol and pentanol have higher boiling points (117 and 137°C, respectively), removal required azeotropic distillation with hexane. Compound (**83**) (Fig. 2.8) was also recovered during the purification of (**82**).



83

Figure 2.8: 1-oxo-1-(pentyloxy)propan-2-yl 2-hydroxypropanoate.

The moderate range of yields (56-76 %) can be attributed to the equilibrium of the reaction.

In the ^{1}H NMR spectrum of **82** the H4 protons behave as non-identical and show geminal coupling. Each proton resulting in a pair of triplet of doublets thus appearing as 12 lines at 4.16 ppm (Fig. 2.9).

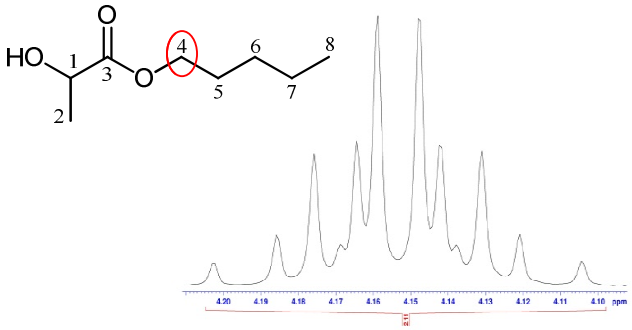
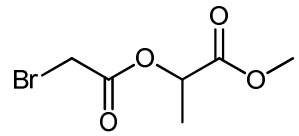


Figure 2.9: Coupling pattern by diastereotopic protons.

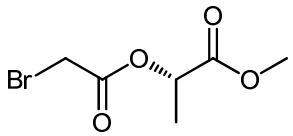
2.2.1.2 Preparation of Alkylating Agent:

The synthesis of the alkylating agent by the acylation of the secondary alcohol was carried out by two different methods. The methyl, butyl and pentyl esters (**84**, **85** and **88**-**90**) were prepared using a Na_2CO_3 method whereas ethyl esters were synthesized using an Al_2O_3 method.[19] The alumina method is quicker and easier while the Na_2CO_3 one is cleaner but both methods gave comparative yields (Table 2.4). The alumina method includes the addition of bromoacetyl bromide (2.0 eq.) to a mixture of the secondary alcohol and Al_2O_3 (1.5 eq.) at RT. This reaction mixture was sealed with a stopper and maintained at RT (unstirred) for 3 h. The RM was washed and filtered with EtOAc which was then removed by distillation to yield the final product.

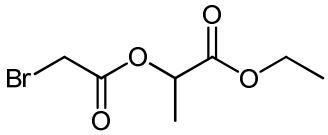
Table 2.4: Yield for bromoesters.



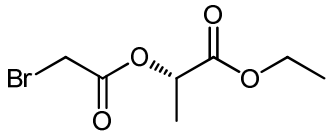
84 (32%)



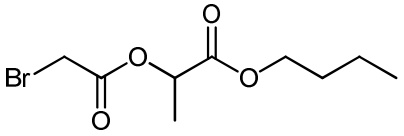
85 (37%)



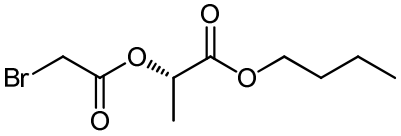
86 (82%)



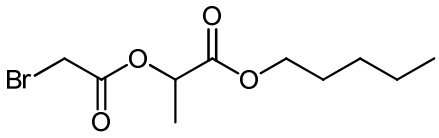
87 (85%)



88 (85%)



89 (80%)



90 (81%)

The low yields for (**84**) and (**85**) (i.e. 32 and 37% respectively) can be attributed to the solubility of compounds in water (as being the methyl esters) which means they have been washed out during the aqueous wash cycle. Furthermore, this observation was consistent with the literature.[6] All compounds (**84**-**90**) were obtained as liquids at room temperature. The acylation can be confirmed by ^{1}H NMR with the presence of the methylene peak at H1 (Fig. 2.10) around 3.80-3.90 ppm or with the two distinct peaks for esters (C2 and C5) in the ^{13}C NMR spectrum. A general trend shows C5 is more deshielded than C2.

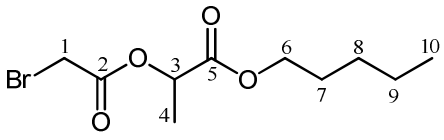
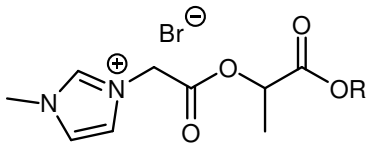


Figure 2.10: Pentyl-2-[(2-bromoacetyl)oxy]propanoate (**90**).

2.3.1.3 Preparation of Bromide IL:

The synthesis of the bromide salt was carried out according to the literature method[2d] as discussed in section 2.2.2. Compounds **91a**-**97a** were synthesized in good yields (74-94 %) (Table 2.5). Only **92a** was found to be a solid with a melting point of 110-112°C whereas **96a** was obtained as a gel.

Table 2.5: Bromide ionic liquids. (stereochemistry is denoted in parentheses).



Compound	R	Yield (%)
91a	Methyl (*RS*)	87
92a	Methyl (*S*)	75
93a	Ethyl (*RS*)	74
94a	Ethyl (*S*)	74
95a	Butyl (*RS*)	89
96a	Butyl (*S*)	75
97a	Pentyl (*RS*)	94

All three enantiopure compounds (i.e. **92a**, **94a** & **96a**) were found to be laevorotatory for Na-D line at 20°C. The ^{1}H NMR spectrum for **92a** (Fig. 2.11) exhibits two sets of doublets for H5 protons, each one showing geminal coupling with J = 17.6 Hz which indicates that both H5 protons are non-identical.

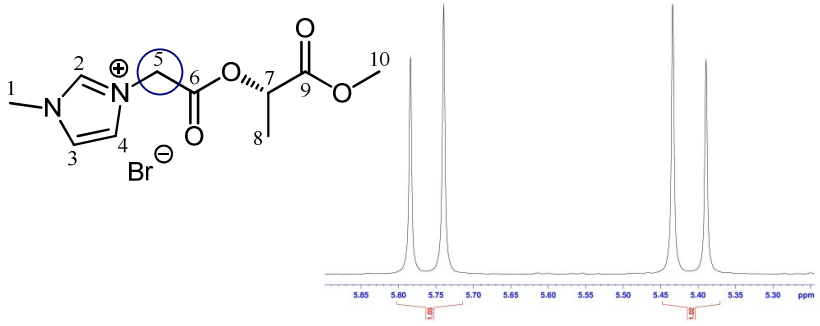


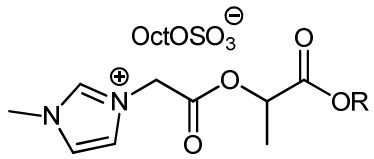
Figure 2.11: Distereotropic protons showing roofing/tilting effect.

It is noteworthy that such distereotropic signals were not observed in alkylating agent **85** despite having the same chiral centre. The $\Delta\upsilon/J$ value is 8 in this case hence it is a first order spectrum.[8]

2.3.1.4 Anion Metathesis:

The lactate based ILs were synthesized for the purpose of biodegradation studies and so mainly [$OctOSO_3$] salts were prepared as opposed to a wide spectrum of salts with different counterions. The compounds **91c**-**97c** were synthesized (Table 2.6) according to literature procedure[2d] as discussed earlier in section 2.2.3.2.

Table 2.6: [$OctOSO_3$] ionic liquids. (stereochemistry is denoted in parentheses).



Compound	R	Yield (%)
91c	Methyl (*RS*)	76
92c	Methyl (*S*)	79
93c	Ethyl (*RS*)	85
94c	Ethyl (*S*)	81
95c	Butyl (*RS*)	81
96c	Butyl (*S*)	82
97c	Pentyl (*RS*)	87

All compounds were obtained as liquids in good yields (76-87 %). The aromatic H2 protons showed a slight upfield shift (200 Hz) in the ^{1}H NMR spectrum than their corresponding bromide ILs. The infra-red spectra exhibits the presence of -S=O with a sharp band at ~ 1050 cm^{-1}.

2.3.2 Mandelate based ILs:

The synthesis of mandelic acid based IL was carried out in five steps (Scheme 2.3). As the starting materials **98** and **99** (Fig. 2.12) are expensive, it was decided to synthesize them and the mono-substituted mandelic acids **100**, **101**, **102**, **103** were bought in from Sigma-Aldrich.

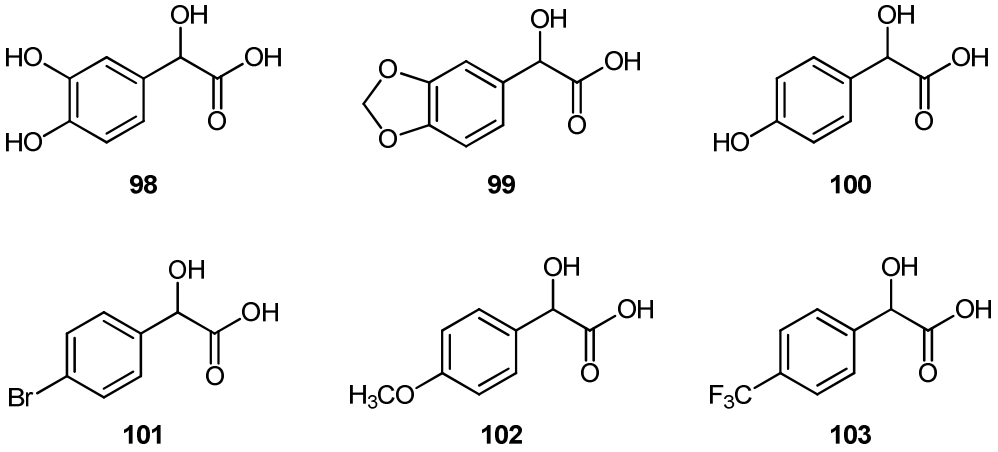
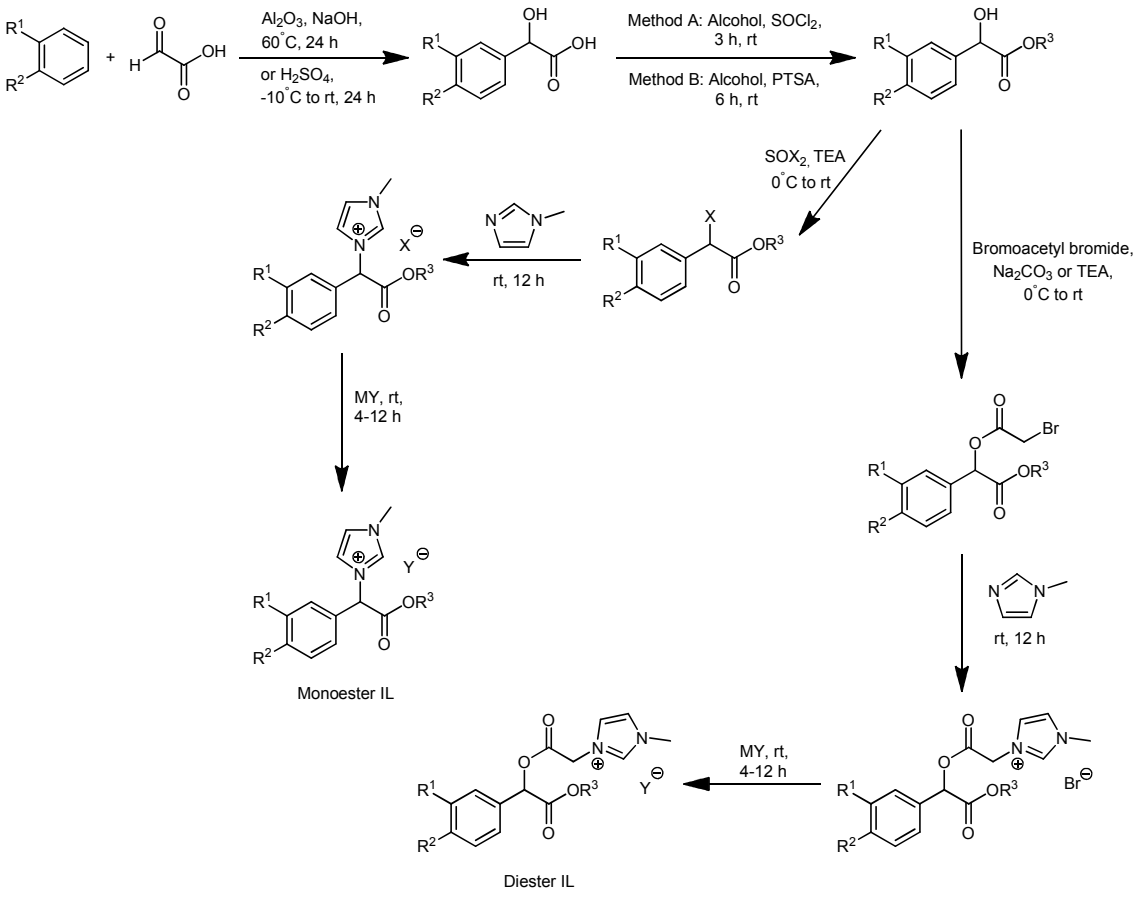


Figure 2.12: Substituted mandelic acids.

The second step involved the conversion of the acids into esters by Fischer-Speier method. Here onwards the IL synthetic route splits into two branches. In route A, the ester was halogenated at the α-position with thionyl halide. The S_N2 reaction of this α-halo ester with 1-methyimidazole/pyridine then allows the preparation of the bromide monoester IL which can be subjected to anion metathesis to tune the properties of the IL. In route B, the secondary alcohol in ester was acylated using bromoacetyl bromide and base. The resultant diester then can react with 1-methyimidazole/pyridine to give the bromide diester IL and subsequent anion metathesis gave the IL with the desired anion. Although the first monoester IL was obtained serendipitously, this class was found to possess low toxicity which will be discussed in chapter 3. The comparison of toxicity and biodegradation data of both monoester ILs and their diester counterparts will enable us to comment firmly on the role of the additional ester group.



Scheme 2.3: General synthetic route for imidazolium based mono- and diester ILs.

2.3.2.1 Synthesis mandelic acids:

Carboxylic acids **98** and **99** were prepared according to literature methods[20] with slight modifications. The synthesis of **98** is comprised of electrophilic aromatic substitution of glyoxylic acid and catechol under basic conditions. This is also a modification of a Friedel-Craft reaction where glyoxylic acid is activated by neutral alumina (Fig. 2.13). A solution of catechol, glyoxylic acid (1.02 eq.) and neutral alumina (0.44 eq.) in aq. NaOH (1.77 eq.) was heated to 60°C for 24 h. Upon cooling the reaction mixture was filtered, acidified to pH ~ 4 and extracted with ethyl acetate to remove any unreacted catechol. The aq. layer was further acidified to pH 1 and extracted with ethyl acetate while the organic layer was evaporated and purified to obtain **98** as a brown solid in 67 % yield. In some cases, the alkaline reaction mixture was acidified directly to pH 1 and extracted repeatedly with toluene to remove the

unreacted catechol. The alkaline conditions enhance the electron rich character of the phenyl ring through the formation of phenoxide which activates both the *ortho* and *para* positions, however, only *para* substituted products were formed in the reaction which was consistent with the reference literature.[20]

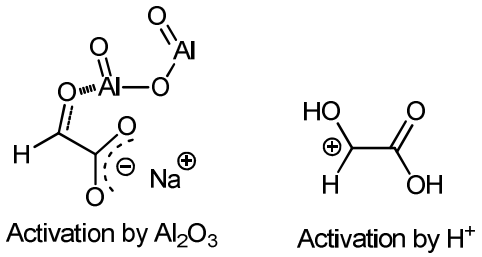
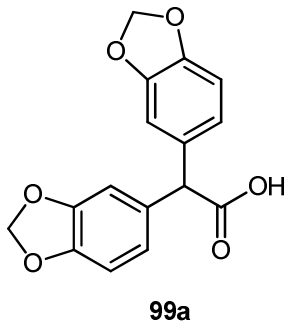


Figure 2.13: Activation of aldehyde by Lewis acid and proton.

Alternatively, the synthesis of **99** follows an electrophilic aromatic substitution in acidic conditions. Here, the catechol is protected with a methylene group hence alkaline condition would not affect the electronic character of phenyl ring. Activation of glyoxylic acid occures via protonation of the aldehyde (Fig. 2.13) and the process involves the addition of 1,2-(methylenedioxy)benzene to an aqueous mixture of glyoxylic acid (1.03 eq.), H_2SO_4 (1.83 eq.) at -10°C. The reaction mixture was then stirred at -10°C for 10 h and at RT for 14 h before extraction with ethyl acetate. The organic layer was concentrated and residue was purified by column chromatography (SiO_2, EtOAc:Hexane; 20:80) to obtain **99** in 72 % yield. A double addition compound **99a** was also isolated in 5 % yield (Fig. 2.14).



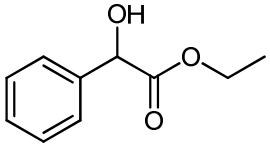
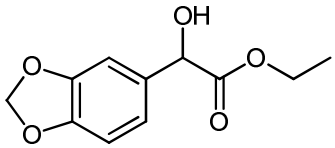
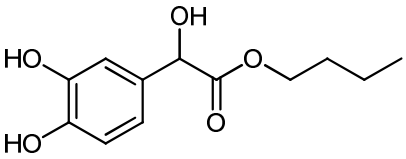
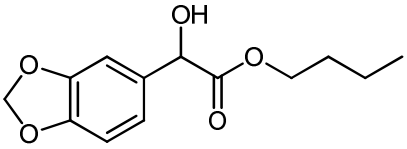
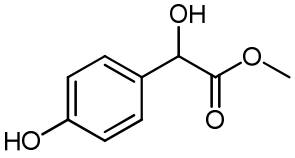
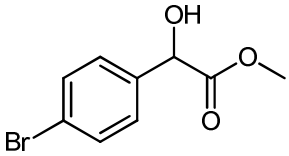
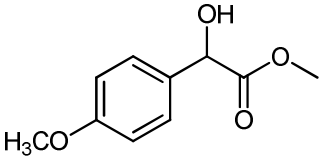
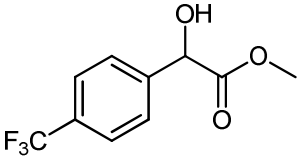
99a

Figure 2.14: 2,2-*bis*(2H-1,3-benzodioxol-5-yl)acetic acid (**99a**).

2.3.2.2 Fischer-Speier esterification:

A range of different esters was prepared by Fischer-Speier esterification methods.

Table 2.7: List of mandelate esters.

Compound	Structure	Yield (%)	Melting point (°C)
104		98	N.A.
105		79	42-44
106		54	88-90
107		95	47-49
108		80	135-137
109		98	56-58
110		97	37-38
111		97	48-50

The disubstituted mandelate esters were prepared by using thionyl chloride and monosubstituted esters were synthesized by using *p*-toluenesulfonic acid (PTSA). The list of esters with yield and melting points is tabulated below (Table 2.7). When thionyl chloride is added to the alcohol, HCl gas is liberated which acts as a catalyst for the reaction. Substituted mandelic acids were dissolved in excess of alcohol followed by slow addition of $SOCl_2$ (0.5 eq.) at RT, the reaction mixture was stirred at RT for 3 h and then solvent was removed by rotary evaporation. Residue was then dissolved in water and extracted with ethyl acetate. Purification of the crude product by column chromatography gave the esters (**105**-**107**) in moderate to good yields (54-95 %). The ^{1}H NMR spectrum of **107** shows a doublet of doublets for the H8 proton (Fig. 2.15) at 6.89 ppm with J = 8.4 and 1.8 Hz. As a result the H4 and H7 couple with H8 and exhibit two doublets at 7.00 and 6.73 ppm with corresponding coupling constants.

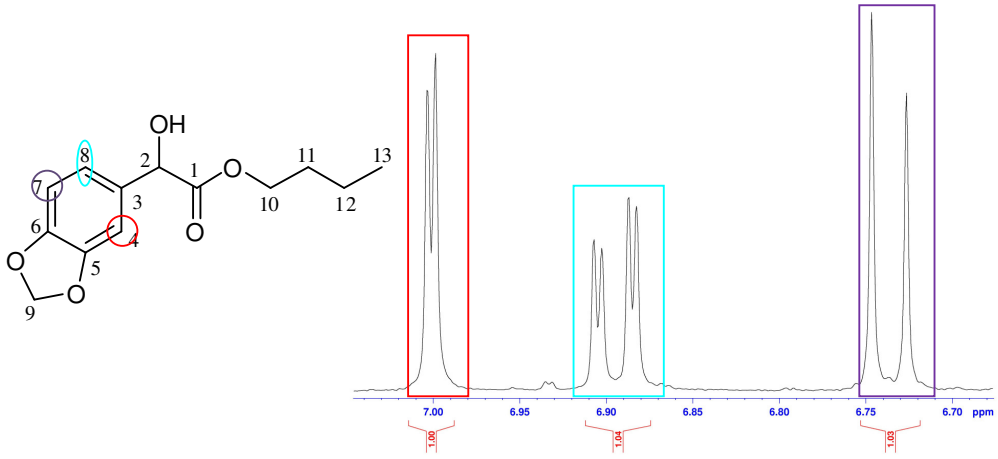


Figure 2.15: Butyl 2-(2H-1,3-benzodioxol-5-yl)-2-hydroxyacetate (**107**); and aromatic region from its ^{1}H NMR spectrum.

The H10 protons are diastereotropic hence undergo geminal coupling showing two sets of triplets of doublets i.e. 12 lines however the resolution of peaks are solvent dependent (Fig. 2.16).

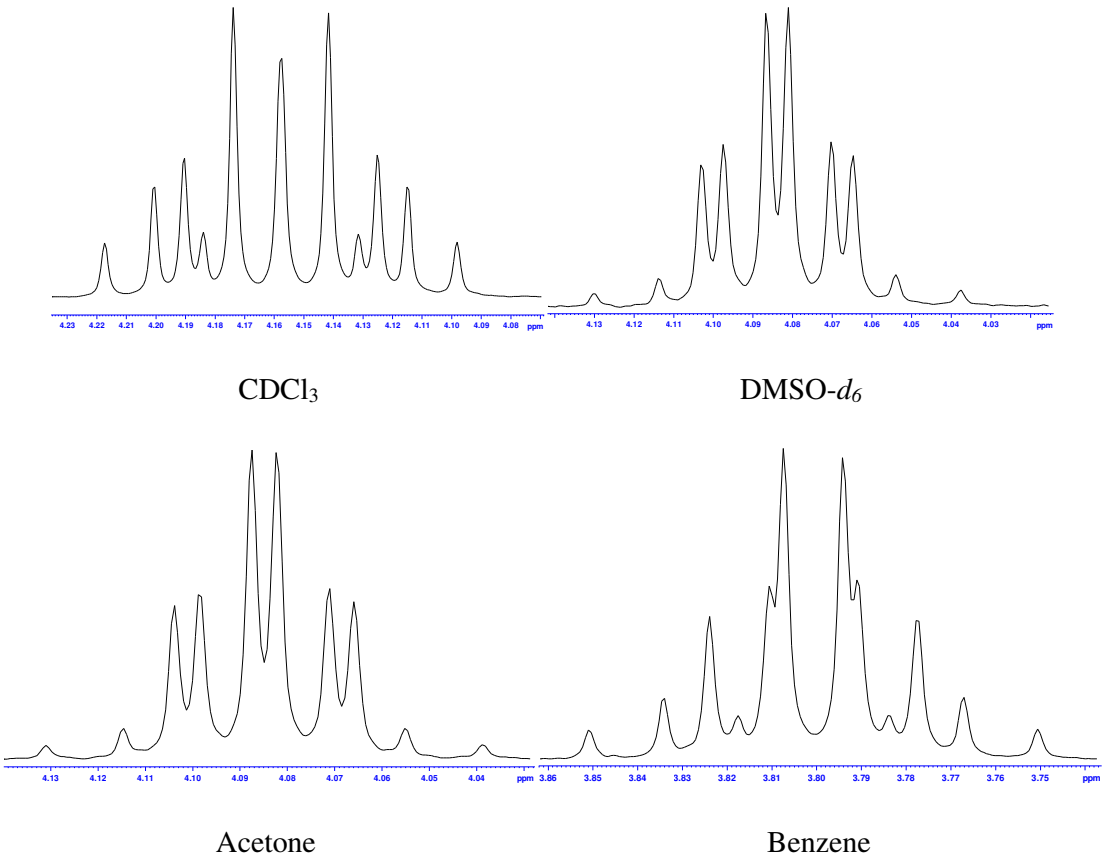


Figure 2.16: H10 protons resolution in different solvents.

A temperature experiment was run on a sample of **107** dissolved in DMSO-d6 to study the effect of temperature on the coupling pattern. The spectra were obtained between a range of 20-70°C. It was observed that with increasing temperature, two sets of triplets of doublets resolved into a simple triplet with a coupling constant 6.6 Hz. This observation was consistent with the fact that at higher temperatures the vibrational-rotational energy increases and σ-bonds rotate faster.[21] Thus, both H10 protons experience the same environment and behave identically (Fig. 2.17).

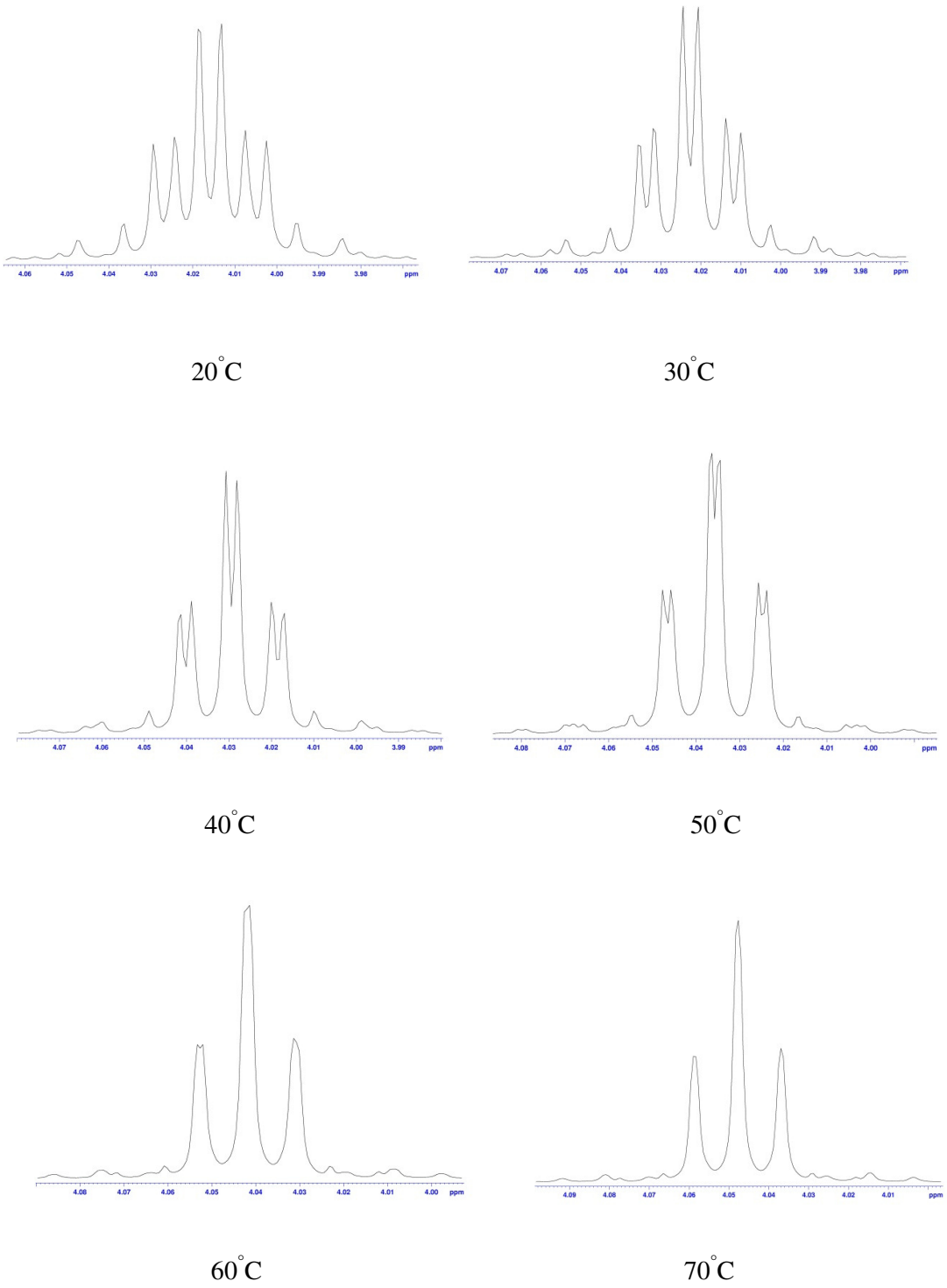


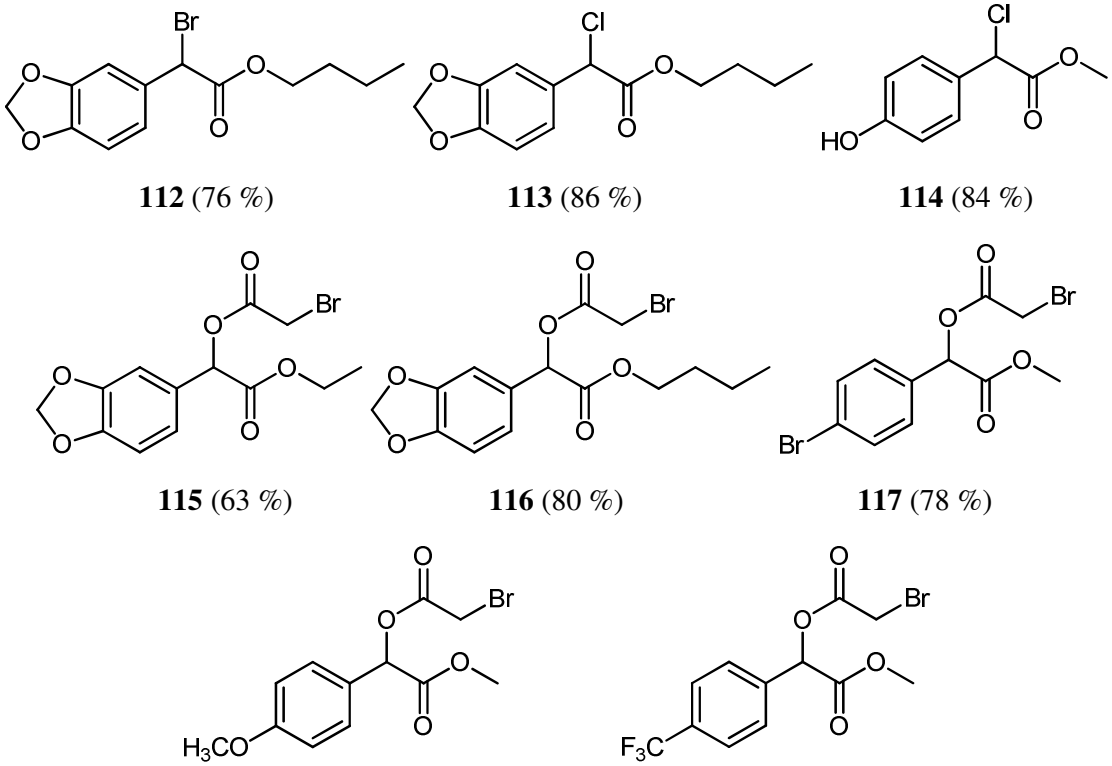
Figure 2.17: H10 peak at various temperatures in DMSO-d_6.

The PTSA method is quite similar to thionyl chloride method except a longer reaction time is required (6 h). Compounds **104** and **108**-**111** were synthesized using corresponding alcohol

and PTSA according to this method resulted in excellent yields (97-98 %). The mechanism of reaction includes the protonation of the carboxyl group followed by nucleophilic attack of the alcohol. A tetrahedral transition state breaks down into the products with subsequent removal of a water molecule. The reason for the low yield of **106** (54 %) could possibly be the solubility of the product in water due to two phenol and one alcohol group. Melting points of **106** (88-90°C) and **108** (135-137°C) observed are higher than expected due to hydrogen bonding.

2.3.2.3 Preparation of the Alkylating Agent:

This includes two methods, a α-haloester synthesis, and *O*-acylation to obtain α-bromodiester. α-Bromo- or chloroesters were prepared as precursors for monoester ILs whereas α-bromodiesters would yield diester ILs upon reaction with 1-methylimidazole/pyridine. In the case of the α-haloester, the halogenation at the benzylic position occurs via a *meso* substitution of the alcohol by the halide.



112 (76 %) **113** (86 %) **114** (84 %)

115 (63 %) **116** (80 %) **117** (78 %)

118 (67 %) **119** (75 %)

Figure 2.18: Mandelate alkylating agents; yields are shown in parentheses.

The process includes the addition of thionyl bromide/chloride (1.0 eq.) to the mixture of alcohol and TEA (1.2 eq.) in dichloromethane at 0°C and the reaction was maintained at RT for 3 h. The organic layer was then washed with water, the DCM removed by rotary evaporation and the residual product was purified by column chromatography (SiO_2, EtOAc:Hexane; 20:80) to obtain the product in good yield (76-86 %). All three compounds (**112**-**114**) (Fig. 2.18) were synthesized by this method and found to be liquids. The mechanism includes the nucleophilic attack of the alcohol on the thionyl halide which makes the alcohol a good leaving group. Triethylamine promotes deprotonation of alcohol, and subsequently, the halide attacks the bromanesulfinate intermediate (at benzylic position) from the rear side followed by departure of the leaving group (Fig. 2.19). An advantage of this process is that the by-products formed are Et_3HNBr and SO_2 which are easy to remove from the reaction mixture.

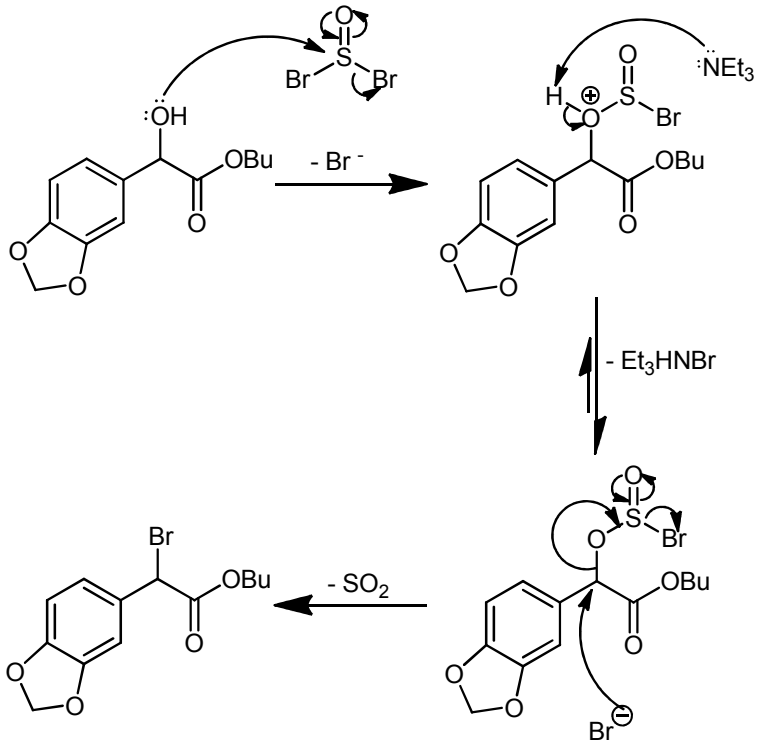


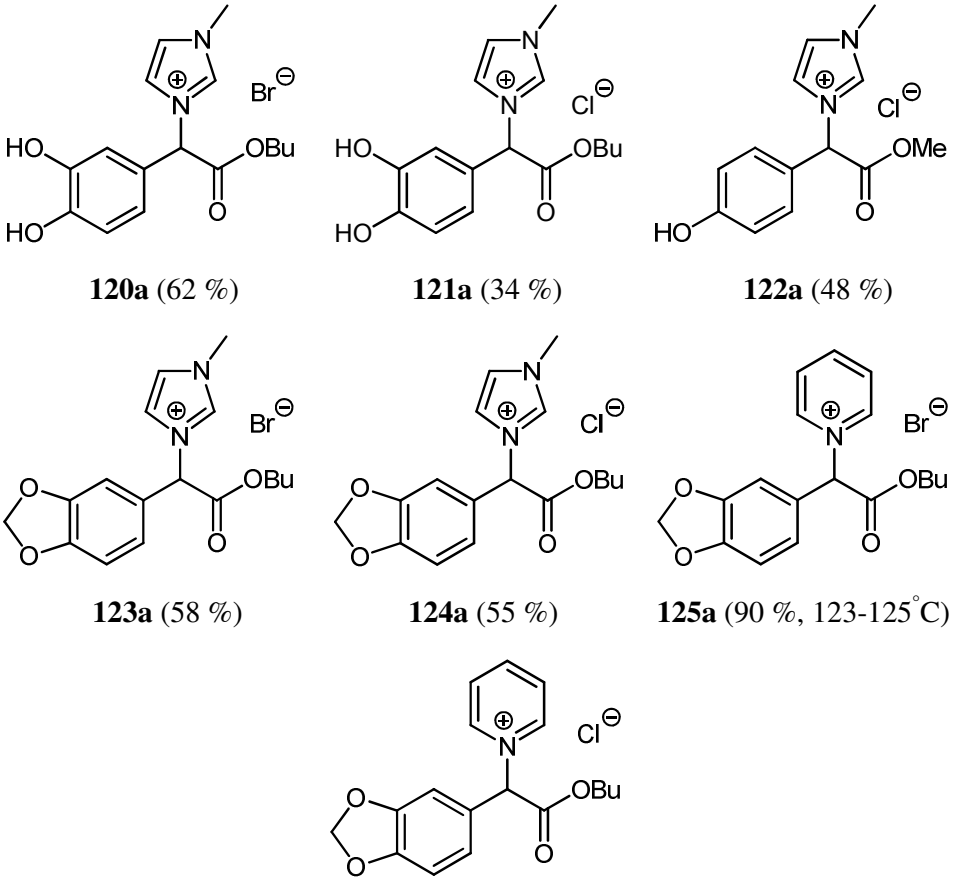
Figure 2.19: Mechanism of bromination.

Compounds **115**-**119** were prepared by acylation of the corresponding alcohols (**105**, **107** and **109**-**111**) according to the literature method[2d] as discussed in section 2.2.1. Triethylamine was applied as a base for **115** and **116** while **117**-**119** were prepared using sodium carbonate. The reactions resulted in moderate yields (63-80 %) giving all compounds in liquid state at RT.

2.3.2.4 Halide ILs:

(A) Monoester ILs:

Although, synthesized compounds are novel (*vide infra*), this class of compounds is known.[22] The monoester ILs **120a** and **121a** were prepared from **106** by one pot synthesis using thionyl bromide and thionyl chloride respectively (Fig. 2.20).[23] Butyl alcohol (**106**) was dissolved in a solution of 1-methylimidazole (2.0 eq.) in DCM followed by the dropwise addition of the thionyl halide (1.0 eq.) at 0°C. The reaction was maintained at RT for 24 h, concentrated by rotary evaporation and purified by column chromatography to obtain the ILs **120a** and **121a** in moderate yield (62 and 34 %, respectively).



120a (62 %) **121a** (34 %) **122a** (48 %)

123a (58 %) **124a** (55 %) **125a** (90 %, 123-125°C)

126a (87 %, 96-98°C)

Figure 2.20: Monoester halide ILs; yields and melting points (if solid at RT) are given in parentheses.

A low yield was obtained in the case of **121a** due to the use of 1.0 eq. 1-methylimidazole which functions as both an acid binder and nucleophile. So by this method a step was avoided

that saved time, energy and solvents. The compounds **122a**-**126a** were synthesized according to the literature procedure[2d] to obtain ILs in fair to excellent yields (48-90 %). In the case of **125a** and **126a** pyridine was employed as a nucleophile instead of 1-methylimidazole. These were the only solid products obtained among the monoester ILs with melting points of 123-125°C and 96-98°C, respectively (Fig. 2.20). The aromatic regions from the ^{1}H NMR spectra of **123a** and **125a** are shown below (Fig. 2.21).

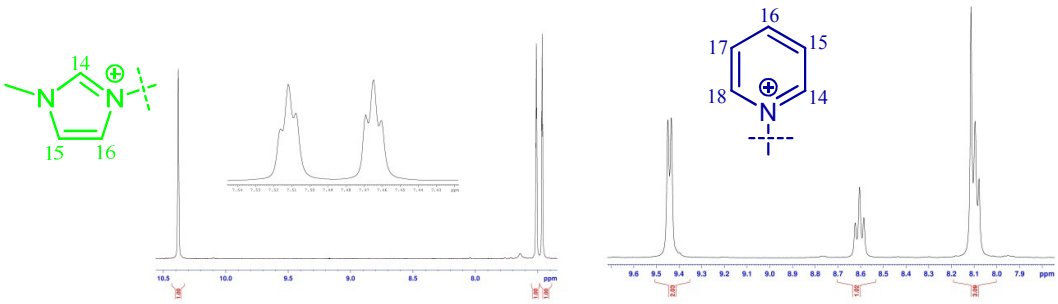
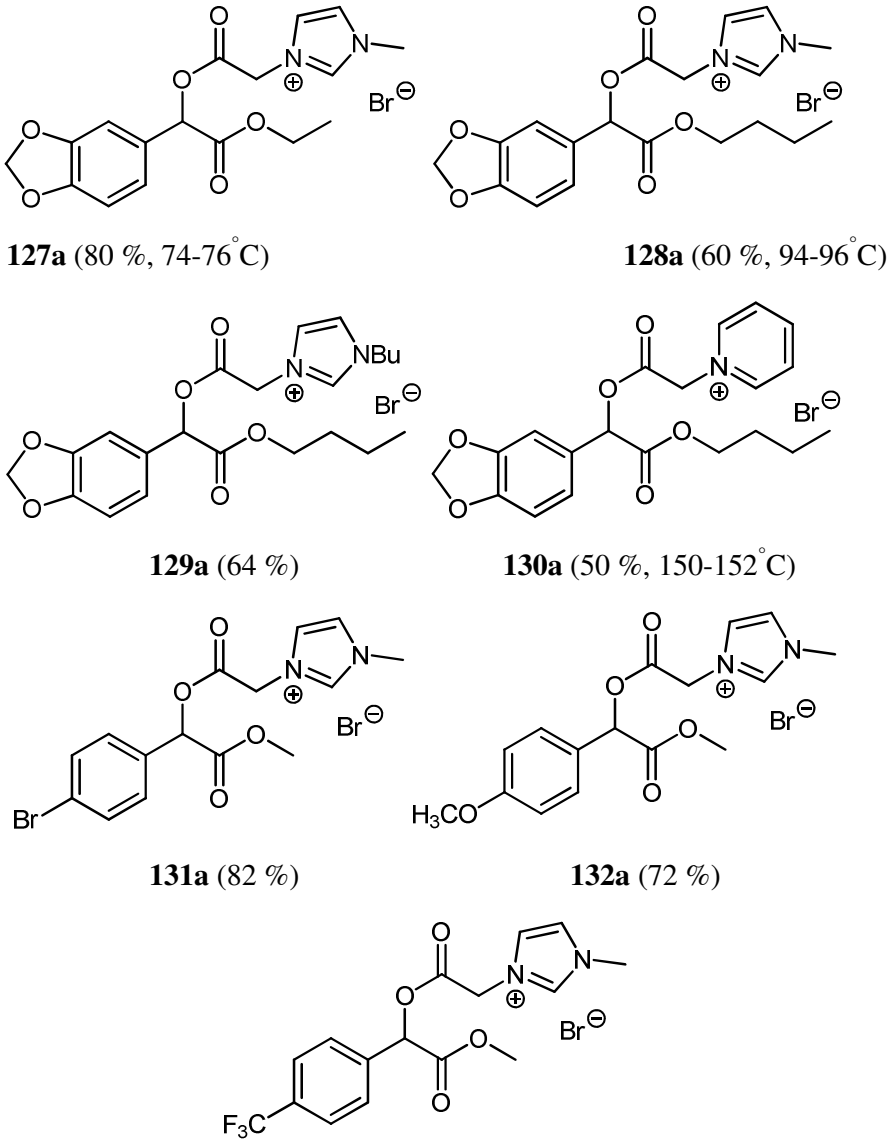


Figure 2.21: The aromatic region from ^{1}H NMR spectra of **123a** (left) and **125a** (right).

Already shown in section 2.2.2 is that bromide anions cause farthest shift in the case of the -NCHN- proton (except for the acetate anion). A similar shift was shown for pyridinium based ILs although not to the same extent as 1-methyl imidazolium ILs. The protons H14 and H18 (Fig. 2.21) appeared to be a doublet at 9.44 ppm with respect to H15 and H17 with J = 6.0 Hz. The apical proton H16 exhibited a triplet at 8.61 ppm with J = 7.6 Hz which must be a merged doublet of doublet shown for H15 and H17. The IL **123a** exhibit two triplets for H15 and H16 protons at 7.51 and 7.47 ppm respectively with J = 1.6 Hz. In this case both H15 and H16 couple and with H14 as well.

(B) Diester IL:

The diester ILs were prepared simply by S_N2 reaction of the alkylating agent and 1-methylimidazole/pyridine in diethyl ether.[2d] Out of seven compounds three were butyl esters, three methyl esters and an ethyl ester. In the case of **127a**, **128a** and **131a**-**133a** 1-methylimidazole while for **129a** and **130a** 1-butylimidazole and pyridine were utilised as nucleophiles respectively (Fig. 2.22).



127a (80 %, 74-76°C)

128a (60 %, 94-96°C)

129a (64 %)

130a (50 %, 150-152°C)

131a (82 %)

132a (72 %)

133a (88 %, 128-130°C)

Figure 2.22: Diester ILs; yields and melting points are shown in parentheses

Compounds **127a**, **128a**, **130a** and **133a** were found to be solid and all seven compounds were obtained in moderate to good yields (50-88 %). A low yield for **130a** (50 %) could not be improved by carrying out reaction at reflux temperature in diethyl ether and another reaction using THF as a solvent. This observation was in contrast with the yields of monoester ILs **125a** and **126a** where pyridine displaces secondary alkyl bromide/chloride resulting 90 % and 87 % yields respectively. The main reason to choose three different cation cores and esters was to compare the effects on toxicity and biodegradability of the ILs. Removal of traces of

water was performed under high vacuum (0.1 mbar) for 8-10 days, however, heating at ~ 40-50°C was required in some cases (e.g. **128a** and **130a**).

2.3.2.5 Anion exchange:

(1) [NTf_2] ILs:

Six triflimide salts (i.e. **123b**, **128b**, **129b**, **130b**, **132b**, **133b**) (refer to Fig. 2.20 and 2.22 for cation structure) were prepared in 66-94 % yields according to the literature method[2d] using $LiNTf_2$ and corresponding bromide ILs (Table 2.8).

Table 2.8: Yields for [NTf_2] ILs.

Compound	**Yield** (%)	**Melting point** (°C)
123b	66	46-48
128b	94	N.A.
129b	90	N.A.
130b	73	N.A.
132b	81	N.A.
133b	88	70-72

Out of six compounds, **123b** is a monoester IL while remainder are diester ILs. Compounds **123b** and **133b** were isolated as solids. Anion exchange was confirmed by a quartet given by -CF_3 groups in the ^{13}C NMR spectrum which was supported by the IR spectrum demonstrating -S=O stretching frequency at ~1050 cm^{-1}. An antimicrobial toxicity was assessed for these compounds (See Chapter 3).

(2) [$OctOSO_3$] ILs:

The octyl sulfate ILs were synthesized to evaluate the biodegradability. The process involves addition of solid $NaOctOSO_3$ to the solution of bromide IL in distilled water. After overnight stirring at RT, the aqueous layer was extracted with DCM. The removal of DCM by rotary evaporation resulted in [$OctOSO_3$] ILs (**120c**, **128c**, **129c**, **130c**, **132c**, **133c**) (Table 2.9) in good to excellent yields (41-91 %).

Table 2.9: Yields for [$OctOSO_3$] ILs.

Compound	Yield (%)	Melting point (°C)
120c	41	N.A.
128c	89	55-57
129c	82	49-51
130c	91	N.A.
132c	88	N.A.
133c	87	60-61

Compound **120c** gave low yield (41 %) due to aqueous solubility. This is also the only monoester [$OctOSO_3$] salt in the list. The ^{1}H NMR spectra for all compounds show similar coupling patterns for the cation core as shown for corresponding bromide salts. These compounds were tested for toxicity and biodegradability which will be discussed in chapter 3.

2.4 Miscellaneous:

2.4.1 Fluorinated ILs:

We aim to apply our novel ILs in a range of organic syntheses as solvents and/or catalysts hence it is important that they should endure the (harsh) reaction conditions for instance acidic, basic, photochemical reactions. The ^{1}H NMR spectrum of IL **73f** shows that the α-protons are partly abstracted by a base i.e. -OAc (pKa = 4.76).[24] Hence it was decided to replace the α-proton from monoester ILs with fluorine atom to induce extra chemical stability in IL. Additionally, a new class of compounds can be tested for toxicity and biodegradability. The compound **134** (Fig. 2.23) was prepared according to the literature method[25] using alcohol (**104**), diethylaminosulfur trifluoride (DAST) (**136**) (Fig. 2.23). The DAST (1.8 eq.) was added slowly to a mixture of **104** in DCM at 0°C and the reaction mixture was stirred at RT for 14 h. After work-up of the reaction, the procuct was obtained as a yellow oil in 51 % yield.

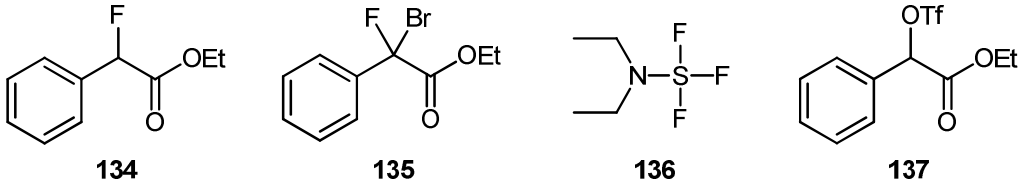


Figure 2.23: Fluorinated products, reagents and intermediates.

A synthesis of **134** was attempted by a reaction of acylated alcohol **137** with tetrabutylammonium fluoride in DCM but unreacted substrate was recovered even after heating at reflux for 2 h. The reaction of **104** with DAST goes through nucleophilic *meso* substitution where fluorine acts as a nucleophile. The ^{1}H NMR spectrum of **134** exhibit a doublet at 5.78 ppm for H2 proton with J = 48.0 Hz which represents a F-H coupling (Fig. 2.24).

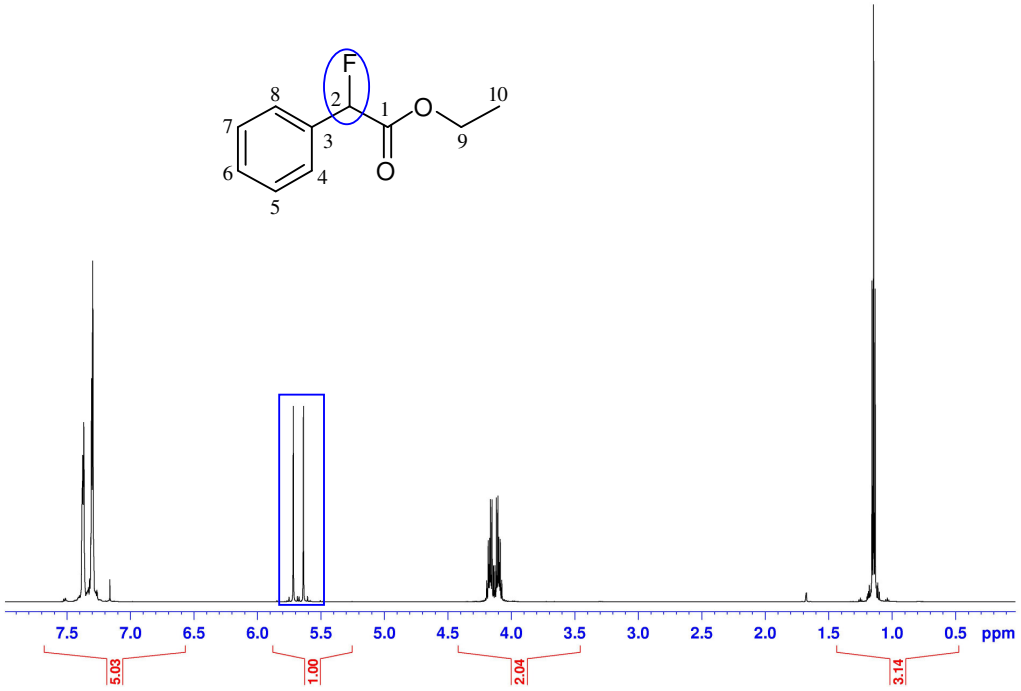


Figure 2.24: The ^{1}H NMR spectrum of compound **134**.

The compound **135** (Fig. 2.23) was synthesized by a photochemical reaction between **134** and *N*-bromosuccinimide (NBS) in CCl_4 at reflux.[26] A solution of **134** and NBS in CCl_4 was irradiated with 150 W mercury lamp at reflux temperature for 5 h (Fig. 2.25). It was observed after 1 h that the reaction mixture turned orange and then became yellow slowly within next 4

h. Reaction completion was confirmed by TLC. The rotary evaporation of the solvent and purification of residue by column chromatography (SiO_2, EtOAc:Hexane; 10:90) gave **135** in 75 % yield.

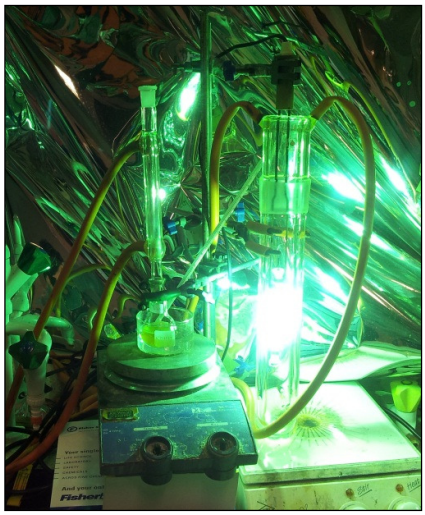


Figure 2.25: The experimental apparatus for photochemical bromination.

The process was reported for α-fluorination of ketones by irradiation with tungsten lamp[26] and was successfully applied for the ester **134** using mercury lamp. A limited number of publications available on geminal dihalogenation with two different halides indicate difficulty in synthesis of such compounds. Figure shows the ^{1}H and ^{13}C NMR spectra of compound **135**. The disappeared doublet from **134** for F-H coupling in the ^{1}H NMR spectrum and downfield shift (89.4 to 96.8 ppm) of C2 carbon in the ^{13}C NMR confirms the bromination at α-position (Fig. 2.26).

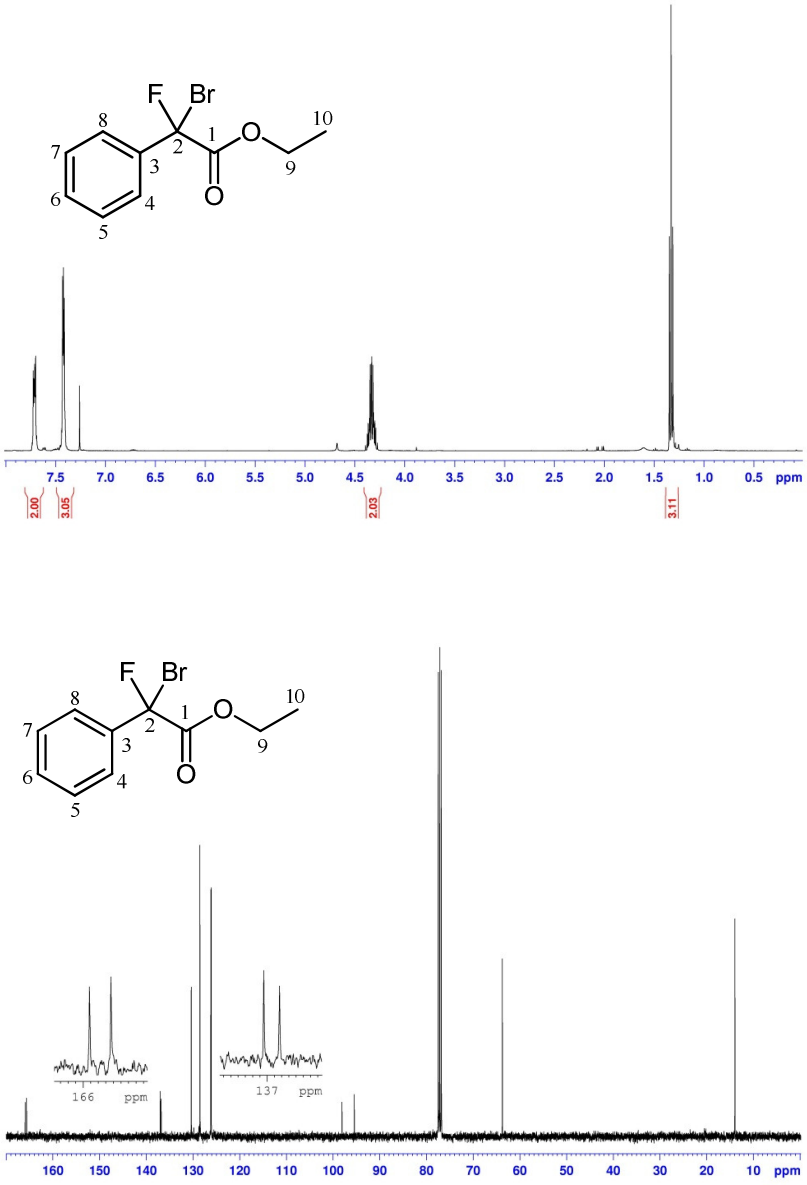


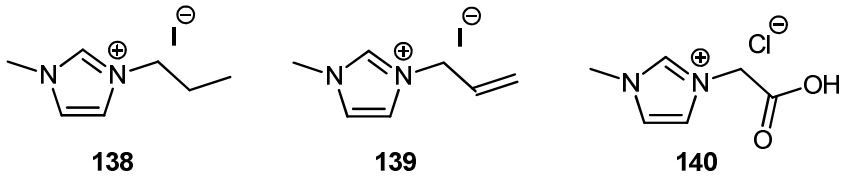
Figure 2.26: The ^{1}H and ^{13}C NMR spectra of compound **135**.

The ^{13}C NMR spectrum shows that C1, C3, C4 and C8 also couples with fluorine atom with J = 28.3, 21.7, 8.0 and 8.0 Hz, respectively.

2.4.2 Commercial ILs:

Ionic liquids **138**, **139** and **140** (Fig. 2.27) are known compounds. Compound **140** was synthesized in 45 % yield according to the literature procedure.[27] The process involves neat

reaction of 1-methylimidazole with chloroacetic acid at 70°C for 3.5 h. The NMR data are in agreement with the reference literature.[27]



138 **139** **140**

Figure 2.27: Compounds **138**, **139** and **140**.

Compounds **138** and **139** are commercially available ILs, commonly employed in dye sensitized solar cell (DSSC) research.[28] These were synthesized with slight modification to the literature procedure.[29] Therein, 1-propyl or 1-allylimidazoles were methylated with methyl iodide in toluene at RT for 32 h. In our case, 1-methylimidazole was alkylated with 1-propyl iodide and 1-allyl iodide in diethyl ether at RT for 12 h to obtain ILs **138** and **140** in 81 % & 76 % yields, respectively. The NMR data is in agreement with reported literature.[29]

2.5 Summary:

As per our plan to synthesize low toxicity and readily biodegradable ionic liquids, twenty seven achiral ILs were prepared that consists of eleven bromide, nine $[NTf_2]^-$, five $[OctOSO_3]^-$ and two iodide salts. Some representative examples, in particular, ester with ether side chain, open chain amide with ether, cyclic amide, cyclic amide with ether were submitted for antimicrobial toxicity screening at our collaborator's lab in Charles University (Czech Republic). Ionic Liquid samples (bromide and $[OctOSO_3]$ salts) were submitted for biodegradation studies to our collaborator's lab in CSIC, Barcelona (Spain). Compounds **69b**, **69d**, **73b**, **73d** were synthesized in bulk quantity to apply into DSSCs (dye-sensitized solar cells). Only one acetate salt (**73f**) was prepared using the literature method[15] to employ in the Tsuji-Trost reaction as a solvent. A new method of synthesis for iodide salts was discovered and applied for the preparation of **69d** and **73d** although, a point of concern is that this is a step down synthesis and increases the E-factor value. Future work should develop a direct synthesis of the iodide.

Twenty one CILs comprising of different classes were prepared including seven lactate based and fourteen substituted mandelate based ILs. Only bromide and $[OctOSO_3]$ salts of lactate ILs were prepared for toxicity and biodegradation studies. Two classes of mandelate ILs were synthesized (i.e. monoester and diester) in five steps. Fisher-Speier esterification was

followed for ester synthesis. Both chloride and bromide salts were prepared in the case of monoester ILs. The diester ILs can be further classified as disubstituted and mono substituted. The monosubstituted mandelates contained both electron donor and withdrawer substituents at *para* position.

Selected examples of each class of CILs were submitted for antimicrobial toxicity screening at our collaborator's lab in Charles University (Czech Republic) and (bromide and [$OctOSO_3$] salts) were submitted for biodegradation studies to our collaborator's lab in CSIC, Barcelona (Spain). CILs (**123a**, **125a**, **128a** and **130a**) were submitted for antialgal toxicity assay at our collaborator's lab in Aveiro (Portugal). Several CILs examples were submitted for additional antibacterial toxicity screening at high concentrations at DCU. The stability, toxicity, comparison of different methods to evaluate toxicity and biodegradation will be discussed in chapter 3.

2.6 Conclusion:

As discussed in section 1.1.1, atom economy is an important green chemistry metric and gives vital information about the greenness of a chemical procedure. The calculation of percentage atom economies for the procedures presented in this thesis were found to be as follows; (a) alkylating agents: 70-95 %; (b) bromide ILs: ~100 %; (c) $[NTf_2]^-$ ILs: 80-92 %; (d) $[OctOSO_3]^-$ ILs: 80-90 %. The new methods for synthesis of iodide ILs from [NTf_2] salts showed low atom economies. i.e. 44 % for **69d** and 42 % for **73d**.

While evaluating the chemical procedure in terms of atom economy, ease of reaction work-up, energy requirements, use of bio-renewable sources, it can be said that these chemical procedures are 'green'. Although the synthesis of intermediates and ILs demands employment of tradiational solvents, these solvents can be recycled when reactions are carried out on bulk scale or alternative methods (e.g. neat reactions) can be found in future to make the process 'greener'. In present situation the preparation of lactic acid based bromide ILs (**91a**-**94a**) are the greenest syntheses given that these procedures use bio-renewable raw materials, and has ~100 % atom economy in the final stage.

In the case of substituted mandelic acid based ILs, the raw materials (2,3-methylenedioxymandelic acid and 2,3-dihydroxymandelic acid) were synthesized in lab due to their high expense. Hence it was five step synthesis of ILs, however, the yields of intermediates and ILs were good (>80 %) to excellent (>90 %).

Overall the bromide ILs were found to be in solid state whereas the $[NTf_2]^-$, $[OctOSO_3]^-$ salts were liquid at RT. Many of the liquid ILs were found to be very thick and viscous. The actual viscocity was not measured due to sample quantity constraints. During the course of work-up the ILs were heated to 40-50°C on rota evaporator and were subjected to high vacuum drying but none of the compounds were found to undergo any chemical or thermal degradation under these conditions indicating their stability and robustness.

This series of 56 ILs, comprising different classes, offer a choice to test representative examples for toxicity & biodegradation and select specific ILs for further applications.

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Chapter 3

Toxicity and Biodegradation

3.1 Introduction:

A number of achiral and chiral ILs were synthesized, characterized and their toxicity and biodegradability were subsequently evaluated. ILs has been recognised as 'greener' and safer solvents and as such the study of their environmental impact is of utmost importance, especially their fate once released into the environment. The toxicity assessment of ILs is an easy guide to estimate their 'greenness' and also provides information on ecological impact. The biodegradation study of ILs thus gives information regarding the degradation and transformation caused to the ILs by microorganisms. These toxicity and biodegradability studies are often carried out in aqueous media; hence it is necessary to assess the stability of the ILs in aqueous solutions.

3.2 Aqueous stability:

The compounds **123a**, **125a**, **128a** and **130a** (Fig. 3.1) were chosen for this study as they best represent the different classes. A 0.178 M solution of **123a** and 0.049 M solutions of **125a**, **128a**, and **130a** were prepared in D_2O and maintained at 25°C for 15 days with ^1H NMR spectra recorded every 24 h.

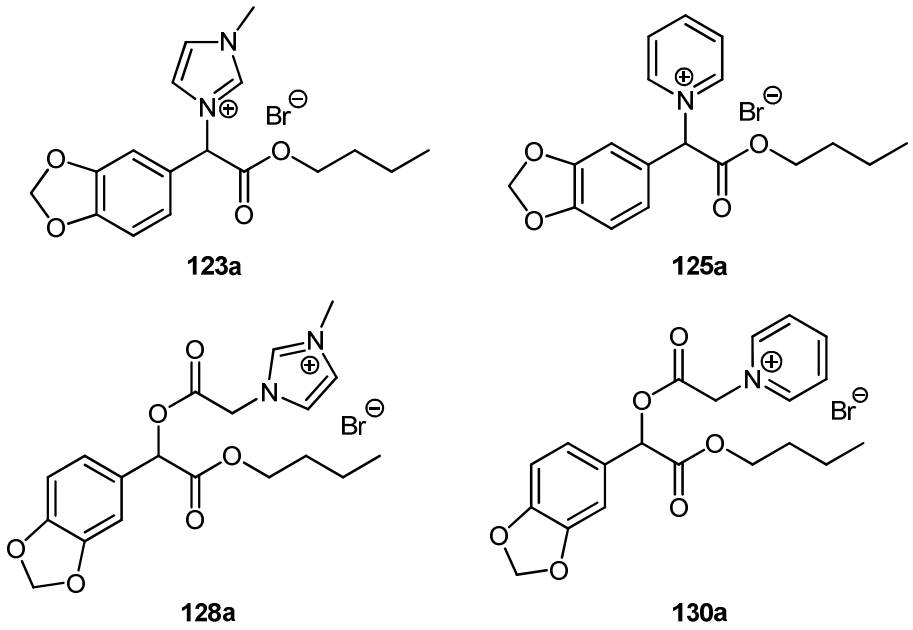


Figure 3.1: ILs used for stability study

Compound **123a** was found to be stable over the period of 15 days for given conditions (Fig. 3.2) whereas **125a** showed slight decomposition after 11 days and was calculated to be 2 % after 15 days (Fig. 3.3).

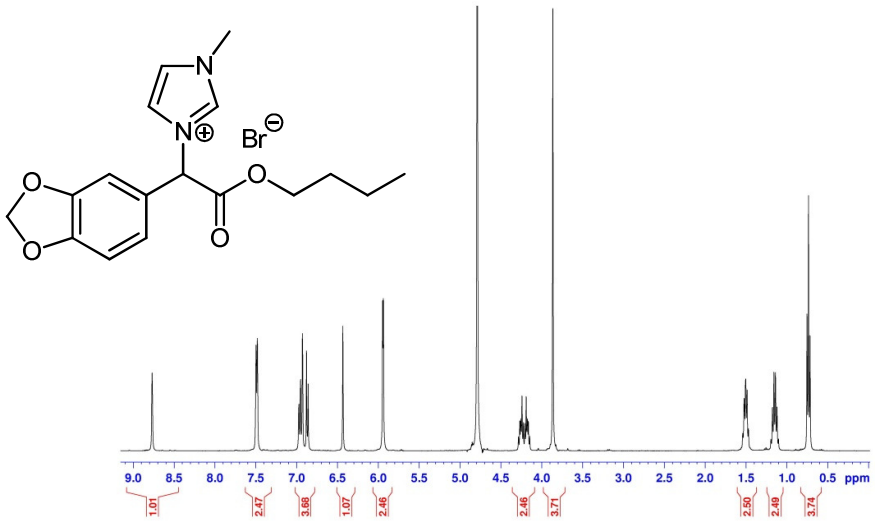


Figure 3.2: ^{1}H NMR of **123a** in D_2O on day 15.

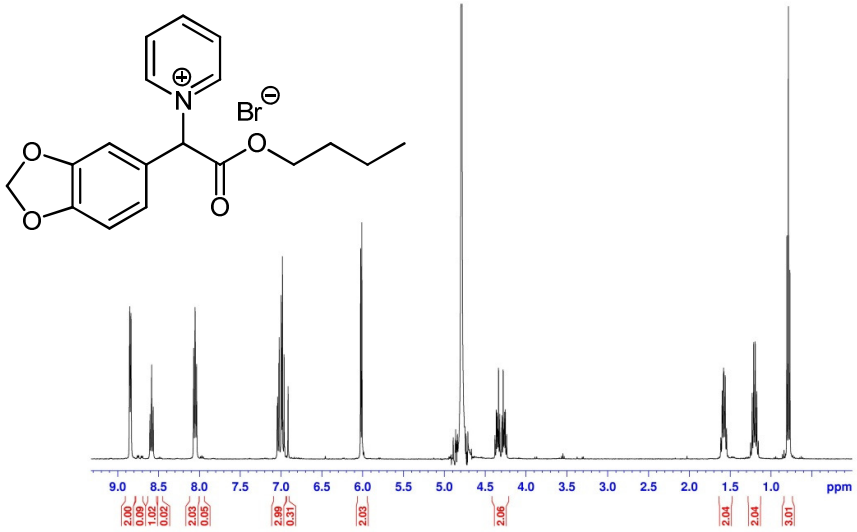
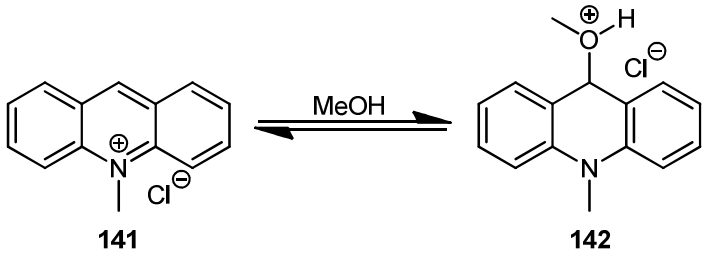


Figure 3.3: ^{1}H NMR of **125a** in D_2O on day 15.

In Fig. 3.2, the NMR spectrum does not show any additional signals to those of **123a** after 15 days. The ^{1}H NMR spectrum for **125a** on day 15 (Fig. 3.3) however shows some small peaks at the baseline. The signals at 8.85, 8.58 and 8.05 ppm correspond to the pyridinium ring in **125a** while the peaks at 8.74, 8.49 and 7.97 ppm correspond to the degradation product. The singlet at 6.91 ppm appears to indicate aromatic protons from the mandelate core of the degraded product. The triplet at 3.54 ppm and its integration when compared to the degradation product peaks in the aromatic region indicate that the degradation might have occurred through ester hydrolysis. A number of publications have discussed the solvent interactions of pyridinium or substituted pyridinium compounds when dissolved in protic solvents.[1] Kano *et al.*[1a] reported the reversible transformation of *N*-methyl acridinium chloride (**141**) to acridane (**142**) in dilute methanol (Fig. 3.4).



141 **142**

Figure 3.4: Reversible reaction of acridinium chloride.

An independent study on rotaxane/calixarene by Grubert *et al.*[1c] also demonstrated similar results. This behaviour of pyridinium compounds was utilised by Connon *et al.*[2] for acetalization of aldehydes who propose an acid catalyst was generated *in situ* from a pyridinium IL and methanol (Fig. 3.5).

With reference to the literature data, it was proposed that such a mechanism was also possible in the case of the ILs presented in this work in aqueous solutions. Dissolution of compound **125a** in D_2O could lead to *in situ* generation of HBr that can then catalyse the hydrolysis of butyl ester, however, only 2 % degradation was observed after 15 days. This low value of degradation can be attributed to the fact that long chain esters hydrolyse with low reaction rates.[3]

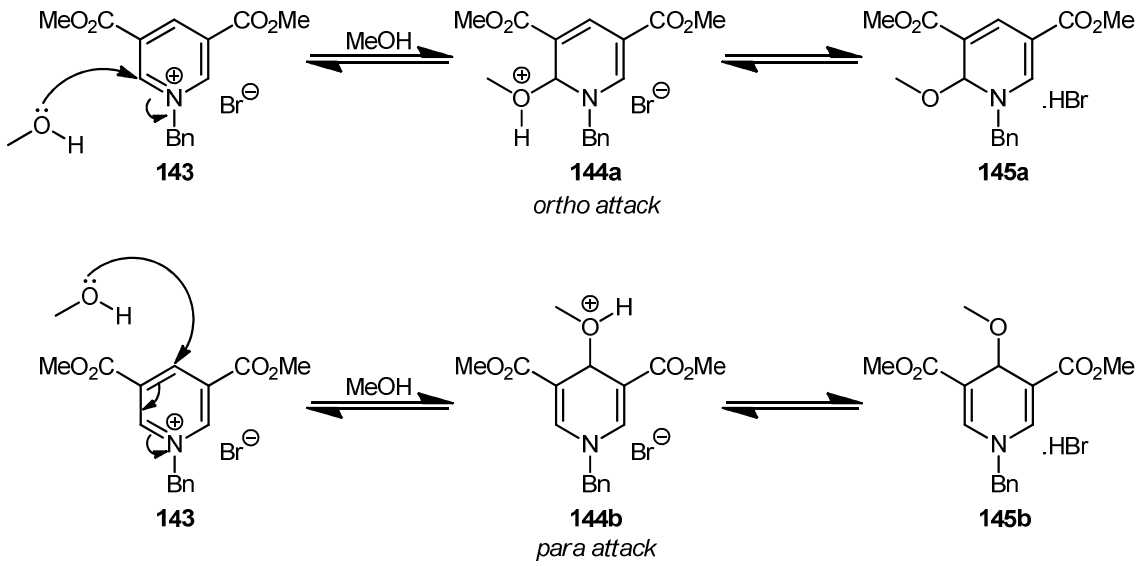


Figure 3.5: Mechanism for generation of Bronsted acid.

In contrast, the diester ILs **128a** and **130a** showed substantial degradation. Compound **128a** was found to be degraded by 4 % on day 1. The ^{1}H NMR spectrum was determined within an hour after dissolution of **128a** in D_2O. The degradation of the IL gradually continued until day 15 demonstrating 81 % decomposition on the final day. The percentage degradation over time is presented in Table 3.1.

Table 3.1: The percentage degradation of **128a.**

Days	**Degradation** (%)
1	4
2	18
4	36
7	58
15	81

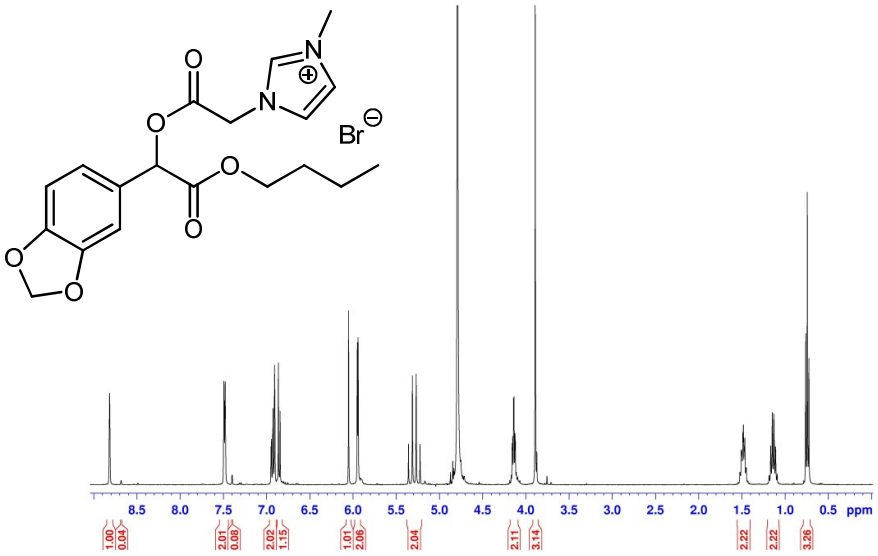


Figure 3.6: ^{1}H NMR of **128a** on day 1.

The degradation of **128a** occurs most likely through the hydrolysis of the diester linkage. The imidazolium IL can react with a protic solvent to produce HBr, similar to the pyridinium ILs. This has been proved by Connon, Gathergood *et al.*[4] who employed an imidazolium ILs in the acetalization reactions. In Fig. 3.6, the signals at 8.81, 7.49 and 7.48 ppm correspond to the imidazolium core from **128a** whilst the weak signals at 8.68, 7.40 5.94 ppm are due to the degraded product.

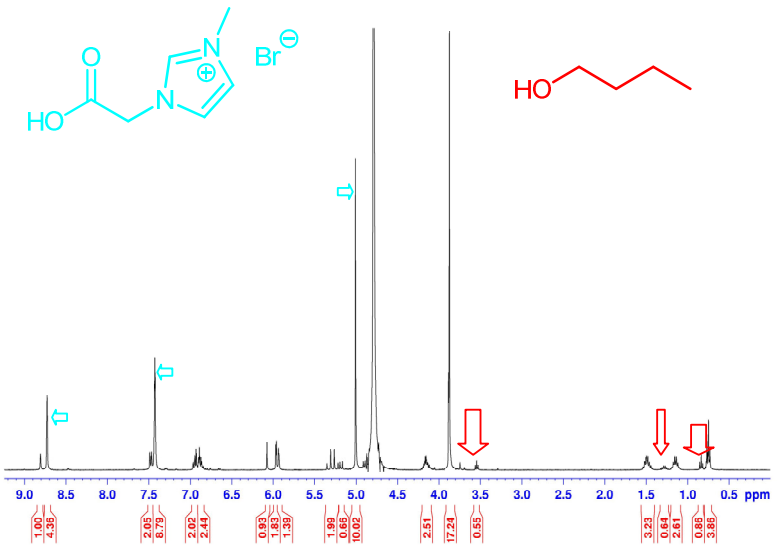
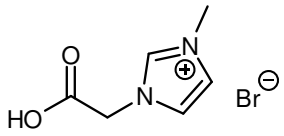


Figure 3.7: Degradation of **128a** on day 15.

The ^{1}H NMR spectrum recorded on day 15 shows 81 % degradation of **128a** and butanol signals (formed after degradation) can be seen prominently (Fig. 3.7). The signals at 3.54, 1.28 and 0.84 ppm could be attributed to butanol which also suggests that both esters have been hydrolysed. The hydrolysis of **128a** was also confirmed by LC-MS analysis where a peak for degradation product **146** (Fig. 3.8) was observed at *m/z* = 141.10.



146

Figure 3.8: 1-(carboxymethyl)-3-methyl-1H-imidazol-3-ium bromide.

The ^{1}H NMR spectrum for compound **130a** showed 7 % degradation after 1 h of dissolution in D_2O (Fig. 3.9). The signals at 8.85, 8.64 and 8.12 ppm correspond to the pyridinium core from **130a** whereas the peaks at 8.74, 8.54, 8.04, 5.92 and 5.22 ppm represent the degraded product.

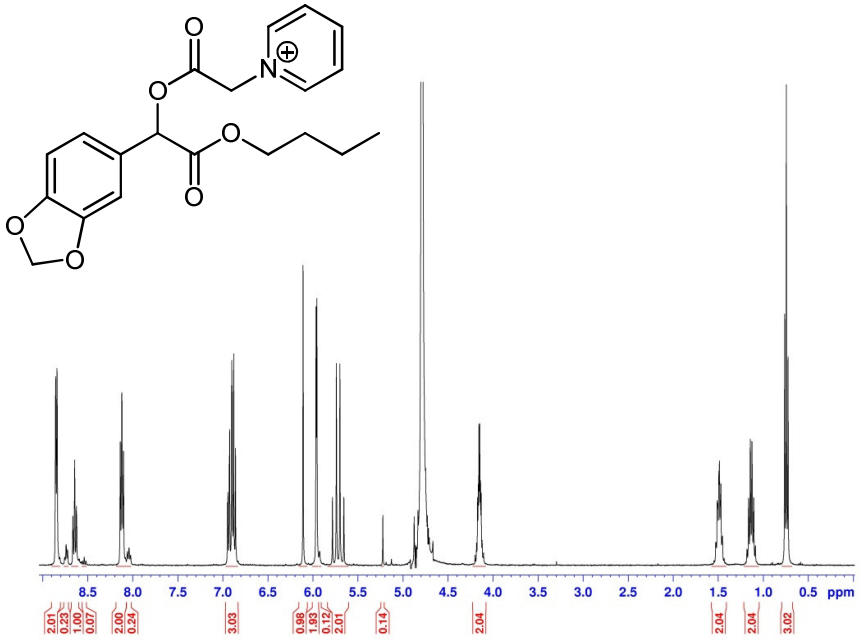


Figure 3.9: ^{1}H NMR of **130a** on day 1.

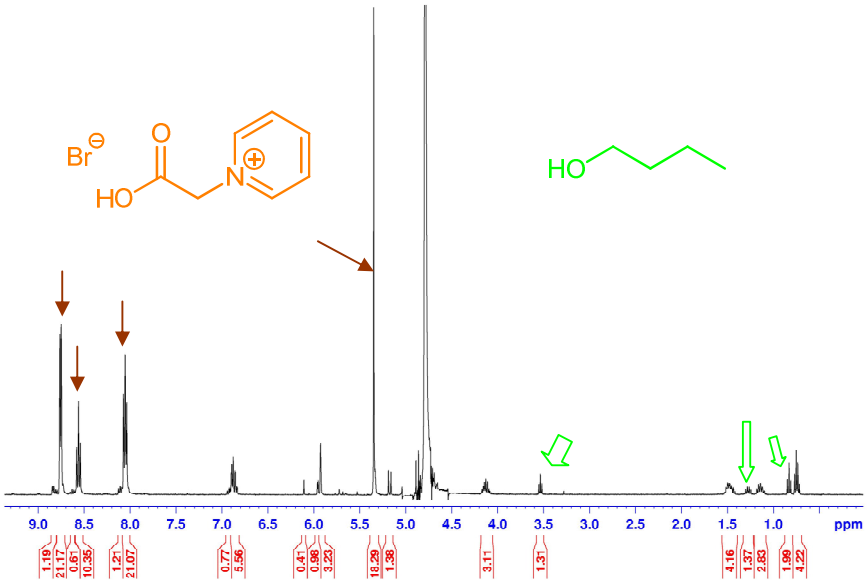


Figure 3.10: ^{1}H NMR of **130a** on day 7.

Surprisingly, 49 % degradation was observed on day 2. The new signals in the ^{1}H NMR spectrum proves that the degradation has occurred through hydrolysis of both ester functionalities (Fig. 3.10). Further analysis of the 1-4 ppm region of the ^{1}H NMR spectrum (Fig. 3.10) revealed that the peaks at 3.54, 1.26 and 0.83 ppm correspond to butanol. With reference to previous experiments and the literature[2] it was postulated that the breakdown of **130a** was catalysed by HBr released from the reaction of **130a** and water. Compound **130a** was degraded completely by day 12, however, the rate of degradation decreased with time. Fig. 3.11 depicts the extent of degradation of **128a** and **130a** with respect to time.

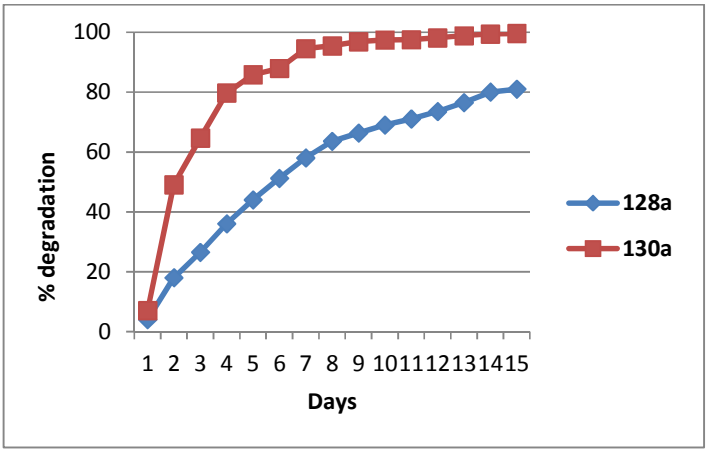


Figure 3.11: The rate of degradation of **128a** and **130a** in D_2O at 25°C.

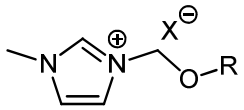
3.3 Toxicity:

3.3.1 Introduction:

The conventional solvents employed in current day chemical industry are a cause of major concern due to their toxicity to both process operators and the environment as well as their volatile and flammable nature making them a potential explosion hazard.[5] The deleterious effects of such solvents on the environment, in particular, atmospheric emissions and contamination of aqueous effluents, are making the usage of these solvents prohibitive. Thus researchers have developed alternative 'green' solvents (discussed in chapter 1) which can overcome the limitations of these conventional solvents. Ionic liquids belong to this same class of alterative solvents. Hence the toxicity assessment of the ionic liquids becomes significant if they are to replace conventional solvents. A number of toxicity studies have been carried out on different classes of ILs including antibacterial, antifungal, antialgal etc.[6,7]

3.3.2 Antibacterial Toxicity:

Bacteria have short generation times hence they are the ideal starting points for toxicity studies. Ionic liquids with different cation cores have been investigated in several types of toxicity studies. The studies by Pernak *et al.*[8] revealed a trend of increasing toxicity with increasing alkyl chain length in the cation core. Authors performed tests on a homologous series of 1-alkoxymethyl-3-methylimidazolium ILs with Cl, $[BF_4]$ and $[PF_6]$ counter ions (Fig. 3.12).



R = C_3-C_{16} (**147-158**)
X = Cl (**a**), $[BF_4]$ (**b**), $[PF_6]$ (**c**)

Figure 3.12: Homologous 1-alkoxymethyl-3-mehtylimidazolium ILs.

The tests were performed using a several strains of cocci (*Staphylococcus epidermidis*, *Micrococcus luteus*, *Staphylococcus* aureus, *Staphylococcus aureus MRSA*, *Enterococcus hirae*) and rods (*Escherichia coli, Proteus vulgaris, Klebsiella pneumoniae, Pseudomonas aeruginosa*) to obtain the minimum inhibitory concentration (MIC/IC_{95}) and minimum

bactericidal concentration (MBC/IC_{95}) values. The benzalkonium chloride compound (BAC), a common biocide, was used as a reference in order to interpret the results. Authors found that all ILs with a side chain greater than six carbon atoms in length to be active against all organisms, and the activity to be dependent upon side chain length and not anion. The chloride salts (**147a**-**149a**) were found to be non-toxic up to 8600 μM concentration while the fluorine containing anions $[BF_4]^-$ (**147b**-**149b**) and $[PF_6]^-$ (**147c**-**149c**) did not show inhibition up to 7000 μM and 5850 μM respectively. The most active ILs against rods and cocci were those with the decyl- side chain (**154**), undecyl- (**155**), dodecyl- (**156**) and tetradecyl- (**157**) with dodecyl- (**156**) being the most active among these. Table 3.2 shows that the most toxic IL found among the test series (**156a-c**) approaches the MIC/IC_{95} values.

Table 3.2: MIC/IC_{95} (μM) values of 3-dodecyloxymethyl-1-methylimidazolium (**156a-c**) vs. BAC

Strain	156a	156b	156c	BAC
M. Luteus	25	21	37	7
S. epidermidis	25	21	18	3
S. aureus	25	21	18	7
MRSA	99	85	73	7
E. hirae	99	85	37	11
E. coli	99	170	73	7
P. vulgaris	197	170	147	22
K. pneumonia	197	170	147	11
P. aeruginosa	395	340	587	54

The antimicrobial toxicity of the ILs involves the regulation of the growth rate of bacteria while interfering with their productivity. The lactic acid producing bacterium *Lactobacillus rhamnosus* was tested against imidazolium ILs [bmim][PF_6], [hmim][PF_6] and [omim][PF_6] to examine if they can be efficient in the extractive fermentation of lactate.[9] The results of these experiments were based on the activity of the bacterium. The amount of glucose consumed was measured, along with the colony forming units (CFUs). The CFU values provide information on the production rate of *Lactobacillus rhamnosus* and these correspond to the glucose consumption, thus indicating that the number of viable cells which produced lactate. The overall results demonstrated that this bacterium survived in all ILs measured, but

possessed a low activity. These results were compared with toluene, for which complete inhibition was noted. There was a little difference found in results shown for the three varying side chain lengths, with [bmim] and [hmim] being approximately equal and showing slightly lower toxicity than [omim] IL.

Vibrio fischeri is a gram negative, rod shaped bacterium commonly found in a symbiotic relationship with squids (Fig. 3.13). This is a popular choice of bacteria to measure toxicity in terms of an acute bioluminescence inhibition assay. Toxicity towards *V. fischeri* can be determined by measuring the difference in light output from the organism. A decrease in observed light output indicates an increase in toxicity. Ranke *et al.*[10] investigated the toxicity of a range of imidazolium ILs against *V. fischeri* and found that the toxicity follows the expected trend, showing a gradual increase in toxicity with an increase in alkyl chain length. This observation was also supported by the studies of Romero & coworkers[11] who performed these tests on several long chain imidazolium ILs bearing alkyl sulfate anions.

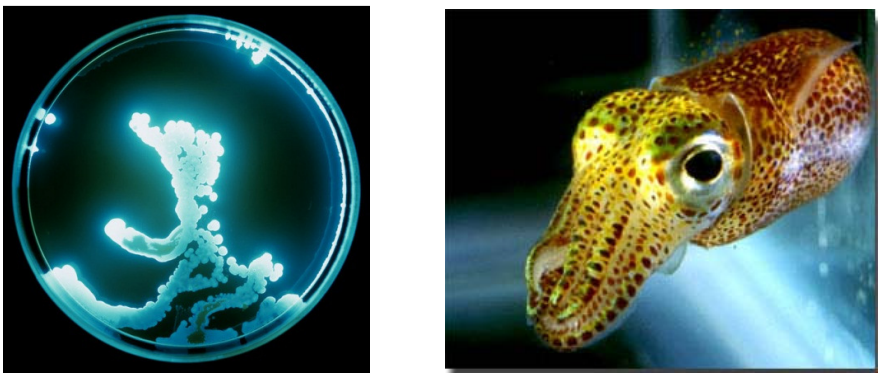


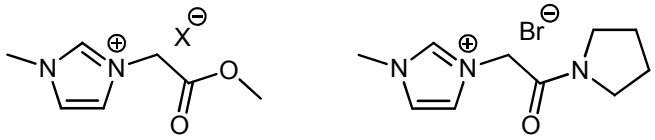
Figure 3.13: *Vibrio fischeri* colonies[12] (left); Hawaiian bobtailed squid[13] (right).

A slight anion effect was noted with which the $[PF_6]^-$ anions appearing to be slightly more toxic compared to $[BF_4]^-$ and Cl^- ILs. However, one exception was observed from this trend. The decyl imidazolium cation combined with the $[BF_4]^-$ anion, demonstrated higher toxicity than its Cl^- and $[PF_6]^-$ counterparts.

3.3.3 Antifungal Toxicity:

Antifungal toxicities of ILs **147**-**158** (**a**-**c**) were measured by Pernak *et al.*[8] against two strains of fungi (*Candida albicans* and *Rhodotorula rubra*). The authors found that similar to their antibacterial results (*vide supra*) the fungi strains also show gradual increase in toxicity with

increase in alkyl chain length. The chloride ILs with propyl, butyl and pentyl chains were non toxic up to 8600 µM concentration whilst the [BF_4] and [PF_6] ILs did not show inhibition up to 7000 and 5850 µM concentrations. Recently, Gathergood and Connon *et al.*[14] reported antifungal toxicity studies of imidazolium based ILs (Fig. 3.14).



159 **160a**

X = Br (**a**), [BF_4] (**b**)

Figure 3.14: Imidazolium based ester and amide ILs.

These ILs were screened against a large array of fungal isolates; *Candida albicans* (ATCC 44859 and ATCC 90028), *Candida parapsilosis*, *Candida krusei* (ATCC 6258 and E28), *Candida tropicalis*, *Candida glabrata*, *Candida lusitaniae*, *Trichosporon beigelii*, *Aspergillus fumigatus*, *Absidia corymbifera* and *Trichophyton mentagrophytes*. No fungal inhibition was observed against the ILs tested up to the highest test concentration of 2000 µM. Kanjilal *et al.*[15] synthesized long chain ester and amide ILs and screened them against five fungal strains, namely *Candida albicans*, *C. rugosa, Saccharomyces cerevisiae*, *Aspergillus flavus* and *A. Niger,* by agar well diffusion method. The test cultures were maintained in potato dextrose agar (PDA) prior to testing, with Amphotericin B, Streptomycin and cetyltrimethylammonium bromide (CTAB) all used as test controls. The toxicity was measured in terms of zones of inhibition.

Table 3.3: Antifungal toxicity of long chain imidazolium ILs.

Fungi	**Zones of inhibition 150 µg [mm]**							
	[ROCOCH$_2$MIm]Br			**[RNHCOCH$_2$MIm]Br**			**Control**	
	R =			**R =**				
	Decyl	**Dodecyl**	**Hexadecyl**	**Decyl**	**Dodecyl**	**Hexadecyl**	**Amphotericin**	**CTAB**
C. albicans	10	17	11	18	20	8	24	12
C. rugosa	12	19	10	19	22	8	-	-
S. cerevisiae	0	21	0	12	15	0	22	0
A. flavus	0	12	12	0	20	23	0	0
A. niger	12	13	0	13	19	10	25	15

Table 3.3 (above) shows that the ILs possessing amide functionality are more toxic than the ester based ILs. A general trend of increasing toxicity with increase in alkyl chain length is consistent. The activity of the dodecyl-substituted imidazolium compounds showed better activity than the decyl- and hexadecyl-substituted compounds, in both the ester- and amide-based ILs. Moreover, the dodecyl-substituted imidazolium compounds displayed better activity than CTAB against all the studied strains.

In 2009, Petkovic and coworkers[16] investigated the toxicity of a series of imidazolium, pyridinium and cholinium based ILs, towards fungi of the Penicilium genus (*Penicillium breviocompactum*, *Penicillium olsonii*, *Penicillium janczewskii*, *Penicillium glandicola*, *Penicillium corylophilum*, *Penicillium glabrum*, *Penicillium restictum*, *Penicillium adametzii*, *Penicillium variabile*, and *Penicillium diversum*). Fungal growth was measured in terms of the absorbance of the medium at 600 nm, given that an increase in absorbance means an increase in growth of fungi. It was found that all strains showed the least tolerance for imidazolium ILs. The increase in lipophilicity (through chain length) was postulated to inhibit the growth of the tested fungi. The environmentally benign cation cholinium exhibited the lowest fungal toxicity, highest MIC and Minimum Fungicidal Concentrations (MFC) values. Studies were carried out to evaluate the antifungal toxicity of the starting materials, namely 1-methylimidazole and pyridine, which inhibited fungal growth by 100 and 60 % respectively.

3.3.4 Antialgal Toxicity:

Algae are primary producers of organic matter required by animals in the fresh water food chain. Thus they play a crucial role in supplying energy for higher trophic levels. The ubiquity and short life cycles of algae makes them interesting candidates to study the toxicological profile of ILs. Cho *et al.*[17a] used *Pseudokirchneriella subcapitata* (Fig. 3.15) to study the effect of different head groups, side chains and anions of ILs on algal growth.

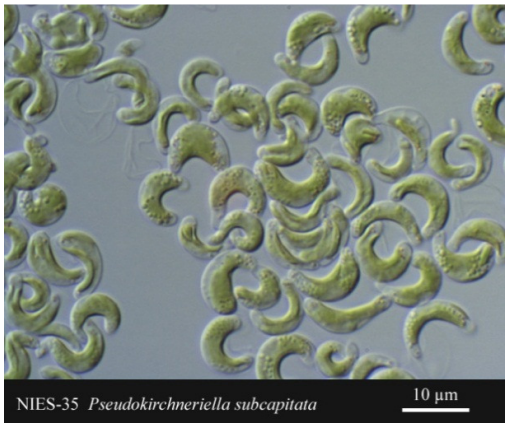


Figure 3.15: *Pseudokirchneriella subcapitata.*[18]

The EC_{50} values were estimated for short term inhibition of photosynthesis of *P. Subcapitata,* when exposed to different salts of imidazolium and pyridinium ILs. The toxicity was measured in terms of absorbance, provided that lesser absorbance is a consequence of more inhibition. The effect of IL toxicity was found to be more significant than photosynthetic performance. A trend of increasing toxicity with increasing alkyl chain length was observed when [pmim], [bmim], [hmim] and [omim] were screened. Out of the anions tested, $[SbF_6]$ was found to be most toxic (EC_{50}:135 µM) with the other anions tested decreasing in toxicity in the order $[SbF_6]^- > [PF_6]^- > [BF_4]^- > [CF_3SO_3]^- > [C_8H_{17}OSO_3]^- > [Br]^- \approx [Cl]^-$.[19]

Table 3.4: EC_{50} values for IL screening with *P. subcapitata* after 96 h exposure.

Ionic Liquids	**EC_{50}** (µM)
[pmim]Br	2137
[bmim]Br	2337
[bmim]Cl	2384
[bmim][BF_4]	2012
[bmim][PF_6]	1318
[bmim][CF_3SO_3]	2188
[bmim][$OctOSO_3$]	2239
[bmim][SbF_6]	135
[hmim]Br	288
[omim]Br	38.2

When Kulacki and Lamberti[20] performed screening of the non-mobile *Scenedesmus quadricauda* and the mobile *Chlamydomonas reinhardtii* freshwater algae in nutrient-rich media and low nutrient groundwater using bromide salts of [bmim], [hmim], and [omim] ILs, the same trend was observed with both algae, in both media tested.

3.4 Antibacterial toxicity of synthesized compounds:

3.4.1 Toxicity for achiral ILs:

In vitro antibacterial activities[21] of a range of achiral ILs (**69**, **71**-**73**, **76**-**78**) (Fig. 3.16) were evaluated on a panel of three CCM strains (**SA**: *Staphylococcus aureus* CCM 4516, **EC**: *Escherichia coli* CCM 4517, **PA**: *Pseudomonas aeruginosa* CCM 1961) and five clinical isolates (**MRSA**: *Staphylococcus aureus* MRSA H 5996/08, **SE**: *Staphylococcus epidermidis* H 6966/08, **EF**: *Enterococcus sp*. J 14365/08, **KP-E**: *Klebsiella pneumoniae* ESBL J 14368/08, **KP**: *Klebsiella pneumoniae* D 11750/08) from the collection of bacterial strains cultured at the Department of Biological and Medical Sciences, Faculty of Pharmacy, Charles University, Hradec Kralove, Czech Republic. The aforementioned CCM strains also served as the quality control strains. All the isolates were maintained on Mueller-Hinton dextrose agar, prior to being tested.

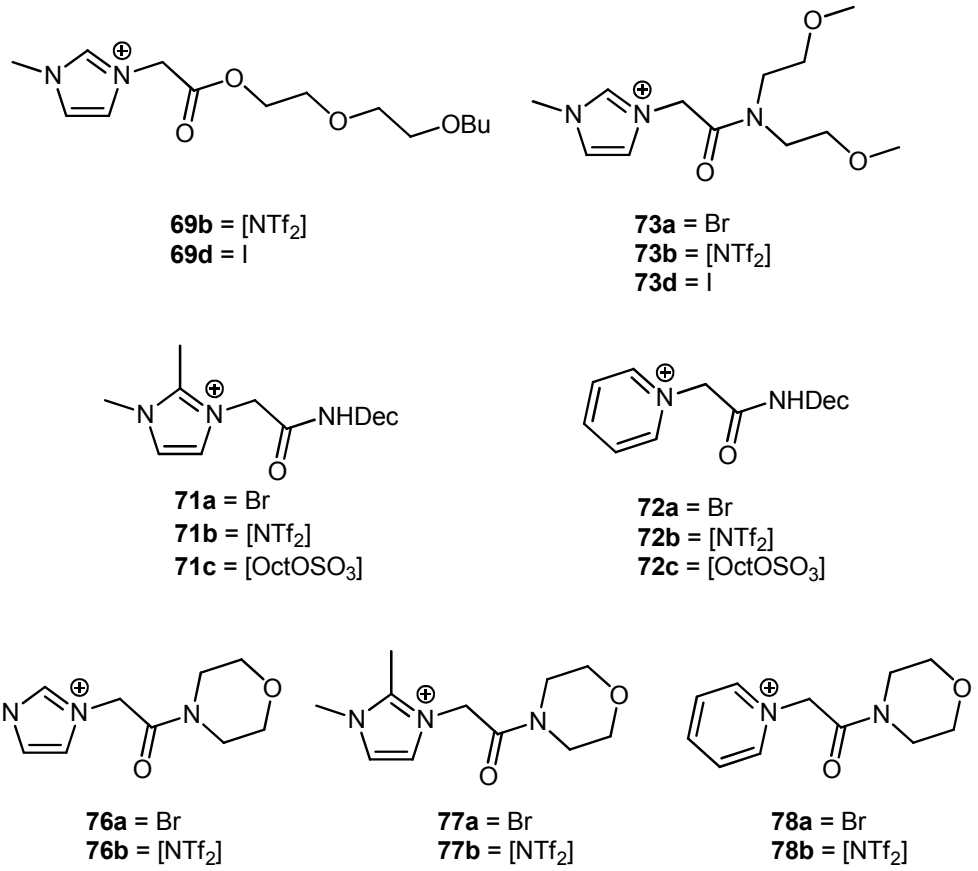


Figure 3.16: The achiral ILs tested for antimicrobial screening.

Out of the achiral ILs tested, only **69b** and **69d** were ester based and the remainder (salts of **71**-**73**, **76**-**78**) were amide based achiral ILs. The results from table 3.5 shows that the bromide ILs (**73a**, **76a**-**78a**) are non toxic up to 2.0 mM/L concentration, except for **71a** and **72b** which are decyl amides. The activity of salts of **71** and **72** was found to be low as expected, which is consistent with reference literature data.[8,15] The lipophilic character of ILs with long alkyl chain [**71**(**a**-**c**) and **72**(**a**-**c**)] enables them to cross the bio-membrane of cell, thus showing more activity compared to others.[22] The iodide ILs **69d** and **73d** were also found to be non-toxic up to 2.0 mM i.e maximum test concentration. The $[NTf_2]^-$ salt **69b** was tested at maximum concentration 1.0 mM and found to inhibit both *S. epidermis* at 0.5 mM concentration and *K. pneumoniae* at 1.0 mM after 24 h. This ester containing IL (**69b**) was also tested by Deng *et al*.[23] against a number of bacterial strains, including *E. coli,* and found the MIC value to be 6.4 mM. The authors furthermore concluded that such classes of ester ILs, containing ether chains, have higher inhibitory concentration in the range of 5-20 mM depending on length of the ester side chain. When comparing the results of **71a**-**71c**, the effect

of the anion component seems to be less pronounced. However, for Gram negative bacteria IL **71b** showed lower IC_{95} values compared to **71a** and **71b**. The pyridinium IL **72a** showed slightly higher inhibitory concentration than **71a** but the trend was reversed for $[OctOSO_3]^-$ salts **71c** and **72c.** The corresponding $[NTf_2]$ ILs **71b** and **72b** seem to behave in a similar way, with both Gram positive and Gram negative bacteria.

Table 3.5: Antibacterial toxicity results for achiral ILs.

No.	Bacteria strain	Time (h)	MIC/IC_{95} (mM)							
			73a-b,d 76a-b, 77a-b, 78a-b, 69d	**69b**	**71a**	**71b**	**71c**	**72a**	**72b**	**72c**
1.	**SA**	24h	> 2.0	> 1.0	**0.0625**	**0.0625**	**0.03125**	**0.125**	**0.03125**	**0.03125**
		48h	> 2.0	> 1.0	**0.125**	**0.0625**	**0.03125**	**0.125**	**0.0625**	**0.03125**
2.	**MRSA**	24h	> 2.0	> 1.0	**0.125**	**0.125**	**0.125**	**0.125**	**0.125**	**0.0625**
		48h	> 2.0	> 1.0	**0.125**	**0.125**	**0.125**	**0.125**	**0.125**	**0.0625**
3.	**SE**	24h	> 2.0	**0.5**	**0.03125**	**0.25**	**0.25**	**0.125**	**0.125**	**0.0625**
		48h	> 2.0	> 1.0	**0.0625**	**0.25**	**0.50**	**0.125**	**0.125**	**0.0625**
4.	**EF**	24h	> 2.0	> 1.0	**0.125**	**0.0625**	**0.125**	**0.125**	**0.0625**	**0.0625**
		48h	> 2.0	> 1.0	**0.125**	**0.125**	**0.125**	**0.25**	**0.125**	**0.0625**
5.	**EC**	24h	> 2.0	> 1.0	**0.25**	**0.25**	**0.25**	**0.125**	**0.125**	**0.0625**
		48h	> 2.0	> 1.0	**0.50**	**0.25**	**0.25**	**0.125**	**0.125**	**0.0625**
6.	**KP**	24h	> 2.0	**1.0**	**0.50**	**0.25**	**0.50**	**0.50**	**0.25**	**0.25**
		48h	> 2.0	> 1.0	**1.0**	**0.25**	**0.50**	**0.50**	**0.25**	**0.25**
7.	**KP-E**	24h	> 2.0	> 1.0	**1.0**	**0.25**	**1.0**	**0.50**	**0.125**	**0.50**
		48h	> 2.0	> 1.0	**1.0**	**0.25**	**1.0**	**0.50**	**0.125**	**0.50**
8.	**PA**	24h	> 2.0	> 1.0	**1.0**	**1.0**	**2.0**	**0.50**	**1.0**	**0.50**
		48h	> 2.0	> 1.0	**1.0**	> 1.0	**2.0**	**0.50**	**1.0**	**1.0**

3.4.2 Toxicity studies of Lactate and Mandelate ILs:

Overall, thirty chiral ILs (salts of **91**-**97**, **123**, **125**, **128**-**133**) (Fig. 3.17) were screened for antibacterial tests which included fourteen lactate based and remaining mandelate based ILs. The mandelate ILs include two monoester and fourteen diester ILs. The tests were carried out using DMSO as the test medium. The results are presented in table 3.6.

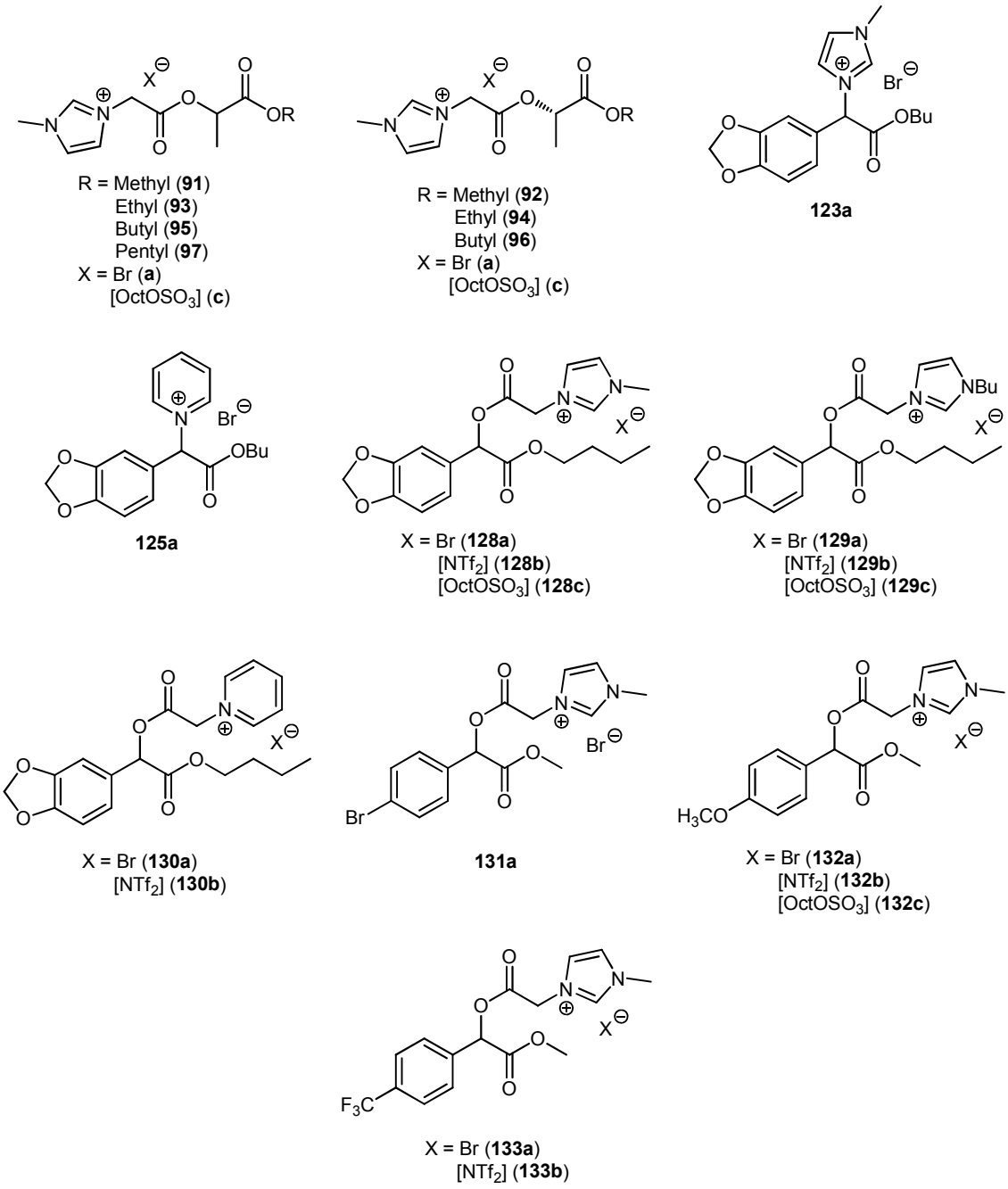


Figure 3.17: Lactate and mandelate based ILs for antimicrobial screening.

Table 3.6: Antibacterial toxicity results for chiral ILs containing lactate and mandelate core.

No.	Bacteria strain	Time (h)	MIC/IC_{95} (mM)						
			91a-97a,123a, 125a, 129a, 131a-133a, 133b, 91c, 97c, 129c	**129b, 92c-96c**	**130b, 132b**	**128a**	**128b**	**128c**	**130a**
1.	**SA**	24h	> 2.0	> 1.0	> 0.5	> 2.0	> 1.0	**2.0**	> 2.0
		48h	> 2.0	> 1.0	> 0.5	> 2.0	> 1.0	**2.0**	> 2.0
2.	**MRSA**	24h	> 2.0	> 1.0	> 0.5	> 2.0	> 1.0	**2.0**	> 2.0
		48h	> 2.0	> 1.0	> 0.5	> 2.0	> 1.0	**2.0**	> 2.0
3.	**SE**	24h	> 2.0	> 1.0	> 0.5	**1.0**	**0.5**	> 2.0	**2.0**
		48h	> 2.0	> 1.0	> 0.5	**2.0**	> 1.0	> 2.0	> 2.0
4.	**EF**	24h	> 2.0	> 1.0	> 0.5	> 2.0	> 1.0	> 2.0	> 2.0
		48h	> 2.0	> 1.0	> 0.5	> 2.0	> 1.0	> 2.0	> 2.0
5.	**EC**	24h	> 2.0	> 1.0	> 0.5	> 2.0	> 1.0	> 2.0	> 2.0
		48h	> 2.0	> 1.0	> 0.5	> 2.0	> 1.0	> 2.0	> 2.0
6.	**KP**	24h	> 2.0	> 1.0	> 0.5	> 2.0	> 1.0	> 2.0	> 2.0
		48h	> 2.0	> 1.0	> 0.5	> 2.0	> 1.0	> 2.0	> 2.0
7.	**KP-E**	24h	> 2.0	> 1.0	> 0.5	> 2.0	> 1.0	> 2.0	> 2.0
		48h	> 2.0	> 1.0	> 0.5	> 2.0	> 1.0	> 2.0	> 2.0
8.	**PA**	24h	> 2.0	> 1.0	> 0.5	> 2.0	> 1.0	> 2.0	> 2.0
		48h	> 2.0	> 1.0	> 0.5	> 2.0	> 1.0	> 2.0	> 2.0

The results presented in table 3.6 shows that all lactate ILs, containing bromide counter-ion, (**91a**-**97a**) and the $[OctOSO_3]^-$ salts (**91c**, **97c**) were non-toxic up to 2.0 mM concentration. ILs **92c**-**96c** did not show inhibition when tested at 1.0 mM concentration. The mono substituted mandelate ILs (**131a**-**133a, 133b**), which are methyl esters, were also non-toxic up to 2 mM concentration. The $[NTf_2]^-$ IL **132b** was tested at 0.5 mM concentration limit and found to show no inhibition to any of the bacteria. The monoester mandelate ILs **123a** and **125a** did not display any inhibition up to 2mM concentration although they possess a butyl ester group, thus having higher lipophilicity than methyl ester ILs (**131a**-**133a**).

The di-substituted mandelate ILs **128a** and **130a** showed a marginal toxicity towards *S. epidermis* after 24 h. Here, it can be seen that **128a** inhibits the growth of this Gram positive bacteria at 1.0 mM after 24 h and 2.0 mM after 48 h. There is an explanation in that the IL itself shows higher toxicity towards bacteria, but the metabolites formed after 24 h do not show any antibacterial activity. We have seen in section 3.2 (*vide supra*) that **128a** and **130a** undergo chemical degradation through hydrolysis. Although this experiment was carried out in DMSO (100 %), the media was supplemented with buffer of pH = 7.4. Thus the possibility of hydrolysis can't be ruled out as in aqueous stability studies we have seen that **128a** hydrolysed by 18 % degradation after 24 h whereas **130a** degrades by 49 %. In the case of **130a** only, growth inhibition was observed for *S. epidermis* after 24 h at 1.0 mM, which clearly suggests that even though **130a** hydrolyses the metabolites are non-toxic at 2 mM concentration. The [$OctOSO_3$] salt **128c** gave borderline inhibition of bacteria *S. aureus* and MRSA *S. aureus* at 2.0 mM. The overall results show that both Mandelate and Lactate ILs are non-toxic towards bacteria, with some exceptions. It is noteworthy that inhibition was observed only in the case of Gram positive bacteria.

3.5 Antifungal toxicity of synthesized compounds:

3.5.1 Toxicity studies of achiral ILs:

In vitro antifungal activities of the compounds (salts of **69**, **71**-**73**, **76**-**78**) (Fig. 3.16) were evaluated on a panel of four ATCC strains (**CA1**: *Candida albicans* ATCC 44859, **CA2**: *Candida albicans* ATCC 90028, **CP**: *Candida parapsilosis* ATCC 22019, **CK1**: *Candida krusei* ATCC 6258) and eight clinical isolates of yeasts (**CK2**: *Candida krusei* E28, **CT**: *Candida tropicalis* 156, **CG**: *Candida glabrata* 20/I, **CL**: *Candida lusitaniae* 2446/I, **TA**: *Trichosporon asahii* 1188) and filamentous fungi (**AF**: *Aspergillus fumigatus* 231, **AC**: *Absidia corymbifera* 272, **TM**: *Trichophyton mentagrophytes* 445) from the collection of fungal strains cultured at the Department of Biological and Medical Sciences, Faculty of Pharmacy, Charles University, Hradec Králové, Czech Republic. Three of the above ATCC strains (*C. albicans* ATCC 90028, *C. parapsilosis* ATCC 22019, *C. krusei* ATCC 6258) also served as the quality control strains. All the isolates were maintained on Sabouraud dextrose agar prior to being tested. Minimum inhibitory concentrations (MICs) were determined by the micro-dilution format from the NCCLS M27-A guidelines.[21] In the case of the *T. mentagrophytes,* readings were taken after 72 and 120 h and MIC/IC_{50} values were calculated for *A. fumigatus, A. corymbifera and T. mentagrophytes* while for all other strains MIC/IC_{80} values were calculated after 24 and 48 h of exposure to ILs.

Table 3.7: Results for antifungal study of achiral ILs.

No	Fungi strain	Time (h)	MIC/IC_{80}.IC_{50} (mM)[a]							
			69d, **73a-b**, **73d**, **76-78** (**a**, **b**)	**69b**	**71a**	**71b**	**71c**	**72a**	**72b**	**72c**
1.	**CA1**	24h	> 2.0	**1.0**	**0.125**	**0.250**	**0.125**	**0.125**	**0.250**	**0.125**
		48h	> 2.0	> 1.0	**0.250**	**0.250**	**0.125**	**0.250**	**0.5**	**0.125**
2.	**CA2**	24h	> 2.0	> 1.0	**0.125**	**0.250**	**0.125**	**0.125**	**0.250**	**0.125**
		48h	> 2.0	> 1.0	**0.125**	**0.250**	**0.125**	**0.250**	**0.250**	**0.125**
3.	**CP**	24h	> 2.0	> 1.0	**0.0625**	**0.0625**	**0.125**	**0.0625**	**0.0625**	**0.0625**
		48h	> 2.0	> 1.0	**0.0625**	**0.125**	**0.125**	**0.0625**	**0.125**	**0.0625**
4.	**CK1**	24h	> 2.0	> 1.0	**0.0078**	**0.0313**	**0.0313**	**0.0156**	**0.0156**	**0.0078**
		48h	> 2.0	> 1.0	**0.0078**	**0.0313**	**0.0625**	**0.0156**	**0.0156**	**0.0156**
5.	**CK2**	24h	> 2.0	> 1.0	**0.0039**	**0.0156**	**0.0313**	**0.0156**	**0.0039**	**0.0039**
		48h	> 2.0	> 1.0	**0.0039**	**0.0313**	**0.0625**	**0.0156**	**0.0156**	**0.0078**
6.	**CT**	24h	> 2.0	**1.0**	**0.0039**	**0.0156**	**0.0313**	**0.0156**	**0.0156**	**0.0039**
		48h	> 2.0	> 1.0	**0.0039**	**0.0313**	**0.0625**	**0.0156**	**0.0156**	**0.0039**
7.	**CG**	24h	> 2.0	> 1.0	**0.0313**	**0.0625**	**0.125**	**0.125**	**0.0625**	**0.0625**
		48h	> 2.0	> 1.0	**0.0625**	**0.125**	**0.125**	**0.125**	**0.125**	**0.125**
8.	**CL**	24h	> 2.0	> 1.0	**0.250**	**0.250**	**0.250**	**0.250**	**0.250**	**0.125**
		48h	> 2.0	> 1.0	**0.250**	**0.250**	**0.250**	**0.250**	**0.250**	**0.125**
9.	**TA**	24h	> 2.0	**0.5**	**0.250**	**0.250**	**0.250**	**0.250**	**0.250**	**0.125**
		48h	> 2.0	> 1.0	**0.250**	**0.5**	**0.250**	**0.250**	**0.5**	**0.125**
10.	**AF**	24h	> 2.0	> 1.0	**0.250**	**0.250**	**0.250**	**0.250**	**0.250**	**0.125**
		48h	> 2.0	> 1.0	**0.250**	**0.5**	**0.250**	**0.250**	**0.250**	**0.125**
11.	**AC**	24h	> 2.0	> 1.0	**0.250**	> 1.0	**1.0**	**0.125**	> 0.5	**1.0**
		48h	> 2.0	> 1.0	**0.250**	> 1.0	**1.0**	**0.250**	> 0.5	**1.0**
12.	**TM**	72h	> 2.0	> 1.0	**0.250**	**0.250**	**0.125**	**0.250**	**0.250**	**0.125**
		120h	> 2.0	> 1.0	**0.250**	**0.250**	**0.125**	**0.250**	**0.250**	**0.125**

[a] IC_{50} values were assessed for AF, AC and TM. For all other fungi strains IC_{80} values were evaluated.

Seventeen achiral ILs were screened for antifungal toxicity (Fig. 3.17). The results from table 3.7 indicate that the imidazolium ILs, with amide side chain containing ether groups (**73a**-**b**, **73d**), were non-toxic up to 2 mM concentration. The ester IL **69d** also did not exhibit any inhibition to the fungal growth, which is supported by the findings of Deng and coworkers.[23] The $[NTf_2]^-$ salt **69b** was tested at 1.0 mM concentration and found to be toxic for *C. albicans*, *C. tropicalis* and *T. asahii* after 24 h, but after 48 h again the IL did not exhibit toxicity. This behaviour was also observed in the case of antibacterial studies and can be explained as the IL itself may be toxic, but after 48 h the metabolites formed are not. One more explanation can be that on prolonged exposure the fungi adapt themselves to the surroundings. Pernak and co-workers reported that some fungi can change their metabolic pathway upon exposure to ILs, by changing their cell biochemistry.[8c]

The decyl amide ILs (**71a**-**c** and **72a**-**c**) showed high antifungal activity as expected. The $[NTf_2]$ salts **71b** and **72b** were found to be non-toxic only towards filamentous fungi (*A. Corymbifera)* up to the maximum test concentration i.e 1.0 and 0.5 mM respectively. The effect of both the cation and anion was less pronounced. All six ILs (**71a**-**c** and **72a**-**c**) showed high antifungal toxicity especially, in the case of *C. parapsilosis, C. krusei, C. krusei, C. tropicalis* and *C. glabrata*. This was also observed for antibacterial studies. Other amide ILs (**76a**-**b**, **78a**-**b**) were non-toxic up to a test concentration of 2.0 mM.

3.5.2 Toxicity studies using Lactate and Mandelate ILs:

Thirty chiral ILs, including lactate and mandelate salts, were screened for antifungal toxicity at Charles University (Czech Republic) using twelve strains of fungi. MIC/IC_{50} values were calculated the case of the *T. mentagrophytes* after 72 and 120 h and for *A. fumigatus*, *A. corymbifera* after 24 and 48 h. For all other strains MIC/IC_{80} values were evaluated after 24 and 48 h of exposure to ILs. The results presented in Table 3.8 in general, show that ILs tested were non-toxic up to maximum test concentration, with some exceptions. All the bromide salts of lactate ILs (**91a**-**97a**) and the $[OctOSO_3]^-$ salts (**91c**, **97c**) did not show inhibition up to 2.0 mM concentration. The monosubstituted mandelate ILs (**131a**-**133a**) did not inhibit bacterial growth up to 2.0 mM. The monoester IL **123a** was found to be non-toxic whilst **125a** showed growth inhibition for *C. albicans* and *C. lusitaniae* at 2.0 mM concentration. The disubstituted ILs **128a** and **130a** behaved in a similar way towards yeast (*C. krusei*, *C. tropicalis*, *C. glabrata, C. lusitaniae, T. asahii*) and filamentous fungi (*A. fumigatus*, *A. corymbifera, T. mentagrophytes*) indicating structure-toxicity relationship.

Table 3.8: Antifungal studies using lactate and mandelate ILs.

No	Fungi strain	Time (h)	MIC/IC_{80}.IC_{50} (mM)[a]							
			91a-97a, 123a,129a, 131a-133a, 133b, 91c, 97c,	**128b, 129b, 92c-96c, 132c**	**130b, 132b**	**125a**	**128a**	**128c**	**129c**	**130a**
1.	**CA1**	24h	> 2.0	> 1.0	> 0.5	**2.0**	**2.0**	**2.0**	**2.0**	**2.0**
		48h	> 2.0	> 1.0	> 0.5	**2.0**	> 2.0	**2.0**	> 2.0	**2.0**
2.	**CA2**	24h	> 2.0	> 1.0	> 0.5	> 2.0	**2.0**	**2.0**	**2.0**	**2.0**
		48h	> 2.0	> 1.0	> 0.5	> 2.0	> 2.0	> 2.0	> 2.0	> 2.0
3.	**CP**	24h	> 2.0	> 1.0	> 0.5	> 2.0	**2.0**	**2.0**	**2.0**	**2.0**
		48h	> 2.0	> 1.0	> 0.5	> 2.0	> 2.0	> 2.0	> 2.0	> 2.0
4.	**CK1**	24h	> 2.0	> 1.0	> 0.5	> 2.0	> 2.0	**2.0**	**2.0**	**2.0**
		48h	> 2.0	> 1.0	> 0.5	> 2.0	> 2.0	**2.0**	> 2.0	> 2.0
5.	**CK2**	24h	> 2.0	> 1.0	> 0.5	> 2.0	> 2.0	**2.0**	**2.0**	> 2.0
		48h	> 2.0	> 1.0	> 0.5	> 2.0	> 2.0	**2.0**	> 2.0	> 2.0
6.	**CT**	24h	> 2.0	> 1.0	> 0.5	**2.0**	> 2.0	**2.0**	**2.0**	> 2.0
		48h	> 2.0	> 1.0	> 0.5	> 2.0	> 2.0	> 2.0	> 2.0	> 2.0
7.	**CG**	24h	> 2.0	> 1.0	> 0.5	> 2.0	**2.0**	**2.0**	**2.0**	**2.0**
		48h	> 2.0	> 1.0	> 0.5	> 2.0	> 2.0	**2.0**	> 2.0	> 2.0
8.	**CL**	24h	> 2.0	> 1.0	> 0.5	**2.0**	**2.0**	**2.0**	**2.0**	**2.0**
		48h	> 2.0	> 1.0	> 0.5	**2.0**	> 2.0	> 2.0	> 2.0	> 2.0
9.	**TA**	24h	> 2.0	> 1.0	> 0.5	> 2.0	**1.0**	**1.0**	**1.0**	**0.5**
		48h	> 2.0	> 1.0	> 0.5	> 2.0	**2.0**	**2.0**	> 2.0	**2.0**
10.	**AF**	24h	> 2.0	> 1.0	> 0.5	> 2.0	**2.0**	**2.0**	**2.0**	**2.0**
		48h	> 2.0	> 1.0	> 0.5	> 2.0	> 2.0	> 2.0	**2.0**	> 2.0
11.	**AC**	24h	> 2.0	> 1.0	> 0.5	> 2.0	**2.0**	**2.0**	**2.0**	**2.0**
		48h	> 2.0	> 1.0	> 0.5	> 2.0	**2.0**	**2.0**	> 2.0	**2.0**
12.	**TM**	72h	> 2.0	> 1.0	> 0.5	> 2.0	**1.0**	**0.5**	**1.0**	**1.0**
		120h	> 2.0	> 1.0	> 0.5	> 2.0	**1.0**	**0.5**	**1.0**	**1.0**

[a] For AF, AC and TM, IC_{50} values while for all other fungi strains IC_{80} values were evaluated.

The only difference between these two ILs is the cation core i.e **128a** contains imidazolium whereas **130a** possess pyridinium core. On the other hand, a similar compound, but with a 1-butylimidzolium core (**129a**) has been found to be non-toxic with $IC_{80/50}$ >2.0 mM. With the variable maximum test concentrations of different salts of the same cation, it is difficult to compare the overall effect of the anion. But the comparison between bromide IL (**128a**) and its $[OctOSO_3]^-$ salt (**128c**) reveals that the $[OctOSO_3]^-$ salt has higher antifungal toxicity to all types of fungi.

3.6 Antibacterial toxicity studies at higher concentration:

In collaboration with the Biotechnology Department at DCU, four achiral ILs (**69d**, **73d**, **77a**, **78a**) (Fig. 3.16) and five chiral ILs (**123a**, **125a**, **128a**, **130a** and **133a**) (Fig. 3.17) were screened against five bacteria strains: Gram-positive (*Bacillus subtilis*) and Gram-negative (*Escherichia coli*, *Pseudomonas fluorescence*, *Pseudomonas putida* CP1, *Pseudomonas putida* KT2440) (Table 3.5, entries 1-9). IL toxicity determination was based on bacterial growth inhibition in a 24 hour assay and was expressed as IC_{50} values. The maximum test concentration for ILs **69d**, **73d**, **123a**, **125a** and **133a** was 200 mM whereas amide based achiral ILs (**77a**, **78a**) were tested at 50 mM. The test concentration for **128a** and **130a** was 150 mM and 6.25 mM respectively. The low test concentration was chosen due to the low aqueous solubility (0.013 g/mL) of **130a**. The IC_{50} value ranges are presented in Table 3.9

Table 3.9: Antibacterial screening of achiral and chiral ILs.

Ionic Liquids	IC_{50} (mM)				
	E. coli	***B. subtilis***	***P. fluorescens***	***P. putida* (CP1)**	***P. putida* (KT 2440)**
69d	50-100	50-100	50-100	50-100	50-100
73d	>200	>200	>200	>200	>200
77a	>50	>50	>50	>50	>50
78a	25-50	>50	>50	25-50	>50
123a	25-50	25-50	25-50	25-50	25-50
125a	25-50	25-50	25-50	25-50	25-50
128a	37.5-75	37.5-75	75-150	75-150	75-150
130a	3.13-6.25	>6.25[a]	>6.25[a]	3.13-6.25	3.13-6.25
133a	3.13-6.25	3.13-6.25	3.13-6.25	3.13-6.25	3.13-6.25

[a] Solubility limit; IC_{50} value greater than solubility in media.

Among the achiral ILs, **69d** and **73d** are iodide salts and Table 3.9 shows that the half maximal inhibitory concentration values are higher for these two compounds. The ester IL **69d** has an IC_{50} value between 50-100 mM for all strains tested. Previously, we have seen that the $[NTf_2]^-$ salt of same cation has shown MIC value of 6.4 mM for several strains of bacteria including *E. coli*.[15] In our antibacterial studies, the aforementioned ILs (**69d**, **73d**) were found to be non-toxic at 2.0 mM concentration. Compound **73d** did not exhibit toxicity up to 200 mM. The amide based IL, containing imidazolium core (**77a**), was found to be non-toxic up to the max. test concentration 50 mM, whereas the IL with pyridinium core (**78a**) shows inhibition of bacteria *E. coli* and *P. putida* (CP1) in the range 25-50 mM.

Out of the five chiral ILs tested, the compounds **123a** and **125a** exhibited similar IC_{50} value range for all bacteria screened i.e. 25-50 mM. Both ILs have similar structure except for the cation core. The diester IL **128a** showed IC_{50} value between 37.5-75 mM when screened against Gram positive bacteria *B. subtilis* and Gram negative bacteria *E. coli,* while the range is higher (75-150 mM) for the remaining three bacterial strains. In contrast to the similar results between **123a** and **125a**, the compounds **128a** and **130a** exhibit a completely different scenario. The IL **130a** was showed to be most toxic among the disubstituted Mandelate ILs possessing O-CH_2-O linkage on the aromatic ring. However, this does not affect the growth of *B. subtilis* and Gram negative bacteria *P. fluorescence* up to a max. test concentration 6.25 mM. This compound was screened at low test concentration due to its low solubility in Milton broth. The only monosubstituted mandelate IL screened (**133a**) was found to be the most toxic IL in the table, inhibiting all strains of bacteria between the ranges 3.13-6.25 mM. Analysis of Table 3.9 across the rows reveals that Gram-negative bacterium *E. coli* and the Gram-positive bacterium *B. subtilis* exhibit similar IC_{50} values, which is in contrast with previously reported results for common ionic liquids.[24]

3.7 Antialgal Toxicity Studies:

We have seen in previous sections that the mandelate ILs (**123a**, **125a** and **128a**) show low antimicrobial toxicity. Hence aiming to explore in more detail the effects of these mono- and diester ILs (**123a**, **125a**, **128a** and **130a**), their effects towards two freshwater green algae, namely *P. subcapitata* and *Chlorella vulgaris* (*C. vulgaris*), were investigated and the toxicity results presented in Table 3.10.

Table 3.10: EC_{50} values ($mg.L^{-1}$ and μM) the ILs tested towards two freshwater microalgae (*P. subcapitata* and *C. vulgaris*).

Ionic Liquids	EC_{50} (mg/L) (lower limit; upper limit)		EC_{50} (μM) (lower limit; upper limit)	
	P. subcapitata	***C. vulgaris***	***P. subcapitata***	***C. vulgaris***
123a (M_w: 397.3)	24.1 (17.5; 30.7)	251 (225; 277)	61 (44; 77)	632 (566; 698)
125a (M_w: 394.3)	196 (155; 237)	344 (266; 422)	497 (393; 601)	873 (675; 1070)
128a (M_w: 455.3)	7.1 (6.0; 8.1)	19.9 (16.2; 23.6)	16 (13; 18)	44 (36; 52)
130a (M_w: 452.3)	16.6 (14.1; 19.7)	109 (85; 140)	37 (31; 44)	241 (188; 310)

These two distinct species of algae were used to determine (i) the effect of the mandelate ILs synthesized on a more complex trophic level and (ii) the effect of these ionic structures with respect to different species of the same trophic level. The results reported in Table 3.10 show the trend of low toxicity in descending order for both *P. subcapitata* and *C. Vulgaris* as, **125a < 123a < 130a < 128a**

According to Passino's classification,[24] these ILs are included in different categories and dependent on the algae species investigated. Thus, for the *P. subcapitata*, the IL **128a** can be classified as slightly toxic (1-10 mg/L), a moderately toxic label can be attributed to the ILs **123a** and **130a** (10-100 mg/L) while **125a** can be considered as low toxicity (100-1000 mg/L). The *C. vulgaris* is less sensitive to these ionic liquids, with **128a** categorized as moderately toxic whereas **123a**, **125a** and **130a** exhibiting low toxicity. These ILs appear to have an impact on algae different from the ordinary ionic liquids previously described in the literature[25] that we propose is related to the high complexity (c.f. [bmim]Br) of their chemical structures.

Table 3.11: Toxicity of dialkylimidazolium halides towards fresh water green algae.[26,27]

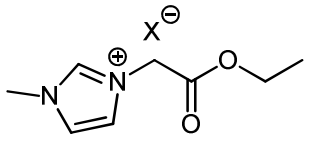
IL	Mol. wt. (g/mol)	Algae tested	EC_{50} (mg/L)	EC_{50} (µM)
N,*N*-dimethyl-*N*-octadecyl-1-octadecanaminium chloride $[N_{1,1,18,18}]Cl$	586.502	*P. subcapitata*	0.46	0.784
3-decyl-1-methyl-1H-imidazolium chloride [dmim]Cl	258.831	*S. vacuolatus*	7.05×10^{-5}	2.72×10^{-4}
1-methyl-3-tetradecyl-1H-imidazolium chloride [tdmim]Cl	314.937	*S. vacuolatus*	9.25×10^{-4}	2.94×10^{-3}

When these results were compared with those of other ILs (Table 3.11) on the basis of M_w and/or carbon content, it was found that mandelate based ILs were 10^5-10^6 times less toxic. However, there are two differing variables in this study (i) chloride anion instead of bromide and (ii) a different alga was screened i. e. *S. vacuolatus*. However, the results of this study can be used as a rough guide.

3.8 Biodegradation:

3.8.1 Introduction:

Gathergood and Scammells were first to design and synthesize biodegradable ILs. Considering Boethling's suggestions[28-31] and observations from biodegradation studies of surfactants, which indicated that the unbranched long alkyl chains and hydrolysable sites in a molecule increase biodegradation,[32] they prepared several ester and amide based imidazolium ILs (including **161a**-**b**).[33] These functional groups were chosen in order to retain important properties of ILs (i.e. melting point <100°C) while having a hydrolysable site in the molecule. Both Sturm test (OECD 301B) and closed Bottle Test (OECD 301D) were performed on new ILs **161a-b** (Fig. 3.18) along with commercial [bmim] ILs, for comparison.

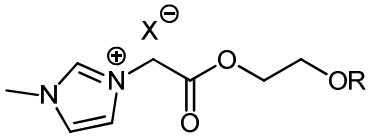


X = Br (**161a**)
= $[BF_4]$ (**161b**)

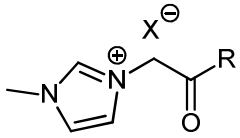
Figure 3.18: Ester based imidazolium ILs

In the Sturm test, the biodegradability was calculated in terms of the amount of CO_2 evolved from wastewater microorganisms in an aerobic aqueous medium containing the IL to be tested. A CO_2 evolution of 60 % was the threshold value to pass this test and ILs are required to pass this value (60%) to be termed as "readily biodegradable". Compounds **161a**, **161b** and [bmim][PF_6] displayed 48, 59 and 60 % degradation. After these preliminary tests, more comprehensive tests were performed using the 'closed bottle test' which involves inoculation of waste water microorganisms in an aerobic aqueous medium. Sodium *n*-dodecyl sulfate (SDS) was used as reference standard and depletion of dissolved molecular oxygen was measured up to 28 days. The ester based IL (**161a**) exhibited 19 % biodegradation compared to 0 % in the case of [bmim][BF_4] and [bmim][PF_6], however, a significant difference was observed between the results of two different test methods. The authors continued this research and synthesized propyl ester based ILs with a wide range of anions, in particular Br^-, $[BF_4]^-$, $[PF_6]^-$, $[NTf_2]^-$, $[N(CN)_2]^-$, and $[OctOSO_3]^-$.[34] The 'closed bottle' biodegradation tests were performed on these ILs and compared with the results of [bmim] based ILs possessing similar anions. The results clearly revealed that incorporation of ester functionality increased the biodegradability of ILs, with all ILs showing 10-50 % biodegradation. In the case of [bmim] based ILs <10 % biodegradation was observed, except for a $[OctOSO_3]^-$ salt (~25 %).

In 2009, Morrissey *et al.*[35] (from the same group) reported the biodegradation studies of a number of ester and amide based ILs containing Br^- and $[OctOSO_3]^-$ anions. ILs which possess an ester and amide side chain with ether functionalities are shown in Fig. 3.19. The biodegradation was evaluated using the 'CO_2 headspace test' (ISO 14593), which measures biodegradability in terms of CO_2 evolution during metabolism of IL by microbes.



R = $-CH_3$ (**162**)
= $-CH_2CH_2$ (**68**)
= $-CH_2CH_2OCH_2CH_3$ (**163**)
= $-CH_2CH_2OCH_2CH_2CH_3$ (**164**)
= $-CH_2CH_2OCH_2CH_2CH_2CH_3$ (**69**)
X = Br (**a**)
= $[OctOSO_3]$ (**b**)



R = Pyrrolidine (**165**)
= $-NHCH_2CH_2OCH_3$ (**166**)
= $-NHCH_2CH_2CH_2OCH_3$ (**167**)
= $-N(CH_2CH_2OCH_3)_2$ (**73**)
X = Br (**a**)
= [OctOSO3] (**b**)

Figure 3.19: Long chain ester and amide based ILs including ether examples.

The results showed that all $[OctOSO_3]^-$ salts **68b**, **69b**, **162-164b** exhibit ~ 60 % biodegradation, whereas the amide based ILs[35] (**73b**, **165b**-**167b**) displayed 30-40 % biodegradation. The low values in the case of amide ILs were attributed to low reaction kinetics of enzymatic hydrolysis of amide functionalities.

Stolte *et al.*[36] investigated the primary biodegradation of imidazolium and pyridinium ILs using activated sludge microbes, according to a modified version of OECD guideline 301 D.

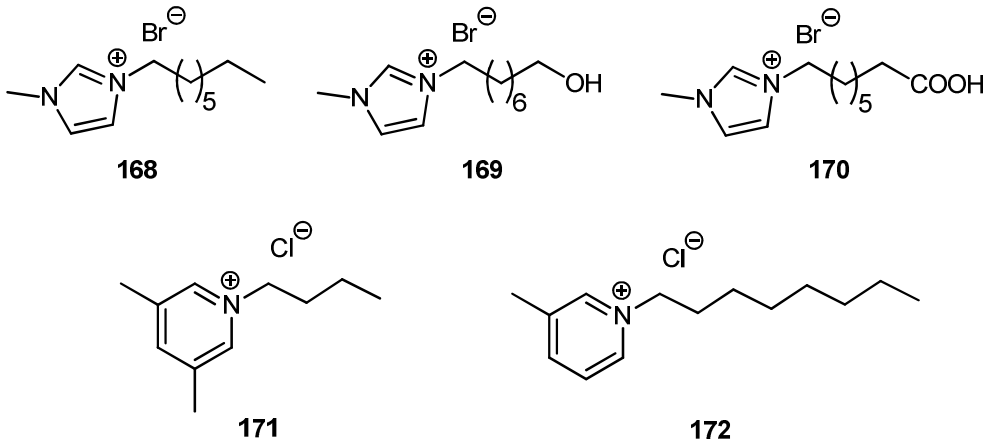


Figure 3.20: Imidazolium and Pyridinium based ILs.

A wide range of imidazolium and pyridinium based ILs (including **168**-**172**) were studied and it was found that ILs **168**-**172** undergo 100 % degradation after 31 days. This observation was consistent with the study of Doherty and co-workers.[37] The short chain ILs containing ether, nitrile and alcohol functional groups displayed 0 % biodegradation. The metabolites from the breakdown of **172** were studied, which revealed the pathway of biodegradation. Authors stated that the transformation of the alkyl chain starts with the oxidation of the terminal methyl group (ω-oxidation) catalysed probably by mono-oxygenases, e.g. by bacterial cytochrome P450 systems. The alcohol formed is subsequently oxidised by dehydrogenases, via aldehydes, to carboxylic acids. The resulting carboxylic acids then can undergo β-oxidation and the two released carbon fragments can enter the tricarboxylic acid cycle as acetylCo-A.

This postulate can be linked to the low biodegradation observed by Harjani *et al.*[38] where authors studied a number of imidazolium ILs bearing alcohol, olefin, benzyl and sulphonate functionalities at the terminal carbon. These ILs exhibited <5 % biodegradation despite

possessing $[OctOSO_3]^-$ anion, which is known to increase biodegradation. This group further investigated the biodegradability of a number of nicotinate ester and nicotinamide based ILs (Fig. 3.21).

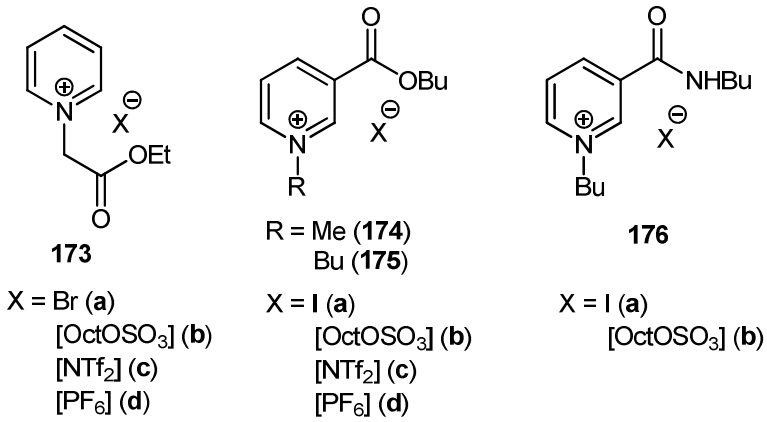


Figure 3.21: Nicotinate ester and nicotinamide based ILs.

The biodegradability was evaluated using the CO_2 headspace test. All salts of **173, 174** and **175b** were found to be readily biodegradable, whereas **176b** displayed 30 % biodegradation after 28 days, as expected. Further studies resulted in a 10-20% decrease in biodegradability of ILs, when an ester functionality on the pyridinium ring was replaced with an ether side chain.[39]

Limited data are available on the biodegradation of ammonium ILs. When *mono*, *bis* and *tris* (2-hydroxyethyl)ammonium lactate ionic liquids were tested for biodegradability using the BOD method[40], all ILs were found to be readily biodegradable (60-95%).[41] Interesting results were obtained when NAILs (naphthenic acid ILs) were screened for biodegradation.[42] In this case, carboxylates of various cores were chosen as anions for ILs for instance; alicyclic carboxylate, salicylate and lithocholate. Eight out of ten ILs (**177a-f** and **177i-j**) (Fig. 3.22) were found to be 'readily biodegradable' (60-83%), when tested using closed bottle test.[42]

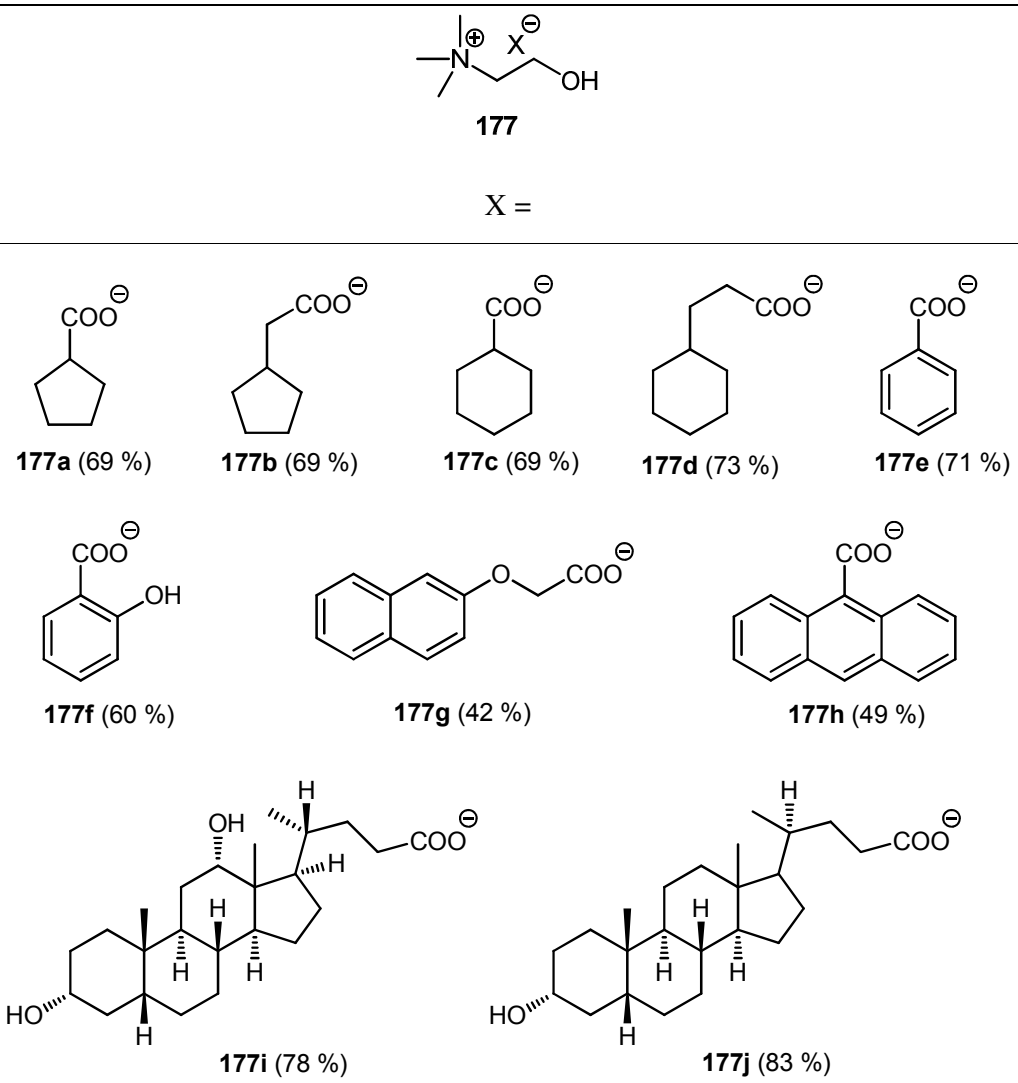


Figure 3.22: NAILs based ionic liquids; biodegradation values are given in parentheses.

The ILs possessing 2-naphthoxyacetate (**177g**) and anthracene-9-carboxylate (**177h**) anions demonstrated 42 and 49 % biodegradation after 28 days, which was attributed to the plausible toxicity of these anions towards micro-organisms.

3.8.2 Biodegradation study of synthesized ILs:

Twenty one ILs were screened for biodegradation studies (Fig. 3.23).

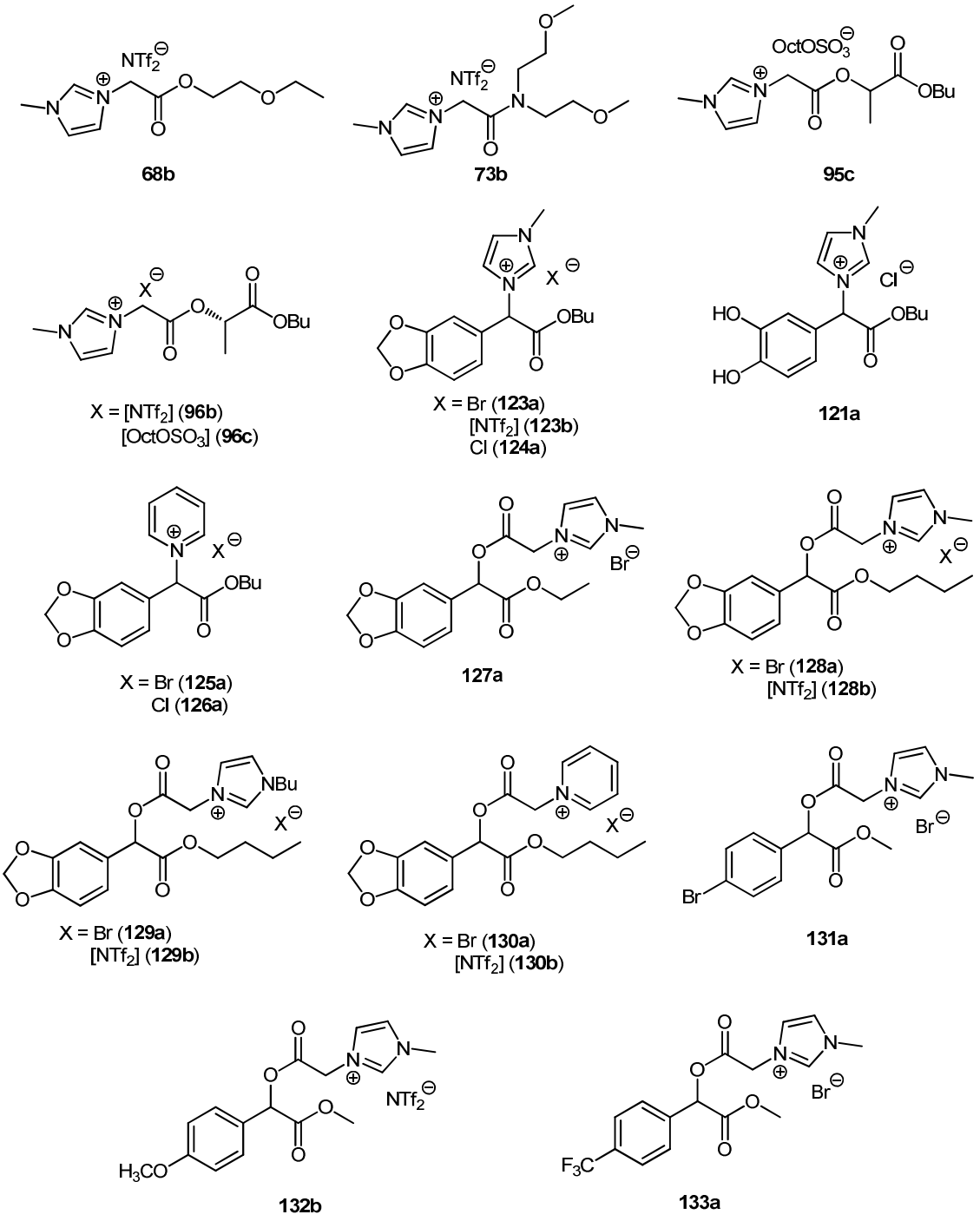


Figure 3.23: ILs screened for biodegradation study.

This panel of ILs was chosen in order to study the effect of monoester and diester functionalities on biodegradation, along with mono and di-substitution on the phenyl ring. The tests were carried out by the CO_2 headspace method (ISO 14593), using 20 mg C /L concentration of the ILs above. Sodium *n*-dodecyl sulfate was used as a reference standard.

The obtained results are classified according to the percentage biodegradation and presented below.

3.8.2.1: Readily Biodegradable ILs.

Table 3.12 lists the six compounds that were found to be readily biodegradable (>60 %; according to ISO requirements). The *R,S*-lactate based IL, **95c** possessing $[OctOSO_3]^-$ anion showed 62 % biodegradation. The $[OctOSO_3]^-$ salts are generally known to be readily biodegradable,[34,35] in part due to the high propensity for the $[OctOSO_3]^-$ ion to biodegrade. Control experiments (SDS/**95c** mixture) were performed to determine whether the **95c** was toxic to the inoculum. No inhibition of SDS biodegradation was observed.

Table 3.12: Results for readily biodegradable ILs (by CO_2 headspace method; ISO 14593).[a]

IL	**Biodegradation** (%)			
	6 days	**13 days**	**21 days**	**28 days**
SDS	73	91	92	93±2.5
95c	52	57	61	62±1.0
128a	17	21	61	60±2.2
128b	11	46	52	60±0.9
130a	35	59	63	75±3.7
130b	26	51	73	80±1.5
132b	33	64	63	64±0.9

[a] IL initial concentration= 20 mg C/L; 95% confidence limits calculated from 4 replicate experiments

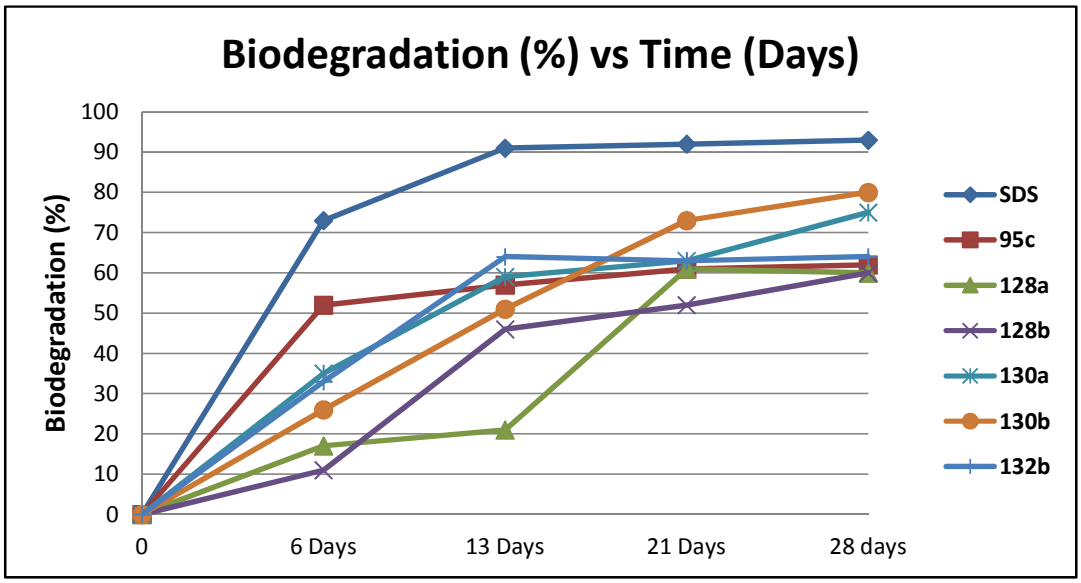


Figure 3.24: Graph of readily biodegradable ILs (by CO_2 headspace method; ISO 14593).

The pyridinium ILs both **130a** (Br^- salt) and **130b** ($[NTf_2]^-$ salt) demonstrated 75 % and 80 % biodegradation respectively, indicating that both are readily biodegradable. Neither was toxic to inoculum in control biodegradation test. We postulate that the **130a-b** are hydrolysed to **179** and **180a-b** (Fig. 3.25), and both these metabolites are readily biodegradable. This postulation is supported by the aqueous stability studies (section 3.2) where 100 % hydrolysis of **130a** was observed in 15 days when tested at 25°C. Further evidence to support the higher biodegradation of the pyridinium metabolite **180a** (c.f. imidazolium metabolite **178a**) is found from results published by Harjani *et. al.*[38] for the pyridinium IL **173a** (87 % by CO_2 headspace test; ISO 14593). The authors attributed the higher value of biodegradation to presence of ester functionality and tendency of pyridine ring to mineralize. To enable a clearer understanding of the biodegradation of the ILs, results of Br^- (**130a**) and $[NTf_2]^-$ (**130b**) salts were compared. While the $[NTf_2]^-$ contains two carbon atoms (c.f. Br), we would expect similar biodegradation values, as long as the toxicity of the ILs is independent of the anion. Imidazolium derivatives **128a** and **128b** also are readily biodegradable, (60 %) and (60 %) respectively, however, the values obtained in the CO_2 headspace test (ISO 14593) are lower than recorded for the pyridinium ILs (**130a-b**). Previously, we have determined the biodegradation of the Cl^- salt of **178a**, and recorded low to negligible CO_2 evolution in the CO_2 headspace test (ISO 14593). As the **128a-b** is postulated to breakdown via hydrolysis to metabolites **178a** and **179** (Fig. 3.25), this supports our hypothesis that **179** is readily

biodegradable and **128a**-**b** also, albeit with a recalcitrant metabolite **178a**. The postulation of hydrolytic breakdown of **128a**-**b** can be further supported by aqueous stability study of **128a** (section 3.2) which demonstrated 81 % breakdown after 15 days at 25°C.

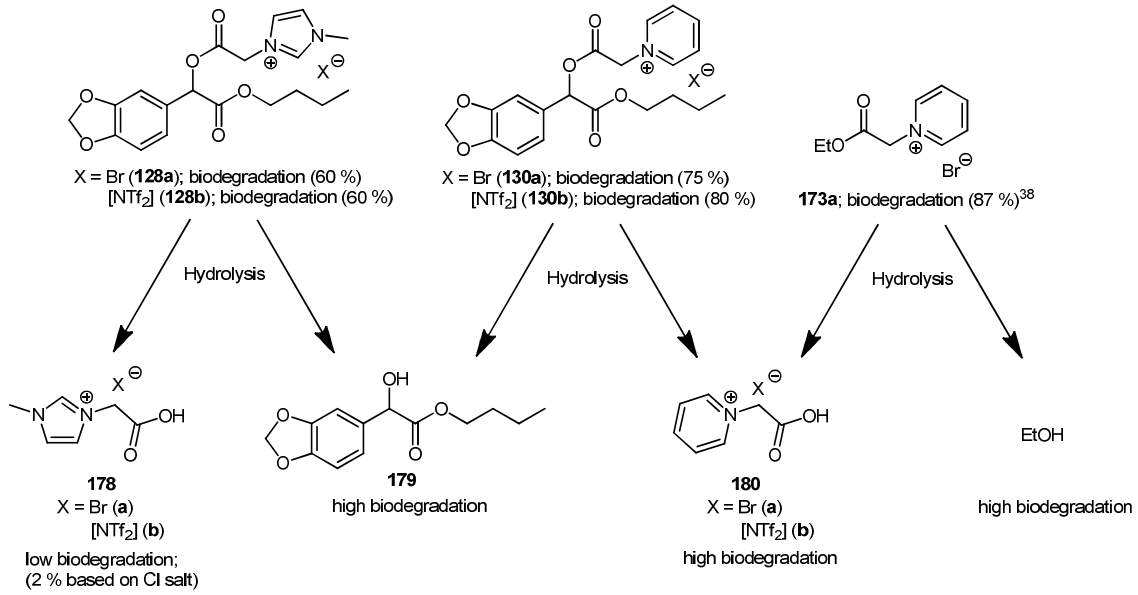


Figure 3.25: Hydrolysed products of **128a** and **130a**.

After breakdown of ILs the resultant mandelate core may follow standard metabolic pathway as shown in Fig. 3.26. The mandelate core containing protected catechol functionality may undergo deprotection through oxidation leaving behind the catechol moiety which breaks down to pyruvic acid, ultimately.

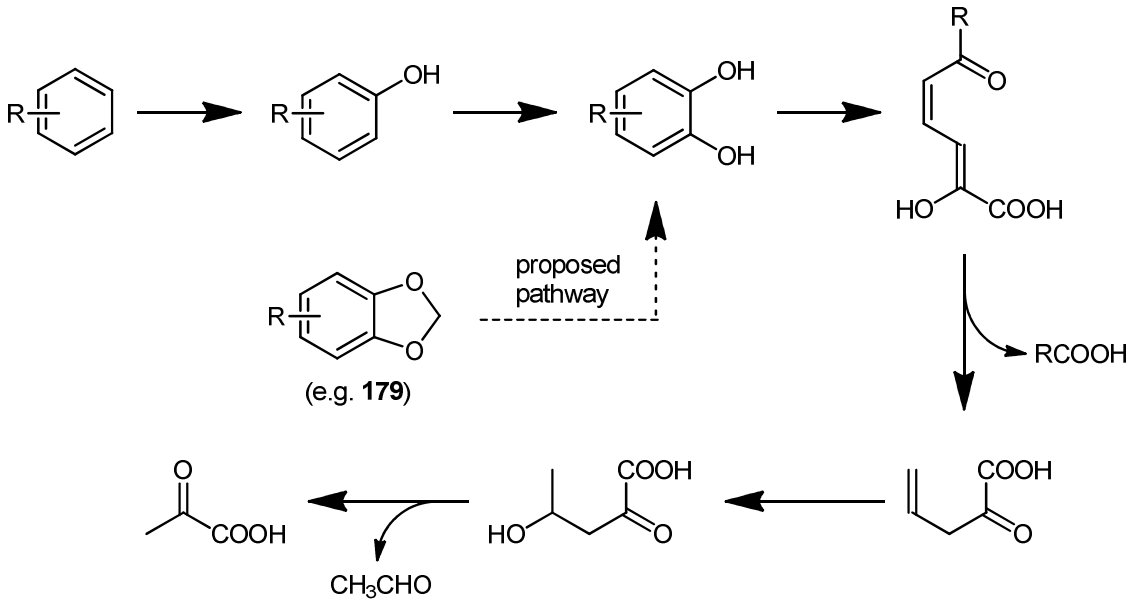


Figure 3.26: Metabolic pathway of biodegradation through enzymatic oxidation of substituted phenyl ring[43] and proposed entry point from metabolite **179**.

Compound **132b** possessing methyl protected phenol showed 64 % biodegradation. Fig. 3.27 represents proposed breakdown pathway for **132b**. The hydrolysis of secondary ester yields **178b** and mandelate derivative **181**. The Cl^- salt of **178b** was shown to be resistant towards biodegradation (2 %, CO_2 headspace test; ISO 14593), during our studies. The metabolite **181** may undergo enzymatic oxidation by enzyme 'catechol dioxygenase'[44] according to the general metabolic pathway shown in Fig. 3.26. Although one of the metabolites (**178b**) from primary biodegradation shows poor biodegradation, we propose further breakdown of **181** enables compound **132b** to be classed readily biodegradable (ISO 14593).

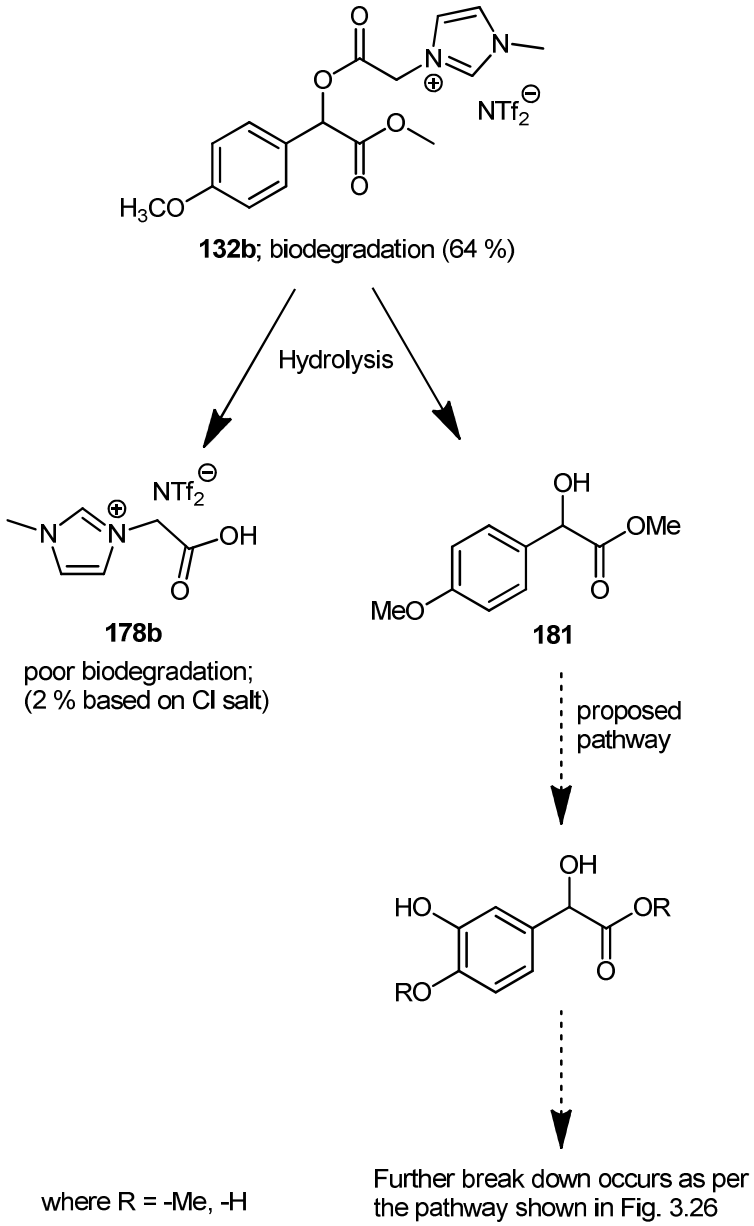


Figure 3.27: Proposed breakdown pathway for **132b**.

3.8.2.2: Moderately Biodegradable ILs.

Table 3.13 presents moderate biodegradability results (21-59 %) obtained for ten ILs. The $[NTf_2]^-$ IL, **68b** displayed 32 % biodegradation. The $[OctOSO_3]^-$ salt of **68** was screened for biodegradation previously in our group, which showed 55 % biodegradation.[35] A significant drop from 55 to 32 % can be attributed to the low biodegradability and low carbon content of anion $[NTf_2]^-$, as compared to $[OctOSO_3]^-$. The *S*-Lactate salts, **96b** and **96c** exhibited 40 and

58 % biodegradation, respectively. The comparison of results for **95c** (*R,S*-lactate, Table 3.12) and **96c** indicates that there is no significant difference between enantiopure and racemic IL.

Table 3.13: Results for moderately biodegradable ILs (by CO_2 headspace method; ISO 14593).[a]

IL	**Biodegradation** (%)			
	6 days	**13 days**	**21 days**	**28 days**
SDS	73	91	92	93±2.5
68b	28	28	35	32±0.6
96b	27	25	39	40±0.5
96c	48	57	58	58±3.0
121a	18	29	43	36±5.1
123b	20	26	27	25±2.8
125a	15	22	29	28±2.3
126a	13	20	27	32±5.0
127a	13	36	42	37±4.3
129a	30	35	37	46±5.2
129b	7	43	51	49±1.7

[a] IL initial concentration = 20 mg C/L; 95% confidence limits calculated from 4 replicate experiments

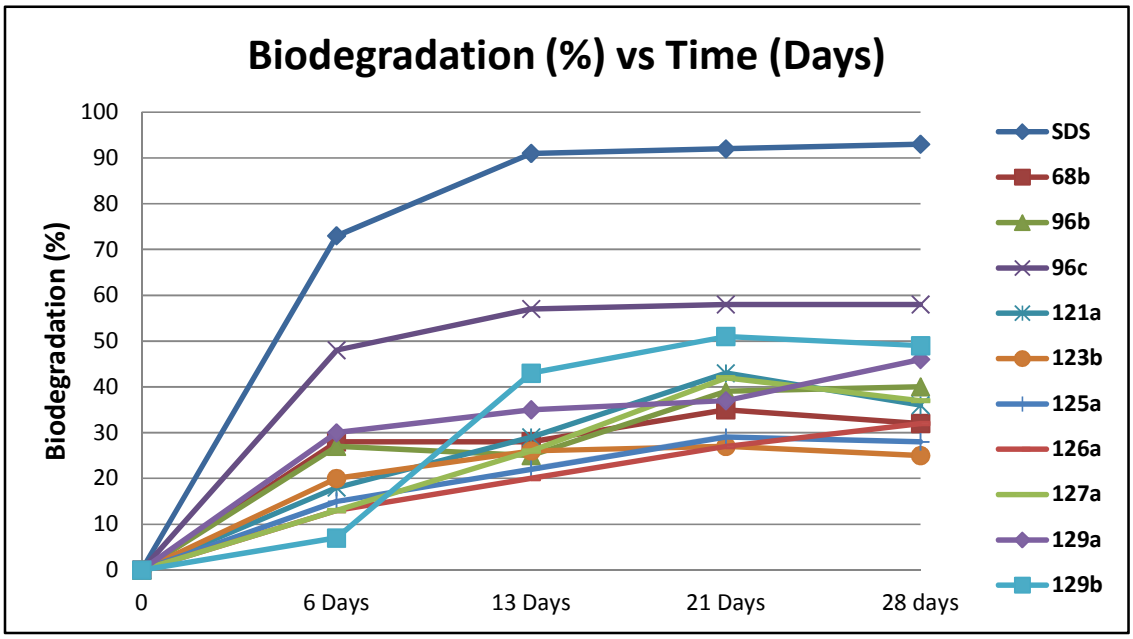


Figure 3.28: Graph of moderately biodegradable (21-59 %) ILs (by CO_2 headspace method; ISO 14593).

The catechol based IL **121a** showed 36 % biodegradation which was unexpectedly low because a molecule possessing a catechol functionality, should facilitate biodegradation, according to the pathway shown in Fig. 3.26 and our own results for ILs **128a-b** and **130a-b**. Here, we postulate that the breakdown of compound **121a** occurred via hydrolysis of the butyl ester and further biodegradation of the resulting carboxylate was inhibited (Fig. 3.29). Our hypothesis is that the catechol moiety **182** is too sterically hindered and lacks the co-ordination sphere for Fe (III) from the 'catechol dioxygenase' enzyme to bind.[44b,45] The 25-36 % biodegradation value (CO_2 headspace test-ISO 14593) can be attributed to the conversion of butanol formed due to enzymatic hydrolysis.

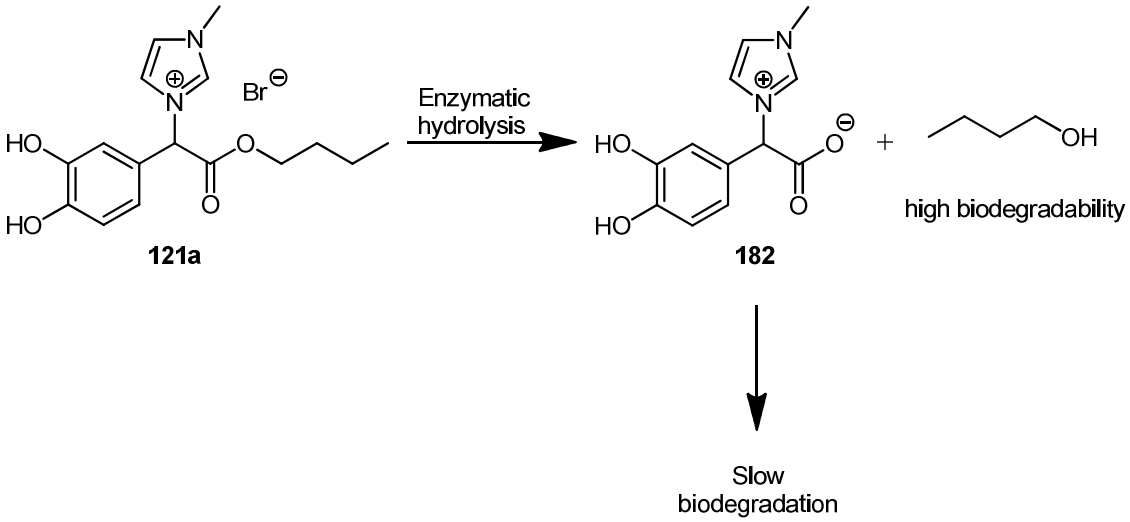


Figure 3.29: Plausible pathway to support slow biodegradation of **121a**.

The monoester compounds **123b** and **125a**, both possessing methylene di-oxy (-OCH_2O-) linkage displayed 25 and 28 % biodegradation respectively. Compound **125a** containing pyridinium core showed moderate biodegradability probably due to the same reason as in the case of **121a**. If the CO_2 evolved was due to breakdown of the aromatic ring having the butyl ester intact, then we would observe significantly lower biodegradation for these methylenedioxy series. This was not observed, thus further supporting our claims that the butyl ester is cleaved. The Cl^- salt **126a** (same cation from **125a**) showed 32 % biodegradation after 28 days which suggests that the effect of two different halides is less significant.

In the case of ethyl ester IL **127a**, 42 % biodegradation was observed after 21 days, which reduced to 37 %. This suggests that the metabolites formed after 21 days did not show further breakdown. Compounds **129a** and **129b** possessing 1-butylimidazolium core demonstrated 46 and 49 % biodegradation respectively. The studies by Stolte *et al.*[36] already have revealed that 1-methylimidazolium core showed 0 % biodegradation after 31 days. Hence 1-butylimidazole may not break down easily, thus reducing the overall biodegradability of the compound. Here, both Br^- (**129a**) and $[NTf_2]^-$ (**129b**) salts displayed analogous biodegradability as similar in the cases of **128a**-**b** and **130a**-**b** (Table 3.12).

3.8.2.3: Low Biodegradability ILs.

Table 3.14 shows the low biodegradation (0-20 %) results obtained for five ILs. The achiral IL **73b** exhibited low (3 %) biodegradation as expected due to the amide functionality, which generally presents low kinetics for hydrolysis.

Table 3.14: Results for low biodegradation ILs (by CO_2 headspace method; ISO 14593).[a]

IL	**Biodegradation** (%)			
	6 days	**13 days**	**20 days**	**28 days**
SDS	71	91	87	89±2.5
73b	0	0	1	3±1.6
123a	14	18	21	16±0.6
124a	14	19	22	18±5.5
131a	3	5	7	4±0.4
133a	3	5	6	3±0.7

[a] IL initial concentration = 20 mg C/L; 95% confidence limits calculated from 4 replicate experiments.

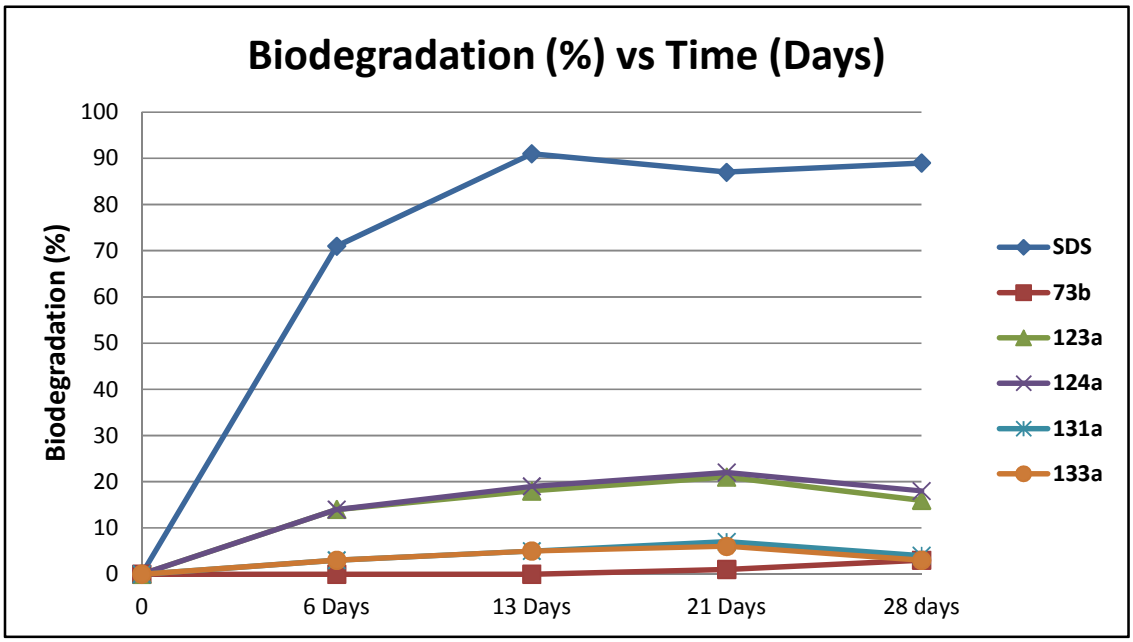


Figure 3.30: Graph of low biodegradable (0-20 %) ILs (by CO_2 headspace method; ISO 14593).

The monoester compounds **123a** (Br^- salt) and **124a** (Cl^- salt) showed 16 and 18 % biodegradation respectively. The aqueous stability study of **123a** (section 3.2) revealed that this compound did not hydrolyse after 15 days at 25°C. This resistance towards hydrolysis accounts for the low biodegradation values obtained for **123a** and **124a**. Again the effect of two different halides on biodegradation was found to be less pronounced. The monosubstituted ILs **131a** and **133a** displayed 4 and 3 % biodegradation respectively. Although these are methyl ester ILs and contains two ester functionalities, the breakdown of the phenyl ring would be necessary to obtain higher values as in these cases, more carbon content resides within the phenyl ring. Fig. 3.31 shows the proposed pathway for breakdown of **131a** and **133a**. The primary biodegradation gives the metabolites **178a** and mandelate derivative. We already have seen that **178a** shows poor biodegradation (Fig. 3.25), hence the percentage biodegradation now depends on breakdown of mandelate core. In the case of **133a,** the $-CF_3$ group withdraws electron density from the phenyl ring in the mandelate core through a negative inductive effect (-I effect) causing lower reactivity of the aromatic system towards enzymatic oxidation (Fig. 3.31), thus resisting biodegradation by this pathway. While for compound **131a**, the scenario is different as phenyl ring experiences both resonance (+R) and inductive (-I) effects due to the bromo- substituent. But the often limiting factor in the

biodegradation of aryl halide possessing compounds is the enzymatic conversion of the halide into a phenolic functionality. The process is usually slow and hence adversely affects the rate of biodegradation.[30,31] This general observation by Boethling accounts for low biodegradation obtained in the case of **131a** (Fig. 3.31). Thus poor biodegradability of metabolites formed by primary biodegradation of **131a** and **133a** gives overall low biodegradation values.

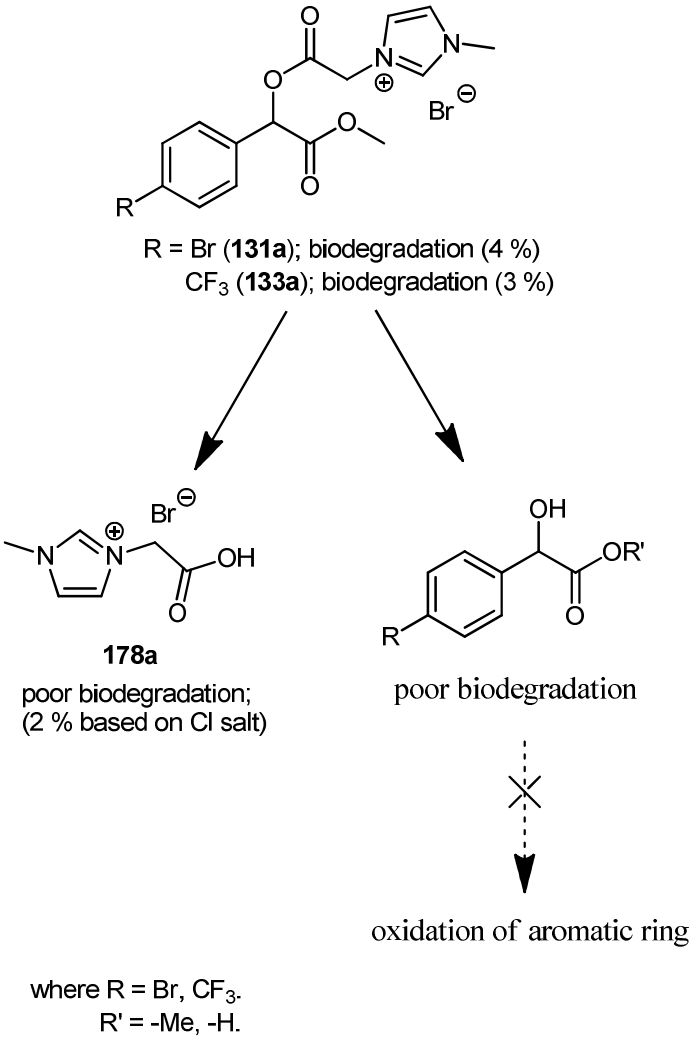


Figure 3.31: Proposed breakdown pathway for **131a** and **133a** (ISO 14593 data shown).

3.9 Summary:

Seventeen achiral ILs (salts of **69**, **71**-**73** and **76**-**78**) (Fig. 3.16) and thirty chiral ILs (salts of **91**-**97**, **123**, **125**, **128**-**130**) (Fig. 3.17) were screened for antimicrobial toxicity. The achiral ILs consisted of ester side chain with ether, long chain alkyl amides, amide with ether side

chain and cyclic amides with ether chain. All ILs with decyl side chains (**71a-c**, **72a-c**) were found to exhibit high antibacterial and antifungal activity. On the other hand, amide ILs containing a morpholine ring (**76a,b**-**78a,b**) did not exhibit any antimicrobial toxicity. The iodide ILs (**69d**, **73d**) were non-toxic at a maximum test concentration of 2.0 mM. The antibacterial tests at higher concentrations revealed that the IC_{50} value for **73d** is higher than 200 mM whereas in case of **69d** it is between 50-100 mM.

Out of the thirty chiral ILs, fourteen were lactate based ILs containing both racemic and *S* isomer components. The bromide and $[OctOSO_3]^-$ salts (**91a,c**-**97a,c**) were found to be non toxic in antimicrobial screening up to corresponding maximum test concentrations. As the actual IC_{80}/IC_{95} values were above the limit, comments on effect of anion type and enantioselectivity effects of the compounds could not be made.

Four Mandelate based ILs (**123a**, **125a**, **128a** and **130a**) were investigated for stability in D_2O. Monoester IL **123a** was found to be most stable amongst screened ILs, showing no degradation till day 15 at 25°C, while another monoester IL was degrading by 2 % by day 15. The diester ILs (**128a** and **130a)** showed significant degradation in 15 days i.e. 81 % and 100 % respectively. Pyridinium IL was surprisingly found to degrade by 49 % on day 2. The antimicrobial screening shows that **130a** possess toxicity only towards yeasts (*C. glabrata, C. lusitaniae, T. asahii*) and filamentous fungi (*A. fumigatus, A. corymbifera, T. mentagrophytes*) suggesting that eventhough the IL has a rapid degradation rate in water, the metabolites are non-toxic except against a few strains of fungi. The IL **128a** generally was non-toxic for bacteria, but marginally toxic towards yeasts (*C. glabrata, C. lusitaniae, T. asahii*) and filamentous fungi (*A. fumigatus, A. corymbifera, T. mentagrophytes*). The bromide salts of monosubstituted Mandelate ILs (**131a**-**133a**) were non-toxic throughout the antimicrobial tests. The antibacterial screening at higher concentrations revealed that only **130a** was toxic towards five strains of bacteria between 3.13-6.25 mM concentration, whereas all others (**123a**, **125a** and **128a**) have higher IC_{50} values. The antifungal screening of **123a**, **125a, 128a** and **130a** against fresh water algae *P. subcapitata* and *C. vulgaris* showed that monoester ILs **125a** exhibited low toxicity, **123a** and **130a** were moderately toxic whilst diester ILs **128a** was slightly toxic, according to Passino's classification. Further investigation revealed that generalisation is not possible in this study and the toxicities observed are specific to the strain employed in the tests.

Overall twenty one ILs were screened in this biodegradation study, out of which eleven were halides, eight $[NTf_2]^-$ examples based and two $[OctOSO_3]^-$ salts. The studies were carried out using the 'CO_2 headspace test' (ISO-14593) with sodium *n*-dodecyl sulfate as the reference

standard. All compounds were non-toxic to inoculum in control biodegradation tests. Overall six compounds were found to be readily biodegradable. The $[OctOSO_3]^-$ salt **95c** demonstrated 62 % biodegradability as expected due high propensity of $[OctOSO_3]^-$ ion to biodegrade. Pyridinium base ILs **130a**-**b** exhibited 75 and 80 % biodegradation respectively and we proposed that metabolites **179** and **180a** obtained from primary biodegradation are readily biodegradable. The imidazolium ILs **128a-b,** both displayed 60 % biodegradability, the lower value was attributed to poor biodegradability of one of the metabolites (**178a**).

Monoester ILs **121a**, **123b**, **125a** and **126a** displayed moderate biodegradability which was proposed to be due to biodegradation of butanol. The other metabolite, containing mandelate core (**182**) seems to be sterically hindered inhibiting enzymatic oxidation. In general, the diester ILs displayed higher biodegradation values than monoester ILs. The effect of two different halides (i.e. Br^- and Cl^-) on biodegradation was found to be negligible. The monosubstituted mandelic ILs (**131a**, **133a**) were found to be resistant towards biodegradation due to poor biodegradability of metabolite **178a** and resistance of mandelate core towards enzymatic oxidation. When $[NTf_2]^-$ salts were studied, overall it was found that they exhibited slightly higher biodegradation than their bromide salts. All three $[NTf_2]^-$ ILs (**128b**, **130b** and **132b**) were found to be readily biodegradable.

In the case of lactate $[OctOSO_3]^-$ ILs, the enantiopure salt (**96c**) displayed a similar value (58 %) to the racemic salt **95c** (62 %) indicating the parity of enzymes for these compounds. The amide based achiral IL **73b** showed negligible biodegradation (3 %) as expected due to resistance of amides towards enzyme catalysed hydrolysis. The overall results were satisfactory and indicated that not only the substitution on phenyl ring but also the number of ester moieties in the molecule, cation core and the anion type greatly affects the biodegradation of ILs.

Finally, we conclude that the aim of synthesizing novel low toxicity and readily biodegradable lactate and mandelate based ILs was achieved and further applications of these ILs were investigated.

3.10 Conclusion:

Out of fourty seven ILs tested in toxicity studies, the amide ILs possessing decyl chain (**71a**-**c** and **72a**-**c**) were found to be most toxic (low MIC values) against both bacteria (8 strains) and

fungi (12 strains). Whilst the lactate based ILs (**91a**-**97a**) were found to be least toxic (high MIC values) to the eight strains of bacteria and twelve strains of fungi. Although it is well known that toxicity is strain specific, we can make an arbitrary comment that increase in the lipophilic character of the IL may increase antimicrobial and antialgae toxicity. The comment can be supported by an observation that with increasing lipophilicity the penetration ability of organic compound through the cell membrane increases. While designing the low toxicity ILs one shall remember that the ILs possessing oxygen functionalities (i.e. ether and/or ester) were found to be less toxic to bacteria, fungi and algae. We have seen in the presented work that the butyl esters of lactate and mandalate core were non-toxic upto 2 mM whereas the decyl amides demonstrated high antimicrobial activity. Hence long side chains should be avoided as they increase the lipophilic character of the IL.

Out of twenty one ILs tested in biodegradation studies, the pyridinium IL **130b** exhibited maximum biodegradation (80 %) while amide IL **73b** showed lowest biodegradation (3 %). The aqueous stability studies had already shown the degradation behaviour of the mono- and diester ILs. The biodegradation data was found to be consistent with the outcomes of aqueous stability study. It was observed that ether, ester functionality, $[OctOSO_3]^-$ anion, catechol ring, pyridinium core facilitate the biodegradation process. While presence of amide functional group, aromatic ring with bromo/trifluoromethyl substituents resist the biodegradation process. Some factors such as steric bulk, lack of co-ordination sphere, presence of 1-alkylimidazole also contribute to lower the biodegradation of ILs.

Biodegradation of ILs is not strain specific hence the design of biodegradable ILs presents its own challanges. One can design readily biodegradable ILs by following Boethling's guidelines, however every compound is unique and experimental data is essential, before classifying biodegradable.[30,31] The IL shall possess phenyl/aryl rings, unbranched alkyl chains, enzymatically hydrolysable sites (for instance ester, alcohols, phenols, aldehydes) and anions like $[OctOSO_3]^-$ which helps the biodegradability. At the same time the branched alkyl chains, fused ring systems, substituents such as bromo-, nitro- must be avoided which resist the biodegradability. Alongwith the aforementioned rules, one must consider the probable toxicity, stability and synthetic viability of the chemical structure while designing the ILs. Considering the Boethling's guidelines and results from current work, several biodegradable ILs are suggested for the future work (Fig. 3.32).

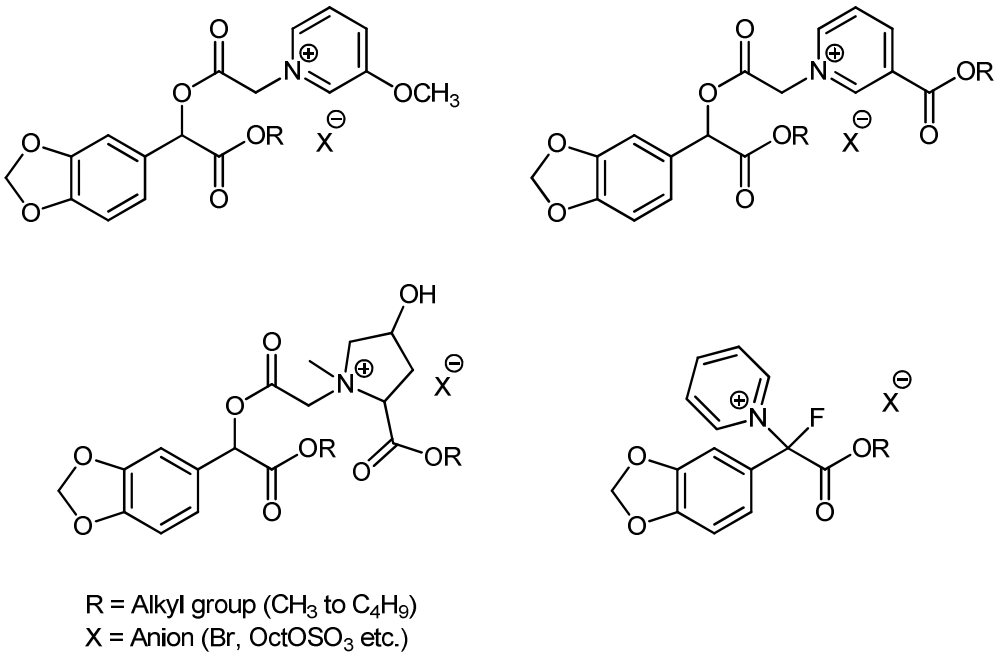


Figure 3.32: Design of ionic liquids for the future work.

Incorporation of ether and ester groups in pyridinium core would facilitate the biodegradability and break down will occur at a faster rate. In our recent studies,[46] tetrabutylammonium 4-hydroxyprolinate was found to be readily biodegradable. In this case 4-hydroxy proline ester has been included as part of the cation. The substitution of acidic proton at α-position with fluorine we postulate would increase the chemical stablity of the IL, but biodegradation data of these ILs is required to determine if these are readily biodegradable (or not).

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Chapter 4

Tsuji-Trost Reactions

4.1 Introduction:

The Tsuji-Trost reaction is one of the classical coupling methods to form C-C bonds using transition metal catalysts. A special feature of this reaction is the replacement of the leaving group on the allylic carbon with a range of suitable nucleophiles, thus it holds importance in synthesizing allyl substituted organic molecules.[1] Asymmetric Tsuji-Trost reactions are significant for synthesis of enantiopure drug molecules.[2] Ionic liquids have been investigated heavily as reaction media in transition metal catalysis for over a decade mainly because of their properties such as low vapour pressure,[3] non-flammability, high boiling point, high dielectric constant etc. There are many examples displaying the use of ILs in hydrogenation,[4] Heck,[5] Suzuki,[6] carbonyl-ene[7] and Diels-Alder reactions.[8]

A number of attempts have been made to apply ionic liquids in Tsuji-Trost reactions[9-15] as well as reactions using chitosan supported catalysts,[16] microwave assisted reactions,[17] and reactions in ionic liquids-organic solvent biphasic media.[18] Toma *et al.*[19,20] reported enantioselective Tsuji-Trost reactions in [bmim][PF_6] using a range of homochiral ferrocenyl phoshphine ligands.

Ionic liquids are considered as alternatives for conventional solvents hence evaluation of the toxicity and biodegradability of ionic liquids is a necessary step and gives added advantage in their applications. Reported data on the toxicity of [bmim] based ionic liquids shows that they are less toxic than conventional solvents (e.g. DCM, DMF).[21] The amide based ionic liquids synthesized in our group were found to have lower antimicrobial toxicity than [bmim] ILs.[22] Luczak *et al.*[22] tested the antimicrobial toxocity of [bmim][NTf_2] and found that the growth of *E. coli* was inhibited at MIC/IC_{95} = 2 mM concentration. The MIC/IC_{95} value for *Staphylococcus aureus* was observed to be > 2 mM whereas in our case the [NTf_2] salts **69b**, **73b, 75b** and **77b** were non-toxic up to 2 mM concentraton for eight strains of bacteria (see chapter 3). We reported the application of such ILs in hydrogenation reactions in our previous publication.[23]

4.2 Results and Discussion:

We have seen in the toxicity section (chapter 3) that the achiral ILs **69b**, **73b** and **77b** were non-toxic up to 2.0 mM concentration. Also these ILs are liquids at RT, facilitating their application as solvent in the reactions (Fig. 4.1).

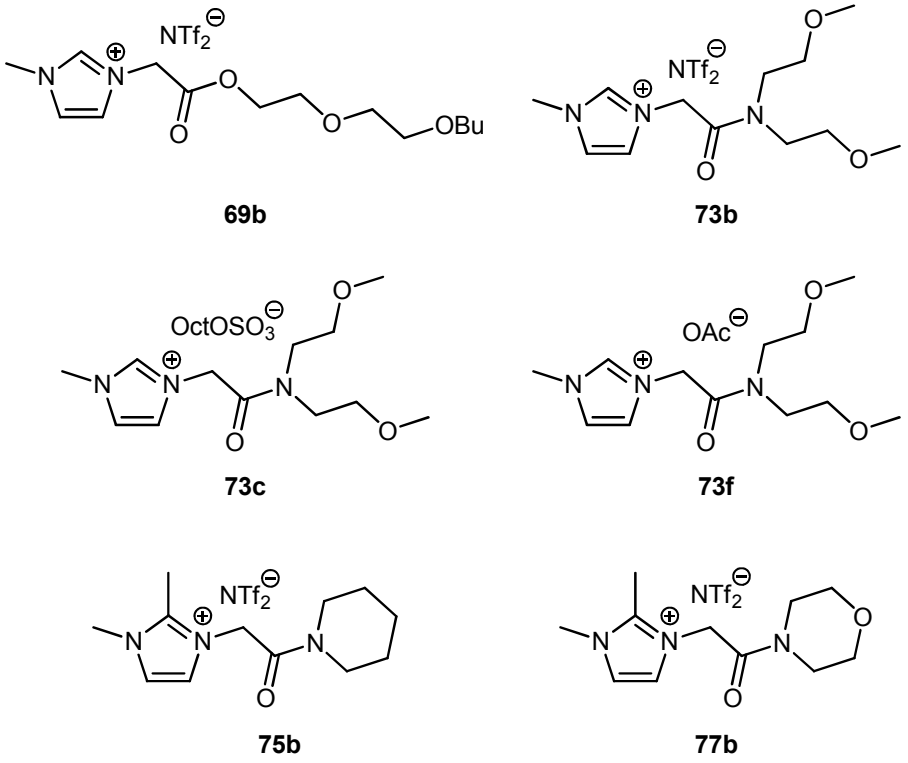
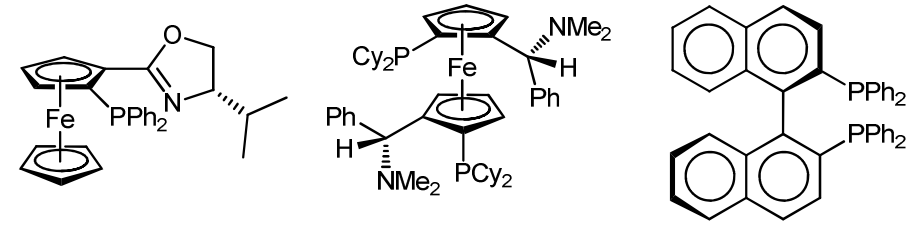


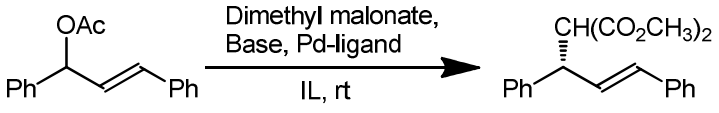
Figure 4.1: Ionic liquids used in the Tsuji-Trost reactions.



(*S,S*)-*i*Pr-phospherrox **163** | Mandyphos ligand **164** | *R*-BINAP **165**

Figure 4.2: Catalysts used for the Tsuji-Trost reaction.

The Tsuji-Trost reactions were performed at RT, under argon atmosphere, using (*E*)-1,3-diphenylallyl acetate as a substrate, dimethyl malonate as nucleophile (2.0 eq.), homochiral ferrocenyl phosphine based ligands (8 mol%) (Fig. 4.2), $Pd_2(dba)_3$ (2 mol%) as Pd^0 source and potassium carbonate (2.0 eq.) as base (Scheme 4.1). The results are shown in Table 4.1.



161 **162**

Scheme 4.1: Tsuji-Trost reaction of (*E*)-1,3-diphenylallyl acetate.

The starting point of this work was to repeat the best result obtained by Toma *et al.*[20] This was successfully repeated giving 31 % yield with 86 % enantioselectivity towards the *S*-isomer. The [bmim] salt was then replaced with our low antimicrobial toxicity ILs. An ester IL **69b** gave good enantioselectivity but with poor yield (entry 2), whereas amide IL containing ether linkage gave the best *ee* (96 %) in the reported work howver with 21 % yield (entry 3). To study the reaction kinetics, we carried out reactions for 5 h. A reaction in **73b** retained the enantioselectivity (94 %) with a very poor yield (11 %) (entry 4).

Table 4.1: Results of Tsuji-Trost reactions by K_2CO_3 method.

Entry	IL	Temp. (°C)	Time (h)	Yield (%)	*ee* (%) (*S*)
1	[bmim][PF_6]	RT	15	31	86
2	**69b**	RT	15	27	80
3	**73b**	RT	15	21	96
4	**73b**	RT	05	11	94
5	**73b**[a]	RT	15	29	88
6	**73b**[b]	RT	15	26	85
7	**69b**	40	05	20	74
8	**69b**	40	15	12	77
9	**69b**	60	05	24	66
10	**73b**	40	05	37	92
11	**73b**	40	15	37	92
12	**73b**	60	05	32	88
13	**73b**	60	15	39	80

Reaction conditions: The reaction was performed under Ar atmosphere at RT using dimethyl malonate (2.0 eq.), $Pd_2(dba)_3$ (2 mol%), (*S,S*)-^{i}Pr-phospherrox (8 mol%), K_2CO_3 (2.0 eq.), IL (1.0 eq.); [a] DIPEA (2.0 eq.), [b] mandyphos ligand (8 mol%).

The dissolution of potassium carbonate in **73b** was observed to be low as this is an inorganic salt and excess (2.0 eq.) was used in the reaction. Hence it was replaced with *N,N*-di-*iso*propylethylamine, but a similar yield with a lower *ee* was observed (entry 5). In another

experiment, the phospherrox ligand was replaced with a ligand from the mandyphos family (Fig. 4.2) which gave 26 % yield with 85 % enantioselectivity. The temperature effect on the yield and *ee* was investigated which revealed that the IL **69b** gave poor performance in terms of both yield and enantioselectivity (entries 7-9) whilst **73b** proved to be the better solvent, particularly at 40°C giving 37 % yield and 92 % *ee* (entries 10, 11).The reactions gave poor yields however, with excellent *ee* (88-96 %).

Poor yields were initially attributed to the stability of the enolate intermediate and hence we decided to shift the keto-enolate equilibrium towards the enolate by trapping it *in situ* as a silyl ether (similar to Mukaiyama condensation[24]). Thus using KOAc (2.0 eq.) and *bis*(trimethylsilyl)acetamide (2.0 eq.) the reactions were carried out under similar conditions. Along with being utilised as a base, the other reason in using KOAc in the reaction was to suppress the minor decomposition of starting material (**161**) to the corresponding alcohol, caused by trace amounts of water in the reaction. The reactions were carried out using amide based ILs (Fig. 4.1) with results presented in Table 4.2.

Table 4.2: Results of Tsuji-Trost reactions by KOAc/BSA method.

Entry	IL	Temp. (°C)	Time (h)	Yield (%)	*ee* (%) (*S*)
1	**73b**	RT	15	38	87
2	**73b**[a]	RT	15	61	83
3	**73b**[a]	RT	15	59	86
4	**73b**[b]	RT	15	75	48
5	**77b**	RT	15	47	64
6	**75b**	RT	15	43	94
7	**75b**[a]	RT	15	53	55
8	**73c**	RT	15	58	44
9	**73f**	RT	15	54	49
10	THF	RT	15	61	79
11	THF[a]	RT	15	65	63
12	DMSO	RT	15	62	97
13	DMSO[a]	RT	15	71	91

Reaction conditions: The reactions were performed under Ar atmosphere using IL (1.0 eq.), dimethyl malonate (2.0 eq.), $Pd_2(dba)_3$ (2 mol%), (*S,S*)-^{i}Pr-phospherrox (8 mol%), KOAc (2.0 eq.), *bis*(trimethylsilyl)acetamide (2.0 eq.); [a] $Pd_2(dba)_3$ (4 mol%), [b] *R*-BINAP (8 mol%).

A reaction in **73b** with 2 mol% (Pd^0) catalyst loading (entry 1) gave 38 % yield and 87 % *ee*, and when 4 mol% catalyst was used, the yield was boosted by 23 % with a minor drop in *ee* (83 % obtained) (entry 2). The repeated reaction in **73b** under same conditions gave similar results (entry 3). When the (*S,S*)-^{i}Pr-phospherrox ligand was replaced with *R*-BINAP (8 mol%), the reaction gave moderate yield (75 %) but with a substantial drop in the enantioselectivity (48 %) (entry 4). The IL (**73b**) was replaced with other amide based ILs (**75b** and **77b,** Fig. 4.1) to investigate the effects of structural modifications in the IL solvent, as our main observations lead us to postulate that due to the presence of an ether group in the IL, the catalyst may be more stable resulting in higher enantioselectivity. The IL **77b** is comprised of a cyclic ether moiety whereas **75b** has lack of ether functional group. The results were inconsistent with this theory however as improved result was obtained for **75b** (entry 6, 94 % ee) than for **77b** (entry 5, 64 % ee). Both reactions gave fair yields (43% and 47% respectively, entry 5, vs entry 6). On doubling catalyst loading (entry 7), **75b** gave only 53 % yield with a substantial drop in the enantioselectivity (55 %). The IL **73c** (Fig. 4.1) was shown to possess low antimicrobial toxicity,[25] hence **73c** was employed in a reaction which yielded 58 % product (**162**) with 44 % ee. On the other hand, the acetate IL (**73f**) gave **162** in 54 % yield with 49 % ee (entry 9). Several reactions were performed in conventional solvents for the comparision of the results. A common solvent used for Tsuji-Trost reactions (THF) lead to **162** isolated in 61 % yield with 79 % *ee* (entry 10) while with double catalyst loading (4 mol% Pd^0), gave 65 % yield and 63 % enantioselectivity was achieved (entry 11). A reaction in DMSO gave 62 % yield with excellent *ee* (97 %) (entry 12) and with 4 mol% catalyst loading reaction yield increased to 71 %, giving 91 % enantioselectivity (entry 13).

The mechanism of this reaction involves coordination of the chiral Pd-phospherrox catalyst with the target olefin (**161**) followed by oxidative addition of Pd complex to form a π-allyl complex (Fig. 4.3). S_N2 attack of the formed enolate species of dimethyl malonate on the π-allyl complex causes reduction of Pd^{II} to Pd^0. Subsequent decomplexation of the Pd-phospherrox catalyst yields product (**162**).[26] In this case the π-allyl complex possesses C_2 symmetry, hence S_N2 attack of enolate at either of the allyl termini would give the same product.

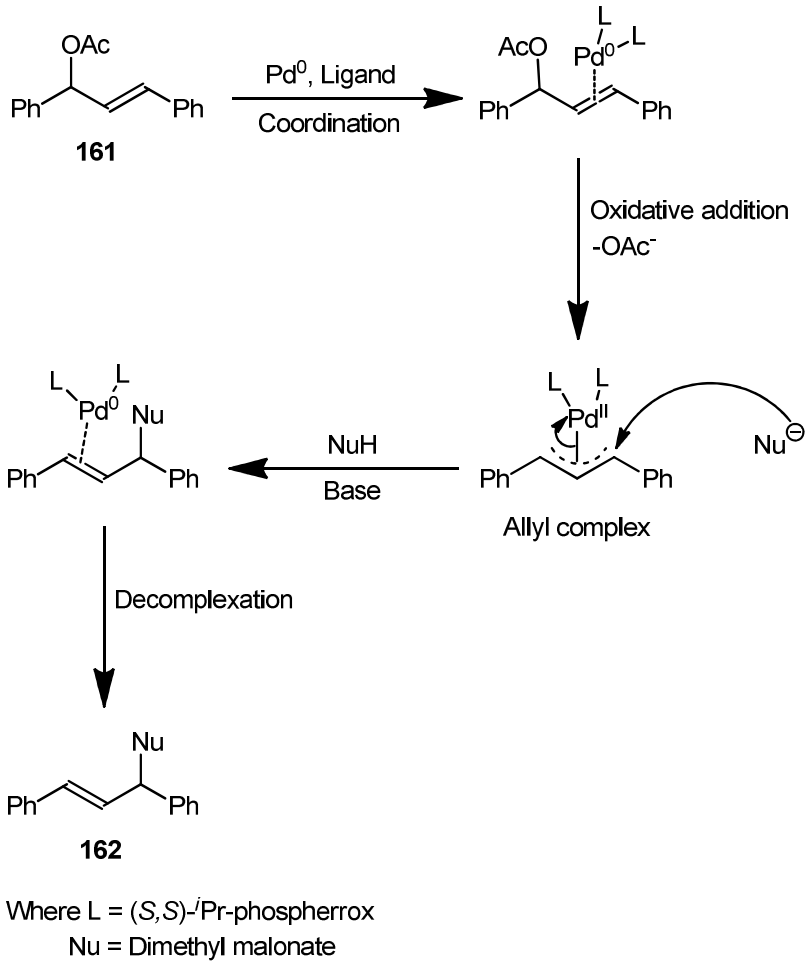


Figure 4.3: Mechanism of Tsuji-Trost reaction.

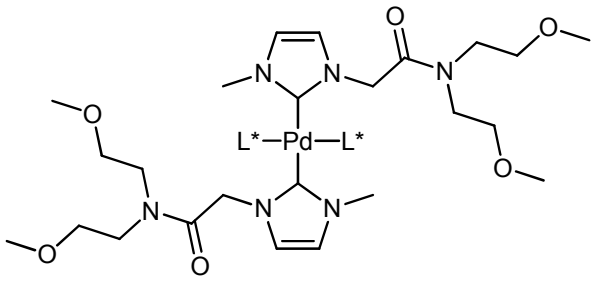
4.3 Summary:

A range of low antimicrobial toxicity ILs (**69b**, **73b-c**, **73f**, **75b** and **77b**) were employed in Tsuji-Trost reactions of (*E*)-1,3-diphenylallyl acetate (**161**). The reactions were performed using two methods i.e K_2CO_3 method and KOAc/BSA method. The ester based IL **69b** gave poor yields of **162** (12-27 %) with moderate to good *ee* (66-80 %). The amide based IL **73b** exhibited excellent enantioselectivities (88-96 %) by K_2CO_3 method but with poor yields (21-29 %) whereas by KOAc/BSA method, reactions gave fair to moderate yields (38-61 %) with good enantioselectivities (83-87 %). When piperidine based IL (**75b**) was used as a solvent, fair yield (43 %) with excellent enantioselectivity (94 %) was obtained. The temperature studies revealed that at higher temperature reactions with IL **69b** showed a decrease in both yield and *ee*, whilst the reactions with **73b** showed 16 % increase in the yield with a minimal

decrease in enantioselectivity. The experiments with lower reaction time displayed decreased yields suggesting slow reaction kinetics within the reactions.

4.4 Conclusion:

Reactions were carried out using two methods consisting two different bases. In the K_2CO_3 method, 96 % *ee* was obtained with 21 % yield using amide IL **73b**. The second best result by this method was at 40°C which gave 92 % *ee* with 37 % yield. Whilst in KOAc/*bis*(trimethylsilyl)acetamide method, IL **75b** gave 94 % *ee* with 43 % yield and IL **73b** showed 87 % *ee* with 38 % yield. While preparing the catalyst, the Pd-source and (*S,S*)-^{i}Pr-phosferrox were heated in IL at 80°C. It is well known that at higher temperature and under basic conditions imidazole ILs form carbene complex with Pd. In some cases these carbene complexes have been found to be more reactive than the original catalyst (see section 1.8.4).



L* = (*S,S*)-^{i}Pr-phosferrox

Figure 4.4: Carbene-Pd complex.

Hence in this case it can be said that IL forms a carbene complex with Pd while providing the added stability to the catalyst (Fig. 4.4). The low yields obtained in these reactions can be attributed to the mass transfer effects resulting from high viscosities of applied ILs.

The KOAc/BSA method is advantageous in terms of yields, especially, with 4 mol% (Pd^0) catalyst loading. The conventional solvents, THF and DMSO showed moderate yields and excellent enantioselectivities. However, from a toxicity point of view our ILs proved to be 'greener' and safer. Also these ILs have the potential to be further optimised for this reaction to give improved yields and enantioselectivities.

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Chapter 5
Conclusion

Atom economy is an important green chemistry metric and gives vital information about the greenness of a chemical procedure. The calculation of percentage atom economies for the procedures presented in this thesis were found to be as follows; (a) alkylating agents: 70-95 %; (b) bromide ILs: ~100 %; (c) $[NTf_2]^-$ ILs: 80-92 %; (d) $[OctOSO_3]^-$ ILs: 80-90 %. The new methods for synthesis of iodide ILs from $[NTf_2]$ salts showed low atom economies. i.e. 44 % for **69d** and 42 % for **73d**.

While evaluating the chemical procedure in terms of atom economy, ease of reaction work-up, energy requirements, use of bio-renewable sources, it can be said that these chemical procedures are 'green'. Although the synthesis of intermediates and ILs demands employment of traditional solvents, these solvents can be recycled when reactions are carried out on bulk scale or alternative methods (e.g. neat reactions) can be found in future to make the process 'greener'. In present situation the preparation of lactic acid based bromide ILs (**91a**-**94a**) are the greenest syntheses given that these procedures use bio-renewable raw materials, and has ~100 % atom economy in the final stage.

In the case of substituted mandelic acid based ILs, the raw materials (2,3-methylenedioxymandelic acid and 2,3-dihydroxymandelic acid) were synthesized in lab due to their high expense. Hence it was five step synthesis of ILs, however, the yields of intermediates and ILs were good (>80 %) to excellent (>90 %).

Overall the bromide ILs were found to be in solid state whereas the $[NTf_2]^-$, $[OctOSO_3]^-$ salts were liquid at RT. Many of the liquid ILs were found to be very thick and viscous. The actual viscosity was not measured due to sample quantity constraints. During the course of work-up the ILs were heated to 40-50 $^{\circ}$C on rota evaporator and were subjected to high vacuum drying but none of the compounds were found to undergo any chemical or thermal degradation under these conditions indicating their stability and robustness.

This series of 56 ILs, comprising different classes, offer a choice to test representative examples for toxicity & biodegradation and select specific ILs for further applications.

Out of fourty seven ILs tested in toxicity studies, the amide ILs possessing decyl chain (**71a**-**c** and **72a**-**c**) were found to be most toxic (low MIC values) against both bacteria (8 strains) and fungi (12 strains). Whilst the lactate based ILs (**91a**-**97a**) were found to be least toxic (high MIC values) to the eight strains of bacteria and twelve strains of fungi. Although it is well known that toxicity is strain specific, we can make an arbitrary comment that increase in the

lipophilic character of the IL may increase antimicrobial and antialgal toxicity. The comment can be supported by an observation that with increasing lipophilicity the penetration ability of organic compound through the cell membrane increases. While designing the low toxicity ILs one shall remember that the ILs possessing oxygen functionalities (i.e. ether and/or ester) were found to be less toxic to bacteria, fungi and algae. We have seen in the presented work that the butyl esters of lactate and mandelate core were non-toxic up to 2 mM whereas the decyl amides demonstrated high antimicrobial activity. Hence long side chains should be avoided as they increase the lipophilic character of the IL.

Out of twenty one ILs tested in biodegradation studies, the pyridinium IL **130b** exhibited maximum biodegradation (80 %) while amide IL **73b** showed lowest biodegradation (3 %). The aqueous stability studies had already shown the degradation behaviour of the mono- and diester ILs. The biodegradation data was found to be consistent with the outcomes of aqueous stability study. It was observed that ether, ester functionality, $[OctOSO_3]^-$ anion, catechol ring, pyridinium core facilitate the biodegradation process. While presence of amide functional group, aromatic ring with bromo/trifluoromethyl substituents resist the biodegradation process. Some factors such as steric bulk, lack of co-ordination sphere, presence of 1-alkylimidazole also contribute to lower the biodegradation of ILs.

Biodegradation of ILs is not strain specific hence the design of biodegradable ILs presents its own challenges. One can design readily biodegradable ILs by following Boethling's guidelines, however every compound is unique and experimental data is essential, before classifying biodegradable.[30,31] The IL shall possess phenyl/aryl rings, unbranched alkyl chains, enzymatically hydrolysable sites (for instance ester, alcohols, phenols, aldehydes) and anions like $[OctOSO_3]^-$ which helps the biodegradability. At the same time the branched alkyl chains, fused ring systems, substituents such as bromo-, nitro- must be avoided which resist the biodegradability. Alonwith the aforementioned rules, one must consider the probable toxicity, stability and synthetic viability of the chemical structure while designing the ILs. Considering the Boethling's guidelines and results from current work, several biodegradable ILs are suggested for the future work (Fig. 5.1).

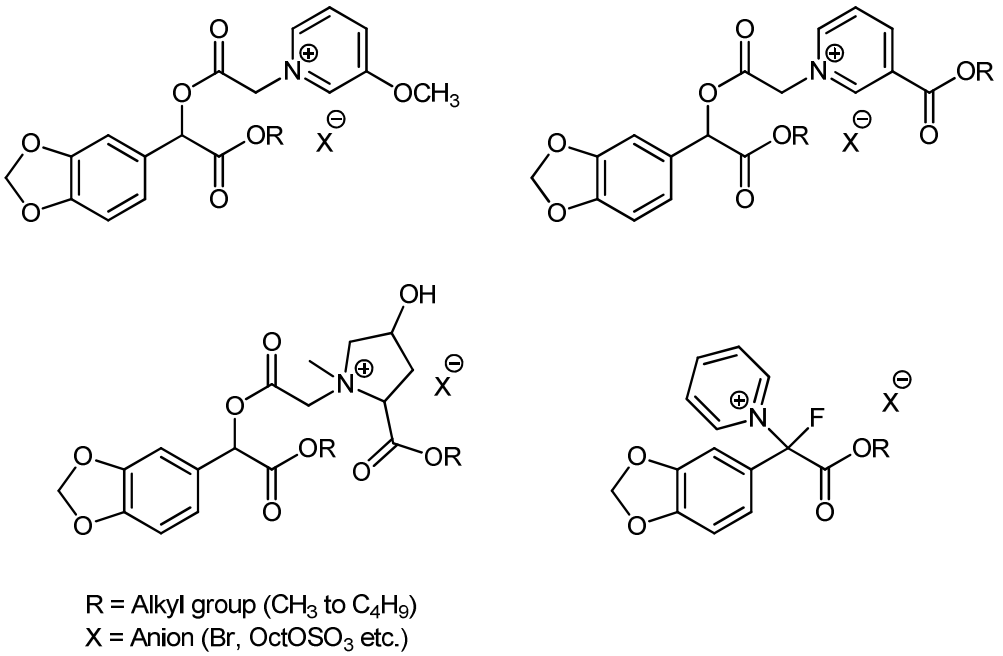
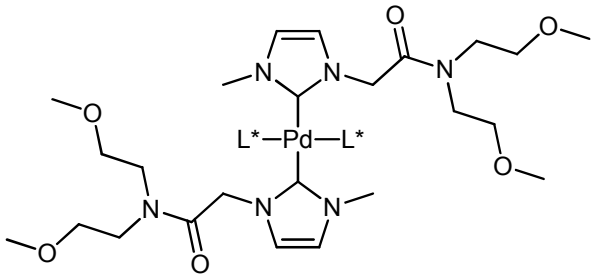


Figure 5.1: Design of ionic liquids for the future work.

Incorporation of ether and ester groups in pyridinium core would facilitate the biodegradability and break down will occur at a faster rate. In our recent studies,[46] tetrabutylammonium 4-hydroxyprolinate was found to be readily biodegradable. In this case 4-hydroxy proline ester has been included as part of the cation. The substitution of acidic proton at α-position with fluorine we postulate would increase the chemical stability of the IL, but biodegradation data of these ILs is required to determine if these are readily biodegradable (or not).

The Tsuji-Trost reactions were carried out using two methods consisting two different bases. In the K_2CO_3 method, 96 % *ee* was obtained with 21 % yield using amide IL **73b**. The second best result by this method was at 40°C which gave 92 % *ee* with 37 % yield. Whilst in KOAc/*bis*(trimethylsilyl)acetamide method, IL **75b** gave 94 % *ee* with 43 % yield and IL **73b** showed 87 % *ee* with 38 % yield. While preparing the catalyst, the Pd-source and (*S,S*)-^{i}Pr-phosferrox were heated in IL at 80°C. It is well known that at higher temperature and under basic conditions imidazole ILs form carbene complex with Pd. In some cases these carbene complexes have been found to be more reactive than the original catalyst (see section 1.8.4).



L* = (*S*,*S*)-^{i}Pr-phosferrox

Figure 5.2: Carbene-Pd complex.

Hence in this case it can be said that IL forms a carbene complex with Pd while providing the added stability to the catalyst (Fig. 5.2). The low yields obtained in these reactions can be attributed to the mass transfer effects resulting from high viscosities of applied ILs.

The KOAc/BSA method is advantageous in terms of yields, especially, with 4 mol% (Pd^0) catalyst loading. The conventional solvents, THF and DMSO showed moderate yields and excellent enantioselectivities. However, from a toxicity point of view our ILs proved to be 'greener' and safer. Also these ILs have the potential to be further optimised for this reaction to give improved yields and enantioselectivities.

Finally, we conclude that our aim of synthesizing low toxicity and readily biodegradable ionic liquids was achieved successfully. Fifty six novel chiral and achiral ILs were prepared and representative examples were tested for toxicity and biodegradability studies. Six achiral ILs were chosen to employ as reaction media in Tsuji-Trost reactions while nine achiral ILs are being tested for applications in dye-sensitized solar cells as electrolyte media.

Chapter 6
Experimental

6.1 Introduction:

6.1.1 Chemicals:

All chemicals were used from Sigma Aldrich, with the exceptions of lithium *bis*(trifluromethanesulfonyl) imide ($LiNTf_2$) which was purchased from Solvionic. Sodium octyl sulphate ($NaOctSO_4$) was synthesized according to the litereature method.[1] Methanol, hexane and triethylamine were dried over molecular sieves and distilled before use. 1-butanol, 1-pentanol and 1-octanol were dried over molecular sieves and used without further purification. Diethyl ether was dried over sodium metal wire (checked with benzophenone) and distilled before use. DCM was dried over calcium hydride, and distilled before use. Riedel de Haën silica gel was used for flash and thin layer chromatography. Sodium carbonate (Na_2CO_3), ammonium chloride (NH_4Cl), calcium chloride anhydrous ($CaCl_2{\cdot}2H_2O$) and Magnesium sulphate heptahydrate ($MgSO_4.7H_2O$) were obtained from Riedel de Haën. and Fluka respectively.

6.1.2 NMR Analysis

The NMR analysis was carried out on a Bruker 400 MHz and 600 MHz spectrometers, operating at 400, 600 MHz for ^{1}H NMR and 100, 150 MHz for ^{13}C NMR, in deuterated chloroform, DMSO, acetone, benzene or water. Chemical shifts are measured in parts per million (ppm) and coupling constants (*J*) are measured in Hertz (Hz). Numbering of specific protons and carbons of the compounds is assigned for all intermediates and ionic liquids. Splitting patterns are noted as follows:

s: singlet; d: doublet; t: triplet; q: quartet; dd: doublet of doublets; dt: doublet of triplets;

tt: triplet of triplets; tq: triplet of quartets; bs: broad singlet.

6.1.3 IR analysis

All IR analysis was carried out on a Perkin Elmer FT-IR spectrum GX spectrometer with neat samples.

6.1.4 Optical Rotation

All optical rotation measurements were carried out on a Perkin Elmer 343 Polarimeter in chloroform or ethanol at 20 $^{\circ}C$ and the values are expressed in degrees.

6.1.5 Melting point

All melting point (uncorrected) measurements were carried out on a Griffin melting point apparatus and values are expressed in degrees celcius ($^{\circ}$C).

6.1.6 Mass Spectrometry

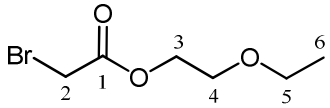
The HRMS analysis was carried out in our collaborator's laboratory at Cork using Waters Micromass LCT Premier mass spectrometer (Instrument number KD 160) at capillary voltage 3.52 kV. HMRS was obtained for all halide ionic liquids and after anion metathesis only LRMS was obtained for analogues composed of the same cation. The analysis of both chiral and achiral α-bromo ester and α-bromo amide alkylating agents was unsuccessful hence not reported.

6.2 Achiral Ionic Liquids:

6.2.1 Alkylating agents:

General Proceedure A: Preparation of achiral α-bromoesters[2]

2-Ethoxyethyl-2-bromoacetate (62)[2]



To a stirred solution of ethoxyethanol (20.04 g, 222.4 mmol) in CH_2Cl_2 (100 mL) at -5 ^oC was added sodium carbonate (28.22 g, 266.2 mmol) followed by bromoacetyl bromide (21.4 mL, 244.1 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. Then reaction mixture was filtered and washed with saturated sodium bicarbonate (50 mL) and brine solution (3 × 50 mL). The organic phase was then concentrated by rotary evaporation and crude product was purified by column chromatography (SiO_2, EtOAc:Hexane, 20:80) to obtain the title compound (**62**) as a colourless liquid in 97 % yield (45.67 g, 216.4 mmol).

Molecular formula: $C_6H_{11}BrO_3$

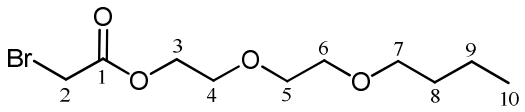
Molecular weight: 211.05 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 4.30 (t, *J* = 4.6 Hz, 2H, *H3*), 3.86 (s, 2H, *H2*), 3.64 (t, *J* = 4.6 Hz, 2H, *H4*), 3.52 (q, *J* = 7.0 Hz, 2H, *H5*), 1.20 (t, *J* = 7.0 Hz, 3H, *H6*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 167.21 (*C*OO, *C1*), 67.87 (O*C*H_2, *C3*), 66.61 (*C*H_2O, *C4*), 65.37 (O*C*H_2, *C5*), 25.90 (*C*H_2, *C2*), 15.04 (*C*H_3, *C6*).

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[2]

2-(2-Butoxyethoxy)ethyl-2-bromoacetate (63)[2]



The title compound (**63**) was prepared from di(ethyleneglycol)-*n*-butylether (23.83 g, 146.9 mmol), sodium carbonate (23.35 g, 220.3 mmol) and bromoacetyl bromide (15.4 mL, 176

mmol) according to general procedure A to afford as a colourless liquid in 98 % yield (40.82 g, 144.2 mmol).

Molecular formula: $C_{10}H_{19}BrO_4$

Molecular weight: 283.16 g/mol

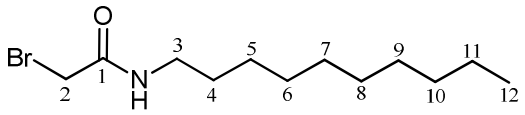
^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.26 (t, *J* = 4.8 Hz, 2H, *H3*), 3.82 (s, 2H, *H2*), 3.67 (t, *J* = 4.8 Hz, 2H, *H4*), 3.60-3.57(m, 2H, *H5*), 3.53-3.50 (m, 2H, *H6*), 3.39 (t, *J* = 6.8 Hz, 2H, *H7*), 1.50 (tt, *J* = 7.4, 6.8 Hz, 2H, *H8*), 1.30 (qt, *J* = 7.4, 7.2 Hz, 2H, *H9*), 0.85 (t, *J* = 7.2 Hz, 3H, *H10*).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 167.19 (*C*OO, *C1*), 71.18 (O*C*H$_2$, *C7*), 70.63 (O*CH$_2$*, *C5*), 70.01 (O*CH$_2$*, *C6*), 68.70 (O*CH$_2$*, *C4*), 65.31 (O*CH$_2$*, *C3*), 31.65 (N*C*H$_2$, *C8*), 25.85 (*C*H$_2$, *C2*), 19.23 (*C*H$_2$, *C9*), 13.89 (*C*H$_3$, *C10*).

IR (neat, cm^{-1}): 2958, 2933, 2867, 1738, 1279, 1107, 1035, 962, 864, 666.

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[2]

2-Bromo-N-decylacetamide (64)[3]



The title compound (**64**) was prepared from *n*-decylamine (12.65 g, 80.4 mmol), sodium carbonate (10.23 g, 96.5 mmol) and bromoacetyl bromide (8.40 mL, 96.5 mmol) according to general procedure A as a pale yellow solid in 67 % yield (14.90 g, 53.6 mmol).

Molecular formula: $C_{12}H_{24}BrNO$

Molecular weight: 278.23 g/mol

Melting point: 42-44 °C

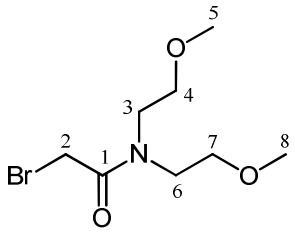
^{1}H NMR (400 MHz, $CDCl_3$) ppm: 6.43 (bs, 1H, N*H*), 3.85 (s, 2H, *H2*), 3.25 (dt, *J* = 7.2, 6.0 Hz, 2H, *H3*), 1.51 (tt, *J* = 7.2, 6.8 Hz, 2H, *H4*), 1.32-1.19 (m, 14 H, *H5-H11*), 0.85 (t, *J* = 6.8 Hz, 3H, *H12*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 165.42 (*C*O,*C2*), 40.36 (HN*C*H_2,*C4*), 31.95 (*C*H_2,*C5*), 29.60 (*C*H_2), 29.58 (*C*H_2), 29.44 (*C*H_2), 29.37 (*C*H_2), 29.32 (*C*H_2), 29.26 (*C*H_2,*C2*), 26.89 (*C*H_2), 22.75 (*C*H_2), 14.20 (*C*H_3,*C12*).

IR (neat, cm^{-1}): 3276, 2919, 2851, 1675, 1636, 1555, 1470, 1434, 1322, 1212, 941, 717.

^{1}H, ^{13}C-NMR spectra and melting point are in agreement with the literature data.[3]

2-Bromo-*N*,*N*-*bis*(2-methoxyethyl)acetamide (65)[4]



To a stirred solution of *bis*(2-methoxyethyl)amine (40.10 g, 301.1 mmol) in CH_2Cl_2 (500 mL) at −78 °C was added triethylamine (48.51 g, 479.4 mmol) followed by bromoacetyl bromide (34.8 mL, 400 mmol). The reaction mixture was stirred at −78 °C for 5 h. Then reaction mixture was washed with 10 % NH_4Cl solution (200 mL), 10 % sodium bicarbonate (200 mL), water (200 mL) and brine solution (200 mL). The organic phase was then dried over anhydrous $MgSO_4$, filtered and concentrated under high vacuum to obtain the title compound (**65**) as a brown liquid in 76 % yield (58.15 g, 228.8 mmol).

Molecular formula: $C_8H_{16}BrNO_3$

Molecular weight: 254.12 g/mol

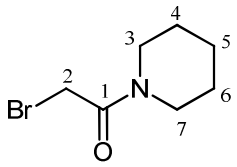
^{1}H NMR (400 MHz, $CDCl_3$) ppm: 3.96 (s, 2H, *H2*), 3.59 (t, *J* = 5.2 Hz, 2H, *H3/H6*), 3.52-3.48 (m, 4H, *H3/H6, H4/C7*), 3.48 (t, *J* = 5.2 Hz, 2H, *H4/H7*), 3.28 (s, 6H, *H5, H8*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 167.66 (*C*OO, *C1*), 70.70 (O*C*H_2, *C4/C7*), 70.28 (O*C*H_2, *C4/C7*), 59.09 (O*C*H_3, *C5/C8*), 58.89 (O*C*H_3, *C5/C8*), 50.05 (N*C*H_2, *C3/C6*), 46.83 (N*C*H_2, *C3/C6*), 27.25 (*C*H_2, *C2*).

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[4]

IR (neat, cm^{-1}): 2984, 2929, 2890, 1643, 1456, 1419, 1365, 1189, 1112, 1012, 964, 825, 708.

2-Bromo-1-(piperidin-1-yl)ethan-1-one (66)



The title compound (**66**) was prepared from piperidine (30.12 g, 345.7 mmol), sodium carbonate (35.68 g, 336.6 mmol) and bromoacetyl bromide (23.4 mL, 269 mmol) according to the general procedure A as a colourless liquid in 78 % yield (36.25 g, 175.9 mmol).

Molecular formula: $C_7H_{12}BrNO$

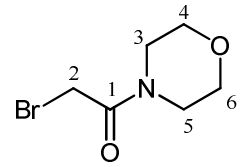
Molecular weight: 206.08 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 3.82 (s, 2H, *H2*), 3.51 (t, *J* = 5.6 Hz, 2H, *H3/H7*), 3.40 (t, *J* = 5.6 Hz, 2H, *H3/H7*), 1.63-1.60 (m, 4H, *H4/ H6, H5*), 1.55-1.49 (m, 2H, *H4/H6*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 164.98 (*C*ON, *C1*), 47.91 (N*C*H$_2$, *C3/C7*), 43.23 (N*C*H$_2$, *C3/C7*), 26.25 (*C*H$_2$, *C4/C6*), 26.19 (*C*H$_2$, *C2*), 25.37 (*C*H$_2$, *C*5), 24.26 (*C*H$_2$, *C4/C6*).

IR (neat, cm^{-1}): 2936, 2856, 1634, 1443, 1367, 1272, 1258, 1211, 1129, 1101, 1020, 953, 852, 714.

2-Bromo-1-(morpholin-4-yl)ethan-1-one (67)



The title compound (**67**) was prepared from morpholine (30.12 g, 345.7 mmol), sodium carbonate (54.97 g, 518.59 mmol) and bromoacetyl bromide (36.2 mL, 415 mmol) according to the general procedure A as a colourless liquid in 85 % yield (61.06 g, 293.5 mmol).

Molecular formula: $C_6H_{10}BrNO_2$

Molecular weight: 208.05 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 3.78 (s, 2H, *H2*), 3.63 (t, *J* = 4.8 Hz, 2H, *H4/H5*), 3.58 (t, *J* = 4.8 Hz, 2H, *H4/H5*), 3.51 (t, *J* = 4.8 Hz, 2H, *H3/H6*), 3.42 (t, *J* = 4.8 Hz, 2H, *H3/H6*).

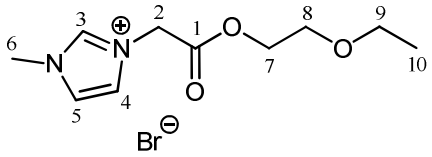
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 165.27 (*C*OO, *C1*), 66.35 (O*C*H$_2$, *C4/C5*), 66.14 (O*C*H$_2$, *C4/C5*), 46.92 (N*C*H$_2$, *C3/C6*), 42.19 (N*C*H$_2$, *C3/C6*), 25.48 (*C*H$_2$, *C2*).

IR (neat, cm^{-1}): 2966, 2857, 1636, 1459, 1436, 1361, 1274, 1217, 1109, 1068, 1036, 964, 846, 719.

6.2.2 Bromide Ionic Liquids:

General Procedure B: Preparation of achiral bromide ILs[2]

3-[2-(2-Ethoxyethoxy)-2-oxoethyl]-1-methyl-1H-imidazol-3-ium bromide (68a)[2]



To a stirred solution of 2-ethoxyethyl-2-bromoacetate (**62**) (45.67 g, 216.4 mmol) in diethyl ether (200 mL), 1-methylimidazole (17.77 g, 216.4 mmol) was added dropwise at RT under a N_2 atmosphere. After stirring overnight the white solid of product was separated from the solvent by decantation. The solid was washed with diethyl ether (5 x 100 mL) and dried under high vacuum to obtain the title compound (**68a**) as white solid in 91 % yield (57.96 g, 197.7 mmol).

Molecular formula: $C_{10}H_{17}BrN_2O_3$

Molecular weight: 293.16 g/mol

Melting Point: 24-26 $^{\circ}$C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 10.28 (s, 1H, *H3*), 7.55 (t, *J* = 1.8 Hz, 1H, *H4/H5*), 7.40 (t, *J* = 1.8 Hz, 1H, *H4/H5*), 5.52 (s, 2H, *H2*), 4.35 (t, *J* = 4.8 Hz, 2H, *H7*), 4.01 (s, 3H, *H6*), 3.67 (t, *J* = 4.8 Hz, 2H, *H8*), 3.53 (q, *J* = 7.0 Hz, 2H, *H9*), 1.20 (t, *J* = 7.0 Hz, 3H, *H10*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 166.09 (*C*OO, *C1*), 137.82 (Ar*C*H, *C3*), 123.74 (Ar*C*H, *C4/C5*), 123.16 (Ar*C*H, *C4/C5*), 67.49 (O*C*H_2, *C8*), 66.40 (O*C*H_2, *C9*), 65.50 (O*C*H_2, *C7*), 50.03 (N*C*H_2, *C2*), 36.71 (N*C*H_3, *C6*), 14.88 (*C*H_3, *C10*).

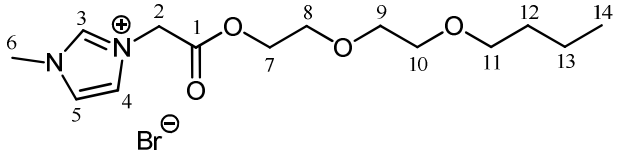
IR (neat, cm^{-1}): 3411, 3152, 3085, 2975, 1747, 1632, 1576, 1437, 1378, 1217, 1174, 1115, 1025, 875.

HRMS (ESI$^+$, *m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{10}H_{17}N_2O_3^+$, requires = 213.1231, found = 213.1239.

MS (*m/z*): 213.10 $[M\text{-}Br^-]^+$

^{1}H, ^{13}C-NMR spectra and melting point are in agreement with the literature data.[2]

3-{2-[2-(2-Butoxyethoxy)ethoxy]-2-oxoethyl}-1-methyl-1H-imidazol-3-ium bromide (69a)[2]



The title compound (**69a**) was prepared from 1-methylimidazole (5.85 g, 71.3 mmol) and 2-(2-butoxyethoxy)ethyl-2-bromoacetate (**63**) (20.18 g, 71.3 mmol) according to the general procedure B to afford a white solid in 90 % yield (23.5 g, 63.3 mmol).

Molecular formula: $C_{14}H_{25}BrN_2O_4$

Molecular weight: 365.26 g/mol

Melting Point: 78-80 °C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 10.13 (s, 1H, *H3*), 7.68 (t, *J* = 1.8, Hz, 1H, *H4/H5*), 7.51 (t, *J* = 1.8, Hz, 1H, *H4/H5*), 5.50 (s, 2H, *H2*), 4.33 (t, *J* = 4.8 Hz, 2H, *H7*), 4.06 (s, 3H, *H6*), 3.71 (t, *J* = 4.8 Hz, 2H, *H8*), 3.61 (t, *J* = 5.2 Hz, 2H, *H9*), 3.55 (t, *J* = 5.2 Hz, 2H, *H10*), 3.42 (t, *J* = 6.8 Hz, 2H, *H11*), 1.51 (tt, *J* = 7.6, 6.8 Hz, 2H, *H12*), 1.31 (tq, *J* = 7.6, 7.4 Hz, 2H, *H13*), 0.87 (t, *J* = 7.4 Hz, 3H, *H14*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 166.19 (*C*OO, *C1*), 138.05 (Ar*C*H, *C3*), 123.91 (Ar*C*H, *C4/C5*), 123.15 (Ar*C*H, *C4/C5*), 71.09 (O*C*H$_2$, *C11*), 70.49 (O*C*H$_2$, *C9*), 69.84 (O*C*H$_2$, *C10*), 68.45 (O*C*H$_2$, *C8*), 65.53 (O*C*H$_2$, *C7*), 50.14 (N*C*H$_2$, C2), 36.84 (N*C*H$_3$, *C6*), 31.53 (*C*H$_2$, *C12*), 19.14 (*C*H$_2$, *C13*), 13.86 (*C*H$_3$, *C14*).

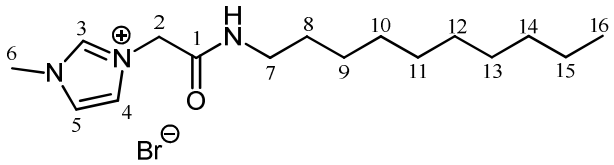
IR (neat, cm^{-1}): 3134, 3094, 2954, 2871, 1752, 1577, 1567, 1448, 1370, 1341, 1281, 1236, 1219, 1193, 1169, 1128, 1096, 1044, 967, 881, 850, 770, 713.

HRMS (ESI$^+$,*m/z*): Calculated for [M-Br$^-$]$^+$, $C_{14}H_{25}N_2O_4^+$, requires = 285.1814, found = 285.1803.

MS (*m/z*): 285.20 [M-Br$^-$]$^+$

^{1}H, ^{13}C-NMR spectra and melting point are in agreement with the literature data.[2]

3-[(Decylcarbamoyl)methyl]-1-methyl-1H-imidazol-3-ium bromide (70a)[3]



The title compound (**70a**) was prepared from 1-methylimidazole (0.68 g, 8.28 mmol) and alkylating agnt (**64**) (2.30 g, 8.3 mmol) according to the general procedure B to obtain a white solid in 90 % yield (2.69 g, 7.5 mmol).

Molecular formula: $C_{16}H_{30}BrN_3O$

Molecular weight: 360.33 g/mol

Melting Point: 94-96 °C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.76 (s, 1H, *H3*), 8.56 (t, *J* = 6.0 Hz, 1H, *NH*), 7.62 (t, *J* = 1.6 Hz, 1H, *H4/H5*), 7.25 (t, *J* = 1.6 Hz, 1H, *H4/H5*), 5.35 (s, 2H, *H2*), 4.02 (s, 3H, *H6*), 3.19 (td, *J* = 7.2, 6.0 Hz, 2H, *H7*), 1.54 (tt, *J* = 7.2, 6.8 Hz, 2H, *H8*), 1.30-1.18 (m, 14H, *H9-15*), 0.85 (t, *J* = 6.8 Hz, 3H, *H16*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 164.34 (*C*O, *C1*), 137.58 (N*C*HN, *C3*), 123.90 (N*C*H, *C4/C5*), 122.52 (N*C*H, *C4/C5*), 51.90 (N*C*H_2, *C2*), 40.21 (HN*C*H_2, *C7*), 36.89 (N*C*H_3, *C6*), 31.98 (*C*H_2, *C8*), 29.67 (*C*H_2), 29.66 (*C*H_2), 29.40 (*C*H_2), 29.36 (*C*H_2), 29.21 (*C*H_2), 27.15 (*C*H_2), 22.77 (*C*H_2), 14.22 (*C*H_3, *C16*).

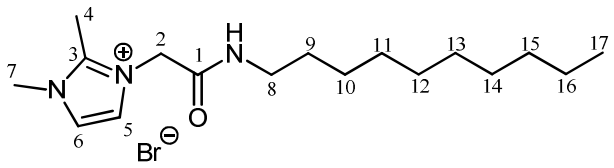
IR (neat, cm^{-1}): 3450, 2981, 1693, 1608, 1512, 1435, 1292, 1173, 1030, 827.

HRMS (ESI^+,*m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{16}H_{30}N_3O^+$, requires = 280.2383, found = 280.2389.

MS (*m/z*): 280.20 $[M\text{-}Br^-]^+$

^{1}H, ^{13}C-NMR spectra and melting point are in agreement with the literature data.[3]

3-[(Decylcarbamoyl)methyl]-1,2-dimethyl-1H-imidazol-3-ium bromide (71a)



The title compound (**71a**) was prepared from 1,2-dimethylimidazole (1.82 g, 18.9 mmol) and alkylating agnt (**64**) (5.27 g, 18.9 mmol) according to the general procedure B to afford a white solid in 91 % yield (6.48 g, 17.3 mmol).

Molecular formula: $C_{17}H_{32}BrN_3O$

Molecular weight: 374.36 g/mol

Melting point: 120-122 °C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 8.72 (t, *J* = 5.8 Hz, 1H, *NH*), 7.65 (d, *J* = 2.0 Hz, 1H, *H5/H6*), 7.33 (d, *J* = 2.0 Hz, 1H, *H5/H6*), 5.26 (s, 2H, *H2*), 3.88 (s, 3H, *H7*), 3.18 (td, *J* = 7.6, 5.8 Hz, 2H, *H8*), 2.78 (s, 3H, *H4*), 1.55 (tt, *J* = 7.6, 7.2 Hz, 2H, *H9*), 1.27-1.21 (m, 14H, *H10-16*), 0.84 (t, *J* = 7.2 Hz, 3H, *H17*).

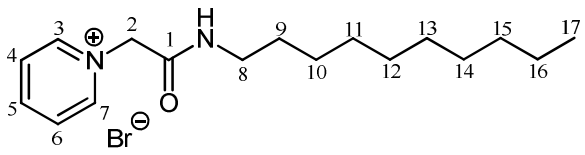
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 164.37 (*C*O, *C1*), 145.46 (N*C*N, *C3*), 122.80 (N*C*H, *C5/C6*), 122.04 (N*C*H, *C5/C6*), 51.13 (N*C*H_2, *C2*), 40.12 (HN*C*H_2, *C8*), 35.97 (N*C*H_3, *C7*), 31.96 (*C*H_2, *C9*), 29.65 (*C*H_2), 29.64 (*C*H_2), 29.38 (*C*H_2), 29.33 (*C*H_2), 29.22 (*C*H_2), 27.14 (*C*H_2), 22.75 (*C*H_2), 14.20 (*C*H_3, *C17*), 11.14 (*C*H_3, *C4*).

IR (neat, cm^{-1}): 3419, 3218, 2920, 1691, 1671, 1638, 1565, 1487, 1252, 1090, 782.

HRMS (ESI$^+$,*m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{17}H_{32}N_3O^+$, requires = 294.2539, found = 294.2542.

MS (*m/z*): 294.20 $[M\text{-}Br^-]^+$

1-[(Decylcarbamoyl)methyl]pyridin-1-ium bromide (72a)



The title compound (**72a**) was prepared from pyridine (1.58 g, 20.02 mmol) and alkylating agnt (**64**) (5.56 g, 20.0 mmol) according to the general procedure B to obtain a white solid in 97 % yield (6.90 g, 19.3 mmol).

Molecular formula: $C_{17}H_{29}BrN_2O$

Molecular weight: 357.33 g/mol

Melting point: 168-169 °C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.28 (dd, *J* = 5.5, 1.6 Hz, 2H, *H3, H7*), 8.80 (t, *J* = 5.6 Hz, 1H, *NH*), 8.47 (tt, *J* = 7.6, 1.6 Hz, 1H, *H5*), 8.05 (dd, J = 7.6, 5.5 Hz, 2H, *H4, H6*), 5.95 (s, 2H, *H2*), 3.21 (td, *J* = 7.2, 5.6 Hz, 2H, *H8*), 1.55 (tt, *J* = 7.6, 7.2 Hz, 2H, *H9*), 1.28-1.21 (m, 14H, *H10-16*), 0.85 (t, *J* = 7.2 Hz, 3H, *H17*).

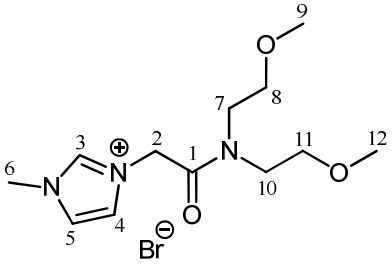
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 163.37 (*C*O, *C1*), 146.03 (2Ar*C*H, *C3, C7*), 145.41 (Ar*C*H, *C5*), 127.82 (2Ar*C*H, *C4/C6*), 62.52 (N*C*H_2, *C2*), 40.46 (HN*C*H_2, *C8*), 31.97 (*C*H_2), 29.66 (*C*H_2), 29.63 (*C*H_2), 29.39 (*C*H_2), 29.32 (*C*H_2), 29.14 (*C*H_2), 27.13 (*C*H_2), 22.76 (*C*H_2), 14.21 (*C*H_3, *C17*).

IR (neat, cm^{-1}): 3418, 3218, 2921, 2851, 1671, 1637, 1566, 1486, 1342, 1251, 1090, 782.

HRMS (ESI^+,*m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{17}H_{29}N_2O^+$, requires = 277.2274, found = 277.2280.

MS (*m/z*): 277.20 $[M\text{-}Br^-]^+$

3-{[*bis*(2-Methoxyethyl)carbamoyl]methyl}-1-methyl-1H-imidazol-3-ium bromide (73a)[2]



The title compound (**73a**) was prepared from 1-methylimidazole (23.06 g, 280.8 mmol) and 2-bromo-*N*,*N*-*bis*-(2-methoxyethyl) acetamide (**65**) (71.37 g, 280.9 mmol) according to the general procedure B to obtain a yellow solid in 83 % yield (78.04 g, 232.1 mmol).

Molecular formula: $C_{12}H_{22}BrN_3O_3$

Molecular weight: 336.23 g/mol

Melting Point: 68-70 °C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.76 (s, 1H, *H3*), 7.47 (t, *J* = 1.6 Hz, 1H, *H4/H5*), 7.41 (t, *J* = 1.6 Hz, 1H, *H4/H5*), 5.57 (s, 2H, *H2*), 3.98 (s, 3H, *H6*), 3.62 (t, *J* = 4.8 Hz, 2H, *H7/H10*), 3.49 (t, *J* = 4.8 Hz, 2H, *H8/H11*), 3.47 (t, *J* = 4.8 Hz, 2H, *H8/H11*), 3.41(t, *J* = 4.8 Hz, 2H, *H7/H10*), 3.28 (s, 3H, *H9/H12*), 3.23 (s, 3H, H9/*H12*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 165.62 (*C*OO, *C1*), 138.01 (Ar*C*H, *C3*), 123.99 (Ar*C*H, *C4/C5*), 122.61 (Ar*C*H, *C4/C5*), 70.30 (O*C*H_2, *C8/C11*), 70.04 (O*C*H_2, *C8/C11*), 59.19 (O*C*H_3, *C9/C12*), 58.80 (O*C*H_3, *C9/C12*), 50.61 (N*C*H_2, *C2*), 48.59 (N*C*H_2, *C7/C10*), 46.68 (N*C*H_2, *C7/C10*), 36.73 (N*C*H_3, *C6*).

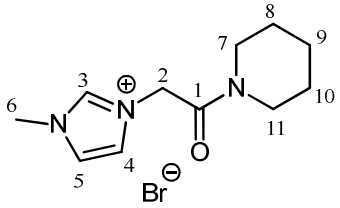
IR (neat, cm^{-1}): 3420, 3078, 2930, 1651, 1570, 1470, 1424, 1350, 1175, 1111, 1014, 922, 827, 727.

HRMS (ESI$^+$,*m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{12}H_{22}N_3O_3^+$, requires = 256.1661, found = 256.1653.

MS (*m/z*): 256.20 $[M\text{-}Br^-]^+$

^{1}H, ^{13}C-NMR spectra and melting point are in agreement with the literature data.[2]

1-Methyl-3-[2-(piperidin-1-yl)-2-oxoethyl]-1H-imidazol-3-ium bromide (74a)



The title compound (**74a**) was prepared from 1-methylimidazole (1.65 mL, 20.77 mmol) and 2-bromo-1-(piperidin-1-yl)ethan-1-one (**66**) (4.28 g, 20.8 mmol) according to the general procedure B to obtain a white solid in 89 % yield (5.33 g, 18.5 mmol).

Molecular formula: $C_{11}H_{18}BrN_3O$

Molecular weight: 288.18 g/mol

Melting Point: 96-98°C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.89 (s, 1H, *H3*), 7.56 (t, *J* = 1.8 Hz, 1H, *H4/5*), 7.35 (d, *J* = 1.8 Hz, 1H, *H4/H5*), 5.68 (s, 2H, *H2*), 4.01 (s, 3H, *H6*), 3.52-3.49 (m, 4H, *H7, H11*), 1.73-1.62 (m, 4H, *H8/H10, H9*), 1.58-1.53 (m, 2H, *H8/H10*).

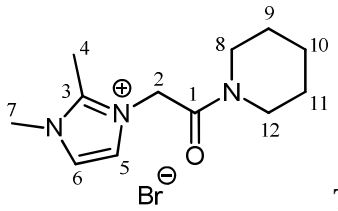
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 162.52 (*C*OO, *C1*), 138.36 (Ar*C*H, *C3*), 124.59 (ArN*C*H, *C4/C5*), 122.15 (Ar*C*H, *C4/C5*), 50.86 (N*C*H_2, *C2*), 46.37 (N*C*H_2, *C7/C11*), 43.70 (N*C*H_2, *C7/C11*), 36.83 (N*C*H_3, *C6*), 26.32 (*C*H_2, *C8/C10*), 25.38 (*C*H_2, *C9*), 24.25 (*C*H_2, *C8/C10*).

IR (neat, cm^{-1}): 3420, 3100, 3065, 2951, 2924, 2860, 1648, 1565, 1454, 1410, 1320, 1252, 1229, 1167, 1127, 1019, 959, 854, 787.

HRMS (ESI$^+$,*m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{11}H_{18}N_3O^+$, requires = 208.1444, found = 208.1442.

MS (*m/z*): 208.10 $[M\text{-}Br^-]^+$

1,2-Dimethyl-3-[2-(piperidin-1-yl)-2-oxoethyl]-1H-imidazol-3-ium bromide (75a)



The title compound (**75a**) was prepared from 1,2-dimethylimidazole (2.99 g, 31.1 mmol) and 2-bromo-1-(piperidin-1-yl)ethan-1-one (**66**) (6.41 g, 31.1 mmol) according to the general procedure B to obtain a white solid in 87 % yield (8.17 g, 27.0 mmol).

Molecular formula: $C_{12}H_{20}BrN_3O$

Molecular weight: 302.21 g/mol

Melting Point: 135-137 °C

^{1}H NMR (400 MHz, DMSO-d_6) ppm: 7.64 (d, *J* = 2.0 Hz, 1H, *H5/H6*), 7.55 (d, *J* = 2.0 Hz, 1H, *H5/H6*), 5.35 (s, 2H, *H2*), 3.81 (s, 3H, *H7*), 3.45-3.42 (m, 4H, *H8, H12*), 2.49 (s, 3H, *H4*), 1.64-1.69 (m, 4H, *H9/ H11, H10*), 1.49-1.47 (m, 2H, *H9/H11*).

^{13}C NMR (100 MHz, DMSO-d_6) ppm: 162.80 (*C*OO, *C1*), 145.83 (Ar*C*, *C3*), 122.36 (ArN*C*H, *C5/C6*), 121.92 (Ar*C*H, *C5/C6*), 49.14 (N*C*H_2, *C2*), 45.22 (N*C*H_2, *C8/C12*), 42.71

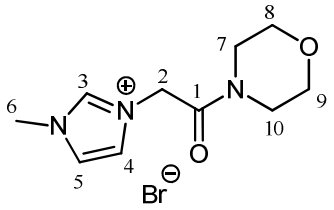
(N*C*H_2, *C8/C12*), 34.84 (N*C*H_3, *C7*), 25.71 (*C*H_2, *C9/C11*), 25.14 (*C*H_2, *C10*), 23.74 (*C*H_2, *C9/C11*), 9.39 (CH_3, *C4*).

IR (neat, cm^{-1}): 3131, 3077, 2940, 2860, 1640, 1589, 1542, 1475, 1439, 1418, 1325, 1278, 1253, 1232, 1166, 1144, 1112, 1019, 962, 817, 764, 752.

HRMS (ESI^+,*m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{12}H_{20}N_3O^+$, requires = 222.1601, found = 222.1600.

MS (*m/z*): 222.10 $[M\text{-}Br^-]^+$

1-Methyl-3-[2-(morpholin-4-yl)-2-oxoethyl]-1H-imidazol-3-ium bromide (76a)



The title compound (**76a**) was prepared from 1-methylimidazole (23.37 mL, 293 mmol) and 2-bromo-1-(morpholin-4-yl)ethan-1-one (**67**) (61.06 g, 293.5 mmol) according to the general procedure B to obtain a white solid in 85 % yield (72.29 g, 249.1 mmol).

Molecular formula: $C_{10}H_{16}BrN_3O_2$

Molecular weight: 290.16 g/mol

Melting Point: 170-172 °C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.65 (s, 1H, *H3*), 7.64 (t, *J* = 1.6 Hz, 1H, *H4/H5*), 7.38 (t, *J* = 1.6 Hz, 1H, *H4/H5*), 5.75 (s, 2H, *H2*), 3.98 (s, 3H, *H6*), 3.76 (t, *J* = 4.8 Hz, 2H, *H8/H9*), 3.64 (t, *J* = 4.8 Hz, 2H, *H8/H9*), 3.59 (t, *J* = 4.8, Hz, 2H, *H7/H10*), 3.52 (t, *J* = 4.8, Hz, 2H, *H7/H10*).

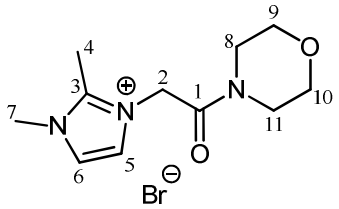
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 163.34 (*C*ON, *C1*), 137.94 (N*C*HN, *C3*), 124.56 (N*C*H, *C4/C5*), 122.33 (N*C*H, *C4/C5*), 66.50 (O*C*H_2, *C8/C9*), 66.40 (O*C*H_2, *C8/C9*), 50.75 (N*C*H_2CO, C2), 45.51 (N*C*H_2, *C7/C10*), 42.67 (N*C*H_2, *C7/C10*), 36.83 (N*C*H_3, *C6*).

IR (neat, cm^{-1}): 3364, 3076, 2864, 1640, 1574, 1425, 1242, 1165, 1113, 1042, 959, 857.

HRMS (ESI$^+$,*m/z*): Calculated for [M-Br$^-$]$^+$, $C_{10}H_{16}N_3O_2^+$, requires = 210.1237, found = 210.1232.

MS (*m/z*): 210.10 [M-Br$^-$]$^+$

1,2-Dimethyl-3-[2-(morpholin-4-yl)-2-oxoethyl]-1H-imidazol-3-ium bromide (77a)



The title compound (**77a**) was prepared from 1,2-dimethylimidazole (3.42 g, 35.6 mmol) and 2-bromo-1-(morpholin-4-yl)ethan-1-one (**67**) (7.40 g, 35.6 mmol) according to the general procedure B to afford a white solid in 95 % yield (10.24 g, 33.7 mmol).

Molecular formula: $C_{11}H_{18}BrN_3O_2$

Molecular weight: 304.18 g/mol

Melting Point: 224-226°C

^{1}H NMR (400 MHz, DMSO-*d*$_6$) ppm: 7.65 (d, *J* = 2.0 Hz, 1H, *H5/H6*), 7.55 (d, *J* = 2.0 Hz, 1H, *H5/H6*), 5.39 (s, 2H, *H2*), 3.81 (s, 3H, *H7*), 3.68 (t, *J* = 5.0 Hz, 2H, *H9/H10*), 3.59 (t, *J* = 5.0 Hz, 2H, *H9/H10*), 3.48 (t, *J* = 5.0 Hz, 2H, *H8/H11*), 3.45 (t, *J* = 5.0, Hz, 2H, *H8/H11*), 2.51 (s, 3H, *H4*).

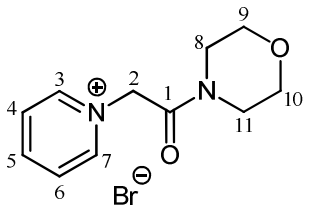
^{13}C NMR (100 MHz, DMSO-*d*$_6$) ppm: 163.56 (*C*ON, *C1*), 145.90 (N*C*N, *C3*), 122.27 (N*C*H, *C5/C6*), 121.99 (N*C*H, *C5/C6*), 65.88 (O*C*H$_2$, *C9/C10*), 65.79 (O*C*H$_2$, *C9/C10*), 49.07 (N*C*H$_2$CO, C2), 44.72 (N*C*H$_2$, *C8/C11*), 42.08 (N*C*H$_2$, *C8/C11*), 34.86 (N*C*H$_3$, *C7*), 9.44 (C*C*H3, *C4*).

IR (neat, cm^{-1}): 2961, 2858, 1667, 1652, 1540, 1417, 1354, 1244, 1113, 1039, 818.

HRMS (ESI$^+$,*m/z*): Calculated for [M-Br$^-$]$^+$, $C_{11}H_{18}N_3O_2^+$, requires = 224.1394, found = 224.1395.

MS (*m/z*): 224.10 [M-Br$^-$]$^+$

1-[2-(Morpholin-4-yl)-2-oxoethyl]pyridin-1-ium bromide (78a)



The title compound (**78a**) was prepared from pyridine (2.39 g, 30.2 mmol) and 2-bromo-1-(morpholin-4-yl)ethan-1-one (**67**) (6.28 g, 30.2 mmol) according to the general procedure B to obtain a white solid in 94 % yield (8.11 g, 28.2 mmol).

Molecular formula: $C_{11}H_{15}BrN_2O_2$

Molecular weight: 287.15 g/mol

Melting Point: 95-97°C

^{1}H NMR (400 MHz, DMSO-d_6) ppm: 8.99 (d, *J* = 6.8 Hz, 2H, *H3, H7*), 8.69 (t, *J* = 7.6 Hz, 1H, *H5*), 8.22 (dd, J = 7.6, 6.8 Hz, 2H, *H4, H6*), 5.88 (s, 2H, *H2*), 3.72 (t, *J* = 4.8 Hz, 2H, *H9/H10*), 3.61 (t, *J* = 4.8 Hz, 2H, *H9/H10*), 3.50 (t, *J* = 4.8 Hz, 2H, *H8/H11*), 3.47 (t, *J* = 4.8, Hz, 2H, *H8/H11*).

^{13}C NMR (100 MHz, DMSO-d_6) ppm: 163.46 (*C*ON, *C1*), 146.34 (2Ar*C*H, *C3/ H7*), 146.28 (Ar*C*H, *C5*), 127.58 (2Ar*C*H, *C4/C6*), 65.83 (O*C*H$_2$, *C9/C10*), 65.72 (O*C*H$_2$, *C9/C10*), 61.13 (N*C*H$_2$CO, C2), 44.78 (N*C*H$_2$, *C8/C11*), 42.28 (N*C*H$_2$, *C8/C11*).

IR (neat, cm^{-1}): 2961, 2864, 1646, 1633, 1484, 1425, 1243, 1207, 1112, 1045, 855, 763.

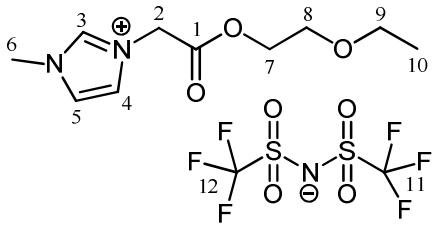
HRMS (ESI$^+$,*m/z*): Calculated for [M-Br$^-$]$^+$, $C_{11}H_{15}N_2O_2^+$, requires = 207.1128, found = 207.1125.

MS (*m/z*): 207.10 [M-Br$^-$]$^+$

6.2.3 [NTf_2] Ionic Liquids:

General Procedure C: Preparation of the achiral [NTf_2] ILs[2]

3-[2-(2-Ethoxyethoxy)-2-oxoethyl]-1-methyl-1H-imidazol-3-ium *bis*(trifluoromethylsulfonyl)imide (68b)[2]



To a stirred solution of bromide salt (**68a**) (11.25 g, 38.4 mmol) in distilled water (50 mL), $LiNTf_2$ was added (11.02 g, 38.4 mmol) at RT. After stirring for 4 h at RT the liquid product was separated from the water by decantation. The liquid was washed with distilled water (3 × 50 mL) and dried under high vacuum to obtain the title compound (**68b**) as a colourless oil in 91 % yield (17.13 g, 34.7 mmol).

Molecular formula: $C_{12}H_{17}F_6N_3O_7S_2$

Molecular weight: 493.4 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 8.72 (s, 1H, *H3*), 7.38 (t, *J* = 1.8 Hz, 1H, *H4/H5*), 7.34 (t, *J* = 1.8 Hz, 1H, *H4/H5*), 5.00 (s, 2H, *H2*), 4.33 (t, *J* = 4.6 Hz, 2H, *H7*), 3.91 (s, 3H, *H6*), 3.68 (t, *J* = 4.6 Hz, 2H, *H8*), 3.50 (q, *J* = 7.0 Hz, 2H, *H9*), 1.17 (t, *J* = 7.0 Hz, 3H, *H10*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 165.89 (*C*OO, *C1*), 137.60 (Ar*C*H, *C3*), 123.97 (Ar*C*H, *C4/C5*), 123.46 (Ar*C*H, *C4/C5*), 119.82 (q, *J* =319 Hz, 2*C*F_3's, *C11, C12*), 67.71 (O*C*H_2, *C8*), 66.73 (O*C*H_2, *C9*), 66.00 (O*C*H_2, *C7*), 49.99 (N*C*H_2, *C2*), 36.58 (N*C*H_3, *C6*), 15.06 (*C*H_3, *C10*).

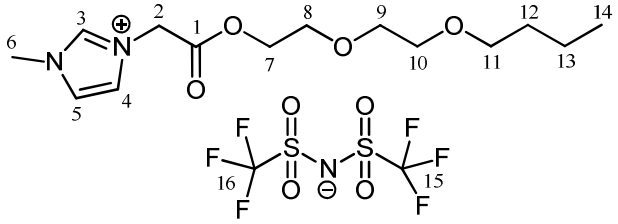
^{19}F NMR (376 MHz, $CDCl_3$) ppm: - 79.35 (6*F*)

IR (neat, cm^{-1}): 3163, 3126, 2979, 1754, 1569, 1439, 1347, 1174, 1131, 1051, 789, 740.

MS (*m/z*): 213.10 $[M\text{-}NTf_2^-]^+$

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[2]

3-{2-[2-(2-Butoxyethoxy)ethoxy]-2-oxoethyl}-1-methyl-1H-imidazol-3-ium *bis*(trifluoromethylsulfonyl)imide (69b)[2]



The title compound (**69b**) was prepared from bromide IL (**69a**) (126.03 g, 345.0 mmol) and $LiNTf_2$ (108.97 g, 379.6 mmol) according to the general procedure C to obtain a colourless oil in 80 % yield (155.39 g, 274.8 mmol).

Molecular formula: $C_{16}H_{25}F_6N_3O_8S_2$

Molecular weight: 565.51 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 8.74 (s, 1H, *H3*), 7.39 (t, *J* = 1.6 Hz, 1H, *H4/H5*), 7.34 (t, *J* = 1.6 Hz, 1H, *H4/H5*), 5.00 (s, 2H, *H2*), 4.33 (t, *J* = 4.8 Hz, 2H, *H7*), 3.92 (s, 3H, *H6*), 3.70 (t, *J* = 4.8 Hz, 2H, *H8*), 3.61 (t, *J* = 4.8 Hz, 2H, *H9*), 3.56 (t, *J* = 4.8 Hz, 2H, *H10*), 3.43 (t, *J* = 6.8 Hz, 2H, *H11*), 1.52 (tt, *J* = 7.6, 6.8 Hz, 2H, *H12*), 1.32 (tq, *J* = 7.6, 7.2 Hz, 2H, *H13*), 0.88 (t, *J* = 7.2 Hz, 3H, *H14*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 165.84 (*C*OO, *C1*), 137.49 (Ar*C*H, *C3*), 123.97 (Ar*C*H, *C4/C5*), 123.44 (Ar*C*H, *C4/C5*), 119.76 (q, *J* = 320 Hz, 2*C*F_3, *C15, C16*), 71.18 (O*C*H_2, *C11*), 70.56 (O*C*H_2, *C9*), 69.92 (O*C*H_2, *C10*), 68.43 (O*C*H_2, *C8*), 65.74 (O*C*H_2, *C7*), 49.86 (*C*H_2, *C2*), 36.47 (N*C*H_3, *C6*), 31.66 (*C*H_2, *C12*), 19.25 (*C*H_2, *C13*), 13.90 (*C*H_3, *C14*).

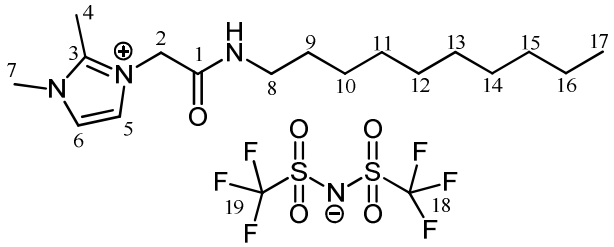
^{19}F NMR (376 MHz, $CDCl_3$) ppm: -79.20 (6*F*).

IR (neat, cm^{-1}): 3162, 2964, 2873, 1765, 1569, 1348, 1331, 1177, 1133, 1053, 976, 789, 740.

MS (*m/z*): 285.15 $(M\text{-}NTf_2^-)^+$

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[2]

3-[(Decylcarbamoyl)methyl]-1,2-dimethyl-1H-imidazol-3-ium *bis*(trifluoromethylsulfonyl)imide (71b)



The title compound (**71b**) was prepared from bromide salt (**71a**) (2.22 g, 5.9 mmol) and $LiNTf_2$ (1.70 g, 5.9 mmol) according to the general procedure C to obtain a white solid in 97 % yield (3.30 g, 5.7 mmol).

Molecular formula: $C_{19}H_{32}F_6N_4O_5S_2$

Molecular weight: 574.60 g/mol

Melting Point: 53-55°C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 7.26 (d, *J* = 2.0 Hz, 1H, *H5/H6*), 7.13 (d, *J* = 2.0 Hz, 1H, *H5/H6*), 6.89 (t, *J* = 6.0 Hz, 1H, N*H*), 4.86 (s, 2H, *H2*), 3.81 (s, 3H, *H7*), 3.18 (dt, *J* = 7.2, 6.0 Hz, 2H, *H8*), 2.60 (s, 3H, *H4*), 1.51 (tt, *J* = 7.6, 7.2 Hz, 2H, *H9*), 1.31-1.25 (m, 14H, *H10-16*), 0.87 (t, *J* = 7.2 Hz, 3H, *H17*).

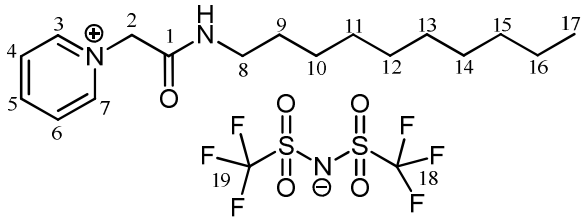
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 163.82 (*C*O, *C1*), 145.68 (N*C*N, *C3*), 122.80 (N*C*H, *C5/C6*), 121.96 (N*C*H, *C5/C6*), 119.41 (q, *J* = 319 Hz, 2*C*F_3's, *C18, C19*), 50.64 (N*C*H_2, *C2*), 40.36 (HN*C*H_2, *C8*), 35.58 (N*C*H_3, *C7*), 32.01 (*C*H_2, *C9*), 29.67 (*C*H_2), 29.61 (*C*H_2), 29.43 (*C*H_2), 29.33 (*C*H_2), 29.14 (*C*H_2), 26.94 (*C*H_2), 22.81 (*C*H_2), 14.25 (*C*H_3, *C17*), 10.13 (*C*H_3, *C4*).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -78.94 (6*F*)

IR (neat, cm^{-1}): 2981, 2972, 1734, 1668, 1608, 1512, 1434, 1247, 1172, 1111, 1030, 981.

MS (*m/z*): 294.25 $(M\text{-}NTf_2^-)^+$

1-[(Decylcarbamoyl)methyl]pyridin-1-ium *bis*(trifluoromethylsulfonyl)imide (72b)



The title compound (**72b**) was prepared from bromide salt (**72a**) (2.33 g, 6.5 mmol) and $LiNTf_2$ (1.87 g, 6.5 mmol) according to the general procedure C to obtain a white solid in 94 % yield (3.41 g, 6.1 mmol).

Molecular formula: $C_{19}H_{29}F_6N_3O_5S_2$

Molecular weight: 557.57 g/mol

Melting Point: 70-72°C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 8.77 (d, *J* = 6.8 Hz, 2H, *H3, H7*), 8.50 (t, *J* = 7.8 Hz, 1H, *H5*), 8.02 (dd, *J* = 7.8, 6.8 Hz, 2H, *H4, H6*), 7.08 (t, *J* = 6.0 Hz, 1H, *NH*), 5.35 (s, 2H, *H2*), 3.25 (dt, *J* = 7.2, 6.0 Hz, 2H, *H8*), 1.52 (tt, *J* = 7.6, 7.2 Hz, 2H, *H9*), 1.31-1.24 (m, 14H, *H10-16*), 0.87 (t, *J* = 7.2 Hz, 3H, *H17*).

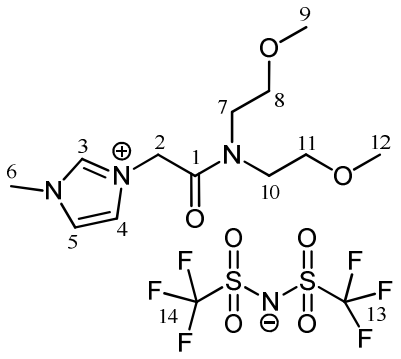
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 162.72 (*C*O,*C1*), 145.09 (Ar*C*H,*C5*), 145.88 (2Ar*C*H, *C3, C7*), 127.97 (2Ar*C*H,*C4/C6*), 119.79 (q, *J* = 319.0 Hz, 2*C*F_3's, *C18, C19*), 62.42 (N*C*H_2, *C2*), 40.68 (HN*C*H_2, *C8*), 32.01 (*C*H_2), 29.67 (*C*H_2), 29.58 (*C*H_2), 29.42 (*C*H_2), 29.31 (*C*H_2), 29.02 (*C*H_2), 26.91 (*C*H_2), 22.81 (*C*H_2), 14.24 (*C*H_3, *C17*).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -78.91 (6*F*)

IR (neat, cm^{-1}): 3429, 2969, 1727, 1665, 1609, 1509, 1449, 1250, 1169, 1078, 1027, 977.

MS (*m/z*): 277.70 $(M\text{-}NTf_2^-)^+$

3-{[*bis*(2-Methoxyethyl)carbamoyl]methyl}-1-methyl-1H-imidazol-3-ium *bis*(trifluoromethylsulfonyl)imide (73b)



The title compound (**73b**) was prepared from bromide salt (**73a**) (74.99 g, 223 mmol) and $LiNTf_2$ (66.82 g, 232.7 mmol) according to the general procedure C to obtain a yellow oil in 74 % yield (88.64 g, 165.2 mmol).

Molecular formula: $C_{14}H_{22}F_6N_4O_7S_2$

Molecular weight: 536.47 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 8.63 (s, 1H, *H3*), 7.27 (t, *J* = 1.8 Hz, 1H, *H4/H5*), 7.26 (t, *J* = 1.8 Hz, 1H, *H4/H5*), 5.24 (s, 2H, *H2*), 3.91 (s, 3H, *H6*), 3.58 (t, *J* = 4.8 Hz, 2H, *H7/H10*), 3.57-3.52 (m, 4H, *H7/H10*, *H8/H11*), 3.49 (t, *J* = 4.8 Hz, 2H, *H6/H11*), 3.34 (s, 3H, *H9/H12*), 3.30 (s, 3H, *H9/H12*).

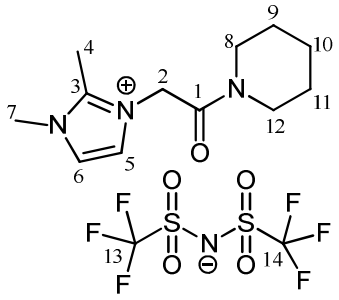
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 165.17 (*C*OO, *C1*), 137.68 (Ar*C*H, *C3*), 124.26 (Ar*C*H, *C4/C5*), 122.72 (Ar*C*H, *C4/C5*), 119.86 (q, *J* = 319 Hz, 2*C*F_3's, *C13, C14*), 70.52 (O*C*H_2, *C8/C11*), 69.99 (O*C*H_2, *C8/C11*), 59.16 (O*C*H_3, *C9/C12*), 58.89 (O*C*H_3, *C9/C12*), 50.52 (N*C*H_2, *C2*), 48.63 (N*C*H_2, *C7/C10*), 46.89 (N*C*H_2, *C7/C10*), 36.45 (N*C*H_3, *C6*).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -78.97 (6*F*)

IR (neat, cm^{-1}): 3161, 2938, 2898, 1659, 1575, 1473, 1427, 1348, 1330, 1175, 1133, 1116, 1052, 830, 789, 739.

MS (*m/z*): 256.15 $(M\text{-}NTf_2^-)^+$

1,2-Dimethyl-3-[2-oxo-2-(piperidin-1-yl)ethyl]-1H-imidazol-3-ium *bis*(trifluoromethylsulfonyl)imide (75b)



The title compound (**75b**) was prepared from bromide salt (**75a**) (1.84 g, 6.09 mmol) and $LiNTf_2$ (1.75 g, 6.09 mmol) according to the general procedure C to obtain a colourless liquid in 89 % yield (2.72 g, 5.42 mmol).

Molecular formula: $C_{14}H_{20}F_6N_4O_5S_2$

Molecular weight: 502.45 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 7.16 (bs, 2H, *H5, H6*), 5.01 (s, 2H, *H2*), 3.76 (s, 3H, *H7*), 3.50 (t, *J* = 5.6 Hz, 2H, *H8/H12*), 3.40 (t, *J* = 5.6 Hz, 2H, *H8/H12*), 2.46 (s, 3H, *H4*), 1.66-1.63 (m, 4H, *H9/ H11, H10*), 1.55 (tt, *J* = 5.6, 4.8 Hz, 2H, *H9/H11*).

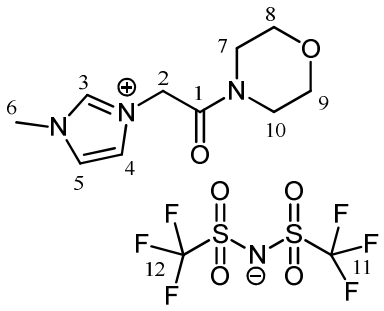
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 161.82 (*C*O, *C1*), 145.89 (Ar*C*H, *C3*), 122.71 (ArN*C*H, *C5/C6*), 121.81 (Ar*C*H, *C5/C6*), 119.81 (q, *J* = 319.0 Hz, 2*C*F_3's, *C13, C14*), 49.87 (N*C*H_2, *C2*), 45.91 (N*C*H_2, *C8/C12*), 43.65 (N*C*H_2, *C8/C12*), 35.36 (N*C*H_3, *C7*), 26.03 (*C*H_2, *C9/C11*), 25.37 (*C*H_2, *C10*), 24.12 (*C*H_2, *C9/C11*), 9.86 (CH_3, *C4*).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -78.84 (6*F*)

IR (neat, cm^{-1}): 2982, 1735, 1688, 1667, 1608, 1512, 1435, 1292, 1248, 1173, 1111, 1030, 827.

MS (*m/z*): 222.10 $[M\text{-}NTf_2^-]^+$

1-Methyl-3-[2-(morpholin-4-yl)-2-oxoethyl]-1H-imidazol-3-ium *bis*(trifluoromethylsulfonyl)imide (76b)



The title compound (**76b**) was prepared from bromide salt (**76a**) (88.12 g, 303.7 mmol) and $LiNTf_2$ (95.93 g, 334.1 mmol) according to the general procedure C to afford a crystalline white solid 62 % yield (92.30 g, 188.2 mmol).

Molecular formula: $C_{12}H_{16}F_6N_4O_6S_2$

Molecular weight: 490.4 g/mol

Melting Point: 63-65°C

^{1}H NMR (400 MHz, DMSO-d_6): 9.41 (s, 1H, *H3*), 8.16 (t, *J* = 1.6 Hz, 1H, *H4/H5*), 8.10 (t, *J* = 1.6 Hz, 1H, *H4/H5*), 5.95 (s, 2H, *H2*), 4.57 (s, 3H, *H6*), 4.14 (t, *J* = 4.8 Hz, 2H, *H8/H9*), 4.08 (t, *J* = 4.8 Hz, 2H, *H8/H9*), 4.03-3.99 (m, 4H, *H7, H10*).

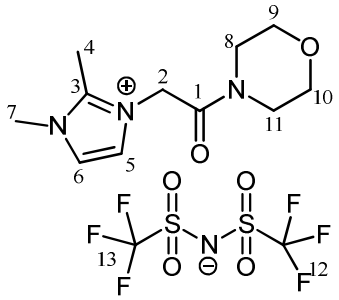
^{13}C NMR (100 MHz, DMSO-d_6): 163.93 (*C*ON, *C1*), 137.91 (N*C*HN, *C3*), 124.04 (N*C*H, *C4/C5*), 123.00 (N*C*H, *C4/C5*), 119.56 (q, *J* =320 Hz, 2*C*F_3's, *C11, C12*), 65.95 (O*C*H_2, *C8/C9*), 65.83 (O*C*H_2, *C8/C9*), 49.99 (N*C*H_2CO, *C2*), 44.70 (N*C*H_2, *C7/C10*), 42.14 (N*C*H_2, *C7/C10*), 35.87 (N*C*H_3, *C6*).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -78.99 (6*F*)

IR (neat, cm^{-1}): 3164, 3109, 3000, 2872, 1656, 1579, 1564, 1475, 1440, 1348, 1328, 1275, 1184, 1136, 1108, 1050, 1033, 975, 845, 807, 771, 740.

MS (*m/z*): 210.10 $[M\text{-}NTf_2^-]^+$

1,2-Dimethyl-3-[2-(morpholin-4-yl)-2-oxoethyl]-1H-imidazol-3-ium *bis*(trifluoromethylsulfonyl)imide (77b)



The title compound (**77b**) was prepared from bromide salt (**77a**) (2.46 g, 8.09 mmol) and $LiNTf_2$ (2.32 g, 8.09 mmol) according to the general procedure C to obtain a colourless liquid in 76 % yield (3.08 g, 6.11 mmol).

Molecular formula: $C_{13}H_{18}F_6N_4O_6S_2$

Molecular weight: 504.43 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 7.21 (d, *J* = 2.4 Hz, 1H, *H5/H6*), 7.16 (d, *J* = 2.4 Hz, 1H, *H5/H6*), 5.09 (s, 2H, *H2*), 3.79 (s, 3H, *H7*), 3.74 (t, *J* = 4.8 Hz, 2H, *H9/H10*), 3.70 (t, *J* = 4.8 Hz, 2H, *H9/H10*), 3.58 (t, *J* = 4.8 Hz, 2H, *H8/H11*), 3.52 (t, *J* = 4.8, Hz, 2H, *H8/H11*), 2.51 (s, 3H, *H4*).

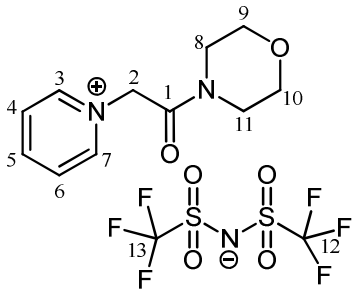
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 162.61 (*C*ON, *C1*), 146.07 (N*C*N, *C3*), 122.87 (N*C*H, *C5/C6*), 121.86 (N*C*H, *C5/C6*), 119.84 (q, *J* =320 Hz, 2*C*F_3's, *C12, C13*), 66.53 (O*C*H_2, *C9/C10*), 66.36 (O*C*H_2, *C9/C10*), 49.85 (N*C*H_2CO, C2), 45.20 (N*C*H_2, *C8/C11*), 42.76 (N*C*H_2, *C8/C11*), 35.52 (N*C*H_3, *C7*), 10.01 (C*C*H3, *C4*).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -78.99 (6*F*)

IR (neat, cm^{-1}): 2976, 1661, 1595, 1543, 1470, 1347, 1328, 1177, 1133, 1112, 1051, 739.

MS (*m/z*): 224.10 $[M\text{-}NTf_2^-]^+$

1-[2-(Morpholin-4-yl)-2-oxoethyl]pyridin-1-ium *bis*(trifluoromethylsulfonyl)imide (78b)



The title compound (**78b**) was prepared from bromide salt (**78a**) (2.72 g, 9.5 mmol) and $LiNTf_2$ (2.72 g, 9.5 mmol) according to the general procedure C to obtain a colourless liquid in 71 % yield (3.28 g, 6.7 mmol).

Molecular formula: $C_{13}H_{15}F_6N_3O_6S_2$

Molecular weight: 487.40 g/mol

^{1}H NMR (400 MHz, DMSO-d_6) ppm: 8.91 (d, *J* = 6.8 Hz, 2H, *H3, H7*), 8.68 (t, *J* = 7.8 Hz, 1H, *H5*), 8.20 (dd, J = 7.8, 6.8 Hz, 2H, *H4, H6*), 5.75 (s, 2H, *H2*), 3.71 (t, *J* = 5.2 Hz, 2H, *H9/H10*), 3.62 (t, *J* = 5.2 Hz, 2H, *H9/H10*), 3.50-3.47 (m, 4H, *H8, H11*).

^{13}C NMR (100 MHz, DMSO-d_6) ppm: 163.44 (*C*ON, *C1*), 146.38 (2Ar*C*H, *C3, H7*), 146.27 (Ar*C*H, *C5*), 127.59 (2Ar*C*H, *C4, C6*), 119.49 (q, *J* =320 Hz, 2*C*F_3's, *C12, C13*), 65.85 (O*C*H_2, *C9/C10*), 65.70 (O*C*H_2, *C9/C10*), 61.15 (N*C*H_2CO, *C2*), 44.75 (N*C*H_2, *C8/C11*), 42.28 (N*C*H_2, *C8/C11*).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -79.16 (6*F*)

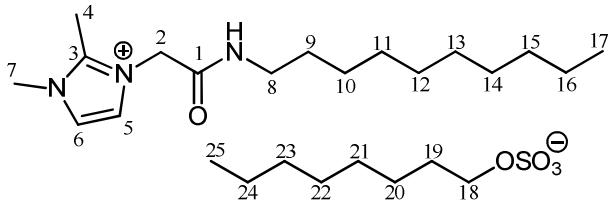
IR (neat, cm^{-1}): 2978, 1662, 1493, 1466, 1347, 1328, 1178, 1132, 1112, 1049, 850, 755.

MS (*m/z*): 207.10 $[M\text{-}NTf_2^-]^+$

6.2.4 [$OctOSO_3$] Ionic Liquids:

General Procedure D: Preparation of the achiral [$OctOSO_3$] ILs[2]

3-[(Decylcarbamoyl)methyl]-1,2-dimethyl-1H-imidazol-3-ium octyl sulfate (71c)



To a stirred solution of bromide salt (**71a**) (2.02 g, 5.4 mmol), in distilled water (10 mL) was added in one portion sodium octyl sulphate (1.25 g, 5.4 mmol). The mixture was stirred overnight, then the water was evaporated by rotary evaporation. The crude product was dissolved in DCM (25 mL) and washed with water (3 x 5 mL). The product was then dried by rotary evaporation and under high vacuum to afford a white gel in 71 % yield (1.94 g, 3.9 mmol).

Molecular formula: $C_{25}H_{49}N_3O_5S$

Molecular weight: 503.74 g/mol

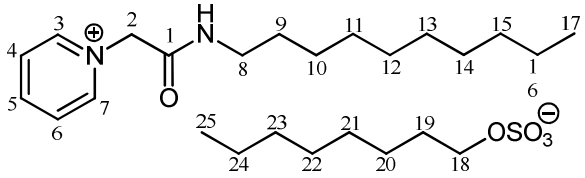
^{1}H NMR (400 MHz, $CDCl_3$) ppm: 8.01 (t, *J* = 6.2 Hz, 1H, *NH*), 7.28 (d, *J* = 2.0 Hz, 1H, *H5/H6*), 7.27 (d, *J* = 2.0 Hz, 1H, *H5/H6*), 4.79 (s, 2H, *H2*), 3.74 (t, *J* = 7.0 Hz, 2H, *H18*), 3.65 (s, 3H, *H7*), 2.95 (td, *J* = 7.2, 6.2 Hz, 2H, *H8*), 2.44 (s, 3H, *H4*), 1.42 (tt, *J* = 7.6, 7.2 Hz, 2H, *H9*), 1.31 (tt, *J* = 7.6, 7.0 Hz, 2H, *H19*), 1.15-1.03 (m, 24H, *H10-16, H20-24*), 0.65 (t, *J* = 7.2 Hz, 6H, *H17, H25*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 164.21 (*C*O, *C1*), 144.97 (N*C*N, *C3*), 121.97 (2N*C*H, *C5, C6*), 67.27 (N*C*H_2, *C2*), 49.90 (HN*C*H_2, *C8*), 39.58 (*C*H_2), 34.96 (*C*H_3, *C7*), 31.46 (*C*H_2), 31.39 (*C*H_2), 29.19 (2*C*H_2), 29.10 (*C*H_2), 28.93 (2*C*H_2), 28.89 (*C*H_2), 28.85 (*C*H_2), 28.79 (*C*H_2), 26.61 (*C*H_2), 25.49 (*C*H_2), 22.22 (*C*H_2), 22.20 (*C*H_2), 13.66 (2*C*H_3, *C17, C25*), 9.59 (*C*H_3, *C4*).

IR (neat, cm^{-1}): 3453, 2960, 1736, 1649, 1630, 1480, 1238, 1210, 1153, 1027, 922, 757.

MS (*m/z*): 294.20 [M-$OctOSO_3^-$]$^+$

1-[(Decylcarbamoyl)methyl]pyridin-1-ium octyl sulfate (72c)



The title compound (**72c**) was prepared using bromide salt (**72a**) (1.91 g, 5.4 mmol), sodium octyl sulphate (1.24 g, 5.4 mmol) and distilled water (10 mL) according to general procedure D to obtain a white gel in 75 % yield (1.95 g, 4.0 mmol).

Molecular formula: $C_{25}H_{46}N_2O_5S$

Molecular weight: 486.71 g/mol

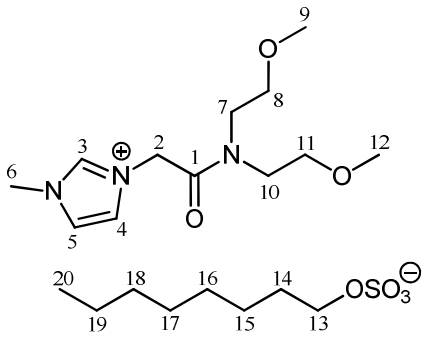
^{1}H NMR (400 MHz, $CDCl_3$) ppm: 8.83 (dd, *J* = 6.8, 1.2 Hz, 2H, *H3, H7*), 8.35 (tt, *J* = 8.0, 1.2 Hz, 1H, *H5*), 8.15 (t, *J* = 6.0 Hz, 1H, *NH*), 7.88 (dd, J = 8.0, 6.8 Hz, 2H, *H4, H6*), 5.41 (s, 2H, *H2*), 3.79 (t, *J* = 6.6 Hz, 2H, *H18*), 2.98 (td, *J* = 7.2, 6.0 Hz, 2H, *H8*), 1.43 (tt, *J* = 7.6, 7.2 Hz, 2H, *H9*), 1.33 (tt, *J* = 7.2, 6.6 Hz, 2H, *H19*), 1.13-1.03 (m, 24H, *H10-16, H20-24*), 0.65 (t, *J* = 7.2 Hz, 6H, *H17*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 163.25 (*C*O, *C1*), 145.66 (2Ar*C*H, *C3, C7*), 145.49 (Ar*C*H, *C5*), 127.47 (2Ar*C*H, *C4, C6*), 67.50 (O*C*H_2, *C18*), 61.65 (N*C*H_2, *C2*), 39.89 (*C*H_2), 31.45 (*C*H_2), 31.39 (*C*H_2), 29.19 (*C*H_2), 29.10 (*C*H_2), 28.94 (2*C*H_2), 28.90 (*C*H_2), 28.85 (2*C*H_2), 28.71 (*C*H_2), 26.61 (*C*H_2), 25.49 (*C*H_2), 22.22 (*C*H_2), 22.20 (*C*H_2), 13.65 (2*C*H_3, *C17, C25*).

IR (neat, cm^{-1}): 2981, 1737, 1644, 1608, 1512, 1435, 1292, 1247, 1173, 1111, 1030, 827.

MS (*m/z*): 277.70 $[M\text{-}OctOSO_3^-]^+$

3-{[*bis*(2-Methoxyethyl)carbamoyl]methyl}-1-methyl-1H-imidazol-3-ium octyl sulfate (73c)[4]



The title compound (**73c**) was prepared using bromide salt (**73a**) (2.16 g, 6.4 mmol), sodium octyl sulphate (1.49 g, 6.4 mmol) and distilled water (15 mL) according to general procedure D to obtain a brown oil in 54 % yield (1.61 g, 3.5 mmol).

Molecular formula: $C_{20}H_{39}N_3O_7S$

Molecular weight: 465.61 g/mol

^{1}H NMR (600 MHz, $CDCl_3$) ppm: 9.19 (s, 1H), 7.39 (t, *J* = 1.8 Hz, 1H), 7.30 (t, *J* = 1.8 Hz, 1H), 5.36 (s, 2H), 3.94 (t, *J* = 6.8 Hz, 2H), 3.91 (s, 3H), 3.59 (t, *J* = 4.8 Hz, 2H), 3.51-3.44 (m, 6H), 3.31 (s, 3H), 3.26 (s, 3H), 1.59 (tt, *J* = 7.2, 6.8 Hz, 2H), 1.32-1.15 (m, 10H), 0.80 (t, *J* = 6.8 Hz, 3H).

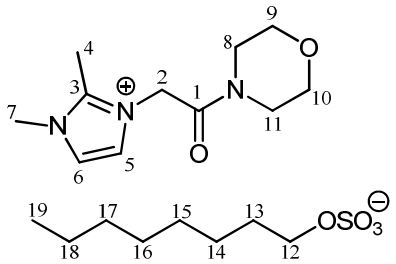
^{13}C NMR (150 MHz, $CDCl_3$) ppm: 165.63, 138.64, 124.00, 122.69, 70.48, 70.13, 67.64, 59.11, 58.82, 50.29, 48.53, 46.84, 36.35, 31.79, 29.53, 29.34, 29.23, 25.88, 22.62, 14.09.

IR (neat, cm^{-1}): 3480, 3112, 2926, 1653, 1575, 1472, 1428, 1220, 1119, 1016.

MS (*m/z*): 256.10 $(M\text{-}OctOSO_3^-)^+$

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[4]

1,2-Dimethyl-3-[2-(morpholin-4-yl)-2-oxoethyl]-1H-imidazol-3-ium octyl sulfate (77c)



The title compound (**77c**) was prepared using bromide salt (**77a**) (2.23 g, 7.3 mmol), sodium octyl sulphate (1.70 g, 7.3 mmol) and distilled water (10 mL) according to general procedure D to obtain a colourless liquid in 79 % yield (2.52 g, 5.8 mmol).

Molecular formula: $C_{19}H_{35}N_3O_6S$

Molecular weight: 433.56 g/mol

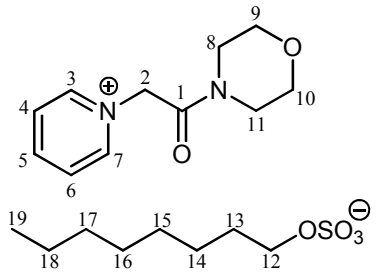
^{1}H NMR (400 MHz, $CDCl_3$) ppm: 7.49 (d, *J* = 2.0 Hz, 1H, *H5/H6*), 7.30 (d, *J* = 2.0 Hz, 1H, *H5/H6*), 5.44 (s, 2H, *H2*), 3.94 (t, *J* = 7.0 Hz, 2H, *H12*), 3.81 (s, 3H, *H7*), 3.77 (t, *J* = 5.2 Hz, 2H, *H9/H10*), 3.68 (t, *J* = 5.2 Hz, 2H, *H9/H10*), 3.63 (t, *J* = 5.2 Hz, 2H, *H8/H11*), 3.52 (t, *J* = 5.2, Hz, 2H, *H8/H11*), 2.56 (s, 3H, *H4*), 1.61 (tt, *J* = 8.0, 7.0 Hz, 2H, *H13*), 1.34-1.23 (m, 10H, *H14-18*), 0.85 (t, *J* = 7.2 Hz, 3H, *H19*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 163.60 (*C*ON, *C1*), 146.06 (N*C*N, *C3*), 122.57 (N*C*H, *C5/C6*), 122.34 (N*C*H, *C5/C6*), 65.48 (O*C*H_2, *C9/C10*), 65.78 (O*C*H_2, *C9/C10*), 65.50 (O*C*H_2, *C12*), 49.07 (N*C*H_2CO, C2), 44.72 (N*C*H_2, *C8/C11*), 42.08 (N*C*H_2, *C8/C11*), 34.86 (N*C*H_3, *C7*), 31.78 (*C*H_2), 29.51 (*C*H_2), 29.22 (*C*H_2), 28.30 (*C*H_2), 25.81 (*C*H_2), 22.60 (*C*H_2), 14.09 (*C*H_3), 9.44 (C*C*H_3, *C4*).

IR (neat, cm^{-1}): 2927, 1709, 1658, 1594, 1543, 1429, 1362, 1219, 1114, 1038, 956, 790.

MS (*m/z*): 224.10 $[M\text{-}OctOSO_3^-]^+$

1-[2-(Morpholin-4-yl)-2-oxoethyl]pyridin-1-ium octyl sulfate (78c)



The title compound (**78c**) was prepared using bromide salt (**78a**) (2.29 g, 7.98 mmol), sodium octyl sulphate (1.85 g, 7.98 mmol) and distilled water (10 mL) according to general procedure D to obtain a colourless liquid in 73 % yield (2.43 g, 5.84 mmol).

Molecular formula: $C_{19}H_{32}N_2O_6S$

Molecular weight: 416.53 g/mol

^{1}H NMR (400 MHz, DMSO-d_6) ppm: 8.93 (d, *J* = 6.8 Hz, 2H, *H3, H7*), 8.37 (t, *J* = 7.4 Hz, 1H, *H5*), 7.89 (dd, *J* = 7.4, 6.8 Hz, 2H, *H4, H6*), 5.94 (s, 2H, *H2*), 3.87 (t, *J* = 7.0 Hz, 2H, *H12*), 3.69 (t, *J* = 4.8 Hz, 2H, *H9/H10*), 3.58 (t, *J* = 4.8 Hz, 2H, *H9/H10*), 3.50 (t, J = 4.8, 2H, *H8/H11*), 3.46 (t, *J* = 4.8 Hz, 2H, *H8/H11*), 1.52 (tt, *J* = 7.6, 7.0 Hz, 2H, *H13*), 1.22 (m, 10 H, *H14-18*), 0.77 (t, *J* = 7.2 Hz, 3H, *H19*).

^{13}C NMR (100 MHz, DMSO-d_6) ppm: 163.65 (*C*ON, *C1*), 146.31 (2Ar*C*H, *C3, H7*), 146.12 (Ar*C*H, *C5*), 127.29 (2Ar*C*H, *C4, C6*), 65.83 (O*C*H$_2$, *C9/C10*), 65.71 (O*C*H$_2$, *C9/C10*), 65.55 (O*C*H$_2$, *C12*), 61.15 (N*C*H$_2$CO, *C2*), 44.75 (N*C*H$_2$, *C8/C11*), 42.28 (N*C*H$_2$, *C8/C11*), 31.56 (*C*H$_2$), 29.46 (*C*H$_2$), 29.29 (*C*H$_2$), 28.21 (*C*H$_2$), 25.76 (*C*H$_2$), 22.34 (*C*H$_2$), 14.26 (*C*H$_3$).

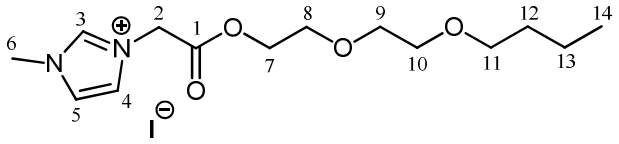
IR (neat, cm^{-1}): 2926, 1709, 1661, 1639, 1467, 1362, 1244, 1219, 1113, 1040, 957, 758.

MS (*m/z*): 207.10 [M-OctOSO$_3^-$]$^+$

6.2.5 Iodide Ionic Liquids:

General Procedure E: Preparation of the achiral iodide ILs

3-{2-[2-(2-Butoxyethoxy)ethoxy]-2-oxoethyl}-1-methyl-1H-imidazol-3-ium iodide (69d)



To a stirred solution of [NTf$_2$] salt (**69b**) (88.64 g, 156.7 mmol) in DCM (100 mL) was added a solution of tetrabutylammonium iodide (63.69 g, 172.4 mmol) in DCM (100 mL) slowly at RT. After stirring for 3 h at RT the solvent was evaporated completely, the residue was dissolved in distilled water (100 mL). The aq. solution was washed with DCM (50 mL) and then evaporated on rota evaporator, dried under high vacuum to afford the title compound (**69d**) as yellow solid in 66 % yield (42.81 g, 103.8 mmol).

Molecular formula: $C_{14}H_{25}IN_2O_4$

Molecular weight: 412.26 g/mol

Melting Point: 52-54°C

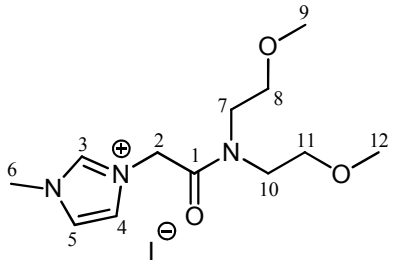
^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.63 (s, 1H, *H3*), 7.68 (t, *J* = 1.8 Hz, 1H, *H4/H5*), 7.58 (t, *J* = 1.8 Hz, 1H, *H4/H5*), 5.37 (s, 2H, *H2*), 4.29 (t, *J* = 4.8 Hz, 2H, *H7*), 4.02 (s, 3H, *H6*), 3.67 (t, *J* = 4.8 Hz, 2H, *H8*), 3.56 (t, *J* = 4.4 Hz, 2H, *H9*), 3.50 (t, *J* = 4.4 Hz, 2H, *H10*), 3.36 (t, *J* = 6.8 Hz, 2H, *H11*), 1.45 (tt, *J* = 7.6, 6.8 Hz, 2H, *H12*), 1.25 (tq, *J* = 7.6, 7.2 Hz, 2H, *H13*), 0.82 (t, *J* = 7.2 Hz, 3H, *H14*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 165.86 (*C*OO, *C1*), 137.53 (Ar*C*H, *C3*), 123.93 (Ar*C*H, *C4/C5*), 123.24 (Ar*C*H, *C4/C5*), 71.03 (O*C*H$_2$, *C11*), 70.45 (O*C*H$_2$, *C9*), 69.80 (O*C*H$_2$, *C10*), 68.42 (O*C*H$_2$, *C8*), 65.63 (O*C*H$_2$, *C7*), 50.46 (*C*H$_2$, *C2*), 37.21 (N*C*H$_3$, *C6*), 31.48 (*C*H$_2$, *C12*), 19.09 (*C*H$_2$, *C13*), 13.83 (*C*H$_3$, *C14*).

IR (neat, cm^{-1}): 3131, 3100, 2955, 2934, 2869, 1751, 1633, 1577, 1565, 1450, 1430, 1340, 1220, 1196, 1172, 1127, 1094, 1044, 969, 869, 841, 765.

MS (*m/z*): 285.20 $(M\text{-}I^-)^+$

3-{[*bis*(2-Methoxyethyl)carbamoyl]methyl}-1-methyl-1H-imidazol-3-ium iodide (73d)



The title compound (**73d**) was prepared from [NTf_2] salt (**73b**) (99.8 g, 186.0 mmol), tetrabutylammonium iodide (77.6 g, 210.1 mmol) and DCM (300 mL) according to the general procedure E as a brown solid in 74 % yield (52.97 g, 138.3 mmol).

Molecular formula: $C_{12}H_{22}IN_3O_3$

Molecular weight: 383.23 g/mol

Melting Point: 48-50°C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.54 (s, 1H, *H3*), 7.45 (d, *J* = 2.4 Hz, 1H, *H4/H5*), 7.44 (d, *J* = 2.4 Hz, 1H, *H4/H5*), 5.59 (s, 2H, *H2*), 4.03 (s, 3H, *H6*), 3.67 (t, *J* = 4.8 Hz, 2H, *H7/H10*), 3.55-3.52 (m, 4H, *H7/H10, H8/H11*), 3.48 (t, *J* = 4.8 Hz, 2H, *H8/H11*), 3.35 (s, 3H, *H9/H12*), 3.29 (s, 3H, H9/*H12*).

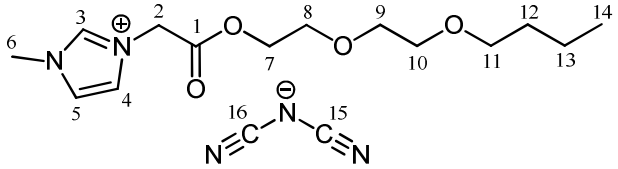
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 165.12 (*C*OO, *C1*), 137.66 (Ar*C*H, *C3*), 124.10 (Ar*C*H, *C4/C5*), 122.60 (Ar*C*H, *C4/C5*), 70.44 (O*C*H_2, *C8/C11*), 70.05 (O*C*H_2, *C8/C11*), 59.32 (O*C*H_3, *C9/C12*), 58.88 (O*C*H_3, *C9/C12*), 50.85 (N*C*H_2, *C2*), 48.84 (N*C*H_2, *C7/C10*), 46.87 (N*C*H_2, *C7/C10*), 37.07 (N*C*H_3, *C6*).

IR (neat, cm^{-1}): 3149, 3101, 2921, 2889, 1662, 1651, 1562, 1472, 1423, 1341, 1195, 1169, 1118, 1095, 1069, 1031, 1003, 831, 804, 751.

MS (*m/z*): 256.10 $[M\text{-}I^-]^+$

6.2.6 $[N(CN)_2]$ Ionic Liquids:

3-{2-[2-(2-Butoxyethoxy)ethoxy]-2-oxoethyl}-1-methyl-1H-imidazol-3-ium dicyanamide (69e)[2]



A dry flask was charged with bromide salt (**69a**) (10.52 g, 28.8 mmol) and acetonitrile (100 mL) under a nitrogen atmosphere $NaN(CN)_2$ (2.82 g, 32.7 mmol) was added in one portion and the suspension was stirred vigorously for 4 days at RT. The fine white precipitate was filtered quickly in air and washed with dry acetonitrile (3 x 10 mL). The filtrate and washings were combined, solvent removed by rotary evaporation and then under high vacuum to obtain a off white solid in 97 % yield (9.86 g, 28.1 mmol)

Molecular formula: $C_{16}H_{25}N_5O_4$

Molecular weight: 351.4 g/mol

Melting Point: 58-60°C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.59 (s, 1H, *H3*), 7.60 (t, *J* = 1.6 Hz, 1H, *H4/H5*), 7.49 (t, *J* = 1.6 Hz, 1H, *H4/H5*), 5.31 (s, 2H, *H2*), 4.31 (t, *J* = 4.8 Hz, 2H, *H7*), 4.01 (s, 3H, *H6*), 3.69 (t,

J = 4.8 Hz, 2H, *H8*), 3.58 (t, *J* = 4.4 Hz, 2H, *H9*), 3.53 (t, *J* = 4.4 Hz, 2H, *H10*), 3.38 (t, *J* = 6.8 Hz, 2H, *H11*),1.48 (tt, *J* = 7.2, 6.8 Hz, 2H, *H12*), 1.29 (qt, *J* = 7.6, 7.2 Hz, 2H, *H13*), 0.84 (t, *J* = 7.6 Hz, 3H, *H14*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 166.13 (*C*OO, *C1*), 137.96 (Ar*C*H, *C3*), 123.98 (Ar*C*H, *C4/C5*), 123.27 (Ar*C*H, *C4/C5*), 71.14 (O*C*H$_2$, *C11*), 70.53 (O*C*H$_2$, *C9*), 69.89 (O*C*H$_2$, *C10*), 68.49 (O*C*H$_2$, *C8*), 65.69 (O*C*H$_2$, *C7*), 50.14 (*C*H$_2$, *C2*), 36.83 (N*C*H$_3$, *C6*), 31.60 (*C*H$_2$, *C12*), 19.21 (*C*H$_2$, *C13*), 13.92 (*C*H$_3$, *C14*).

Note: C's from anion are not visible in ^{13}C NMR.

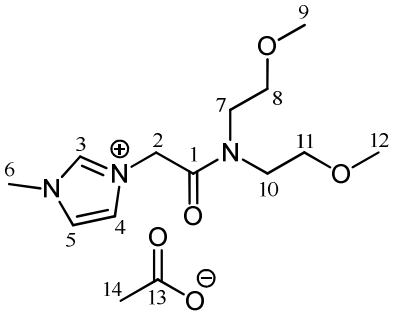
IR (neat, cm^{-1}): 2957, 2933, 2869, 2231, 2194, 2130, 1750, 1628, 1567, 1456, 1375, 1304, 1216, 1175, 1095, 1042, 967, 878, 769.

MS (m/z): 285.20 [M- $N(CN)_2^-$]$^+$

^{1}H and ^{13}C-NMR spectra and melting point are in agreement with the literature data.[2]

6.2.7 [OAc] Ionic Liquids:

3-{[*bis*(2-Methoxyethyl)carbamoyl]methyl}-1-methyl-1H-imidazol-3-ium acetate (73f)



The title compound (**73f**) was synthesized by a slow addition of an aq. bromide solution (**73a**) [(4.22 g, 12.6 mmol) in 10 mL water] into an equimolar $Ag(CH_3COO)$ solution [(2.09 g, 12.6 mmol) in 200 mL water]. The reaction was covered with aluminum foil to prevent the photodegradation of silver acetate. The reaction mixture was stirred at room temperature for 2 h, followed by a removal of AgBr precipitate through filtration. Charcoal was added to the filtrate to remove color and impurities overnight. After filtering off the charcoal, water was removed from the filtrate through rotary evaporation under vacuum at 60 $^{\circ}$C to obtain a colourless oil in 65 % yield (2.56 g, 8.1 mmol).[5]

Molecular formula: $C_{14}H_{25}N_3O_5$

Molecular weight: 315.37 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 11.17 (bs, 1H, *H3*), 7.19 (s, 1H, *H3/H4*), 7.12 (s, 1H, *H3/H4*), 5.58 (s, 2H, *H2*), 3.88 (s, 3H, *H6*), 3.60 (t, *J* = 4.8 Hz, 2H, *H8/H11*), 3.47-3.39 (m, 6H, *H7, H10, H8/H11*), 3.25 (s, 3H, *H9/H12*), 3.22 (s, 3H, *H9/H12*), 1.89 (s, 3H, *H14*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 175.39 (*C*OO, *C13*), 165.99 (*C*OO, *C1*), 141.38 (Ar*C*H, *C3*), 123.70 (Ar*C*H, *C4/C5*), 121.58 (Ar*C*H, *C4/C5*), 70.53 (O*C*H$_2$, *C8/C11*), 70.05 (O*C*H$_2$, *C8/C11*), 59.02 (O*C*H$_3$, *C9/C12*), 58.80 (O*C*H$_3$, *C9/C12*), 49.97 (N*C*H$_2$, *C2*), 48.53 (N*C*H$_2$, *C7/C10*), 46.58 (N*C*H$_2$, *C7/C10*), 36.03 (N*C*H$_3$, *C6*), 25.25 (CO*C*H$_3$, *C14*).

IR (neat, cm^{-1}): 2995, 1648, 1560, 1474, 1400, 1341, 1178, 1109, 1013, 919.

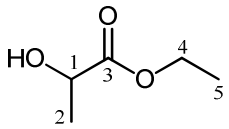
MS (*m/z*): 256.20 $[M\text{-}OAc^-]^+$

6.3 Lactate Ionic Liquids:

6.3.1 Esters:

General procedure F: Preparation of the Lactate esters[4]

Ethyl-2-hydroxypropanoate (79)[4]



To a stirred mixture of lactic acid (21.53 g, 239 mmol) in ethanol (200 mL), thionyl chloride (3.0 mL, 41.1 mmol) was added at RT and reaction was heated to reflux for 8 h. The reaction mixture was cooled to RT and volatiles were removed by rotary evaporation. With the purification by column chromatography (SiO_2, EtOAc:Hexane; 20:80) a pale yellow oil was obtained in 56 % yield (15.80 g, 133.8 mmol).

Molecular formula: $C_5H_{10}O_3$

Molecular weight: 118.13 g/mol

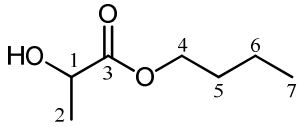
^{1}H NMR (400 MHz, $CDCl_3$) ppm: 4.27-4.22 (m, 3H, *H1, H4*), 2.77(d, *J* = 5.2 Hz, 1H, *OH*), 1.41 (d, *J* = 7.6 Hz, 3H, *H2*), 1.30 (t, *J* = 7.2 Hz, 3H, *H5*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 175.78 (*C*OO, *C3*), 66.93 (*CH*OH, *C1*), 61.53 (O*C*H_2, *C4*), 20.38 (*C*H_2, *C2*), 14.21 (*C*H_3, *C5*).

IR (neat, cm^{-1}): 3466, 2987, 1739, 1452, 1373, 1191, 1124, 1091, 1045, 1018, 861.

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[4]

Butyl-2-hydroxypropanoate (80)[6]



The title compound (**80**) was prepared using lactic acid (11.38 g, 126.3 mmol), butanol (80 mL) and thionyl chloride (4.0 mL, 54.8 mmol) according to the general procedure F as a colourless liquid in 66 % yield (12.25 g, 83.8 mmol).

Molecular formula: $C_7H_{14}O_3$

Molecular weight: 146.18 g/mol

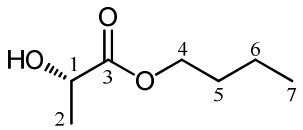
^{1}H NMR (400 MHz, $CDCl_3$) ppm: 4.22 (q, *J* = 6.8 Hz, 1H, *H1*), 4.13 (dt, *J* = 10.8, 6.8 Hz, 2H, *H4*), 3.05 (s, 1H, O*H*), 1.59 (tt, *J* = 7.0, 6.8 Hz, 2H, *H5*), 1.36 (d, *J* = 6.8 Hz, 3H, *H2*), 1.34 (qt, *J* = 7.4, 7.0 Hz, 2H, *H6*), 0.89 (t, *J* = 7.4 Hz, 3H, *H7*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 175.79 (*C*OO, *C3*), 66.70 (*CH*OH, *C1*), 65.35 (O*C*H_2, *C4*), 30.50 (*C*H_2, *C5*), 20.32 (*C*H_2, *C6*), 18.96 (*C*H_3, *C2*), 13.57 (*C*H_3, *C7*).

IR (neat, cm^{-1}): 3458, 2961, 1732, 1460, 1376, 1263, 1205, 1125, 1043, 964, 943, 843.

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[6]

(*S*) Butyl 2-hydroxypropanoate (81)[6]



The title compound (**81**) was preapred using (*S*)-lactic acid (40 % in water) (27.19 g, 120.7 mmol), butanol (200 mL) and thionyl chloride (5.0 mL, 68.5 mmol) according to the general procedure F as a colourless liquid in 71 % yield (12.57 g, 85.99 mmol).

Molecular formula: $C_7H_{14}O_3$

Molecular weight: 146.18 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 4.23 (q, *J* = 6.8 Hz, 1H, *H1*), 4.13 (dt, *J* = 10.8, 6.4 Hz, 2H, *H4*), 3.03 (s, 1H, O*H*), 1.60 (tt, *J* = 7.0, 6.4 Hz, 2H, *H5*), 1.37 (d, *J* = 6.8 Hz, 3H, *H2*), 1.34 (qt, *J* = 7.4, 7.0 Hz, 2H, *H6*), 0.89 (t, *J* =7.4 Hz, 3H, *H7*).

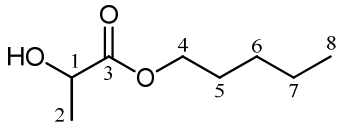
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 175.83 (*C*OO, *C3*), 66.71 (*CH*OH, *C1*), 65.42 (O*C*H_2, *C4*), 30.52 (*C*H_2, *C5*), 20.37 (*C*H_2, *C6*), 18.98 (*C*H_3, *C2*), 13.61 (*C*H_3, *C7*).

IR (neat, cm^{-1}): 3456, 2961, 1732, 1460, 1376, 1284, 1205, 1125, 1043, 943, 843.

$[\alpha]^{20}_D = -7.1^{\circ}$ (2.1 c, $CHCl_3$)

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[6]

Pentyl-2-hydroxypropanoate (82)[6]



The title compound (**82**) was preapred using lactic acid (7.61 g, 84.5 mmol), pentanol (50 mL) and thionyl chloride (3.0 mL, 41.1 mmol) according to the general procedure F as a colourless liquid in 76 % yield (10.3 g, 64.3 mmol).

Molecular formula: $C_8H_{16}O_3$

Molecular weight: 160.21 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 4.25 (q, *J* = 7.0 Hz, 1H, *H1*), 4.16 (dt, *J* = 8.8, 6.8 Hz, 2H, *H4*), 2.85 (s, 1H, O*H*), 1.64 (tt, *J* = 7.2, 6.8 Hz, 2H, *H5*), 1.39 (d, *J* = 7.0 Hz, 3H, *H2*), 1.33-1.30 (m, 4H, *H's 6 and 7*), 0.89 (t, *J* =7.2 Hz, 3H, *H8*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 175.86 (*C*OO, *C3*), 66.73 (*CH*OH, *C1*), 65.79 (O*C*H_2, *C4*), 28.22 (*C*H_2, *C5*), 27.91 (*C*H_2, *C6*), 22.25 (*C*H_2, *C7*), 20.43 (*C*H_3, *C2*), 13.92 (*C*H_3, *C8*).

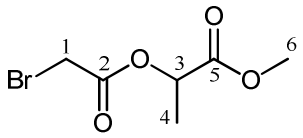
IR (neat, cm^{-1}): 3391, 2958, 2932, 1735, 1461, 1379, 1205, 1129, 1077, 1051, 970, 886.

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[6]

6.3.2 Alkylating agents:

General Procedure G: Preparation of the Lactate based alkylating agents[2]

Methyl 2-[(2-bromoacetyl)oxy]propanoate (84)[4]



To a stirred solution of methyl lactate (2.76 g, 26.5 mmol) in CH_2Cl_2 (25 mL) sodium carbonate (4.22 g, 39.8 mmol) was added, followed by bromoacetyl bromide (2.8 mL, 31.9 mmol) at $0^{\circ}C$. Reaction mixture was allowed to warm to room temperature then stirred for 8 h. The reaction mixture was filtered, washed with 25 mL 10 % $NaHCO_3$ solution, dried over anhydrous $MgSO_4$ and concentrated under high vacuum. The crude product was purified by column chromatography (SiO_2, hexane:EtOAc, 80:20) to obtain the title compound (**84**) as a colourless liquid in 32 % yield (1.92 g, 8.5 mmol).

Molecular formula: $C_6H_9BrO_4$

Molecular weight: 225.04 g/mol

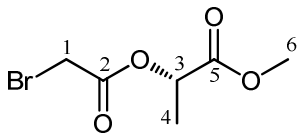
^{1}H NMR (400 MHz, $CDCl_3$) ppm: 5.13 (q, *J* = 7.2 Hz, 1H, *H3*), 3.89 (s, 2H, *H1*), 3.73 (s, 3H, *H6*), 1.50 (d, *J* = 7.2 Hz, 3H, *H4*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 170.47 (*C*OO, *C5*), 166.64 (*C*OO, *C2*), 70.03 (O*C*H, *C3*), 52.54 (O*C*H_3, *C6*), 25.35 (*C*H_2, *C1*), 16.77 (*C*H_3, *C4*).

IR (neat, cm^{-1}): 2958, 1745, 1453, 1405, 1315, 1280, 1225, 1167, 1098, 1047, 981.

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[4]

Methyl-(*2S*)-2-[(2-bromoacetyl)oxy]propanoate (85)



The title compound (**85**) was synthesized using (*S*)-methyl lactate (7.06 g, 67.8 mmol), dry DCM (70 mL), sodium carbonate (10.78 g, 101.7 mmol), and bromoacetyl bromide (7.1 mL, 81.3 mmol) according to general procedure G to afford a colourless liquid in 37 % yield (5.63 g, 25.0 mmol).

Molecular formula: $C_6H_9BrO_4$

Molecular weight: 225.04 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 5.13 (q, *J* = 7.2 Hz, 1H, *H3*), 3.89 (s, 2H, *H1*), 3.74 (s, 3H, *H6*), 1.50 (d, *J* = 7.2 Hz, 3H, *H4*).

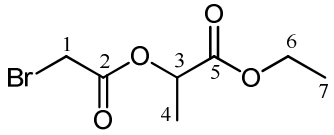
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 170.47 (*C*OO, *C5*), 166.64 (*C*OO, *C2*), 70.03 (O*C*H, *C3*), 52.54 (O*C*H$_3$, *C6*), 25.29 (*C*H$_2$, *C1*), 16.78 (*C*H$_3$, *C4*).

IR (neat, cm^{-1}): 2958, 1741, 1452, 1407, 1314, 1275, 1214, 1132, 1093, 1045, 981, 836.

$[\alpha]^{20}_D$ = -104.5° (0.6 c, $CHCl_3$)

General procedure H: Preparation of Lactate based alkylating agents[7]

Ethyl 2-[(2-bromoacetyl)oxy]propanoate (86)[4]



Bromoacetyl bromide (14.6 mL, 168 mmol) was added, in one portion, to the mixture of alcohol (**79**) (9.91 g, 83.9 mmol) and neutral Al_2O_3 (12.84 g, 125.9 mmol). The resultant dispersion was stoppered tightly and kept aside unstirred at 25 °C, and the progress of the reaction was monitored by TLC. When the reaction was complete, EtOAc (50 mL) was added to the reaction mixture and filtered. The solvent was removed by rotary evaporation to furnish the product in 82 % yield (16.36 g, 68.8 mmol).

Molecular formula: $C_7H_{11}BrO_4$

Molecular weight: 239.06 g/mol

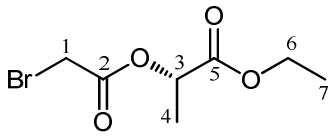
^{1}H NMR (400 MHz, $CDCl_3$) ppm: 5.06 (q, *J* = 7.2 Hz, 1H, *H3*), 4.15 (q, *J* = 7.2 Hz, 2H, *H6*), 3.86 (s, 2H, *H1*), 1.46 (d, *J* = 7.2 Hz, 3H, *H4*), 1.22 (t, *J* = 7.2 Hz, 3H, *H7*),

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 169.95 (*C*OO, *C5*), 166.61 (*C*OO, *C2*), 70.11 (O*C*H, *C3*), 61.59 (*C*H_2, *C6*), 25.37 (*C*H_2, *C1*), 16.71 (*C*H_3, *C4*), 14.05 (*C*H_3, *C7*).

IR (neat, cm^{-1}): 2985, 1739, 1449, 1380, 1370, 1273, 1206, 1132, 1092, 1045, 1017, 960, 860.

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[4]

Ethyl-(*2S*)-2-[(2-bromoacetyl)oxy]propanoate (87)



The title compound (**87**) was synthesized from bromoacetyl bromide (16.1 mL, 185 mmol), alcohol (10.93 g, 92.6 mmol) and neutral Al_2O_3 (14.16 g, 138.9 mmol) according to general procedure H as a yellow oil in 85 % yield (18.66 g, 78.4 mmol).

Molecular formula: $C_7H_{11}BrO_4$

Molecular weight: 239.06 g/mol

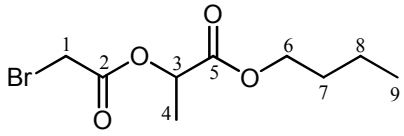
^{1}H NMR (400 MHz, $CDCl_3$) ppm: 5.07 (q, *J* = 7.2 Hz, 1H, *H3*), 4.16 (q, *J* = 7.2 Hz, 2H, *H6*), 3.87 (s, 2H, *H1*), 1.47 (d, *J* = 7.2 Hz, 3H, *H4*), 1.23 (t, *J* = 7.2 Hz, 3H, *H7*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 169.99 (*C*OO, *C5*), 166.65 (*C*OO, *C2*), 70.15 (O*C*H, *C3*), 61.63 (*C*H_2, *C6*), 25.39 (*C*H_2, *C1*), 16.75 (*C*H_3, *C4*), 14.08 (*C*H_3, *C7*).

IR (neat, cm^{-1}): 2986, 1739, 1450, 1380, 1312, 1273, 1206, 1132, 1092, 1045, 1017, 960.

$[\alpha]^{20}_D$ = -38.1° (2.383 c, $CHCl_3$)

Butyl-2-[(2-bromoacetyl)oxy]propanoate (88)[4]



The title compound (**88**) was prepared using butyl lactate (**80**) (7.63 g, 52.2 mmol), DCM (75 mL), sodium carbonate (8.29 g, 78.2 mmol), and bromoacetyl bromide (5.5 mL, 62.62 mmol) according to general procedure G to obtain a pale yellow liquid in 85 % yield (11.78 g, 44.1 mmol).

Molecular formula: $C_9H_{15}BrO_4$

Molecular weight: 267.12 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 5.11 (q, *J* = 7.2 Hz, 1H, *H3*), 4.13 (dt, *J* = 6.8, 6.4 Hz, 2H, *H6*), 3.89 (s, 2H, *H1*), 1.61 (tt, *J* = 7.0, 6.4 Hz, 2H, *H7*), 1.50 (d, *J* = 7.2 Hz, 3H, *H4*), 1.35 (qt, *J* = 7.6, 7.0 Hz, 2H, *H8*), 0.90 (t, *J* = 7.6 Hz, 3H, *H9*).

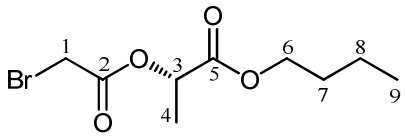
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 175.07 (*C*OO, *C5*), 166.63 (*C*OO, *C2*), 70.15 (*CH*OH, *C3*), 65.45 (O*C*H$_2$, *C6*), 30.46 (*C*H$_2$, *C1*), 25.35 (*C*H$_2$, *C7*), 18.99 (*C*H$_2$, *C8*), 16.78 (*C*H$_3$, *C4*), 13.64 (*C*H$_3$, *C9*).

IR (neat, cm^{-1}): 2962, 1741, 1457, 1351, 1274, 1203, 1132, 1094, 1044, 963, 937, 842.

HRMS (ESI$^+$,*m/z*): Calculated for $[M]^{+1}$, $C_9H_{16}O_4Br^+$, requires = 267.0232, found = 267.0234.

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[4]

Butyl-(*2S*)-2-[(2-bromoacetyl)oxy]propanoate (89)



The title compound (**89**) was prepared using (*S*)-butyl lactate (**81**) (16.55 g, 113.2 mmol), DCM (200 mL), sodium carbonate (18.0 g, 169.8 mmol), and bromoacetyl bromide (11.8 mL, 136 mmol) according to general procedure G to obtain a pale yellow liquid in 80 % yield (24.25 g, 90.8 mmol).

Molecular formula: $C_9H_{15}BrO_4$

Molecular weight: 267.12 g/mol

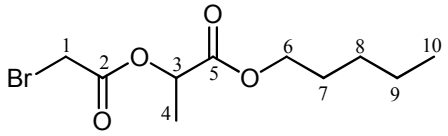
^{1}H NMR (400 MHz, $CDCl_3$) ppm: 5.09 (q, *J* = 7.2 Hz, 1H, *H3*), 4.10 (dt, *J* = 10.8, 6.6 Hz, 2H, *H6*), 3.87 (s, 2H, *H1*), 1.59 (tt, *J* = 7.2, 6.6 Hz, 2H, *H7*), 1.48 (d, *J* = 7.2 Hz, 3H, *H4*), 1.33 (tq, *J* = 7.6, 7.2 Hz, 2H, *H8*), 0.89 (t, *J* = 7.6 Hz, 3H, *H9*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 170.08 (*C*OO, *C5*), 166.64 (*C*OO, *C2*), 70.15 (*CH*, *C3*), 65.45 (O*C*H_2, *C6*), 30.45 (*C*H_2, *C1*), 25.37 (*C*H_2, *C7*), 18.81 (*C*H_2, *C8*), 16.79 (*C*H_3, *C4*), 13.65 (*C*H_3, *C9*).

IR (neat, cm^{-1}): 2962, 1747, 1458, 1312, 1278, 1207, 1134, 1098, 1046, 964.

$[\alpha]^{20}_D$ = -34.9° (1.09 c, $CHCl_3$)

Pentyl-2-[(2-bromoacetyl)oxy]propanoate (90)



The title compound (**90**) was prepared using pentyl lactate (**82**) (2.48 g, 15.5 mmol), DCM (25 mL), sodium carbonate (2.46 g, 23.2 mmol), and bromoacetyl bromide (1.60 mL, 18.58 mmol) according to general procedure G as a colourless liquid in 81 % yield (3.53 g, 12.6 mmol).

Molecular formula: $C_{10}H_{17}BrO_4$

Molecular weight: 281.14 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 5.12 (q, *J* = 7.2 Hz, 1H, *H3*), 4.13 (dt, *J* = 10.8, 6.6 Hz, 2H, *H6*), 3.90 (s, 2H, *H1*), 1.63 (tt, *J* = 7.2, 6.6 Hz, 2H, *H7*), 1.51 (d, *J* = 7.2 Hz, 3H, *H4*), 1.32-1.29 (m, 4H, *H8-9*), 0.88 (t, *J* = 7.2 Hz, 3H, *H10*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 175.86 (*C*OO, *C5*), 166.59 (*C*OO, *C2*), 70.13 (*CH*, *C3*), 65.69 (O*C*H_2, *C6*), 28.11 (*C*H_2, *C1*), 27.86 (*C*H_2, *C7*), 25.34 (*C*H_2, *C8*), 22.21 (*C*H_2, *C9*), 16.76 (*C*H_3, *C4*), 13.91 (*C*H_3, *C10*).

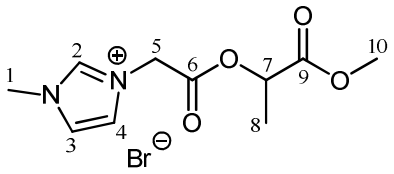
IR (neat, cm^{-1}): 2959, 1743, 1455, 1380, 1274, 1194, 1131, 1093, 1045, 968, 891.

HRMS (ESI^+,*m/z*): Calculated for $[M]^{+1}$, $C_{10}H_{18}O_4Br^+$, requires = 281.0388, found = 281.0399.

6.3.3 Bromide Ionic Liquids:

General Procedure I: Preparation of Lactate based bromide ILs[2]

3-{2-[(1-Methoxy-1-oxopropan-2-yl)oxy]-2-oxoethyl}-1-methyl-1H-imidazol-3-ium bromide (91a)[4]



To a stirred solution of **84** (1.92 g, 8.53 mmol) in diethyl ether (25mL) 1-methylimidazole (700 mg, 8.53 mmol) was added dropwise at RT and the reaction mixture was stirred for 12 h. The viscous liquid which had settled to the bottom of the flask was washed with diethyl ether (5 x 20 mL) and dried under high vacuum to obtain the title compound (**91a**) as a colourless liquid in 87 % yield (2.29 g, 7.46 mmol).

Molecular formula: $C_{10}H_{15}BrN_2O_4$

Molecular weight: 307.14 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 10.04 (s, 1H, *H2*), 7.68 (t, *J* = 1.6 Hz, 1H, *H4*), 7.61 (t, *J* = 1.6 Hz, 1H, *H3*), 5.67 (d, *J* = 17.6 Hz, 1H, *H5*), 5.42 (d, *J* = 17.6 Hz, 1H, *H5*), 5.12 (q, *J* = 7.2 Hz, 1H, *H7*), 4.05 (s, 3H, *H1*), 3.69 (s, 3H, *H10*), 1.48 (d, *J* = 7.2 Hz, 3H, *H8*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 170.05 (*C*OO, *C9*), 166.49 (*C*OO, *C6*), 137.68 (N*C*HN, *C2*), 123.61 (N*C*H, *C3/C4*), 123.49 (N*C*H, *C3/C4*), 69.90 (*C*H, *C7*), 52.43 (N*C*H$_2$, *C5*), 49.16 (O*C*H$_3$, *C10*), 35.98 (N*C*H$_3$, *C1*), 16.64 (*C*H$_3$, *C8*).

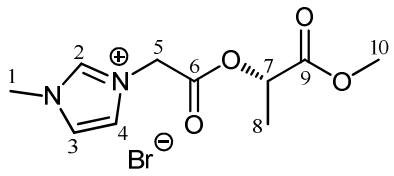
IR (neat, cm^{-1}): 3101, 2957, 1747, 1622, 1578, 1430, 1382, 1230, 1171, 1086, 976, 834, 754.

HRMS (ESI$^+$,*m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{10}H_{15}N_2O_4^+$, requires = 227.1026, found = 227.1022.

MS (*m/z*): 227.10 $[M\text{-}Br^-]^+$

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[4]

3-(2-{[(*2S*)-1-Methoxy-1-oxopropan-2-yl]oxy}-2-oxoethyl)-1-methyl-1H-imidazol-3-ium bromide (92a)



The title compound (**92a**) was prepared from **85** (2.86 g, 12.7 mmol) and 1-methylimidazole (1.05 g, 12.78 mmol) according to the general procedure I to obtain an off white solid in75 % yield (2.92 g, 9.5 mmol).

Molecular formula: $C_{10}H_{15}BrN_2O_4$

Molecular weight: 307.14 g/mol

Melting Point: 110-112°C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 10.22 (s, 1H, *H2*), 7.62 (t, *J* = 1.8 Hz, 1H, *H4*), 7.50 (t, *J* = 1.8 Hz, 1H, *H3*), 5.76 (d, *J* = 17.8 Hz, 1H, *H5*), 5.41 (d, *J* = 17.8 Hz, 1H, *H5*), 5.17 (q, *J* = 7.2 Hz, 1H, *H7*), 4.07 (s, 3H, *H1*), 3.74 (s, 3H, *H10*), 1.53 (d, *J* = 7.2 Hz, 3H, *H8*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 170.35 (*C*OO, *C9*), 165.81 (*C*OO, *C6*), 138.33 (NCHN, *C2*), 123.81 (NCH, *C3/C4*), 123.21 (NCH, *C3/C4*), 70.66 (*C*H, *C7*), 52.82 (NCH2, *C5*), 50.17 (OCH_3, *C10*), 37.00 (NCH_3, *C1*), 16.87 (CH_3, *C8*).

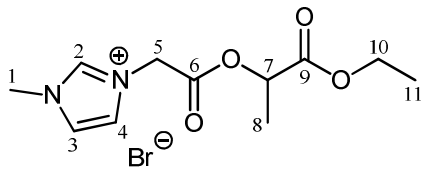
IR (neat, cm^{-1}): 3071, 2952, 1742, 1569, 1454, 1343, 1207, 1165, 1108, 975, 784.

HRMS (ESI$^+$,*m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{10}H_{15}N_2O_4^+$, requires = 227.1026, found = 227.1022.

MS (*m/z*): 227.10 $[M\text{-}Br^-]^+$

$[\alpha]^{20}_D$ = - 43.92° (1.06 c, EtOH)

3-{2-[(1-Ethoxy-1-oxopropan-2-yl)oxy]-2-oxoethyl}-1-methyl-1H-imidazol-3-ium bromide (93a)[4]



The title compound (**93a**) was prepared from **86** (10.48 g, 43.8 mmol) and 1-methylimidazole (3.5 mL, 43.8 mmol) according to the general procedure I to obtain a colourless liquid in 74 % yield (10.47 g, 32.60 mmol).

Molecular formula: $C_{11}H_{17}BrN_2O_4$

Molecular weight: 321.17 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.86 (s, 1H, *H2*), 7.62 (m, 2H, *H3, H4*), 5.57 (d, *J* = 17.6 Hz, 1H, *H5*), 5.35 (d, *J* = 17.6 Hz, 1H, *H5*), 5.02 (q, *J* = 7.2 Hz, 1H, *H7*), 4.06 (q, *J* = 7.2 Hz, 2H, *H10*), 3.98 (s, 3H, *H1*), 1.40 (d, *J* = 7.2 Hz, 3H, *H8*), 1.14 (t, *J* = 7.2 Hz, 3H, *H11*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 169.65 (*C*OO, *C9*), 165.60 (*C*OO, *C6*), 137.84 (N*C*HN, *C2*), 123.66 (N*C*H, *C3/C4*), 123.32 (N*C*H, *C3/C4*), 70.53 (*C*H, *C7*), 61.69 (O*C*H_2, *C10*), 49.92 (N*C*H_2, *C5*), 36.79 (N*C*H_3, *C1*), 16.67 (*C*H_3, *C8*), 13.93 (*C*H_3, *C11*).

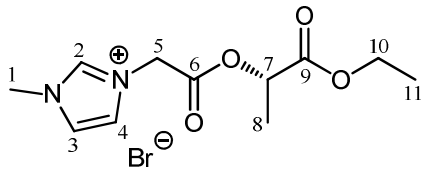
IR (neat, cm^{-1}): 3156, 2983, 1730, 1578, 1375, 1206, 1174, 1125, 1093, 1040, 751.

HRMS (ESI^+, *m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{11}H_{17}N_2O_4^+$, requires = 241.1188, found = 241.1179.

MS (*m/z*): 241.10 $[M\text{-}Br^-]^+$

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[4]

3-(2-{[(*2S*)-1-Ethoxy-1-oxopropan-2-yl]oxy}-2-oxoethyl)-1-methyl-1H-imidazol-3-ium bromide (94a)



The title compound (**94a**) was prepared from **87** (13.35 g, 55.8 mmol) and 1-methylimidazole (4.5 mL, 55.8 mmol) according to the general procedure I to obtain a colourless liquid in 74 % yield (13.35 g, 41.6 mmol).

Molecular formula: $C_{11}H_{17}BrN_2O_4$

Molecular weight: 321.17 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.78 (s, 1H, *H2*), 7.63 (t, *J* = 1.6 Hz, 1H, *H3/4*), 7.61 (t, *J* = 1.6 Hz, 1H, *H3/4*), 5.57 (d, *J* = 17.6 Hz, 1H, *H5*), 5.37 (d, *J* = 17.6 Hz, 1H, *H*5), 5.04 (q, *J* = 7.2 Hz, 1H, *H7*), 4.08 (q, *J* = 7.2 Hz, 2H, *H10*), 3.99 (s, 3H, *H1*), 1.43 (d, *J* = 7.2 Hz, 3H, *H8*), 1.16 (t, *J* = 7.2 Hz, 3H, *H11*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 169.80 (*C*OO, *C9*), 165.75 (*C*OO, *C6*), 137.88 (N*C*HN, *C2*), 123.70 (N*C*H, *C3/C4*), 123.35 (N*C*H, *C3/C4*), 70.55 (*C*H, *C7*), 61.76 (O*C*H$_2$, *C10*), 49.99 (N*C*H$_2$, *C5*), 36.86 (N*C*H$_3$, *C1*), 16.72 (*C*H$_3$, *C8*), 13.98 (*C*H$_3$, *C11*).

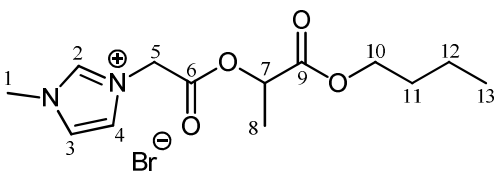
IR (neat, cm^{-1}): 3094, 2982, 1735, 1578, 1450, 1373, 1201, 1174, 1130, 1092, 1045, 1018, 855.

HRMS (ESI$^+$, *m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{11}H_{17}N_2O_4^+$, requires = 241.1188, found = 241.1182.

MS (*m/z*): 241.10 $[M\text{-}Br^-]^+$

$[\alpha]^{20}_D$ = - 37.6° (2.159 c, $CHCl_3$)

3-{2-[(1-Butoxy-1-oxopropan-2-yl)oxy]-2-oxoethyl}-1-methyl-1H-imidazol-3-ium bromide (95a)[4]



The title compound (**95a**) was prepared from **88** (10.93 g, 40.9 mmol) and 1-methylimidazole (3.36 g, 40.9 mmol) according to the general procedure I as a pale yellow liquid in 89 % yield (12.69 g, 36.3 mmol).

Molecular formula: $C_{13}H_{21}BrN_2O_4$

Molecular weight: 349.22 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 10.11 (s, 1H, *H2*), 7.61 (t, *J* = 1.8 Hz, 1H, *H4*), 7.59 (t, *J* = 1.8 Hz, 1H, *H3*), 5.72 (d, *J* = 17.6 Hz, 1H, *H5*), 5.36 (d, *J* = 17.6 Hz, 1H, *H5*), 5.12 (q, *J* = 7.0 Hz, 1H, *H7*), 4.09 (dt, *J* = 10.8, 6.4 Hz, 2H, *H10*), 4.06 (s, 3H, *H1*), 1.57 (tt, *J* = 7.0, 6.4, Hz, 2H, *H11*), 1.49 (d, *J* = 7.0 Hz, 3H, *H8*), 1.31 (qt, *J* = 7.6, 7.0 Hz, 2H, *H12*), 0.88 (t, *J* = 7.6 Hz, 3H, *H13*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 169.87 (*C*OO, *C9*), 165.65 (*C*OO, *C6*), 138.31 (N*C*HN, *C2*), 123.74 (N*C*H, *C3/C4*), 123.26 (N*C*H, *C3/C4*), 70.74 (*C*H, *C7*), 65.68 (N*C*H$_2$, *C5*), 50.12 (O*C*H$_2$, *C10*), 36.97 (N*C*H$_3$, *C1*), 30.41 (*C*H$_2$, *C11*), 18.96 (*C*H$_2$, *C12*), 16.87 (*C*H$_3$, *C8*), 13.66 (*C*H$_3$, *C13*).

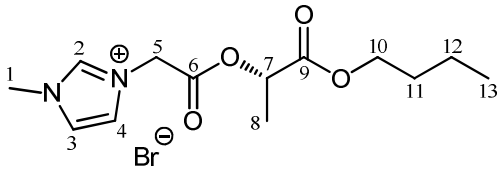
IR (neat, cm^{-1}): 2960, 1742, 1565, 1456, 1373, 1195, 1175, 1132, 1093, 964, 776, 753.

HRMS (ESI$^+$, *m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{13}H_{21}N_2O_4^+$, requires = 269.1501, found = 269.1507.

MS (*m/z*): 269.10 $[M\text{-}Br^-]^+$

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[4]

3-(2-{[(2S)-1-Butoxy-1-oxopropan-2-yl]oxy}-2-oxoethyl)-1-methyl-1H-imidazol-3-ium bromide (96a)



The title compound (**96a**) was prepared from **89** (19.12 g, 71.6 mmol) and 1-methylimidazole (5.87 g, 71.6 mmol) according to the general procedure I to obtain a white gel in 75 % yield (22.08 g, 9.5 mmol).

Molecular formula: $C_{13}H_{21}BrN_2O_4$

Molecular weight: 349.22 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.83 (s, 1H, *H2*), 7.61 (t, *J* = 1.8 Hz, 1H, *H4*), 7.57 (t, *J* = 1.8 Hz, 1H, *H3*), 5.65 (d, *J* = 18 Hz, 1H, *H5*), 5.37 (d, *J* = 18 Hz, 1H, *H5*), 5.11 (q, *J* = 7.2 Hz, 1H, *H7*), 4.09 (dt, *J* = 9.2, 6.6 Hz, 2H, *H10*), 4.04 (s, 3H, *H1*), 1.57 (tt, *J* = 7.0, 6.6 Hz, 2H, *H11*), 1.49 (d, *J* = 7.2 Hz, 3H, *H8*), 1.31 (tq, *J* = 7.6, 7.0 Hz, 2H, *H12*), 0.88 (t, *J* = 7.6 Hz, 3H, *H13*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 175.84 (*C*OO, *C9*), 165.87 (*C*OO, *C6*), 138.16 (N*C*HN, *C2*), 123.75 (N*C*H, *C3/C4*), 123.34 (N*C*H, *C3/C4*), 70.64 (*C*H, *C7*), 65.69 (N*C*H_2, *C5*), 50.15 (O*C*H_2, *C10*), 37.00 (N*C*H_3, *C1*), 30.39 (*C*H_2, *C11*), 18.95 (*C*H_2, *C12*), 16.88 (*C*H_3, *C8*), 13.65 (*C*H_3, *C13*).

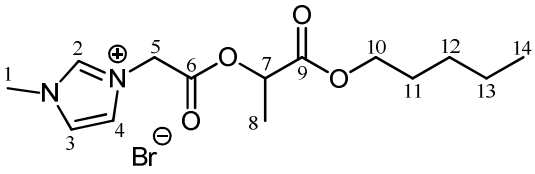
IR (neat, cm^{-1}): 2960, 1741, 1578, 1456, 1374, 1196, 1175, 1132, 1094, 1046, 964, 841, 753, 718.

HRMS (ESI^+, *m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{13}H_{21}N_2O_4^+$, requires = 269.1501, found = 269.1498.

MS (*m/z*): 269.10 $[M\text{-}Br^-]^+$

$[\alpha]^{20}_D = -34.4^{\circ}$ (0.5 c, $CHCl_3$)

1-Methyl-3-(2-oxo-2-{[1-oxo-1-(pentyloxy)propan-2-yl]oxy}ethyl)-1H-imidazol-3-ium bromide (97a)



The title compound (**97a**) was prepared from **90** (3.53 g, 12.6 mmol) and 1-methylimidazole (1.03 g,12.6 mmol) according to the general procedure I to obtain a pale yellow liquid in 94 % yield (4.30 g, 11.8 mmol).

Molecular formula: $C_{14}H_{23}BrN_2O_4$

Molecular weight: 363.25 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 10.23 (s, 1H, *H2*), 7.56 (t, *J* = 1.6 Hz, 1H, *H4*), 7.46 (t, *J* = 1.6 Hz, 1H, *H3*), 5.79 (d, *J* = 17.6 Hz, 1H, *H5*), 5.34 (d, *J* = 17.6 Hz, 1H, *H5*), 5.16 (q, *J* = 7.0 Hz, 1H, *H7*), 4.12 (dt, *J* = 10.8, 6.8 Hz, 2H, *H10*), 4.07 (s, 3H, *H1*), 1.63 (tt, *J* = 6.8, 6.8 Hz,

2H, *H11*), 1.53 (d, *J* = 7.0 Hz, 3H, *H8*), 1.31-1.27 (m, 4H, *H12, H13*), 0.88 (t, *J* = 6.8 Hz, 3H, *H14*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 169.87 (*C*OO, *C9*), 165.59 (*C*OO, *C6*), 138.66 (Ar*C*H, *C2*), 123.67 (Ar*C*H, *C3/C4*), 122.97 (Ar*C*H, *C3/C4*), 70.78 (*CH*, *C7*), 65.99 (O*C*H_2, *C10*), 50.19 (N*C*H_2, *C5*), 36.95 (N*C*H_3, *C1*), 28.12 (*C*H_2, *C11*), 27.85 (*C*H_2, *C12*), 22.21 (*C*H_2, *C13*), 16.85 (*C*H_3, *C8*), 13.93 (*C*H_3, *C14*).

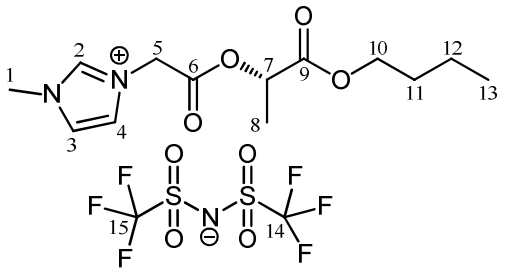
IR (neat, cm^{-1}): 2957, 1743, 1565, 1455, 1373, 1193, 1175, 1093, 1046, 968, 872, 754.

HRMS (ESI$^+$, *m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{14}H_{23}N_2O_4^+$, requires = 283.1658, found = 283.1658.

MS (*m/z*): 283.10 $[M\text{-}Br^-]^+$

6.3.4 [NTf_2] Ionic Liquid:

3-(2-{[(2S)-1-Butoxy-1-oxopropan-2-yl]oxy}-2-oxoethyl)-1-methyl-1H-imidazol-3-ium *bis*(trifluoromethylsulfonyl)imide (96b)



To a stirred solution of (**96a**) (760 mg, 2.16 mmol) in distilled water (10 mL) $LiNTf_2$ (590 mg, 2.06 mmol) was added and reaction mixture was stirred at RT for 4 h. The viscous liquid was washed with distilled water (3 x 10 mL) and dried under high vacuum to afford a colourless liquid in 63 % yield (720 mg, 1.31 mmol).

Molecular formula: $C_{15}H_{21}F_6N_3O_8S_2$

Molecular weight: 549.46 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 8.72 (s, 1H, *H2*), 7.39 (t, *J* = 1.8 Hz, 1H, *H3/H4*), 7.35 (t, *J* = 1.8 Hz, 1H, *H3/H4*), 5.14 (q, *J* = 7.2 Hz, 1H, *H7*), 5.23 (d, *J* = 18 Hz, 1H, *H5*), 5.02 (d, *J* =

18 Hz, 1H, *H5*), 4.14 (dt, *J* = 10.8, 6.6 Hz, 2H, *H10*), 3.94 (s, 3H, *H1*), 1.60 (tt, *J* = 7.0, 6.6, Hz, 2H, *H11*), 1.50 (d, *J* = 7.2 Hz, 3H, *H8*), 1.33 (qt, *J* = 7.6, 7.0 Hz, 2H, *H12*), 0.90 (t, *J* = 7.6 Hz, 3H, *H13*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 169.93 (*C*OO, *C9*), 165.38 (*C*OO, *C6*), 137.46 (N*C*HN, *C2*), 123.87 (N*C*H, *C3/C4*), 123.56 (N*C*H, *C3/C4*), 119.76 (q, 2*C*F_3, *J* = 319 Hz, *C14, C15*), 70.95 (*C*H, *C7*), 65.73 (N*C*H_2, *C5*), 49.75 (O*C*H_2, *C10*), 36.51 (N*C*H_3, *C1*), 30.43 (*C*H_2, *C11*), 18.98 (*C*H_2, *C12*), 16.63 (*C*H_3, *C8*), 13.61 (*C*H_3, *C13*).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -79.20 (6*F*)

$[\alpha]^{20}_{D}$ = -47.6° (0.75 c, $CHCl_3$)

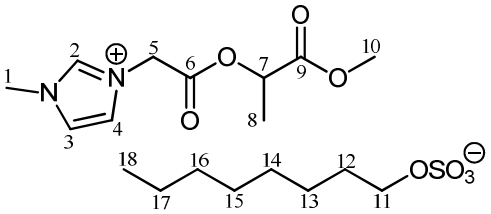
IR (neat, cm^{-1}): 3163, 2966, 1746, 1580, 1459, 1347, 1177, 1133, 1094, 1052, 788.

MS (*m/z*): $[M\text{-}NTf_2^-]^+$

6.3.5 [$OctOSO_3$] Ionic Liquids:

General Procedure J: Preparation of the Lactate based [$OctOSO_3$] ILs.

3-{2-[(1-Methoxy-1-oxopropan-2-yl)oxy]-2-oxoethyl}-1-methyl-1H-imidazol-3-ium octyl sulfate (91c)[4]



To a stirred solution of bromide salt (**91a**) (1.14 g, 3.71 mmol) in distilled water (10 mL) was added sodium octyl sulphate (860 mg, 3.71 mmol) in one portion. The mixture was stirred overnight then the water was removed by the rotary evaporation. The crude product was dissolved in DCM (25 mL) and washed with water (3 x 5 mL). The organic layer was removed by the rotary evaporation and compound (**91c**) dried under high vacuum to obtain a colourless liquid in 76 % yield (1.24 g, 2.84 mmol).

Molecular formula: $C_{18}H_{32}N_2O_8S$

Molecular weight: 436.52 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.35 (s, 1H, *H2*), 7.53 (t, *J* = 1.6 Hz, 1H, *H4*), 7.49 (t, *J* = 1.6 Hz, 1H, *H3*), 5.35 (d, *J* = 16.0 Hz, 1H, *H5*), 5.18 (d, *J* = 16.0 Hz, 1H, *H5*), 5.14 (q, *J* = 7.2 Hz, 1H, *H7*), 3.96-3.93 (m, 5H, *H1, H11*), 3.71 (s, 3H, *H10*), 1.60 (tt, *J* = 7.2, 6.8 Hz, 2H, *H12*), 1.49 (d, *J* = 7.2 Hz, 3H, *H8*), 1.29-1.24 (m, 10H, *H's 13-17*), 0.86 (t, *J* = 6.8 Hz, 3H, *H18*).

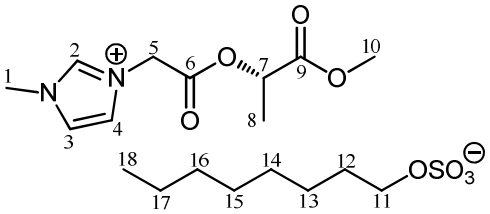
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 170.04 (*C*OO, *C9*), 166.49 (*C*OO, *C6*), 137.72 (N*C*HN, *C2*), 123.64 (N*C*H, *C3/C4*), 123.51 (N*C*H, *C3/C4*), 69.89 (O*C*H$_3$, *C10*), 65.41 (*C*H, *C7*), 52.41 (O*C*H$_2$, *C11*), 49.13 (N*C*H$_2$, *C5*), 35.95 (N*C*H$_3$, *C1*), 31.23 (*C*H$_2$, *C12*), 29.03 (*C*H$_2$), 28.71 (*C*H$_2$), 28.67 (*C*H$_2$), 25.50 (*C*H$_2$), 22.07 (*C*H$_2$), 16.63 (*C*H$_3$, *C8/C18*), 13.95 (*C*H$_3$, *C8/C18*).

IR (neat, cm^{-1}): 3118, 2926, 1749, 1628, 1578, 1456, 1378, 1207,1176, 1057, 977, 905, 837, 789, 755.

MS (*m/z*): 227.10 [M-OctOSO$_3^-$]$^+$

^{1}H, ^{13}C-NMR spectra and melting point are in agreement with the literature data.[4]

3-(2-{[(*2S*)-1-Methoxy-1-oxopropan-2-yl]oxy}-2-oxoethyl)-1-methyl-1H-imidazol-3-ium octyl sulfate (92c)



The title compound (**92c**) was prepared from bromide salt (**92a**) (1.27 g, 4.13 mmol) and sodium octyl sulphate (960 mg, 4.13 mmol) according to the general procedure J to afford a colourless liquid in 79 % yield (1.43 g, 3.28 mmol).

Molecular formula: $C_{18}H_{32}N_2O_8S$

Molecular weight: 436.52 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.41 (s, 1H, *H2*), 7.50 (t, *J* = 1.6 Hz, 1H, *H4*), 7.42 (t, *J* = 1.6 Hz, 1H, *H3*), 5.39 (d, *J* = 17.6 Hz, 1H, *H5*), 5.19 (d, *J* = 17.6 Hz, 1H, *H5*), 5.17 (q, *J* = 7.2

Hz, 1H, *H7*), 3.99 (t, *J* = 7.2 Hz, 2H, *H11*), 3.98 (s, 3H, *H1*), 3.74 (s, 3H, *H10*), 1.63 (tt, *J* = 7.2, 6.8 Hz, 2H, *H12*), 1.53 (d, *J* = 7.2 Hz, 3H, *H8*), 1.28-1.24 (m, 10H, *H's 13-17*), 0.85 (t, *J* = 6.8 Hz, 3H, *H18*).

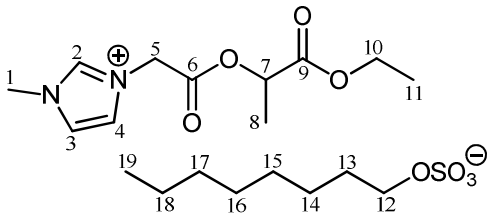
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 170.42 (*C*OO, *C9*), 166.04 (*C*OO *C6*), 138.72 (N*C*HN, *C2*), 123.72 (N*C*H, *C3/C4*), 123.25 (N*C*H, *C3/C4*), 70.58 (O*C*H_3, *C10*), 68.06 (*C*H, *C7*), 52.70 (O*C*H_2, *C11*), 49.75 (N*C*H_2, *C5*), 36.56 (N*C*H_3, *C1*), 31.82 (*C*H_2, *C12*), 29.45 (*C*H_2), 29.34 (*C*H_2), 29.25 (*C*H_2), 25.84 (*C*H_2), 22.65 (*C*H_2), 16.79 (*C*H_3, *C8/C18*), 14.12 (*C*H_3, *C8/C18*).

IR (neat, cm^{-1}): 3099, 2926, 1744, 1569, 1456, 1374, 1206, 1169, 1099, 1035, 976, 757.

MS (*m/z*): 227.10 [M- $OctOSO_3^-$]$^+$

$[\alpha]_D^{20}$ = -19.99° (1.055 c, EtOH)

3-{2-[(1-Ethoxy-1-oxopropan-2-yl)oxy]-2-oxoethyl}-1-methyl-1H-imidazol-3-ium octyl sulfate (93c)



The title compound (**93c**) was prepared from bromide salt (**93a**) (4.59 g, 14.3 mmol) and sodium octyl sulphate (3.32 g, 14.3 mmol) according to the general procedure J to obtain a colourless liquid in 85 % yield (5.46 g, 12.1 mmol).

Molecular formula: $C_{19}H_{34}N_2O_8S$

Molecular weight: 450.55 g/mol

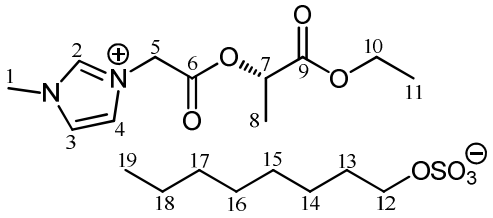
^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.35 (s, 1H, *H2*), 7.50 (t, *J* = 1.8 Hz, 1H, *H3/H4*), 7.47 (t, *J* = 1.8 Hz, 1H, *H3/H4*), 5.37 (d, *J* = 17.6 Hz, 1H, *H5*), 5.17 (d, *J* = 17.6 Hz, 1H, *H5*), 5.12 (q, *J* = 7.0 Hz, 1H, *H7*), 4.16 (q, *J* = 7.2 Hz, 2H, *H10*), 3.97-3.94 (m, 5H, *H1, H12*), 1.61 (tt, *J* = 7.2, 6.8 Hz, 2H, *H13*), 1.50 (d, *J* = 7.0 Hz, 3H, *H8*), 1.33-1.22 (m, 13H, *H's 11, 14-18*), 0.83 (t, *J* = 7.2 Hz, 3H, *H19*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 169.96 (*C*OO, *C9*), 166.05 (*C*OO, *C6*), 138.79 (N*C*HN, *C2*), 123.83 (N*C*H, *C3/C4*), 123.42 (N*C*H, *C3/C4*), 70.73 (O*C*H, *C7*), 67.71 (O*C*H_2, *C12*), 61.86 (O*C*H_2, *C10*), 49.79 (N*C*H_2, *C5*), 36.59 (N*C*H_3, *C1*), 31.87 (*C*H_2), 29.57 (*C*H_2), 29.41 (*C*H_2), 29.31 (*C*H_2), 25.93 (*C*H_2), 22.70 (*C*H_2), 16.83 (*C*H_3, *C8*), 14.17 (*C*H_3, *C11/C19*), 14.15 (*C*H_3, *C11/C19*).

IR (neat, cm^{-1}): 3115, 2927, 1742, 1579, 1568, 1457, 1377, 1182, 1095, 1047, 976, 753.

MS (*m/z*): 241.10 $[M\text{-}OctOSO_3^-]^+$

3-(2-{[(*2S*)-1-Ethoxy-1-oxopropan-2-yl]oxy}-2-oxoethyl)-1-methyl-1H-imidazol-3-ium octyl sulfate (94c)



The title compound (**94c**) was prepared from bromide salt (**94a**) (4.63 g, 14.4 mmol) and sodium octyl sulphate (3.35 g, 14.4 mmol) according to the general procedure J to afford a colourless liquid with in 81 % yield (5.28 g, 11.7 mmol).

Molecular formula: $C_{19}H_{34}N_2O_8S$

Molecular weight: 450.55 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.33 (s, 1H, *H2*), 7.51 (t, *J* = 1.8 Hz, 1H, *H3/H4*), 7.48 (t, *J* = 1.8 Hz, 1H, *H3/H4*), 5.35 (d, *J* = 18 Hz, 1H, *H5*), 5.17 (d, *J* = 18 Hz, 1H, *H5*), 5.12 (q, *J* = 7.0 Hz, 1H, *H7*), 4.15 (q, *J* = 7.2 Hz, 2H, *H10*), 3.97-3.93 (m, 5H, *H1, H12*), 1.60 (tt, *J* = 7.2, 6.8 Hz, 2H, *H13*), 1.49 (d, *J* = 7.0 Hz, 3H, *H8*), 1.32-1.21 (m, 13H, *H11, H14-18*), 0.82 (t, *J* = 7.2 Hz, 3H, *H19*).

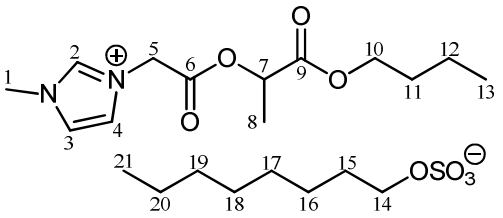
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 169.93 (*C*OO, *C9*), 166.04 (*C*OO, *C6*), 138.71 (N*C*HN, *C2*), 123.83 (N*C*H, *C3/C4*), 123.44 (N*C*H, *C3/C4*), 70.70 (O*C*H, *C7*), 67.79 (O*C*H_2, *C12*), 61.83 (O*C*H_2, *C10*), 49.75 (N*C*H_2, *C5*), 36.55 (N*C*H_3, *C1*), 31.84 (*C*H_2), 29.54 (*C*H_2), 29.38 (*C*H_2), 29.28 (*C*H_2), 25.90 (*C*H_2), 22.67 (*C*H_2), 16.80 (*C*H_3, *C8*), 14.14 (*C*H_3, *C11/C19*), 14.12 (*C*H_3, *C11/C19*).

IR (neat, cm^{-1}): 3115, 2956, 1742, 1578, 1457, 1377, 1345, 1182, 1132, 1047, 1017, 956, 907.

MS (*m/z*): 241.10 $[M\text{-}OctOSO_3^-]^+$

$[\alpha]^{20}_D$ = -30.0° (2.446 c, $CHCl_3$)

3-{2-[(1-Butoxy-1-oxopropan-2-yl)oxy]-2-oxoethyl}-1-methyl-1H-imidazol-3-ium octyl sulfate (95c)[4]



The title compound (**95c**) was prepared from bromide salt (**95a**) (2.35 g, 6.7 mmol) and sodium octyl sulphate (1.56 g, 6.7 mmol) according to the general procedure J to obtain a colourless liquid in 81 % yield (2.61 g, 5.5 mmol).

Molecular formula: $C_{21}H_{38}N_2O_8S$

Molecular weight: 478.6 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.23 (s, 1H, *H2*), 7.49 (t, *J* = 1.8 Hz, 1H, *H4*), 7.48 (t, *J* = 1.8 Hz, 1H, *H3*), 5.29 (d, *J* = 18 Hz, 1H, *H5*), 5.14 (d, *J* = 18 Hz, 1H, *H5*), 5.07 (q, *J* = 7.0 Hz, 1H, *H7*), 4.05 (dt, *J* = 7.2, 6.8 Hz, 2H, *H10*), 3.90 (s, 3H, *H1*), 3.89 (t, *J* = 7.2 Hz, 2H, *H14*), 1.54 (tt, *J* = 7.2, 6.8 Hz, 2H, *H11*), 1.45 (d, *J* = 7.0 Hz, 3H, *H8*), 1.33-1.17 (m, 14H, *H's 12, 15-20*), 0.84 (t, *J* = 7.2 Hz, 3H, *H21*), 0.78 (t, *J* = 6.8 Hz, 3H, *H13*).

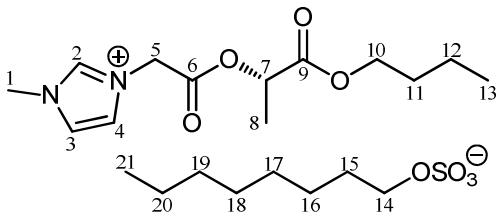
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 169.94 (*C*OO, *C9*), 166.0 (*C*OO, *C6*), 138.45 (N*C*HN, *C2*), 123.77 (N*C*H, *C3/C4*), 123.50 (N*C*H, *C3/C4*), 70.53 (O*C*H_2, *C14*), 67.71 (*C*H, *C7*), 65.50 (O*C*H_2, *C10*), 49.63 (N*C*H_2, *C5*), 36.43 (N*C*H_3, *C1*), 31.75 (*C*H_2, *C11/C15*), 30.37 (*C*H_2, *C11/C15*), 29.43 (*C*H_2), 29.29 (*C*H_2), 29.19 (*C*H_2), 25.81 (*C*H_2), 22.58 (*C*H_2), 18.91 (*C*H_2), 16.76 (*C*H_3, *C8*), 14.04 (*C*H_3, *C13/C21*), 13.58 (*C*H_3, *C13/C21*).

IR (neat, cm^{-1}): 2928, 1749, 1579, 1458, 1377, 1197, 1133, 1096, 1058, 978, 906, 785, 753.

MS (*m/z*): 269.10 $[M\text{-}OctOSO_3^-]^+$

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[4]

3-(2-{[(*2S*)-1-Butoxy-1-oxopropan-2-yl]oxy}-2-oxoethyl)-1-methyl-1H-imidazol-3-ium octyl sulfate (96c)



The title compound (**96c**) was prepared from bromide salt (**96a**) (3.67 g, 10.5 mmol) and sodium octyl sulphate (2.44 g, 10.5 mmol) according to the general procedure J to obtain a colourless liquid in 82 % yield (4.13 g, 8.6 mmol).

Molecular formula: $C_{21}H_{38}N_2O_8S$

Molecular weight: 478.6 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.44 (s, 1H, *H2*), 7.45 (t, *J* = 1.8 Hz, 1H, *H4*), 7.40 (t, *J* = 1.8 Hz, 1H, *H3*), 5.43 (d, *J* = 18 Hz, 1H, *H5*), 5.16 (d, *J* = 18 Hz, 1H, *H5*), 5.15 (q, *J* = 7.0 Hz, 1H, *H7*), 4.13 (dt, *J* = 10.2, 7.0 Hz, 2H, *H10*), 4.0 (t, *J* = 6.8 Hz, 2H, *H14*), 3.99 (s, 3H, *H1*), 1.62 (tt, *J* = 7.6, 7.0 Hz, 2H, *H11*), 1.53 (d, *J* = 7.0 Hz, 3H, *H8*), 1.41-1.24 (m, 14H, *H 12, H15-20*), 0.92 (t, *J* = 7.2 Hz, 3H, *H21*), 0.85 (t, *J* = 6.8 Hz, 3H, *H13*).

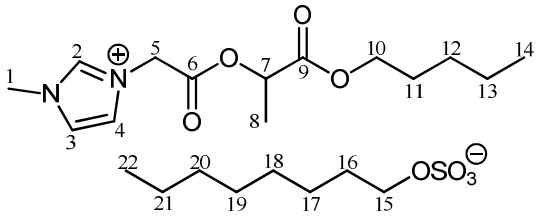
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 169.87 (*C*OO, *C9*), 165.93 (*C*OO, *C6*), 138.50 (N*C*HN, *C2*), 123.73 (N*C*H, *C3/C4*), 123.49 (N*C*H, *C3/C4*), 70.54 (O*C*H_2, *C14*), 67.78 (*C*H, *C7*), 65.46 (O*C*H_2, *C10*), 49.63 (N*C*H_2, *C5*), 36.45 (N*C*H_3, *C1*), 31.74 (*C*H_2, *C11/C15*), 30.36 (*C*H_2, *C11/C15*), 29.41 (*C*H_2), 29.27 (*C*H_2), 29.18 (*C*H_2), 25.79 (*C*H_2), 22.57 (*C*H_2), 18.90 (*C*H_2), 16.75 (*C*H_3, *C8*), 14.04 (*C*H_3, *C13/C21*), 13.58 (*C*H_3, *C13/C21*).

IR (neat, cm^{-1}): 2957, 2928, 1745, 1579, 1458, 1378, 1201, 1179, 1133, 1096, 1057, 977, 906, 789, 753.

MS (*m/z*): 269.10 [M-OctOSO_3^-]$^+$

$[\alpha]_D^{20}$ = -12.3° (1.067 c, EtOH)

1-Methyl-3-(2-oxo-2-{[1-oxo-1-(pentyloxy)propan-2-yl]oxy}ethyl)-1H-imidazol-3-ium octyl sulfate (97c)



The title compound (**97c**) was prepared from bromide salt (**97a**) (1.42 g, 3.91 mmol) and sodium octyl sulphate (910 mg, 3.91 mmol) according to the general procedure J to afford a colourless liquid in 87 % yield (1.68 g, 3.41 mmol).

Molecular formula: $C_{22}H_{40}N_2O_8S$

Molecular weight: 492.63 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.43 (s, 1H, *H2*), 7.48 (t, *J* = 1.8 Hz, 1H, *H4*), 7.44 (t, *J* = 1.8 Hz, 1H, *H3*), 5.40 (d, *J* = 17.6 Hz, 1H, *H5*), 5.151 (d, *J* = 17.6 Hz, 1H, *H5*),5.147 (q, *J* = 7.2 Hz, 1H, *H7*), 4.10 (dt, *J* = 10.8, 6.8 Hz, 2H, *H10*), 3.98 (t, *J* = 7.2 Hz, 2H, *H15*), 3.97 (s, 3H, *H1*), 1.66-1.58 (m, 4H, *H11, H16*), 1.52 (d, *J* = 7.2 Hz, 3H, *H8*), 1.35-1.23 (m, 14H, *H 17-H21, H12, H13*), 0.89-0.83 (m, 6H, *H14,H22*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 169.60 (*C*OO, *C9*), 166.47 (*C*OO, *C6*), 137.71 (N*C*HN, *C2*), 123.61 (N*C*H, *C3/C4*), 123.52 (N*C*H, *C3/C4*), 69.97 (O*C*H_2, *C15*), 65.42 (*C*H, *C7*), 65.05 (O*C*H_2, *C10*), 49.12 (N*C*H_2, *C5*), 35.95 (N*C*H_3, *C1*), 31.23 (*C*H_2, *C11/C16*), 29.03 (*C*H_2, *C11/C16*), 28.71 (*C*H_2), 28.66 (*C*H_2), 27.58 (*C*H_2), 27.29 (*C*H_2), 25.50 (*C*H_2), 22.07 (*C*H_2), 21.64 (*C*H_2), 16.65 (*C*H_3, *C8*), 13.94 (*C*H_3, *C14/C22*), 13.79 (*C*H_3, *C14/C22*).

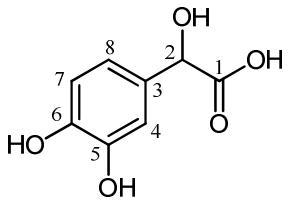
IR (neat, cm^{-1}): 2956, 2927, 1745, 1579, 1458, 1377, 1201, 1133, 1097, 1049, 975, 906, 789, 754.

MS (*m/z*): 283.10 $[M\text{-}OctOSO_3^-]^+$

6.4 Mandelate Ionic Liquids:

6.4.1 Carboxylic Acids:[8]

2-(3,4-Dihydroxyphenyl)-2-hydroxyacetic acid (98)[8]



Catechol (5.10 g, 46.3 mmol) was dissolved in aqueous NaOH (3.21 g, 80.3 mmol in 55 mL of water) and Al_2O_3 (2.04 g, 20.0 mmol) was added. After 5 min glyoxylic acid (50 % aq. solution, 7.12 g, 48.1 mmol) was added and the reaction mixture heated to 60 °C with vigorous stirring and maintained for 24 h at 60°C. After 24 h the reaction mixture was allowed to cool for 10 min, filtered and the filter cake washed with aqueous NaOH solution (1M, 20 mL). The basic washings were combined with the filtrate, acidified to pH ~ 4 with 37 % HCl and extracted with ethyl acetate (2 x 50 mL) to remove unreacted catechol. The aqueous solution was then further acidified to pH 1 and extracted with ethyl acetate (5 x 100 mL). The organic phase was concentrated under high vacuum and residue was purified by column chromatography (SiO_2, MeOH:DCM; 20:80) to obtain a brown solid in 67 % yield (5.70 g, 30.9 mmol).

Molecular formula: $C_8H_8O_5$

Molecular weight: 184.15 g/mol

Melting point: 134-136°C

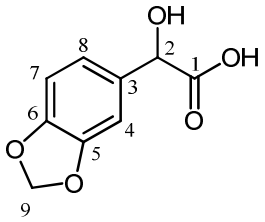
^{1}H NMR (400 MHz, DMSO-d_6) ppm: 12.43 (bs, 1H, O*H* at *C*1), 8.93 (s, 1H, O*H* at *C5/C6*), 8.85 (s, 1H, O*H* at *C5/C6*), 6.79 (d, J = 1.6, 1H, *H4*), 6.66 (d, *J* = 8.0 Hz, 1H, *H7*), 6.64 (dd, *J* = 8.0, 1.6 Hz, 1H, *H8*), 5.71 (bs, 1H, O*H* at *C2*), 4.80 (s, 1H, *H2*).

^{13}C NMR (100 MHz, DMSO-d_6) ppm: 174.44 (*C*OO, *C1*), 144.85 (2Ar*C*, *C5, C6*), 131.06 (Ar*C*, *C3*), 117.80 (Ar*C*H, *C*8), 115.02 (Ar*C*H, *C4/C7*), 114.10 (Ar*C*H, *C4/C7*), 72.08 (*C*HOH, *C2*)

IR (neat, cm^{-1}): 3405, 3333, 3208, 3035, 2909, 1693, 1604, 1534, 1430, 1348, 1280, 1256, 1208, 1189, 1149, 1116, 1084, 980, 879, 867, 803, 709.

^{1}H, ^{13}C-NMR spectra and melting point are in agreement with the literature data.[8]

2-(2H-1,3-Benzodioxol-5-yl)-2-hydroxyacetic acid (99)[8]



A flask was charged with glyoxylic acid solution (50 % in water) (6.25 g, 42.2 mmol), water (1 mL, 55.6 mmol) and at −10 °C conc. sulphuric acid (4.0 mL, 75.1 mmol) was added dropwise to the stirred mixture. 1,2-(methylenedioxy)benzene (5.00 g, 40.9 mmol) was then added dropwise over 1 h at −10 °C. The reaction mixture was stirred at −10 °C for 10 h and then allowed to warm to room temperature and stirring continued for an additional 14 h. Water (50 mL) was added to reaction mixture and product was extracted with ethyl acetate (5 × 75 mL). The organic phase was dried over anhydrous $MgSO_4$, concentrated under high vacuum and purified by column chromatography (SiO_2, EtOAc:Hexane; 20:80) to obtain the title compound (**99**) as an off white solid in 72 % yield (5.74 g, 29.3 mmol).

Molecular formula: $C_9H_8O_5$

Molecular weight: 196.16 g/mol

Melting point: 146-148 °C

^{1}H NMR (400 MHz, DMSO-d_6) ppm: 12.60 (bs, 1H, COO*H*), 6.94 (s, 1H, *H4*), 6.90 (d, *J* = 8.2, Hz, 1H, *H8*), 6.87 (d, *J* = 8.2 Hz, 1 H, *H7*), 5.99 (s 2H, *H9*), 5.81 (bs, 1H, O*H*, C2), 4.94 (s, 1H, *H2*).

^{13}C NMR (100 MHz, DMSO-d_6) ppm: 174.26 (*C*OO, *C1*), 147.17 (Ar*C*, *C5/C6*), 146.79 (ArC, *C5/C6*), 134.24 (Ar*C*, *C3*), 120.23 (Ar*C*H, *C7*), 107.98 (Ar*C*H, *C8*), 107.08 (Ar*C*H, *C4*), 101.02 (O*C*H_2O, *C9*), 72.15 (H*C*OH, *C2*).

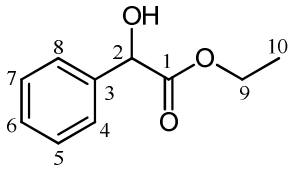
IR (neat, cm^{-1}): 3409, 2907, 1715, 1609, 1501, 1485, 1445, 1357, 1246, 1198, 1121, 1097, 1068, 1046, 937, 811, 747.

^{1}H, ^{13}C-NMR spectra and melting point are in agreement with literature.[8]

6.4.2 Preparation of ester:

General Procedure K: Preparation of Mandelate ester:[9]

Ethyl 2-hydroxy-2-phenylacetate (104)[4]



To a stirred solution of mandelic acid (5.17 g, 33.9 mmol) in ethanol (50 mL) was added *p*-toluenesulfonic acid monohydrate (PTSA) (650 mg, 3.39 mmol) at RT. After stirring for 6 h the reaction mixture was concentrated, added water (50 mL) and the product was extracted with ethyl acetate (5 × 50 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under high vacuum. The crude product was purified by column chromatography (SiO_2, Hexane:EtOAc, 80:20) to obtain a colourless liquid in 98 % yield (6.02 g, 33.4 mmol).

Molecular formula: $C_{10}H_{12}O_3$

Molecular weight: 180.20 g/mol

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.38-7.30 (m, 5H, *H4-H8*), 5.17 (s, 1H, *H2*), 4.29-4.11 (m, 2H, *H9*), 3.81 (bs, 1H, O*H* at C2), 1.21 (t, *J* = 7.2 Hz, 3H, *H10*).

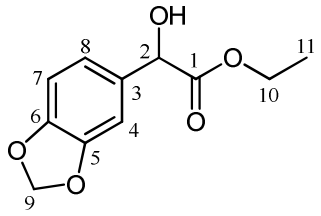
^{13}C NMR (100 MHz, $CDCl_3$, δ): 173.69 (*C*OO, *C1*), 138.46 (Ar*C*, *C3*), 128.57 (2Ar*CH*, *C5,C7*), 128.40 (Ar*C*H, *C6*), 126.57 (2Ar*C*H, *C4,C8*), 72.92 (*C*HOH, *C2*), 62.21(O*C*H$_2$, *C9*), 14.03 (C*C*H$_3$, *C10*).

IR (neat, cm^{-1}): 3453, 2984, 1728, 1689, 1597, 1452, 1200, 1177, 1093, 1066, 1015, 861.

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[4]

General Procedure L: Preparation of Mandelate ester[2]

Ethyl 2-(2H-1,3-benzodioxol-5-yl)-2-hydroxyacetate (105)[10]



To a stirred solution of 3,4-methylenedioxymandelic acid (**99**) (7.87 g, 40.1 mmol) in ethanol (100 mL) was added thionyl chloride (1.0 mL, 13.7 mmol) dropwise at RT. After stirring for 3 h the reaction was quenched with water and the product was extracted with ethyl acetate (5 × 50 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under high vacuum to obtain the title compound (**105**) as a white solid in 79 % yield (7.12 g, 31.8 mmol).

Molecular formula: $C_{11}H_{12}O_5$

Molecular weight: 224.21 g/mol

Melting point: 42-44°C

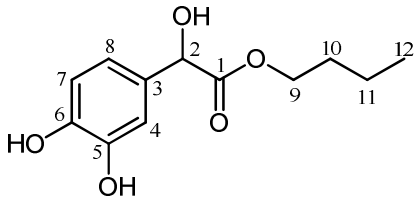
^{1}H NMR (400 MHz, $CDCl_3$) ppm: 6.90 (dd, *J* = 6.8, 1.6 Hz, 1H, *H8*), 6.88 (d, *J* = 1.6 Hz, 1H, *H4*), 6.78 (d, *J* = 6.8 Hz, 1H, *H7*), 5.96 (s, 2H, *H9*), 5.05 (d, *J* = 5.6 Hz, 1H, *H2*), 4.27 (dt, *J* = 10.8, 7.0 Hz, 1H, *H10*), 4.16 (dt, *J* = 10.8, 7.0 Hz, 1H, *H10*), 3.44 (d, *J* = 5.6 Hz, 1H, O*H*, C2), 1.24 (t, *J* = 7.0 Hz, 3H, *H11*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 173.82 (*C*OO, *C1*), 147.99 (Ar*C*, *C5/C6*), 147.84 (Ar*C*, *C5/C6*), 132.42 (Ar*C*, *C3*), 120.47 (Ar*C*H, *C4*/*C8*), 108.40 (Ar*C*H, *C7*), 107.07 (Ar*C*H, *C4*/*C8*), 101.33 (O*C*H_2O, *C9*), 72.74 (*C*HOH, *C2*), 62.43 (O*C*H_2, *C10*), 14.20 (*C*H_3, *C11*).

IR (neat, cm^{-1}): 3657, 2981, 1748, 1733, 1608, 1512, 1434, 1292, 1247, 1172, 1111, 1030, 981, 827.

^{1}H, ^{13}C-NMR spectra and melting point are in agreement with literature.[10]

Butyl 2-(3,4-dihydroxyphenyl)-2-hydroxyacetate (106)



The title compound (**106**) was prepared from 3,4-dihydroxymandelic acid (**98**) (4.04 g, 21.9 mmol), butanol (25 mL) and thionyl chloride (0.40 mL, 5.43 mmol) according to general procedure L to obtain a yellow solid in 54 % yield (2.86 g, 11.9 mmol).

Molecular formula: $C_{12}H_{16}O_5$

Molecular weight: 240.25 g/mol

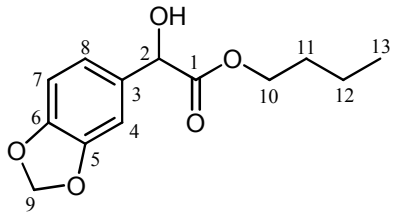
Melting point: 88-90°C

^{1}H NMR (400 MHz, DMSO-d_6) ppm: 8.93 (s, 1H, O*H*, *C*5/*C*6), 8.88 (s, 1H, O*H*, *C*5/*C*6), 6.78 (d, *J* = 1.6 Hz, 1H, *H4*), 6.66 (d, *J* = 8.0 Hz, 1H, *H7*), 6.62 (dd, *J* = 8.0, 1.6 Hz, 1H, *H8*), 5.75 (s, 1H, O*H*, *C*2), 4.89 (s, 1H, *H2*), 4.05-3.97 (m, 2H, *H9*), 1.51-1.44 (m, 2H, *H10*), 1.21 (qt, *J* = 7.6, 7.2 Hz, 2H, *H11*), 0.82 (t, *J* = 7.6 Hz, 3H, *H12*)

^{13}C NMR (100 MHz, DMSO-d_6) ppm: 173.00 (*C*OO, *C1*), 145.04 (Ar*C*, *C5/C6*), 144.99 (Ar*C*, *C5/C6*), 130.64 (Ar*C*, *C3*), 117.81 (Ar*C*H, *C8*), 115.14 (Ar*C*H, *C7*), 114.08 (Ar*C*H, *C4*), 72.24 (*C*HOH, *C2*), 63.76 (O*C*H$_2$, *C10*), 30.14 (*C*H$_2$, *C11*), 18.45 (*C*H$_2$, *C12*), 13.50 (*C*H$_3$, *C13*).

IR (neat, cm^{-1}): 3465, 2960, 1731, 1514, 1235, 1260, 1139, 1024, 803, 764.

Butyl 2-(2H-1,3-benzodioxol-5-yl)-2-hydroxyacetate (107)



The title compound (**107**) was prepared using 3,4-methylenedioxymandelic acid (**99**) (11.06 g, 56.4 mmol), butanol (70 mL) and thionyl chloride (2.1 mL, 28.19 mmol) according to general procedure L as an off white solid in 95 % yield (13.45 g, 53.3 mmol).

Molecular formula: $C_{13}H_{16}O_5$

Molecular weight: 252.26 g/mol

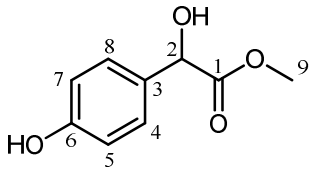
Melting point: 47-49°C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 7.00 (d, *J* = 1.8 Hz, 1H, *H4*), 6.89 (dd, *J* = 8.4, 1.8 Hz, 1H, *H8*), 6.73 (d, *J* = 8.4 Hz, 1H, *H7*), 5.96 (s, 2H, *H9*), 5.06 (s, 1H, *H2*), 4.17 (dt, *J* = 10.8, 6.8 Hz, 1H, *H10*), 4.14 (dt, *J* = 10.8, 6.8 Hz, 1H, *H10*), 3.42 (bs, 1H, O*H* at C2), 1.57 (tt, *J* = 6.8, 6.8 Hz, 2H, *H11*), 1.27 (tq, J = 7.4, 6.8 Hz, 2H, *H12*), 0.87 (t, *J* = 7.4 Hz, 3H, *H13*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 172.68 (*C*OO, *C1*), 147.16 (Ar*C*, *C5/C6*), 146.86 (Ar*C*, *C5/C6*), 133.70 (Ar*C*, *C3*), 120.22 (Ar*C*H, *C8*), 107.99 (Ar*C*H, *C7*), 106.96 (Ar*C*H, *C4*), 101.03 (O*C*H_2O, *C9*), 72.14 (*C*HOH, *C2*), 64.00 (O*C*H_2, *C10*), 30.11 (*C*H_2, *C11*), 18.44 (*C*H_2, *C12*), 13.49 (*C*H_3, *C13*).

IR (neat, cm^{-1}): 3456, 2961, 2946, 2890, 1730, 1498, 1487, 1443, 1397, 1295, 1260, 1233, 1194, 1173, 1100, 1082, 1033, 929, 818, 763.

Methyl-2-hydroxy-2-(4-hydroxyphenyl)acetate (108)[11]



The title compound (**108**) was prepared using 4-hydroxymandelic acid (**100**) (4.99 g, 26.8 mmol), methanol (50 mL) and *p*-toluenesulfonic acid monohydrate (PTSA) (510 mg, 2.68 mmol) according to general procedure K to obtain an off white solid in 80 % yield (3.91 g, 21.5 mmol).

Molecular formula: $C_9H_{10}O_4$

Molecular weight : 182.17 g/mol

Melting point: 135-137°C

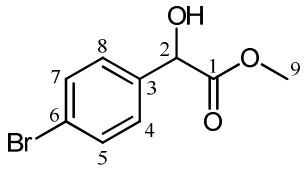
^{1}H NMR (400 MHz, DMSO-d_6) ppm: 9.46 (s, 1H, O*H,* C6), 7.17 (d, *J* = 6.0 Hz, 2H, *H5*, *H7*), 6.72 (d, *J* = 6.0 Hz, 2H, *H4*, *H8*), 5.87 (d, *J* = 3.4 Hz, 1H, O*H* at C2), 5.00 (d, *J* = 3.4 Hz, 1H, *H2*), 3.58 (s, 3H, *H9*).

^{13}C NMR (100 MHz, DMSO-d_6) ppm: 173.47 (*C*OO, *C1*), 157.17 (Ar*C*, *C6*), 130.03 (Ar*C*, *C3*), 128.04 (2Ar*C*H, *C5, C7*), 115.01 (2Ar*C*H, *C4, C8*), 72.08 (*C*HOH, *C2*), 51.66 (O*C*H$_3$, *C9*).

IR (neat, cm^{-1}): 3529, 3231, 3048, 2949, 1732, 1615, 1596, 1517, 1450, 1432, 1326, 1262, 1215, 1190, 1172, 1109, 1076, 980, 827, 814, 758.

^{1}H, ^{13}C-NMR spectra and melting point are in agreement with the literature data.[11]

Methyl-2-(4-bromophenyl)-2-hydroxyacetate (109)[12]



The title compound (**109**) was prepared from 4-bromomandelic acid (**101**) (9.20 g, 39.8 mmol), methanol (100 mL) and *p*-toluenesulfonic acid monohydrate (760 mg, 3.99 mmol) according to general procedure K to obtain an off white solid in 98 % yield (9.56 g, 39.0 mmol).

Molecular formula: $C_9H_9BrO_3$

Molecular weight: 245.07 g/mol

Melting point: 56-58°C

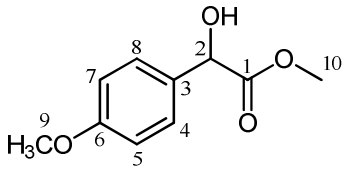
^{1}H NMR (400 MHz, $CDCl_3$) ppm: 7.50 (d, *J* = 8.4 Hz, 2H, *H5, H7*), 7.31 (d, *J* = 8.4 Hz, 2H, *H4, H8*), 5.14 (s, 1H, *H2*), 3.76 (s, 3H, *H9*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 173.81 (*C*OO, *C1*), 137.28 (Ar*C*, *C6*), 131.86 (2Ar*CH*, *C5, C7*), 128.40 (2Ar*CH*, *C4, C8*), 122.68 (Ar*C*, *C3*), 72.34 (*C*HOH, *C2*), 53.39 (O*C*H$_3$, *C9*).

IR (neat, cm^{-1}): 3325, 3000, 2951, 1732, 1592, 1485, 1435, 1407, 1248, 1213, 1197, 1109, 1086, 1003, 980, 828, 761.

^{1}H, ^{13}C-NMR spectra and melting point are in agreement with the literature data.[12]

Methyl-2-hydroxy-2-(4-methoxyphenyl)acetate (110)[12]



The title compound (**110**) was prepared from 4-methoxy mandelic acid (**102**) (1.00 g, 5.49 mmol), methanol (20 mL) and *p*-toluenesulfonic acid monohydrate (110 mg, 0.57 mmol) according to general procedure K to obtain an off white solid in 97 % yield (1.05 g, 5.35 mmol).

Molecular formula: $C_{10}H_{12}O_4$

Molecular weight: 196.20 g/mol

Melting point: 37-38°C

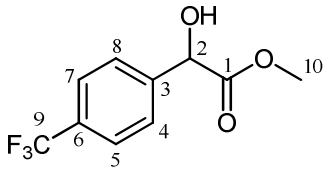
^{1}H NMR (400 MHz, $CDCl_3$) ppm: 7.32 (d, *J* = 8.8 Hz, 2H, *H5, H7*), 6.88 (d, *J* = 8.8 Hz, 2H, *H4, H8*), 5.12 (s, 1H, *H2*), 3.80 (s, 3H, *H9*), 3.74 (s, 3H, *H10*), 3.49 (s, 1H, O*H*, C*2*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 174.45 (*C*OO, *C1*), 159.82 (Ar*C*, *C6*), 130.53 (Ar*C*, *C3*), 128.02 (2Ar*C*H, *C4, C8*), 114.11 (2Ar*C*H, *C5, C7*), 72.56 (*C*HOH, *C2*), 55.38 (O*C*H$_3$, *C9*), 53.08 (O*C*H$_3$, *C10*).

IR (neat, cm^{-1}): 3427, 2969, 1727, 1609, 1509, 1441, 1249, 1168, 1078, 1027, 976, 796.

^{1}H, ^{13}C-NMR spectra and melting point are in agreement with the literature data.[12]

Methyl 2-hydroxy-2-[4-(trifluoromethyl)phenyl]acetate (111)[13]



The title compound (**111**) was synthesized from 4-(trifluoromethyl)mandelic acid (**103**) (9.20 g, 41.79 mmol), methanol (50 mL) and *p*-toluenesulfonic acid monohydrate (790 mg, 4.18 mmol) according to general procedure K to afford an off white solid in 97 % yield (9.48 g, 40.48 mmol).

Molecular formula: $C_{10}H_9F_3O_3$

Molecular weight: 234.17 g/mol

Melting point: 48-50°C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 7.62 (d, *J* = 8.0 Hz, 2H, *H5, H7*), 7.56 (d, *J* = 8.0 Hz, 2H, *H4, H8*), 5.25 (s, 1H, *H2*), 3.77 (s, 3H, *H10*), 3.73 (s, 1H, OH, C2).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 173.57 (*C*OO, *C1*), 142.07 (Ar*C*, *C3*), 130.75 (q, *J* = 31.7 Hz, CF_3*C*, *C6*), 127.04 (2Ar*C*H, *C4, C8*), 125.64 (q, *J* = 8.7 Hz, 2Ar*C*H, *C5, C7*), 124.10 (q, CF_3, *C9*, *J* = 270.3 Hz), 72.73 (*C*HOH, *C2*), 53.46 (O*C*H$_3$, *C10*).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -62.63 (C*F*$_3$)

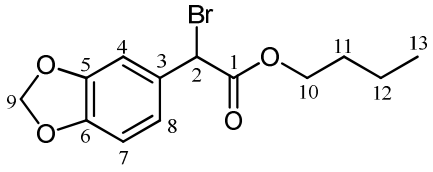
IR (neat, cm^{-1}): 3445, 2964, 1738, 1704, 1618, 1439, 1327, 1158, 1114, 1090, 1065, 1017, 989, 833.

^{1}H, ^{13}C-NMR spectra and melting point are in agreement with the literature data.[13]

6.4.3 Alkylating Agents:

General Procedure M: Preparation of Mandelate based alkylating agents[14]

Butyl-2-(2H-1,3-benzodioxol-5-yl)-2-bromoacetate (112)



To a stirred solution of butyl (3,4-methylenedioxy)mandelate (**107**) (9.04 g, 35.8 mmol) and TEA (6.0 mL, 43 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added thionyl bromide (3.1 mL, 39 mmol) dropwise, and the reaction mixture was allowed to warm to room temperature. After stirring for 3 h the reaction mixture was washed with distilled water (3 × 50 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated under high vacuum. The resulting oil was purified by column chromatography (SiO_2, EA:hexane, 20:80) to obtain the title compound (**112**) as a yellow oil in 76 % yield (8.62 g, 27.3 mmol).

Molecular formula: $C_{13}H_{15}BrO_4$

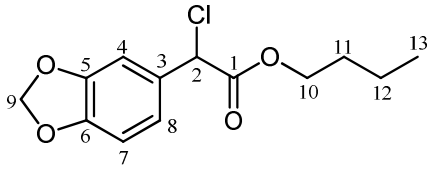
Molecular weight: 315.16 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 7.13 (d, *J* = 2.0 Hz, 1H, *H4*), 6.95 (dd, *J* = 8.0, 2.0 Hz, 1H, *H8*), 6.73 (d, *J* = 8.0 Hz, 1H, *H7*), 5.96 (d, part A of an AB system, *J* = 2.0 Hz, 1H, *H9*), 5.95 (d, part B of an AB system, *J* = 2.0 Hz, 1H, *H9*), 5.29 (s, 1H, *H2*), 4.19 (dt, *J* = 10.8, 6.8 Hz, 1H, *H10*), 4.14 (dt, *J* = 10.8, 6.8 Hz, 1H, *H10*), 1.63 (tt, *J* = 7.4, 6.8 Hz, 2H, *H11*), 1.35 (tq, *J* = 7.4, 7.2 Hz, 2H, *H12*), 0.91 (t, *J* = 7.2 Hz, 3H, *H13*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 168.34 (*C*OO, *C1*), 148.56 (Ar*C*, *C5/C6*), 148.14 (Ar*C*, *C5/C6*), 129.46 (Ar*C*, *C3*), 122.66 (Ar*C*H, *C8*), 109.20 (Ar*C*H, *C7*), 108.12 (Ar*C*H, *C4*), 101.58 (O*C*H$_2$O, *C9*), 66.35 (O*C*H$_2$, *C10*), 47.11 (*C*H, *C2*), 30.41 (*C*H$_2$, *C11*), 19.03 (*C*H$_2$, *C12*), 13.71 (*C*H$_3$, *C13*).

IR (neat, cm^{-1}): 2960, 2875, 1737, 1503, 1489, 1445, 1370, 1315, 1245, 1177, 1139, 1102, 1036, 928, 815, 736.

Butyl-2-(2H-1,3-benzodioxol-5-yl)-2-chloroacetate (113)



The title compound (**113**) was synthesized according to general procedure M using alcohol (**107**) (2.68 g, 10.62 mmol), thionyl chloride (0.77 mL, 10.62 mmol) and TEA (1.48 mL, 10.62 mmol) to obtain a yellow liquid in 86 % yield (2.48 g, 9.16 mmol).

Molecular formula: $C_{13}H_{15}ClO_4$

Molecular weight: 270.71 g/mol

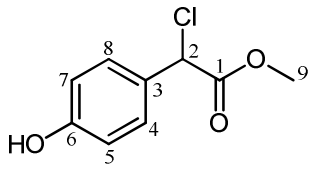
^{1}H NMR (400 MHz, $CDCl_3$) ppm: 7.03 (d, *J* = 1.6 Hz, 1H, *H4*), 6.92 (dd, *J* = 8.0, 1.6 Hz, 1H, *H8*), 6.73 (d, *J* = 8.0 Hz, 1H, *H7*), 5.98 (d, part A of an AB system, *J* = 2.0 Hz, 1H, *H9*), 5.97 (d, part B of an AB system, *J* = 2.0 Hz, 1H, *H9*), 5.26 (s, 1H, *H2*), 4.19 (dt, *J* = 10.8, 6.8Hz, 1H, *H10*), 4.14 (dt, *J* = 10.8, 6.8 Hz, 1H, *H10*), 1.61 (tt, *J* = 7.4, 6.8 Hz, 2H, *H11*), 1.32 (tq, *J* = 7.4, 7.2 Hz, 2H, *H12*), 0.90 (t, *J* = 7.2 Hz, 3H, *H13*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 168.51 (*C*OO, *C1*), 148.58 (Ar*C*, *C5/C6*), 148.20 (Ar*C*, *C5/C6*), 129.59 (Ar*C*, *C3*), 122.16 (Ar*C*H, *C8*), 108.36 (Ar*C*H, *C7*), 108.28 (Ar*C*H, *C4*),

101.60 (O*C*H_2O, *C9*), 66.41 (O*C*H_2, *C10*), 59.24 (*C*H, *C2*), 30.46 (*C*H_2, *C11*), 19.03 (*C*H_2, *C12*), 13.72 (*C*H_3, *C13*).

IR (neat, cm^{-1}): 2961, 1743, 1629, 1504, 1489, 1445, 1368, 1246, 1161, 1036, 928, 803.

Methyl 2-chloro-2-(4-hydroxyphenyl)acetate (114)



To a stirred solution of alcohol (**108**) (690 mg, 3.79 mmol), and DMF (0.1 mL, 1.29 mmol) in DCM (10 mL) was added thionyl chloride (0.28 mL, 3.79 mmol) and reaction mixture was stirred at RT for 3 h. The organic layer was washed with water (5 mL) and volatiles were removed by rotary evaporation. The crude product was purified by column chromatography (SiO_2, MeOH:DCM, 10:90) to obtain a yellow liquid in 84 % yield (0.64 g, 3.17 mmol).

Molecular formula: $C_9H_9ClO_3$

Molecular weight: 200.62 g/mol

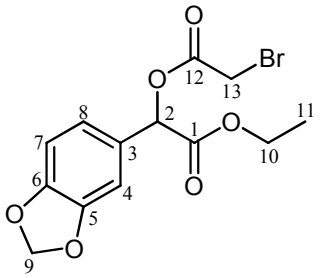
^{1}H NMR (400 MHz, $CDCl_3$) ppm: 8.05 (s, 1H, O*H*), 7.35 (d, *J* = 8.2 Hz, 2H, *H4, H8*), 6.87 (d, *J* = 8.2 Hz, 2H, *H5, H7*), 5.35 (s, 1H, *H2*), 3.78 (s, 3H, *H9*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 172.86 (*C*OO, *C1*), 158.05 (Ar*C*, *C6*), 131.43 (Ar*C*, *C3*), 127.64 (2Ar*C*H, *C5, C7*), 115.37 (2Ar*C*H, *C4, C8*), 59.88 (*C*HOH, *C2*), 51.46 (O*C*H_3, *C9*).

IR (neat, cm^{-1}): 3569, 3233, 3058, 2949, 1739, 1625, 1589, 1537, 1451, 1316, 1272, 1191, 1182, 1075, 981, 847, 815, 768.

General Procedure N: Preparation Mandelate based alkylating agents[2]

Ethyl-2-(2H-1,3-benzodioxol-5-yl)-2-[(2-bromoacetyl)oxy]acetate (115)



To a stirred solution of ethyl-3,4-methylenedioxymandelate (**105**) (6.85 g, 30.6 mmol) in CH_2Cl_2 (75 mL) at 0 °C was added triethylamine (6.38 mL, 45.8 mmol) followed by bromoacetyl bromide (3.19 mL, 36.7 mmol). The reaction mixture was allowed to attain room temperature and stirred overnight. Water (50 mL) was added to the reaction mixture; organic layer was separated and washed with saturated NH_4Cl solution (25 mL), 10 % $NaHCO_3$ solution (25 mL) and saturated brine solution (25 mL), dried over anhydrous $MgSO_4$ and evaporated by rotary evaporation. The crude product was purified by column chromatography (SiO_2, hexane:EtOAc ,90:10) and dried under high vacuum to obtain the title compound (**115**) as a yellow oil in 63 % yield (6.68 g, 19.4 mmol).

Molecular formula: $C_{13}H_{13}BrO_6$

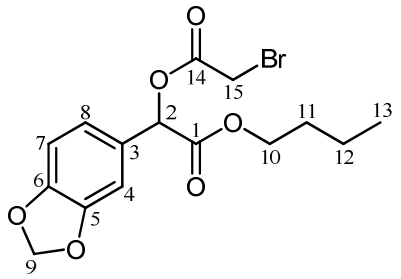
Molecular weight: 345.14 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 6.9255 (dd, *J* = 8.4, 1.6 Hz, 1H, *H8*), 6.9250 (d, *J* = 1.6 Hz, 1H, *H4*), 6.79 (d, *J* = 8.4 Hz, 1H, *H7*), 5.97 (bs, 2H, *H9*), 5.84 (s, 1H, *H2*), 4.23 (dt, *J* = 10.8, 7.2 Hz, 1H, *H10*), 4.15 (dt, *J* = 10.8, 7.2 Hz, 1H, *H10*), 3.96 (d, part A of an AB system, *J* = 14.4 Hz, 1H, *H13*), 3.93 (d, part B of an AB system, *J* = 14.4 Hz, 1H, *H13*), 1.22 (t, *J* = 7.2 Hz, 3H, *H11*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 168.20 (*C*OO, *C1*), 166.66 (*C*OO, *C12*), 148.71 (Ar*C*, *C5/C6*), 148.12 (Ar*C*, *C5/C6*), 126.71 (Ar*C*, *C3*), 122.06 (Ar*C*H, *C8*), 108.55 (Ar*C*H, *C7*), 107.97 (Ar*C*H, *C4*), 101.56 (O*C*H_2O, *C9*), 75.72 (*C*H, *C2*), 62.09 (*C*H_2, *C10*), 25.41 (*C*H_2, *C13*), 14.07 (*C*H_2, *C11*).

IR (neat, cm^{-1}): 2960, 2828, 1736, 1630, 1499, 1480, 1446, 1238, 1210, 1153, 1027, 922.

Butyl-2-(2H-1,3-benzodioxol-5-yl)-2-[(2-bromoacetyl)oxy]acetate (116)



The title compound (**116**) was prepared using butyl-3,4-methylenedioxymandelate (**107**) (6.53 g, 25.9 mmol), CH_2Cl_2 (65 mL), triethylamine (5.4 mL, 38.8 mmol) and bromoacetyl bromide (2.71 mL, 31.06 mmol) according to general procedure N to afford a colourless liquid in 80 % yield (7.72 g, 20.7 mmol).

Molecular formula: $C_{15}H_{17}BrO_6$

Molecular weight: 373.20 g/mol

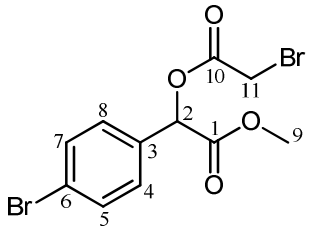
^{1}H NMR (400 MHz, $CDCl_3$) ppm: 6.932 (dd, *J* = 8.4, 1.6 Hz, 1H, *H8*), 6.931 (d, *J* = 1.6 Hz, 1H, *H4*), 6.81 (d, *J* = 8.4 Hz, 1H, *H7*), 5.98 (bs, 2H, *H9*), 5.85 (s, 1H, *H2*), 4.16 (dt, *J* = 10.8, 6.8 Hz, 1H, *H10*), 4.11 (dt, *J* = 10.8, 6.8 Hz, 1H, *H10*), 3.97 (d, part A of an AB system, *J* = 14.4 Hz, 1H, *H15*), 3.94 (d, part B of an AB system, *J* = 14.4 Hz, 1H, *H15*), 1.58 (tt, *J* = 6.8, 6.8 Hz, 2H, *H11*), 1.29 (qt, *J* = 7.4, 6.8 Hz, 2H, *H12*), 0.88 (t, *J* = 7.4 Hz, 3H, *H13*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 168.32 (*C*OO, *C1*), , 166.69 (*C*OO, *C14*), 148.73 (Ar*C*, *C5/C6*), 148.15 (Ar*C*, *C5/C6*), 126.83 (Ar*C*, *C3*), 122.06 (Ar*C*H, *C8*), 108.59 (Ar*C*H, *C7*), 108.00 (Ar*C*H, *C4*), 101.59 (O*C*H$_2$O, *C9*), 75.77 (*C*H, *C2*), 65.82 (*C*H$_2$, *C10*), 30.48 (*C*H$_2$, *C11*), 25.44 (*C*H$_2$, *C15*), 19.00 (*C*H$_2$, *C12*), 13.71 (*C*H$_2$, *C13*).

IR (neat, cm^{-1}): 2961, 2875, 1740, 1504, 1490, 1446, 1337, 1240, 1178, 1101, 1034, 976, 925, 865, 806, 762.

General Procedure O: Preparation of Mandelate based alkylating agent[15]

Methyl-2-[(2-bromoacetyl)oxy]-2-(4-bromophenyl)acetate (117)



To a stirred solution of methyl-2-(4-bromophenyl)-2-hydroxyacetate (**109**) (4.81 g, 19.63 mmol) in CH_2Cl_2 (50 mL) sodium carbonate (3.12 g, 29.43 mmol) was added, followed by bromoacetyl bromide (2.1 mL, 23.6 mmol) at 0°C. Reaction mixture was allowed to warm to room temperature then stirred for 8 h. The reaction mixture was filtered, washed with 25 mL 10 % $NaHCO_3$ solution, dried over anhydrous $MgSO_4$ and concentrated under high vacuum. The crude product was purified by column chromatography (SiO_2, hexane:EtOAc, 80:20) to obtain the title compound (**117**) as a colourless liquid in 78 % yield (5.61 g, 15.33 mmol).

Molecular formula: $C_{11}H_{10}Br_2O_4$

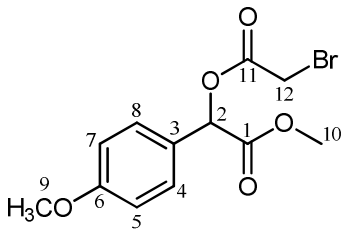
Molecular weight: 366.0 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 7.54 (d, *J* = 8.4 Hz, 2H, *H5, H7*), 7.35 (d, *J* = 8.4 Hz, 2H, *H4, H8*), 5.94 (s, 1H, *H2*), 3.97 (s, 2H, *H11*), 3.73 (s, 3H, *H9*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 168.24 (*C*OO, *C1*), 166.55 (*C*OO, *C10*), 132.22 (2Ar*C*H, *C5, C7*), 132.06 (Ar*C*, *C3*), 129.33 (2Ar*C*H, *C4, C8*), 123.95 (Ar*C*, *C6*), 75.00 (*C*H, *C2*), 53.11 (O*C*H$_3$, *C9*), 25.23 (*C*H$_2$, *C11*).

IR (neat, cm^{-1}): 2956, 1743, 1593, 1489, 1436, 1405, 1345, 1275, 1257, 1215, 1138, 1105, 1070, 1011, 978, 820, 768.

Methyl-2-[(2-bromoacetyl)oxy]-2-(4-methoxyphenyl)acetate (118)



The title compound (**118**) was synthesized using methyl-2-(4-methoxyphenyl)-2-hydroxyacetate (**110**) (1.26 g, 6.42 mmol), CH_2Cl_2 (15 mL), sodium carbonate (1.02 g, 9.63 mmol) and bromoacetyl bromide (0.70 mL, 7.7 mmol) according to general procedure O to afford a colourless liquid in 67 % yield (1.36 g, 4.30 mmol).

Molecular formula: $C_{12}H_{13}BrO_5$

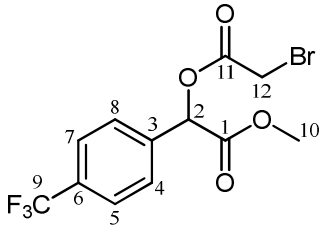
Molecular weight: 317.13 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 7.37 (d, *J* = 8.8 Hz, 2H, *H5, H7*), 7.56 (d, *J* = 8.8 Hz, 2H, *H4, H8*), 5.92 (s, 1H, *H2*), 3.97 (d, *J* = 15.2 Hz, 1H, *H12*), 3.93 (d, *J* = 15.2 Hz, 1H, *H12*), 3.80 (s, 3H, *H9*), 3.71 (s, 3H, *H10*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 168.85 (*C*OO, *C1*), 166.68 (*C*OO, *C11*), 160.53 (Ar*C*H, *C6*), 129.24 (2Ar*C*H, *C4, C8*), 125.00 (Ar*C, C3*), 114.31 (2Ar*C*H, *C5, C7*), 75.39 (*C*H, *C2*), 53.35 (O*C*H_3, *C9*), 52.78 (O*C*H_3, *C10*), 25.46 (*C*H_2, *C12*).

IR (neat, cm^{-1}): 2981, 2889, 1748, 1733, 1608, 1512, 1434, 1292, 1247, 1215, 1172, 1029, 827.

Methyl-2-[(2-bromoacetyl)oxy]-2-[4-(trifluoromethyl)phenyl]acetate (119)



The title compound (**119**) was synthesized using methyl-2-[4-(trifluoromethyl)phenyl]-2-hydroxyacetate (**111**) (9.26 g, 39.5 mmol), CH_2Cl_2 (100 mL), sodium carbonate (6.29 g, 59.3 mmol) and bromoacetyl bromide (4.10 mL, 47.6 mmol) according to general procedure O to afford a colourless liquid in 75 % yield (10.54 g, 29.7 mmol).

Molecular formula: $C_{12}H_{10}BrF_3O_4$

Molecular weight: 355.1 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 7.62 (d, *J* = 8.0 Hz, 2H, *H5, H7*), 7.56 (d, *J* = 8.0 Hz, 2H, *H4, H8*), 5.26 (s, 1H, *H2*), 3.88 (s, 2H, *H12*), 3.77 (s, 3H, *H10*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 173.62 (*C*OO, *C1*), 171.61 (*C*OO, *C11*), 141.98 (Ar*C*H, *C3*), 130.70 (q, *J* = 32 Hz, Ar*C*, *C6*), 127.05 (2Ar*C*H, *C4, C8*), 125.65 (q, *J* = 4.0 Hz, 2Ar*C*H, *C5, C7*), 124.08 (q, J = 270.5, *C*F_3, *C9*), 72.39 (*C*H, *C2*), 53.50 (O*C*H_3, *C9*), 25.46 (*C*H_2, *C10*).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -62.09 (3*F*)

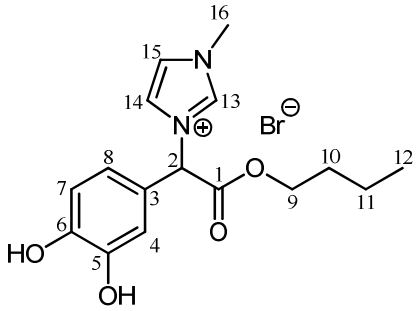
IR (neat, cm^{-1}): 2965, 1731, 1621, 1419, 1323, 1288, 1164, 1116, 1066, 1017, 831.

6.4.4 Bromide Ionic Liquids:

6.4.4.1 Mandelate based Monoester Ionic Liquids:

General Procedure P: Preparation of monoester chloride/bromide ILs[15]

3-[2-Butoxy-1-(3,4-dihydroxyphenyl)-2-oxoethyl]-1-methyl-1H-imidazol-3-ium bromide (120a)



A solution of butyl 3,4-dihydroxy mandelate (**106**) (10.04 g, 41.78 mmol), 1-methylimidazole (6.6 mL, 83.3 mmol) in DCM (200 mL) was stirred at 0^{o}C. Thionyl bromide (3.20 mL, 41.6 mmol) was added drop wise and the reaction mixture was allowed to warm to RT and stirred for 24 h. Completion of reaction was confirmed by TLC. The volatiles were removed via rotary evaporation and the crude product was purified by column chromatography. (SiO_2, 20 % Methanol: 80 % DCM) to obtain a brown oil in 62 % yield (9.97 g, 25.9 mmol).

Molecular formula: $C_{16}H_{21}BrN_2O_4$.

Molecular weight: 385.25 g/mol

^{1}H NMR (400 Hz, DMSO-d_6) ppm: 9.49 (s, 1H, O*H* at *C5/C6*), 9.31 (s, 1H, O*H* at *C5/C6*), 9.11 (s, 1H, *H13*), 7.77 (t, *J* = 2.0 Hz, 1H, *H14/H15*), 7.74 (t, *J* = 2.0 Hz, 1H, *H14/H15*), 6.85 (d, *J* = 2.4 Hz, 1H, *H4*), 6.83 (d, *J* = 8.4 Hz, 1H, *H7*), 6.75 (dd, *J* = 8.4, 2.4 Hz, 1H, *H8*), 6.60

(s, 1H, *H*2), 4.26-4.14 (m, 2H, *H9*), 3.86 (s, 3H, *H16*), 1.59-1.51 (m, 2H, *H10*), 1.23 (qt, *J* = 7.6, 7.2 Hz, 2H, *H11*), 0.83 (t, *J* = 7.6 Hz, 3H, *H12*).

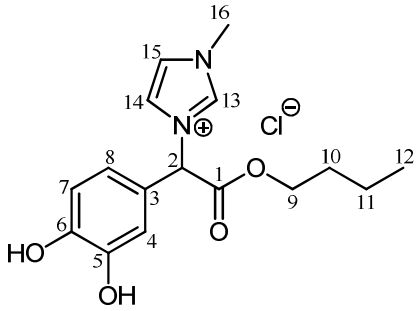
^{13}C NMR (100 Hz, DMSO-d_6) ppm: 167.89 (*C*OO, *C1*), 147.01 (Ar*C*, *C5/C6*), 145.95 (Ar*C*, *C5/C6*), 136.61 (Ar*C*H, *C13*), 123.42 (Ar*C*, *C*3), 122.86 (Ar*C*H, *C14/C15*), 122.31 (Ar*C*H, *C8*), 119.64 (Ar*C*H, *C14/C15*), 116.31 (Ar*C*H, *C7*), 116.03 (Ar*C*H, *C4*), 65.89 (N*C*H, *C2*), 63.52 (O*C*H$_2$, *C9*), 35.95 (N*C*H$_3$, *C16*), 29.77 (*C*H$_2$, *C10*), 18.33 (*C*H$_2$, *C11*), 13.30 (*C*H$_3$, *C12*).

IR (neat, cm^{-1}): 3370, 3138.82, 2959.43, 1740.05, 1602.05, 1580.49, 1549.42, 1527.26, 1447.51, 1278.17, 1197.90, 1162.98, 1118.79, 1085.62, 943.24, 752.19 cm^{-1}

HRMS (ESI$^+$,*m/z*): Calculated for [M-Br$^-$]$^+$, $C_{16}H_{21}N_2O_4^+$, requires = 305.1496, found = 305.1493.

MS (*m/z*): 305.15 [M-Br$^-$]$^+$

3-[2-Butoxy-1-(3,4-dihydroxyphenyl)-2-oxoethyl]-1-methyl-1H-imidazol-3-ium chloride (121a)



The title compound (**121a**) was synthesized from butyl 3,4-dihydroxy mandelate (**106**) (1.04 g, 4.16 mmol), 1-methylimidazole (0.30 mL, 4.16 mmol), thionyl chloride (0.10 mL, 1.04 mmol) and DCM (20 mL) according to general procedure P to obtain a brown oil in 34 % yield (480 mg, 1.40 mmol).

Molecular formula: $C_{16}H_{21}ClN_2O_4$.

Molecular weight: 340.80 g/mol

^{1}H NMR (400 Hz, DMSO-d_6) ppm: 9.55 (s, 1H, O*H* at *C5/C6*), 9.37 (s, 1H, O*H* at *C5/C6*), 9.10 (s, 1H, *H13*), 7.75 (t, *J* = 2.0 Hz, 1H, *H14/H15*), 7.72 (t, *J* = 2.0 Hz, 1H, *H14/H15*), 6.86

(d, *J* = 2.0 Hz, 1H, *H4*), 6.83 (d, *J* = 8.0 Hz, 1H, *H7*), 6.74 (dd, *J* = 8.0, 2.0 Hz, 1H, *H8*), 6.57 (s, 1H, *H2*), 4.25-4.15 (m, 2H, *H9*), 3.78 (s, 3H, *H16*), 1.57-1.52 (m, 2H, *H10*), 1.23 (qt, *J* = 7.6, 7.2 Hz, 2H, *H11*), 0.84 (t, *J* = 7.6 Hz, 3H, *H12*).

^{13}C NMR (100 Hz, DMSO-d_6) ppm: 167.85 (*C*OO, *C1*), 147.01 (Ar*C*, *C5/C6*), 145.95 (Ar*C*, *C5/C6*), 136.58 (Ar*C*H, *C13*), 123.46 (Ar*C*, *C3*), 122.78 (Ar*C*H, *C14/C15*), 122.39 (Ar*C*H, *C8*), 119.71 (Ar*C*H, *C14/C15*), 116.20 (Ar*C*H, *C7*), 115.89 (Ar*C*H, *C4*), 65.91 (N*C*H, *C2*), 63.60 (O*C*H$_2$, *C9*), 35.13 (N*C*H$_3$, *C16*), 29.78 (*C*H$_2$, *C10*), 18.34 (*C*H$_2$, *C11*), 13.37 (*C*H$_3$, *12*).

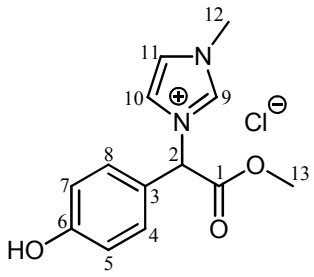
IR (neat, cm^{-1}): 3373, 3141, 2960, 1740, 1601, 1527, 1449, 1280, 1198, 1163, 1120 cm^{-1}

HRMS (ESI$^+$,*m/z*): Calculated for [M-Cl$^-$]$^+$, $C_{16}H_{21}N_2O_4^+$, requires = 305.1496, found = 305.1494.

MS (*m/z*): 305.15 [M-Cl$^-$]$^+$

General Procedure Q: Preparation of monoester bromide/chloride IL[4]

3-[1-(4-Hydroxyphenyl)-2-methoxy-2-oxoethyl]-1-methyl-1H-imidazol-3-ium chloride (122a)



To a stirred solution of **114** (970 mg, 4.82 mmol) in diethyl ether (20 mL) at RT was added 1-methylimidazole (0.40 mL, 4.29 mmol) dropwise and the reaction mixture was stirred for 12 h. The viscous liquid which had settled to the bottom of the flask, was washed with diethyl ether (5 x 20 mL) and dried under high vacuum to give the title compound (**122a**) as a colourless oil in 66 % yield (900 mg, 3.19 mmol).

Molecular formula: $C_{13}H_{15}ClN_2O_3$

Molecular weight: 282.72 g/mol

^{1}H NMR (400 MHz, DMSO-d_6) ppm: 9.45 (s, 1H, O*H*), 9.16 (s, 1H, *H9*), 7.80 (t, *J* = 1.6 Hz, 1H, *H10/H11*), 7.74 (t, *J* = 1.6 Hz, 1H, *H10/H11*), 7.30 (d, *J* = 8.4 Hz, 2H, *H4, H8*), 6.87 (d, *J* = 8.4 Hz, 2H, *H5, H7*), 6.70 (s, 1H, *H2*), 3.85 (s, 3H, *H13*), 3.77 (s, 3H, *H12*).

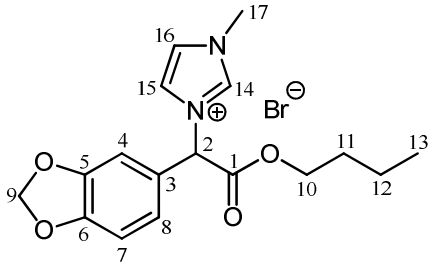
^{13}C NMR (100 MHz, DMSO-d_6) ppm: 172.87 (*C*OO, *C1*), 156.80 (Ar*C*, *C6*), 138.49 (Ar*C*H, *C9*), 131.14 (2Ar*C*H, *C5, C7*), 129.35 (Ar*C*, *C3*), 123.88 (Ar*C*H, *C10/C11*), 122.71 (Ar*C*H, *C10/C11*), 116.31 (2Ar*C*H, *C4, C8*), 75.28 (*C*HOH, *C2*), 51.86 (O*C*H$_3$, *C13*), 37.11 (N*C*H$_3$, *C12*).

IR (neat, cm^{-1}): 3512, 3229, 2941, 1739, 1635, 1576, 1470, 1422, 1321, 1271, 1189, 1142, 1056, 960, 817, 834.

HRMS (ESI$^+$,*m/z*): Calculated for [M-Br$^-$]$^+$, $C_{13}H_{15}N_2O_3^+$, requires = 247.1077, found = 247.1073.

MS (*m/z*): 247.10 [M-Br$^-$]$^+$

3-[1-(2H-1,3-Benzodioxol-5-yl)-2-butoxy-2-oxoethyl]-1-methyl-1H-imidazol-3-ium bromide (123a)



The title compound (**123a**) was prepared using butyl-2-bromo-2-(3,4-methylenedioxyphenyl) acetate (**112**) (2.24 g, 7.11 mmol), diethyl ether (25mL) and 1-methylimidazole (0.60 mL, 7.11 mmol) according to general procedure Q to obtain a brown gel in 58 % yield (1.65 g, 4.15 mmol).

Molecular formula: $C_{17}H_{21}BrN_2O_4$

Molecular weight: 397.26 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 10.38 (s, 1H, *H14*), 7.51 (t, *J* = 1.6 Hz, 1H, *H15/H16*), 7.47 (t, *J* = 1.6 Hz, 1H, *H15/H16*), 7.13 (s, 1H, *H2*), 7.06 (dd, *J* = 8.0, 1.8 Hz, 1H, *H8*), 7.03 (d, *J* = 1.8 Hz, 1H, *H4*), 6.79 (d, *J* = 8.0 Hz, 1H, *H7*), 5.97 (d, part A of an AB system, *J* = 1.2

Hz, 1H, *H9*), 5.96 (d, part B of an AB system, *J* = 1.2 Hz, 1H, *H9*), 4.03 (s, 3H, *H17*), 4.21 (dt, *J* = 10.8, 6.8 Hz, 1H, *H10*), 4.15 (dt, *J* = 10.8, 6.8 Hz, 1H, *H10*), 1.56 (tt, *J* = 7.4, 6.8 Hz, 2H, *H11*), 1.24 (qt, *J* = 7.4, 7.2 Hz, 2H, *H12*), 0.83 (t, *J* = 7.2 Hz, 3H, *H13*).

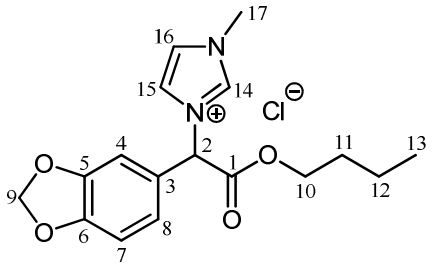
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 167.72 (*C*OO, *C1*), 149.31 (Ar*C*, *C5/C6*), 148.67 (Ar*C*, *C5/C6*), 137.49 (Ar*C*, *C14*), 125.61 (Ar*C*, *C3*), 123.04 (Ar*C*, *C15/C16*), 122.99 (ArCH, C8), 121.77 (Ar*C*, *C15/C16*), 109.20 (Ar*C*H, *C7*), 108.77 (Ar*C*H, *C4*), 101.91 (O*C*H_2O, *C9*), 67.11 (O*C*H_2, *C10*), 63.75 (*C*HN, *C2*), 36.93 (N*C*H_3, *C17*), 30.21 (*C*H_2, *C11*), 18.88 (*C*H_2, *C12*), 13.59 (*C*H_3, *C13*).

IR (neat, cm^{-1}): 3074, 2960, 1741, 1628, 1577, 1552, 1504, 1491, 1447, 1367, 1250, 1234, 1210, 1161, 1105, 1033, 925, 795, 759, 717.

HRMS (ESI^+, *m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{17}H_{21}N_2O_4^+$, requires = 317.1501, found = 317.1510.

MS (*m/z*): 317.10 $[M\text{-}Br^-]^+$

3-[1-(2H-1,3-Benzodioxol-5-yl)-2-butoxy-2-oxoethyl]-1-methyl-1H-imidazol-3-ium chloride (124a)



The title compound (**124a**) was prepared from butyl-2-chloro-2-(3,4-methylenedioxyphenyl) acetate (**113**) (1.16 g, 4.29 mmol), 1-methylimidazole (0.35 mL, 4.29 mmol) and diethyl ether (10 mL) according to representative procedure Q to get a brown gel in 55 % yield (830 mg, 2.36 mmol).

Molecular formula: $C_{17}H_{21}ClN_2O_4$

Molecular weight: 352.81 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 10.47 (s, 1H, *H14*), 7.66 (s, 1H, *H15/H16*), 7.44 (s, 1H, *H15/H16*), 7.13 (s, 1H, *H2*), 6.95-6.93 (m, 2H, *H4, H8*), 6.66 (d, *J* = 8.0 Hz, 1H, *H7*), 5.85 (d,

part A of an AB system, J = 3.2 Hz, 1H, *H9*), 5.84 (d, part B of an AB system, J = 3.2 Hz, 1H, *H9*), 4.05 (m, 2H, *H10*), 3.94 (s, 3H, *H17*), 1.44 (tt, J = 7.4, 6.8 Hz, 2H, *H11*), 1.12 (tq, J = 7.4, 7.2 Hz, 2H, *H*12), 0.71 (t, J = 7.2 Hz, 3H, *H13*).

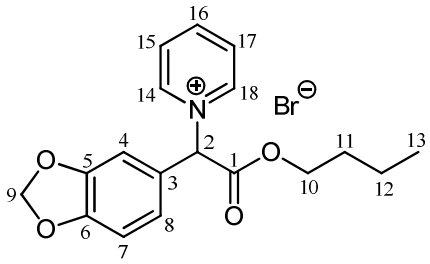
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 167.54 (*C*OO, *C1*), 148.94 (Ar*C*, *C5/C6*), 148.36 (Ar*C*, *C5/C6*), 137.48 (Ar*CH*, *C14*), 125.91 (Ar*C*, *C3*), 123.23 (Ar*C*, *C15/C16*), 122.62 (ArCH, C8), 121.47 (Ar*C*, *C15/C16*), 108.88 (Ar*C*H, *C7*), 108.58 (Ar*C*H, *C4*), 101.65 (O*C*H$_2$O, *C9*), 66.72 (O*C*H$_2$, *C10*), 63.41 (*C*HN, *C2*), 36.54 (N*C*H$_3$, *C17*), 29.99 (*C*H$_2$, *C11*), 18.65 (*C*H$_2$, *C12*), 13.37 (*C*H$_3$, *C13*).

IR (neat, cm^{-1}): 3081, 2960, 1740, 1630, 1577, 1504, 1491, 1448, 1250, 1162, 1032, 924.

HRMS (ESI$^+$,*m/z*): Calculated for [M-Cl$^-$]$^+$, $C_{17}H_{21}N_2O_4^+$, requires = 317.1501, found = 317.1502.

MS (*m/z*): 317.10 [M-Cl$^-$]$^+$

1-[1-(2H-1,3-Benzodioxol-5-yl)-2-butoxy-2-oxoethyl]pyridin-1-ium bromide (125a)



The title compound (**125a**) was prepared using butyl-2-bromo-2-(3,4-methylenedioxyphenyl) acetate (**112**) (2.06 g, 6.54 mmol), pyridine (0.55 mL, 6.54 mmol) and diethyl ether (20mL) according to representative general procedure Q to obtain a white solid in 90 % yield (1.33 g, 3.37 mmol).

Molecular formula: $C_{18}H_{20}BrNO_4$

Molecular weight: 394.26 g/mol

Melting Point: 123-125 ^oC

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.44 (d, J = 6.6 Hz, 2H, *H14, H18*), 8.61 (t, J = 7.4 Hz, 1H, *H16*), 8.11 (s, 1H, *H2*), 8.10 (dd, J = 7.4, 6.6 Hz, 2H, *H15*, *H17*), 7.18 (d, J = 1.6 Hz, 1H, *H4*), 7.15 (dd, J = 8.0, 1.6 Hz, 1H, *H8*), 6.80 (d, J = 8.0 Hz, 1H, *H7*), 5.96 (d, part A of an

AB system, *J* = 4.0 Hz, 1H, *H9*), 5.95 (d, part B of an AB system, *J* = 4.0 Hz, 1H, *H9*), 4.26 (dt, *J* = 10.8, 7.0 Hz, 1H, *H10*), 4.16 (dt, *J* = 10.8, 7.0 Hz, 1H, *H10*), 1.57 (tt, *J* = 7.2, 6.8, 2H, *H11*), 1.23 (qt, *J* = 7.6, 7.0 Hz, 2H, *H12*), 0.81 (t, *J* = 7.6 Hz, 3H, *H13*).

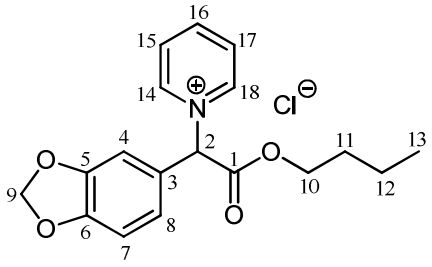
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 167.32 (*C*OO, *C1*), 149.86 (Ar*C C5/C6*), 148.90 (Ar*C C5/C6*), 146.74 (Ar*C*H, *C16*), 144.82 (2Ar*C*H, *C14, C18*), 127.94 (2Ar*C*H, *C15, C17*), 124.26 (Ar*CH*, *C8*), 124.24 (Ar*C*H, *C3*), 109.86 (Ar*C*H, *C4*), 109.31 (Ar*C*H, *C7*), 102.06 (O*C*H_2O, *C9*), 73.17 (*C*HN, *C2*), 67.62 (O*C*H_2, *C10*), 30.13 (*C*H_2, *C11*), 18.83 (*C*H_2, *C12*), 13.53 (*C*H_3, *C13*).

IR (neat, cm^{-1}): 3023, 2960, 1736, 1630, 1498, 1479, 1447, 1369, 1304, 1261, 1239, 1210, 1151, 1108, 1028, 922, 809, 757.

HRMS (ESI$^+$, *m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{18}H_{20}NO_4^+$, requires = 314.1392, found = 314.1404.

MS (*m/z*): 314.10 $(M\text{-}Br^-)^+$

1-[1-(2H-1,3-Benzodioxol-5-yl)-2-butoxy-2-oxoethyl]pyridin-1-ium chloride (126a)



The title compound (**126a**) was prepared using butyl-2-chloro-2-(3,4-methylenedioxyphenyl) acetate (**113**) (1.21 g, 4.5 mmol), pyridine (0.35 mL, 4.47 mmol) and diethyl ether (10mL) according to representative general procedure Q to get a white solid in 87 % yield (1.36 g, 3.9 mmol).

Molecular formula: $C_{18}H_{20}ClNO_4$

Molecular weight: 349.81 g/mol

Melting Point: 96-98°C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.56 (d, *J* = 6.4 Hz, 2H, *H14, H18*), 8.56 (t, *J* = 7.4 Hz, 1H, *H16*), 8.29 (s, 1H, *H2*), 8.08 (dd, *J* = 7.4, 6.4 Hz, 2H, *H15*, *H17*), 7.19 (d, *J* = 1.6 Hz, 1H,

H4), 7.16 (dd, *J* = 8.0, 1.6 Hz, 1H, *H8*), 6.80 (d, *J* = 8.0 Hz, 1H, *H7*), 5.96 (d, part A of an AB system, *J* = 4.0 Hz, 1H, *H9*), 5.95 (d, part B of an AB system, *J* = 4.0 Hz, 1H, *H9*), 4.27 (dt, *J* = 10.8, 7.0 Hz, 1H, *H10*), 4.14 (dt, *J* = 10.8, 7.0 Hz, 1H, *H10*), 1.57 (tt, *J* = 7.2, 6.8, 2H, *H11*), 1.23 (qt, *J* = 7.6, 7.0 Hz, 2H, *H12*), 0.81 (t, *J* = 7.6 Hz, 3H, *H13*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 167.57 (*C*OO, *C1*), 149.80 (Ar*C C5/C6*), 148.89 (Ar*C C5/C6*), 146.46 (Ar*C*H, *C16*), 145.14 (2Ar*C*H, *C14, C18*), 127.87 (2Ar*C*H, *C15, C17*), 124.75 (Ar*CH*, *C8*), 124.19 (Ar*C*H, *C3*), 109.87 (Ar*C*H, *C4*), 109.29 (Ar*C*H, *C7*), 102.04 (O*C*H$_2$O, *C9*), 73.18 (*C*HN, *C2*), 67.57 (O*C*H$_2$, *C10*), 30.15 (*C*H$_2$, *C11*), 18.86 (*C*H$_2$, *C12*), 13.57 (*C*H$_3$, *C13*).

IR (neat, cm^{-1}): 3022, 2959, 1735, 1630, 1499, 1480, 1238, 1210, 1153,1027, 922, 758.

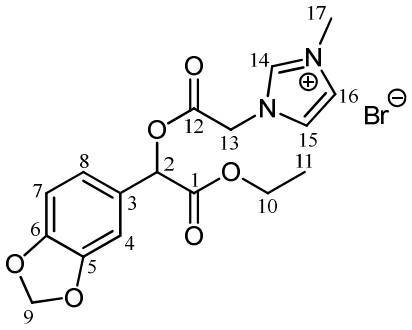
HRMS (ESI$^+$, *m/z*): Calculated for [M-Cl$^-$]$^+$, $C_{18}H_{20}NO_4^+$, requires = 314.1392, found = 314.1383.

MS (*m/z*): 314.10 [M-Cl$^-$]$^+$

6.4.4.2 Diester Ionic Liquids:

General Procedure R: Preparation of diester bromide IL[4]

1-{2-[1-(2H-1,3-Benzodioxol-5-yl)-2-ethoxy-2-oxoethoxy]-2-oxoethyl}-3-methyl-1H-imidazol-3-ium bromide (127a)



To a stirred mixture of ethyl-2-(2-bromoacetoxy)-2-(3,4-methylenedioxyphenyl)acetate (**115**) (1.17 g, 3.4 mmol) in diethyl ether (15 mL) was added 1-methylimidazole (0.25 mL, 3.22 mmol) at RT and stirred for 12 h. The separated product was washed with diethyl ether (5 x 15 mL) and dried under high vacuum to obtain an off white solid in 80 % yield (1.10 g, 4.6 mmol).

Molecular formula: $C_{17}H_{19}BrN_2O_6$

Molecular weight: 427.25 g/mol

Melting point: 74-76°C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 10.21 (s, 1H, *H14*), 7.59 (t, *J* = 1.8 Hz, 1H, *H15/H16*), 7.48 (t, *J* = 1.8 Hz, 1H, *H15/H16*), 6.89 (dd, *J* = 8.0, 1.6 Hz, 1H, *H8*), 6.85 (d, *J* = 1.6 Hz, 1H, *H4*), 6.78 (d, *J* = 8.0 Hz, 1H, *H7*), 5.98 (dd, *J* = 3.2, 3.2 Hz, 2H, *H9*), 5.86 (s, 1H, *H2*), 5.73 (d part A of an AB system, *J* = 18 Hz, 1H, *H13*), 5.47 (d part B of an AB system, *J* = 18 Hz, 1H, *H13*), 4.20 (dt, J = 10.8, 7.0 Hz, 1H, *H10*), 4.11 (dt, J = 10.8, 7.0 Hz, 1H, *H10*), 4.05 (s, 3H, *H17*), 1.20 (t, *J* = 7.0 Hz, 3H, *H11*).

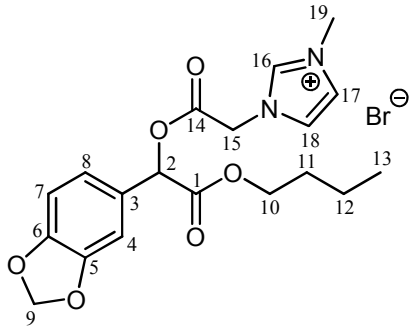
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 168.06 (*C*OO, *C1*), 165.73 (*C*OO, *C12*), 148.94 (Ar*C*, *C5/C6*), 148.18 (Ar*C*, *C5/C6*), 138.66 (Ar*CH*, *C14*), 125.99 (Ar*C*, *C3*), 123.78 (Ar*CH*, *C15/C16*), 123.15 (ArCH, C8), 122.41 (Ar*CH*, *C15/C16*), 108.70 (Ar*C*H, *C7*), 108.09 (Ar*C*H, *C4*), 101.67 (O*CH*$_2$O, *C9*), 76.29 (O*C*H, *C2*), 62.36 (O*CH*$_2$, *C10*), 50.27 (O*CH*$_2$, *C13*), 37.03 (N*C*H$_3$, *C17*), 14.11 (*C*H$_3$, *C11*).

IR (neat, cm^{-1}): 3023, 2960, 1736, 1630, 1489, 1480, 1238, 1210, 1153, 1027, 922, 758.

HRMS (ESI^+, *m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{17}H_{19}N_2O_6^+$, requires = 347.1238 , found = 347.1237.

MS (*m/z*): 347.10 $[M\text{-}Br^-]^+$

1-{2-[1-(2H-1,3-Benzodioxol-5-yl)-2-butoxy-2-oxoethoxy]-2-oxoethyl}-3-methyl-1H-imidazol-3-ium bromide (128a)



The title compound (**128a**) was prepared using butyl-2-(2-bromoacetoxy)-2-(3,4-methylenedioxyphenyl)acetate (**116**) (2.86 g, 7.7 mmol), 1-methylimidazole (0.60 mL, 7.7

mmol) in diethyl ether (50 mL) according to general procedure R to obtain a white solid in 60 % yield (2.11 g, 4.6 mmol).

Molecular formula: $C_{19}H_{23}BrN_2O_6$

Molecular weight: 455.30 g/mol

Melting point: 94-96°C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 10.34 (s, 1H, *H16*), 7.51 (t, *J* = 1.8 Hz, 1H, *H17/H18*), 7.36 (t, *J* = 1.8 Hz, 1H, *H17/H18*), 6.89 (dd, *J* = 8.0, 2.0 Hz, 1H, *H8*), 6.86 (d, *J* = 2.0 Hz, 1H, *H4*), 6.80 (d, *J* = 8.0 Hz, 1H, *H7*), 5.99 (dd, *J* = 3.2, 3.2 Hz, 2H, *H9*), 5.87 (s, 1H, *H2*), 5.77 (d part A of an AB system, *J* = 17.6 Hz, 1H, *H15*), 5.43 (d part B of an AB system, *J* = 17.6 Hz, 1H, *H15*), 4.14 (dt, J = 10.8, 6.8 Hz, 1H, *H10*), 4.10 (dt, J = 10.8, 6.8 Hz, 1H, *H10*), 4.06 (s, 3H, *H19*), 1.55 (tt, *J* = 7.6, 6.8 Hz, 2H, *H11*), 1.25 (tq, *J* = 7.6, 7.2 Hz, 2H, *H12*), 0.86 (t, *J* = 7.2 Hz, 3H, *H13*).

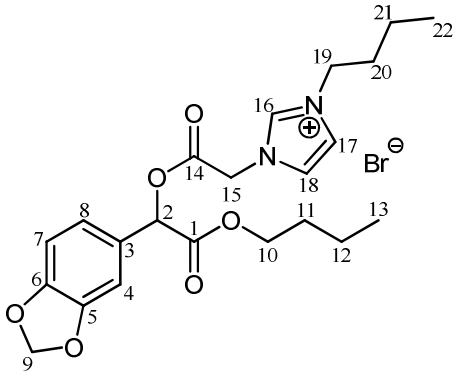
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 167.84 (*C*OO, *C1*), 166.39 (*C*OO, *C14*), 148.23 (Ar*C*, *C5/C6*), 148.57 (Ar*C*, *C5/C6*), 137.76 (Ar*CH*, *C16*), 126.52 (Ar*C*, *C3*), 123.63 (Ar*CH*, *C17/C18*), 123.58 (ArCH, C8), 121.90 (Ar*CH*, *C17/C18*), 108.49 (Ar*C*H, *C7*), 107.77 (Ar*C*H, *C4*), 101.53 (O*CH*$_2$O, *C9*), 74.92 (O*C*H, *C2*), 65.09 (O*CH*$_2$, *C10*), 49.24 (O*CH*$_2$, *C15*), 36.01 (N*C*H$_3$, *C19*), 29.87 (*C*H$_2$, *C11*), 18.26 (*C*H$_2$, *C12*), 13.33 (*C*H$_3$, *C13*).

IR (neat, cm^{-1}): 2961, 1750, 1608, 1580, 1502, 1491, 1449, 1347, 1240, 1190, 1024, 918.

HRMS (ESI$^+$, *m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{19}H_{23}N_2O_6^+$, requires = 375.1556 , found = 375.1559.

MS (m/z): 375.10 $[M\text{-}Br^-]^+$

1-{2-[1-(2H-1,3-Benzodioxol-5-yl)-2-butoxy-2-oxoethoxy]-2-oxoethyl}-3-butyl-1H-imidazol-3-ium bromide (129a)



The title compound (**129a**) was prepared using butyl-2-(2-bromoacetoxy)-2-(3,4-methylenedioxyphenyl)acetate (**116**) (7.82 g, 20.9 mmol), 1-butylimidazole (2.8 mL, 20.9 mmol) and diethyl ether (100 mL) according to general procedure R to obtain a brown liquid in 64 % yield (6.62 g, 13.3 mmol).

Molecular formula: $C_{22}H_{29}BrN_2O_6$

Molecular weight: 497.38 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 10.01(s, 1H, *H16*), 7.4 (t, *J* = 1.8 Hz, 1H, *H17/H18*), 7.51 (t, *J* = 1.8 Hz, 1H, *H17/H18*), 6.77 (dd, *J* = 8.0, 2.0 Hz, 1H, *H8*), 6.73 (d, *J* = 2.0 Hz, 1H, *H4*), 6.66 (d, *J* = 8.0 Hz, 1H, *H7*), 5.86 (dd, *J* = 2.8, 2.8 Hz, 2H, *H9*), 5.74 (s, 1H, *H2*), 5.59 (d part A of an AB system, *J* = 17.6 Hz, 1H, *H15*), 5.41 (d part B of an AB system, *J* = 17.6 Hz, 1H, *H15*), 4.20 (t, 2H, *H19*), 4.03-3.93 (m, 2H, *H10*), 1.80-1.73 (m, 2H, *H20*), 1.46-1.38 (m , 2H, *H11*), 1.27-1.20 (m, 2H, *H21*), 1.17-1.07 (m, 2H, *H12*), 0.81 (t, *J* = 7.6 Hz, 3H, *H22*), 0.73 (t, *J* = 7.2 Hz, 3H, *H13*).

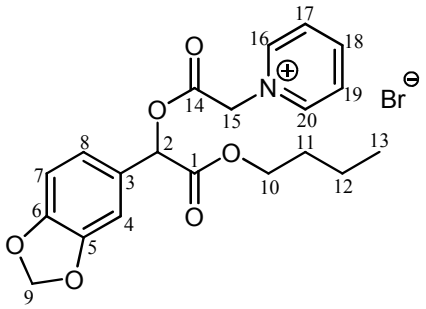
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 173.42 (*C*OO, *C1*), 167.88 (*C*OO, *C14*), 148.52 (Ar*C*, *C5/C6*), 147.82 (Ar*C*, *C5/C6*), 137.46 (Ar*CH*, *C16*), 125.87 (Ar*C*, *C3*), 123.99 (Ar*CH*, *C17/C18*), 123.63 (ArCH, C8), 122.03 (Ar*CH*, *C17/C18*), 108.30 (Ar*C*H, *C7*), 107.70 (Ar*C*H, *C4*), 101.36 (O*CH*$_2$O, *C9*), 75.81 (O*C*H, *C2*), 66.71 (O*CH*$_2$, *C10*), 53.10 (N*C*H2, *C19*), 49.88 (O*CH*$_2$, *C10*), 31.78 (*C*H$_2$, *C11/C20*), 30.17 (*C*H$_2$, *C11/C20*), 19.15 (*C*H$_2$, *C12/C21*), 18.65 (*C*H$_2$, *C12/C21*), 13.33 (*C*H$_3$, *C13/C22*), 13.22 (*C*H$_3$, *C13/C2*).

IR (neat, cm^{-1}): 3143, 3085, 2961, 2935, 1737, 1627, 1566, 1489, 1443, 1237, 1166, 1101, 1034, 750.

HRMS (ESI^+, *m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{22}H_{29}N_2O_6^+$, requires = 417.2020, found = 417.2018.

MS (*m/z*): 417.20 $[M\text{-}Br^-]^+$

1-{2-[1-(2H-1,3-Benzodioxol-5-yl)-2-butoxy-2-oxoethoxy]-2-oxoethyl}pyridin-1-ium bromide (130a)



The title compound (**130a**) was prepared using butyl-2-(2-bromoacetoxy)-2-(3,4-methylenedioxyphenyl)acetate (**116**) (11.56 g, 30.9 mmol), pyridine (2.5 mL, 30.9 mmol) and diethyl ether (150 mL) according to general procedure R to obtain an off white solid in 50 % yield (7.0 g, 15.5 mmol).

Molecular formula: $C_{20}H_{22}BrNO_6$

Molecular weight: 452.23 g/mol

Melting point: 150-152°C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.39 (d, *J* = 6.4 Hz, 2H, *H16, H20*), 8.53 (t, *J* = 8.0 Hz, 1H, *H18*), 8.07 (dd, *J* = 8.0, 6.4 Hz, 2H, *H17, H19*), 6.89 (dd, *J* = 8.0, 2.0 Hz, 1H, *H8*), 6.86 (d, *J* = 2.0 Hz, 1H, *H4*), 6.76 (d, *J* = 8.0 Hz, 1H, *H7*), 6.50 (d part A of an AB system, *J* = 17.2 Hz, 1H, *H15*), 6.21 (d part B of an AB system, *J* = 17.2 Hz, 1H, *H15*), 5.97 (dd, *J* = 4.8, 4.8 Hz, 2H, *H9*), 5.88 (s, 1H, *H2*), 4.10 (dt, *J* = 10.8, 6.8 Hz, 1H, *H10*), 4.07 (dt, *J* = 10.8, 6.8 Hz, 1H, *H10*), 1.52 (tt, *J* = 7.2, 6.8 Hz, 2H, *H11*), 1.22 (qt, *J* = 7.6, 7.2 Hz, 2H, *H12*), 0.83 (t, *J* = 7.6 Hz, 3H, *H13*).

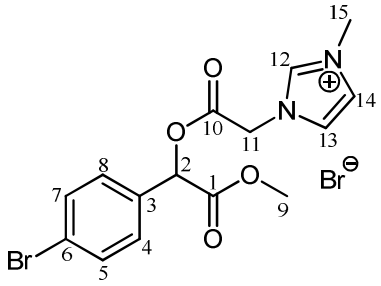
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 168.02 (*C*OO, *C1*), 165.46 (*C*OO, *C14*), 148.87 (Ar*C*, *C5/C6*), 148.12 (Ar*C*, *C5/C6*), 146.70 (2Ar*C*H, *C*16, *C20*), 146.54 (Ar*C*H, *C18*), 127.92 (2Ar*CH*, *C17, C19*), 126.05 (Ar*C*, *C*3), 122.36 (Ar*CH*, *C8*), 108.68 (Ar*C*H, *C7*), 108.12 (Ar*C*H, *C4*), 101.64 (O*CH*$_2$O, *C9*), 76.52 (O*C*H, *C2*), 66.09 (O*CH*$_2$, *C10*), 61.04 (O*CH*$_2$, *C15*), 30.36 (*C*H$_2$, *C11*), 18.90 (*C*H$_2$, *C12*), 13.65 (*C*H$_3$, *C13*).

IR (neat, cm^{-1}): 3135, 3037, 2960, 1746, 1720, 1634, 1576, 1491, 1448, 1367, 1251, 1197, 1177, 1112, 1029, 922, 824, 760.

HRMS (ESI$^+$, *m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{20}H_{22}NO_6^+$, requires = 372.1447, found = 372.1450.

MS (*m/z*): 372.10 $[M\text{-}Br^-]^+$

1-{2-[1-(4-Bromophenyl)-2-methoxy-2-oxoethoxy]-2-oxoethyl}-3-methyl-1H-imidazol-3-ium bromide (131a)



The title compound (**131a**) was prepared using methyl-2-(2-bromoacetoxy)-2-(4-bromophenyl)acetate (**117**) (5.21 g, 14.3 mmol), 1-methylimidazole (1.15 mL, 14.2 mmol) and diethyl ether (25 mL) according to general procedure R to obtain a brown gel in 82 % yield (5.24 g, 11.7 mmol).

Molecular formula: $C_{15}H_{16}Br_2N_2O_4$

Molecular weight: 448.11 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.89 (s, 1H, *H12*), 7.64 (t, *J* = 1.6 Hz, 1H, *H13/H14*), 7.51 (t, *J* = 1.6 Hz, 1H, *H13/H14*), 7.49 (d, *J* = 8.4 Hz, 2H, *H5, H7*), 7.31 (d, *J* = 8.4 Hz, 2H, *H4, H8*), 5.97 (s, 1H, *H2*), 5.75 (d, *J* = 17.2 Hz, 1H, *H11*), 5.55 (d, *J* = 17.2 Hz, 1H, *H11*), 4.01 (s, 3H, *H15*), 3.68 (s, 3H, *H9*).

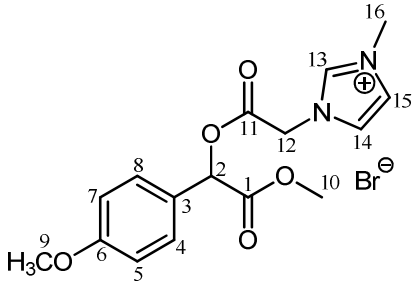
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 168.18 (*C*OO, *C1*), 165.92 (*C*OO, *C10*), 138.21 (Ar*CH*, *C12*), 132.26 (2Ar*CH*, *C5/C7*), 131.75 (Ar*C*, *C3*), 129.56 (2Ar*CH*, *C4, C8*), 124.06 (Ar*C*, *C6*), 123.87 (Ar*C*H, *C13/C14*), 123.39 (Ar*CH*, *C13/C14*), 75.49 (O*C*H, *C2*), 53.32 (O*C*H_3, *C9*), 50.40 (*C*H_2, *C11*), 37.23 (*C*H_3, *C15*).

IR (neat, cm^{-1}): 2961, 1752, 1655, 1224, 1176, 1052, 1024, 820, 757.

HRMS (ESI$^+$, *m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{15}H_{16}BrN_2O_4^+$, requires = 367.0288, found = 367.0276.

MS (*m/z*): 367.05 $[M\text{-}Br^-]^+$

1-{2-[2-Methoxy-1-(4-methoxyphenyl)-2-oxoethoxy]-2-oxoethyl}-3-methyl-1H-imidazol-3-ium bromide (132a)



The title compound (**132a**) was prepared using methyl-2-(2-bromoacetoxy)-2-(4-methoxyphenyl)acetate (**118**) (5.31 g, 16.7 mmol), 1-methylimidazole (1.35 mL, 16.7 mmol) and diethyl ether (25 mL) according to the general procedure R to obtain a brown liquid in 72 % yield (4.83 g, 12.1 mmol).

Molecular formula: $C_{16}H_{19}BrN_2O_5$

Molecular weight: 399.24 g/mol

^{1}H NMR (400 MHz, DMSO-d_6) ppm: 9.17 (s, 1H, *H13*), 7.77 (d, *J* = 1.6 Hz, 1H, *H14/H15*), 7.76 (t, *J* = 1.6 Hz, 1H, *H14/H15*), 7.41 (d, *J* = 8.4 Hz, 2H, *H4, H8*), 7.01 (d, *J* = 8.4 Hz, 2H, *H5/H7*), 6.08 (s, 1H, *H2*), 5.53 (d, *J* = 17.6 Hz, 1H, *H12*), 5.42 (d, *J* = 17.6 Hz, 1H, *H12*), 3.93 (s, 3H, *H9*), 3.78 (s, 3H, *H16*), 3.67 (s, 3H, *H10*).

^{13}C NMR (100 MHz, DMSO-d_6) ppm: 168.54 (*C*OO, *C1*), 166.55 (*C*OO, *C11*), 160.15 (Ar*C*, *C6*), 137.72 (Ar*CH*, *C13*), 129.35 (2Ar*CH*, *C4, C8*), 124.75 (Ar*C*, *C3*), 123.63 (Ar*C*H,

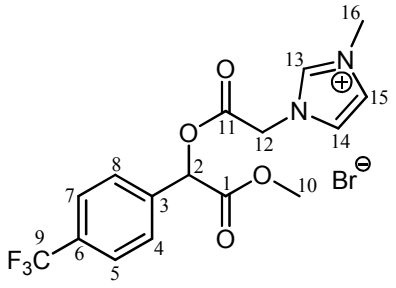
C14/C15), 123.55 (Ar*C*H, *C14/C15*), 114.30 (2Ar*CH*, *C5, C7*), 74.76 (O*C*H, *C2*), 55.26 (O*CH*$_3$, *C9*), 52.66 (O*C*H$_3$, *C10*), 49.19 (*C*H$_2$, C12), 35.99 (*C*H$_3$, *C16*).

IR (neat, cm^{-1}): 3099, 2955, 1735, 1610, 1579, 1511, 1438, 1239, 1171, 1077, 1025, 833.

HRMS (ESI$^+$, *m/z*): Calculated for [M-Br$^-$]$^+$, $C_{16}H_{19}N_2O_5^+$, requires = 319.1289, found = 319.1279.

MS (*m/z*): 319.10 [M-Br$^-$]$^+$

1-(2-{2-Methoxy-2-oxo-1-[4-(trifluoromethyl)phenyl]ethoxy}-2-oxoethyl)-3-methyl-1H-imidazol-3-ium bromide (133a)



The title compound (**133a**) was prepared using methyl-2-(2-bromoacetoxy)-2-[4-(trifluoromethyl)phenyl]acetate (**119**) (6.98 g, 19.7 mmol), 1-methylimidazole (1.6 mL, 19.7 mmol) and diethyl ether (70 mL) according to general procedure R to obtain a white solid in 88 % yield (7.57 g, 17.3 mmol).

Molecular formula: $C_{16}H_{16}BrF_3N_2O_4$

Molecular weight: 437.21 g/mol

Melting point: 128-130°C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 10.24 (s, 1H, *H13*), 7.65 (d, *J* = 8.4 Hz, 2H, *H5, H7*), 7.62 (t, *J* = 1.6 Hz, 1H, *H14/H15*), 7.59 (d, *J* = 8.4 Hz, 2H, *H4, H8*), 7.40 (t, *J* = 1.6 Hz, 1H, *H14/H15*), 6.08 (s, 1H, *H2*), 5.90 (d, *J* = 18.0 Hz, 1H, *H12*), 5.57 (d, *J* = 18.0 Hz, 1H, *H12*), 4.04 (s, 3H, *H16*), 3.73 (s, 3H, *H10*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 173.22 (*C*OO, *C1*), 170.61 (*C*OO, *C11*), 142.00 (Ar*C*H, *C3*), 137.11 (Ar*C*H, *C13*), 131.17 (q, *J* = 32.0 Hz, Ar*C*, *C6*), 128.15 (2Ar*C*H, *C4, C8*), 126.50 (q, *J* = 4.0 Hz, 2Ar*C*H, *C5, C7*), 124.76 (Ar*C*H, *C14/C15*), 124.68 (q, J = 270.5, *C*F$_3$, *C9*),

120.44 (Ar*C*H, *C14/C15*), 72.49 (*C*H, *C2*), 53.70 (O*C*H_3, *C9*), 35.35 (N*C*H_3, *C16*), 24.86 (*C*H_2, *C10*).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -62.46 (3*F*)

IR (neat, cm^{-1}): 3093, 2961, 2925, 1762, 1751, 1621, 1577, 1440, 1419, 1323, 1254, 1226, 1165, 1122, 1063, 1018, 979, 833, 782.

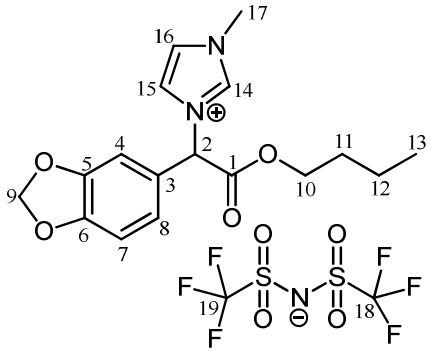
HRMS (ESI^+, *m/z*): Calculated for $[M\text{-}Br^-]^+$, $C_{16}H_{16}F_3N_2O_4^+$, requires = 357.1057, found = 357.1053.

MS (*m/z*): 357.10 $[M\text{-}Br^-]^+$

6.4.5 [NTf_2] Ionic Liquids:

General Procedure S: Preparation of Mandelate based [NTf_2] ILs[4]

3-[1-(2H-1,3-Benzodioxol-5-yl)-2-butoxy-2-oxoethyl]-1-methyl-1H-imidazol-3-ium *bis*(trifluoromethylsulfonyl)imide (123b)



To a stirred solution of bromide salt (**123a**) (450 mg, 1.13 mmol) in distilled water (5 mL) was added $LiNTf_2$ (330 mg, 1.33 mmol) and stirred for 4 h. The solid was washed with distilled water (3 x 5 mL) and dried under high vacuum to obtain a pale yellow solid in 66 % yield (450 mg, 0.75 mmol).

Molecular formula: $C_{19}H_{21}F_6N_3O_8S_2$

Molecular weight: 597.51 g/mol

Melting Point: 46-48 °C

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 8.76 (s, 1H, *H14*), 7.33 (t, *J* = 1.6 Hz, 1H, *H15/H16*), 7.30 (t, *J* = 1.6 Hz, 1H, *H15/H16*), 6.90 (dd, *J* = 8.0, 1.6 Hz, 1H, *H8*), 6.84 (d, *J* = 8.0 Hz, 1H, *H7*), 6.83 (d, *J* = 1.6 Hz, 1H, *H4*), 6.20 (s, 1H, *H2*), 6.005 (d, part A of an AB system, *J* = 1.2 Hz, 1H, *H9*), 6.000 (d, part B of an AB system, *J* = 1.2 Hz, 1H, *H9*), 4.22 (dt, *J* = 10.8, 6.8 Hz, 2H, *H10*), 3.92 (s, 3H, *H17*), 1.59 (tt, *J* = 7.4, 6.8 Hz, 2H, *H11*), 1.26 (tq, *J* = 7.4, 7.2 Hz, 2H, *H12*), 0.85 (t, *J* = 7.2 Hz, 3H, *H13*).

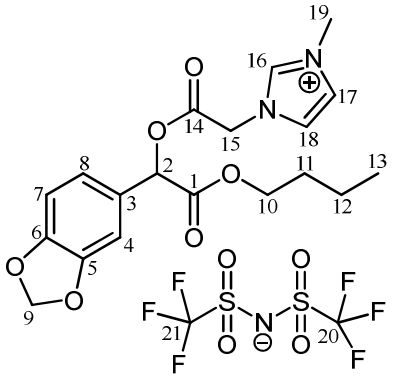
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 167.36 (*C*OO, *C1*), 149.71 (Ar*C*, *C5/C6*), 149.04 (Ar*C*, *C5/C6*), 136.38 (Ar*C*, *C14*), 124.43 (Ar*C*, *C15/C16*), 123.39 (Ar*C*H, *C8*), 123.08 (Ar*C*, *C15/C16*), 122.19 (Ar*C*H, *C3*), 119.83 (q, 2*C*F_3, *J* = 319 Hz, *C18, C19*), 109.41 (Ar*C*H, *C7*), 108.56 (Ar*C*H, *C4*), 102.10 (O*C*H_2O, *C9*), 67.28 (O*C*H_2, *C10*), 64.71 (*C*HN, *C2*), 36.61 (N*C*H_3, *C17*), 30.17 (*C*H_2, *C11*), 18.84 (*C*H_2, *C12*), 13.52 (*C*H_3, *C13*).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -79.22 (6*F*)

IR (neat, cm^{-1}): 3056, 2981, 1736, 1608, 1512, 1435, 1292, 1247, 1215, 1172, 1110, 1030, 982, 827.

MS (*m/z*): 317.10 $[M\text{-}NTf_2^-]^+$

1-{2-[1-(2H-1,3-Benzodioxol-5-yl)-2-butoxy-2-oxoethoxy]-2-oxoethyl}-3-methyl-1H-imidazol-3-ium *bis*(trifluoromethylsulfonyl)imide (128b)



The title compound (**128b**) was prepared using bromide salt (**128a**) (1.0 g, 2.2 mmol), distilled water (5 mL) and $LiNTf_2$ (760 mg, 2.6 mmol) according to the general procedure S to afford a colourless oil in 94 % yield (1.35 g, 2.1 mmol).

Molecular formula: $C_{21}H_{23}F_6N_3O_{10}S_2$

Molecular weight: 655.54 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 8.86 (s, 1H, *H16*), 7.38 (t, *J* = 1.6 Hz, 1H, *H17/H18*), 7.31 (t, *J* = 1.6 Hz, 1H, *H17/H18*), 6.90 (dd, *J* = 8.0, 2.0 Hz, 1H, *H8*), 6.86 (d, *J* = 2.0 Hz, 1H, *H4*), 6.81 (d, *J* = 8.0 Hz, 1H, *H7*), 5.99 (s, 2H, *H9*), 5.87 (s, 1H, *H2*), 5.18 (d part A of an AB system, *J* = 18.0 Hz, 1H, *H15*), 5.12 (d part B of an AB system, *J* = 18.0 Hz, 1H, *H15*), 4.14 (dt, *J* = 10.8, 6.8 Hz, 1H, *H10*), 4.10 (dt, *J* = 10.8, 6.8 Hz, 1H, *H10*), 3.95 (s, 3H, *H19*), 1.55 (tt , *J* = 7.2, 6.8 Hz, 2H, *H11*), 1.25 (qt, *J* = 7.6, 7.2 Hz, 2H, *H12*), 0.85 (t, *J* = 7.6 Hz, 3H, *H13*).

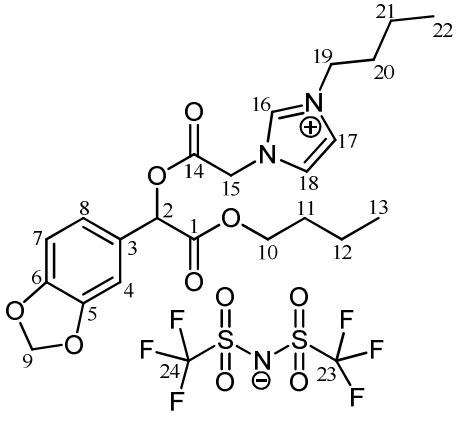
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 168.01 (*C*OO, *C1*), 165.16 (*C*OO, *C14*), 148.92 (Ar*C*, *C5/C6*), 148.16 (Ar*C*, *C5/C6*), 137.83 (Ar*CH*, *C16*), 125.93 (Ar*C*, *C3*), 123.73 (Ar*CH*, *C17/C18*), 123.32 (ArCH, *C8*), 122.26 (Ar*CH*, *C17/C18*), 119.71 (q, 2*C*F_3, *C20, C21*, *J* = 319.2 Hz), 108.59 (Ar*C*H, *C7*), 107.92 (Ar*C*H, *C4*), 101.56 (O*CH*$_2$O, *C9*), 76.36 (O*C*H, *C2*), 66.06 (O*CH*$_2$, *C10*), 49.91 (O*CH*$_2$, *C15*), 36.64 (N*C*H_3, *C19*), 30.31 (*C*H_2, *C11*), 18.81 (*C*H_2, *C12*), 13.48 (*C*H_3, *C13*).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -79.13 (6*F*)

IR (neat, cm^{-1}): 3163, 2965, 1746, 1519, 1348, 1173, 1133, 1053, 1037, 927.

MS (*m/z*): 375.10 $[M\text{-}NTf_2^-]^+$

1-{2-[1-(2H-1,3-Benzodioxol-5-yl)-2-butoxy-2-oxoethoxy]-2-oxoethyl}-3-butyl-1H-imidazol-3-ium *bis*(trifluoromethylsulfonyl)imide (129b)



The title compound (**129b**) was prepared using bromide salt (**129a**) (2.03 g, 4.0 mmol), $LiNTf_2$ (1.27 g, 4.4 mmol) and distilled water (10 mL) according to the general procedure S to afford a yellow oil in 90 % yield (2.53 g, 3.6 mmol).

Molecular formula: $C_{24}H_{29}F_6N_3O_{10}S_2$

Molecular weight: 697.62 g/mol

^{1}H NMR (400 MHz, DMSO-d_6) ppm: 9.21 (s, 1H, *H16*), 7.85 (t, *J* = 1.8 Hz, 1H, *H17/H18*), 7.76 (t, *J* = 1.8 Hz, 1H, *H17/H18*), 6.97-6.94 (m, 3H, *H4, H7, H8*), 6.06 (s, 2H, *H9*), 6.03 (s, 1H, *H2*), 5.48 (d part A of an AB system, *J* = 17.8 Hz, 1H, *H15*), 5.39 (d part B of an AB system, *J* = 17.8 Hz, 1H, *H15*), 4.25 (t, *J* = 7.0 Hz, 2H, *H19*), 4.10 (dt, *J* = 10.8, 6.8 Hz, 2H, *H10*), 1.76 (tt, *J* = 7.6, 7.0 Hz, 2H, *H20*), 1.49 (tt, *J* = 7.6, 6.8 Hz, 2H, *H11*), 1.27-1.15 (m , 4H, *H12, H21*), 0.89 (t, *J* = 7.6 Hz, 3H, *H13/H22*), 0.80 (t, *J* = 7.6 Hz, 3H, *H13/H22*).

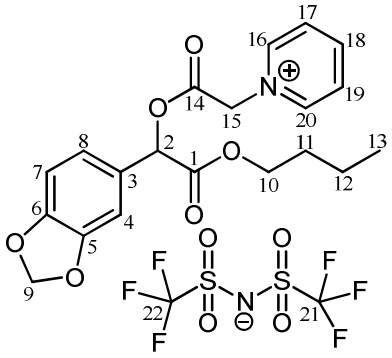
^{13}C NMR (100 MHz, DMSO-d_6) ppm: 168.09 (*C*OO, *C1*), 165.18 (*C*OO, *C14*), 148.92 (Ar*C*, *C5/C6*), 148.16 (Ar*C*, *C5/C6*), 137.32 (Ar*CH*, *C16*), 125.91 (Ar*C*, *C3*), 123.80 (Ar*CH*, *C17/C18*), 122.26 (ArCH, C8), 121.88 (Ar*CH*, *C17/C18*), 119.74 (q, 2*C*F_3, *C20, C21*, *J* = 319 Hz), 108.59 (Ar*C*H, *C7*), 107.90 (Ar*C*H, *C4*), 101.55 (O*C*H_2O, *C9*), 76.33 (O*C*H, *C2*), 66.08 (O*C*H_2, *C10*), 50.36 (N*C*H_2, *C19*), 50.05 (*C*H_2, *C15*), 31.80 (*C*H_2, *C20*), 30.31 (*C*H_2, *C11*), 19.32 (*C*H_2, *C21*), 18.81 (*C*H_2, *C12*), 13.48 (*C*H_3, *C13/C22*), 13.20 (*C*H_3, *C13/C22*).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -79.16 (6*F*).

IR (neat, cm^{-1}): 3153, 2965, 1741, 1611, 1567, 1506, 1491, 1447, 1347, 1180, 1133, 1054, 1037, 929.

MS (*m/z*): 417.20 $[M\text{-}NTf_2^-]^+$

1-{2-[1-(2H-1,3-Benzodioxol-5-yl)-2-butoxy-2-oxoethoxy]-2-oxoethyl}pyridin-1-ium *bis*(trifluoromethylsulfonyl)imide (130b)



The title compound (**130b**) was prepared using bromide salt (**130a**) (1.0 g, 2.2 mmol), $LiNTf_2$ (640 mg, 2.2 mmol) and distilled water (10 mL) according to the general procedure S to afford a brown oil in 73 % yield (1.05 g, 1.6 mmol).

Molecular formula: $C_{22}H_{22}F_6N_2O_{10}S_2$

Molecular weight: 652.54 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 8.78 (d, J = 6.4 Hz, 2H, *H16, H20*), 8.54 (t, *J* = 8.0 Hz, 1H, *H18*), 8.06 (dd, *J* = 8.0, 6.4 Hz, 2H, *H17, H19*), 6.89 (dd, *J* = 8.0, 2.0 Hz, 1H, *H8*), 6.84 (d, *J* = 2.0 Hz, 1H, *H4*), 6.80 (d, *J* = 8.0 Hz, 1H, *H7*), 5.98 (s, 2H, *H9*), 5.89 (s, 1H, *H2*), 5.58 (s, 2H, *H15*), 4.12 (dt, *J* = 10.8, 6.8 Hz, 1H, *H10*), 4.09 (dt, *J* = 10.8, 6.8 Hz, 1H, *H10*), 1.53 (tt, *J* = 7.2, 6.8 Hz, 2H, *H11*), 1.23 (qt, *J* = 7.6, 7.2 Hz, 2H, *H12*), 0.84 (t, *J* = 7.6 Hz, 3H, *H13*).

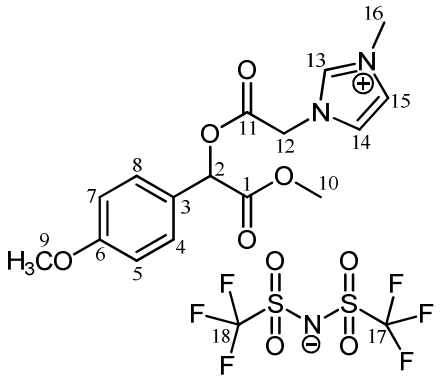
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 167.90 (*C*OO, *C1*), 164.73 (*C*OO, *C14*), 148.98 (Ar*C*, *C5/C6*), 148.17 (Ar*C*, *C5/C6*), 146.73 (Ar*C*H, *C18*), 146.09 (2Ar*C*H, *C16, C20*), 128.32 (2Ar*CH*, *C17, C19*), 125.74 (Ar*C*, *C3*), 122.32 (Ar*CH*, *C8*), 119.67 (q, 2*C*F_3, *C21, C22*, *J* = 319 Hz), 108.61 (Ar*C*H, *C7*), 107.94 (Ar*C*H, *C4*), 101.57 (O*C*H_2O, *C9*), 76.79 (O*C*H, *C2*), 66.15 (O*C*H_2, *C10*), 61.03 (O*C*H_2, *C15*), 30.27 (*C*H_2, *C11*), 18.79 (*C*H_2, *C12*), 13.46 (*C*H_3, *C13*).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -78.91 (6*F*)

IR (neat, cm^{-1}): 3095, 2965, 1740, 1639, 1491, 1447, 1347, 1179, 1132, 1054, 1035, 928, 789.

MS (*m/z*): 372.10 $[M\text{-}NTf_2^-]^+$

1-{2-[2-Methoxy-1-(4-methoxyphenyl)-2-oxoethoxy]-2-oxoethyl}-3-methyl-1H-imidazol-3-ium *bis*(trifluoromethylsulfonyl)imide (132b)



The title compound (**132b**) was prepared using bromide salt (**132a**) (1.50 g, 3.8 mmol), $LiNTf_2$ (1.08 g, 3.8 mmol) and distilled water (10 mL) according to the general procedure S to afford a brown oil in 81 % yield (1.83 g, 3.1 mmol).

Molecular formula: $C_{18}H_{19}F_6N_3O_9S_2$

Molecular weight: 599.48 g/mol

^{1}H NMR (400 MHz,$CDCl_3$) ppm: 8.84 (s, 1H, *H13*), 7.38 (d, *J* = 1.8 Hz, 1H, *H14/H15*), 7.33 (d, *J* = 8.8 Hz, 2H, *H4, H8*),7.29 (t, *J* = 1.6 Hz, 1H, *H14/H15*), 6.91 (d, *J* = 8.8 Hz, 2H, *H5, H7*), 5.95 (s, 1H, *H2*), 5.13 (s, 2H, *H12*), 3.94 (s, 3H, *H9*), 3.81 (s, 3H, *H16*), 3.72 (s, 3H, *H10*).

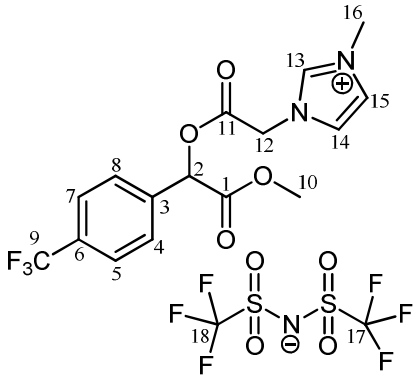
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 168.63 (*C*OO, *C1*), 165.30 (*C*OO, *C11*), 160.81 (Ar*C*, *C6*), 137.65 (Ar*CH*, *C13*), 129.39 (2Ar*CH*, *C4, C8*), 127.93 (Ar*C*, *C3*), 124.32 (Ar*C*H, *C14/C15*), 123.79 (Ar*C*H, *C14/C15*), 119.71 (q, *J* = 319 Hz, 2*C*F_3, *C17, C18*), 114.10 (2Ar*CH*, *C5, C7*), 76.15 (O*C*H, *C2*), 55.36 (O*C*H_3, *C9*), 52.87 (O*C*H_3, *C10*), 49.85 (*C*H_2, C12), 35.55 (*C*H_3, *C16*).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -79.06 (6*F*)

IR (neat, cm^{-1}): 2962, 1749, 1611, 1583, 1515, 1440, 1347, 1170, 1132, 1052, 1028.

MS (*m/z*): 319.10 $[M\text{-}NTf_2^-]^+$

1-(2-{2-Methoxy-2-oxo-1-[4-(trifluoromethyl)phenyl]ethoxy}-2-oxoethyl)-3-methyl-1H-imidazol-3-ium *bis*(trifluoromethylsulfonyl)imide (133b)



The title compound (**133b**) was prepared using bromide salt (**133a**) (440 mg, 1.01 mmol), $LiNTf_2$ (320 mg, 1.11 mmol) and distilled water (5 mL) according to the general procedure S to afford a white solid in 88 % yield (570 mg, 0.89 mmol).

Molecular formula: $C_{18}H_{16}F_9N_3O_8S_2$

Molecular weight: 637.45 g/mol

Melting point: 70-72°C

^{1}H NMR (400 MHz, DMSO-d_6) ppm: 9.13 (s, 1H, *H13*), 7.86 (d, *J* = 8.0 Hz, 2H, *H5,H7*), 7.75 (s, 2H, *H14, H15*), 7.74 (d, *J* = 8.0 Hz, 2H, *H4,H8*), 6.36 (s, 1H, *H2*), 5.56 (d part A of an AB system, *J* = 17.6 Hz, 1H, *H12*), 5.45 (d part B of an AB system, *J* = 17.6 Hz, 1H, *H12*), 3.92 (s, 3H, *H10*), 3.70 (s, 3H, *H16*).

^{13}C NMR (100 MHz, DMSO-d_6) ppm: 167.72 (*C*OO, *C1*), 166.22 (*C*OO, *C11*), 137.80 (Ar*C*, *C13*), 137.50 (Ar*C*, *C3*), 129.83 (q, *J* = 31.5 Hz, Ar*CH*, *C6*), 128.44 (2Ar*CH*, *C4, C8*), 125.85 (q, *J* = 271.5 Hz, *C*F_3, *C9*), 123.60 (q, *J* = 4.0 Hz, 2Ar*C*H, *C5, C7*), 120.54 (Ar*CH, C14/C15*), 118.40 (q, *J* = 319 Hz, 2*C*F3, *C17, C18*), 116.27 (Ar*C*H, *C14/C15*), 74.15 (O*C*H, *C2*), 52.99 (O*C*H_3, *C10*), 49.22 (*C*H_2, C12), 36.00 (*C*H_3, *C16*).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -62.64 (3*F*, C9), -79.23 (6*F*, C17, C18).

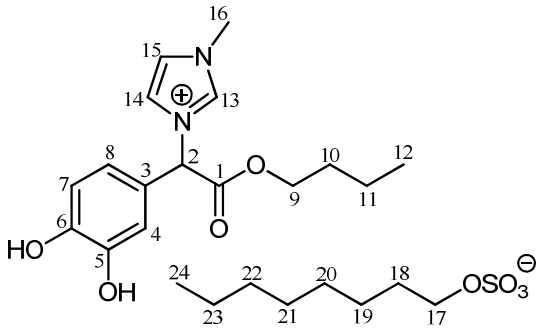
IR (neat, cm^{-1}): 3164, 1748, 1624, 1570, 1441, 1349, 1325, 1175, 1139, 1127, 1052, 1020.

MS (*m/z*): 357.10 $[M\text{-}NTf_2^-]^+$

6.4.6 [$OctOSO_3$] Ionic Liquids:

General Procedure T: Preparation of Mandelate based [$OctOSO_3$] ILs[4]

3-[2-Butoxy-1-(3,4-dihydroxyphenyl)-2-oxoethyl]-1-methyl-1H-imidazol-3-ium octyl sulfate (120c)



To a stirred solution of bromide salt (**120a**) (2.0 g, 5.2 mmol), in distilled water (10 mL) was added sodium octyl sulphate (1.21 g, 5.19 mmol) in one portion. The mixture was stirred overnight, then the water was evaporated on the rotary evaporator. The crude product was dissolved in DCM (25 mL) and washed with water (3 x 5 mL). The product was then dried by rotary evaporation and under high vacuum to obtain a brown oil in 41 % yield (1.10 g, 2.1 mmol).

Molecular formula: $C_{24}H_{38}N_2O_7S$

Molecular weight : 514.63 g/mol

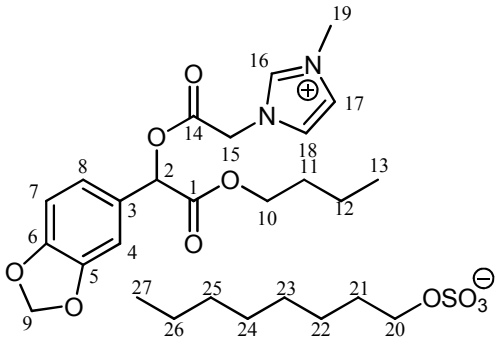
^{1}H NMR (400 Hz, DMSO-d_6) ppm: 9.49 (s, 1H, O*H*, *C5/C6*), 9.31 (s, 1 H, O*H*, *C5/C6*), 9.07 (s, 1H, *H13*), 7.74 (t, *J* = 1.6 Hz, 1H, *H14/H15*), 7.72 (t, *J* = 1.6 Hz, 1H, *H14/H15*), 6.83 (d, *J* = 2.0 Hz, 1H, *H4*), 6.82 (d, *J* = 8.0 Hz, 1H, *H7*), 6.74 (dd, *J* = 8.0, 2.0 Hz, 1H, *H8*), 6.53 (s, 1H, *H2*), 4.26-4.14 (m, 2H, *H9*), 3.86 (s, 3H, *H16*), 3.68 (t, *J* = 6.8 Hz, 2H, *H17*), 1.58-1.45 (m, 4H, *H10, H18*), 1.28-1.19 (m, 12H, *H11, H19, H20, H21, H22, H23*), 0.86 (t, *J* = 7.2 Hz, 3H, *H12/H24*), 0.84 (t, *J* = 7.6 Hz, 3H, *H12/H24*).

^{13}C NMR (100 Hz, DMSO-d_6) ppm: 167.84 (*C*OO, *C1*), 146.98 (Ar*C*, *C5/C6*), 145.93 (Ar*C*, *C5/C6*), 136.58 (Ar*C*H, *C13*), 123.47 (Ar*C*, *C3*), 122.77 (Ar*C*H, *C14/C15*), 122.37 (Ar*C*H, *C8*), 119.77 (Ar*C*H, *C14/C15*), 116.11 (Ar*C*H, *C7*), 115.77 (Ar*C*H, *C4*), 65.91 (N*C*H, *C2*), 65.45 (OCH_2, *C17*), 63.61 (O*C*H_2, *C9*), 35.95 (NCH_3, *C16*), 31.22 (CH_2, *C18*), 29.78 (CH_2, *C10*), 29.03 (CH_2, *C19*), 28.70 (CH_2, *C11*), 28.65 (CH_2, *C20*), 25.50 (CH_2, *C21*), 22.06 (CH_2, *C22*), 18.34 (CH_2, *C23*), 13.93 (CH_3, *C12/C24*), 13.37 (CH_3, *C12/C24*).

IR (neat, cm^{-1}): 3356, 3151, 2928, 1743, 1605, 1524, 1452, 1378, 1191, 1164, 1120, 1057, 955, 908, 798, 753.

MS (*m/z*): 305.15 $[M\text{-}OctOSO_3^-]^+$

1-{2-[1-(2H-1,3-Benzodioxol-5-yl)-2-butoxy-2-oxoethoxy]-2-oxoethyl}-3-methyl-1H-imidazol-3-ium octyl sulfate (128c)



The title compound (**128c**) was prepared using bromide salt (**128a**) (520 mg, 1.09 mmol), sodium octyl sulphate (260 mg, 1.09 mmol) and distilled water (5 mL) according to general procedure T to obtain pale yellow solid in 89 % yield (570 mg, 0.98 mmol).

Molecular formula: $C_{27}H_{40}N_2O_{10}S$

Molecular weight : 584.68 g/mol

Melting point: 55-57°C

^{1}H NMR (400 Hz, $CDCl_3$) ppm: 9.12 (s, 1H, *H16*), 7.75 (t, *J* = 1.6 Hz, 1H, *H17/H18*), 7.73 (t, *J* = 1.6 Hz, 1H, *H17/H18*), 7.00-6.98 (m, 3H, *H4, H7, H8*), 6.07 (s, 2H, *H9*), 6.03 (s, 1H, *H2*), 5.50 (d part A of an AB system, *J* = 17.6 Hz, 1H, *H15*), 5.39 (d part B of an AB system, *J* = 17.6 Hz, 1H, *H15*), 4.10 (dt, *J* = 10.8, 6.8 Hz, 1H, *H10*), 4.09 (dt, *J* = 10.8, 6.8 Hz, 1H, *H10*), 3.91 (s, 3H, *H19*), 3.66 (t, *J* = 6.8 Hz, 2H, *H20*), 1.48 (tt , *J* = 7.6, 6.8 Hz, 2H, *H11*), 1.30-1.15 (m, 14H, *H12, H21-H26*), 0.86 (t, *J* = 6.8 Hz, 3H, *H13*), 0.81 (t, *J* = 7.6 Hz, 3H, *H27*).

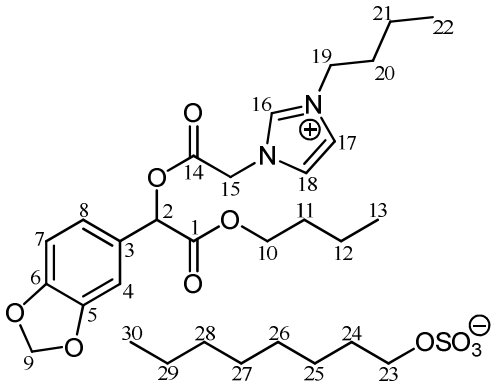
^{13}C NMR (100 Hz, $CDCl_3$) ppm: 168.21 (*C*OO, *C1*), 165.99 (*C*OO, *C14*), 148.87 (Ar*C*, *C5/C6*), 148.16 (Ar*C*, *C5/C6*), 139.08 (Ar*C*H, *C16*), 126.21 (Ar*C*, *C3*), 123.68 (Ar*C*H, *C14/C15*), 123.25 (Ar*C*H, *C8*), 122.31 (Ar*C*H, *C14/C15*), 108.64 (Ar*C*H, *C7*), 108.11 (Ar*C*H, *C4*), 101.63 ($C H_2$, *C9*), 76.19 (O*C*H, *C2*), 68.15 ($C H_2$, *C20*), 66.13 (OCH_2, *C10*), 49.92

(O*C*H_2, *C15*), 36.70 (NCH_3, *C19*), 31.93 (CH_2), 30.50 (CH_2), 29.54 (CH_2), 29.44 (CH_2), 25.93 (CH_2), 22.77 (CH_2), 18.99 (CH_2), 18.95 (CH_2), 14.23 (CH_3, *C13/C27*), 13.68 (CH_3, *C13/C27*).

IR (neat, cm^{-1}): 3402, 2959, 1745, 1636, 1503, 1491, 1447, 1368, 1249, 1196, 1170, 1027, 979, 921.

MS (*m/z*): 375.00 $[M\text{-}OctOSO_3^-]^+$

1-{2-[1-(2H-1,3-Benzodioxol-5-yl)-2-butoxy-2-oxoethoxy]-2-oxoethyl}-3-butyl-1H-imidazol-3-ium octyl sulfate (129c)



The title compound (**129c**) was prepared using bromide salt (**129a**) (2.05 g, 4.12 mmol), sodium octyl sulphate (930 mg, 4.12 mmol) and distilled water (10 mL) according to general procedure T to obtain a pale yellow solid in 82 % yield (2.13 g, 3.39 mmol).

Molecular formula: $C_{30}H_{46}N_2O_{10}S$

Molecular weight: 626.76 g/mol

Melting point: 49-51°C

^{1}H NMR (400 Hz, DMSO-d_6) ppm: 9.22 (s, 1H, *H16*), 7.86 (t, *J* = 1.6 Hz, 1H, *H17/H18*), 7.77 (t, *J* = 1.6 Hz, 1H, *H17/H18*), 7.00-6.98 (m, 3H, *H4, H7, H8*), 6.07 (s, 2H, *H9*), 6.03 (s, 1H, *H2*), 5.49 (d part A of an AB system, *J* = 17.6 Hz, 1H, *H15*), 5.40 (d part B of an AB system, *J* = 17.6 Hz, 1H, *H15*), 4.25 (t, *J* = 7.2 Hz, 2H, *H23*), 4.12-4.09 (m, 2H, *H10*), 3.67 (t, *J* = 6.8 Hz, 2H, *H19*), 1.77-1.75 (m, 2H), 1.50-1.46 (m , 4H), 1.28-1.19 (m, 14H), 0.90 (t, *J* = 7.2 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H), 0.81 (t, *J* = 7.6 Hz, 3H).

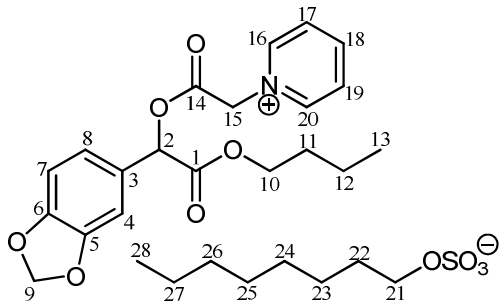
^{13}C NMR (100 Hz, DMSO-d_6) ppm: 168.49 (*C*OO, *C1*), 164.88 (*C*OO, *C14*), 148.32 (Ar*C*, *C5/C6*), 147.36 (Ar*C*, *C5/C6*), 137.51 (Ar*CH*, *C16*), 125.71 (Ar*C*, *C3*), 124.10 (Ar*CH*,

C17/C18), 123.36 (ArCH, C8), 121.89 (Ar*CH*, *C17/C18*), 109.59 (Ar*C*H, *C7*), 108.00 (Ar*C*H, *C4*), 101.56 (O*CH*$_2$O, *C9*), 76.77 (O*C*H, *C2*), 66.48 (O*CH*$_2$, *C10*), 65.45 (OCH$_2$, *C23*), 50.39 (N*CH*$_2$, *C19*), 50.51 (N*CH*$_2$, *C15*), 31.80 (*C*H$_2$), 31.09 (*C*H$_2$) 30.31 (*C*H$_2$), 29.59 (*C*H$_2$), 29.33 (*C*H$_2$), 28.47 (*C*H$_2$), 25.71 (*C*H$_2$), 22.98 (*C*H$_2$), 19.32 (*C*H$_2$), 18.81 (*C*H$_2$), 14.13 (*C*H$_3$), 13.33 (*C*H$_3$), 13.24 (*C*H$_3$).

IR (neat, cm^{-1}): 3150, 2957, 1724, 1563, 1488, 1427, 1249, 1169, 1053, 1017, 975, 815.

MS (*m/z*): 417.20 [M-OctOSO$_3^-$]$^+$

1-{2-[1-(2H-1,3-Benzodioxol-5-yl)-2-butoxy-2-oxoethoxy]-2-oxoethyl}pyridin-1-ium octyl sulfate (130c)



The title compound (**130c**) was prepared using bromide salt (**130a**) (1.58 g, 3.5 mmol), sodium octyl sulphate (810 mg, 3.49 mmol) and distilled water (10 mL) according to the general procedure T to obtain a pale yellow gel in 91 % yield (1.86 g, 3.2 mmol).

Molecular formula: $C_{28}H_{39}NO_{10}S$

Molecular weight: 581.67 g/mol

^{1}H NMR (400 Hz, CDCl$_3$) ppm: 8.95 (d, *J* = 6.2 Hz, 2H, *H16, H20*), 8.40 (t, *J* = 7.8 Hz, 1H, *H18*), 7.96 (dd, *J* = 7.8, 6.2 Hz, 2H, *H17, H19*), 6.85 (dd, *J* = 8.0, 2.0 Hz, 1H, *H8*), 6.82 (d, *J* = 2.0 Hz, 1H, *H4*), 6.73 (d, *J* = 8.0 Hz, 1H, *H7*), 5.92 (dd, J = 3.4, 3.4, 2H, *H9*), 5.90 (s, 1H, *H2*), 5.86 (d part A of an AB system, *J* = 17.6 Hz, 1H, *H15*), 5.71 (d part B of an AB system, *J* = 17.6 Hz, 1H, *H15*), 4.07-4.02 (m, 2H, *H10*), 3.87 (t, *J* = 7.2 Hz, 2H, *H21*), 1.52-1.44 (m, 4H, *H11, H22*), 1.23-1.14 (m, 12H), 0.81 (t, *J* = 7.2 Hz, 3H), 0.78 (t, *J* = 7.6 Hz, 3H).

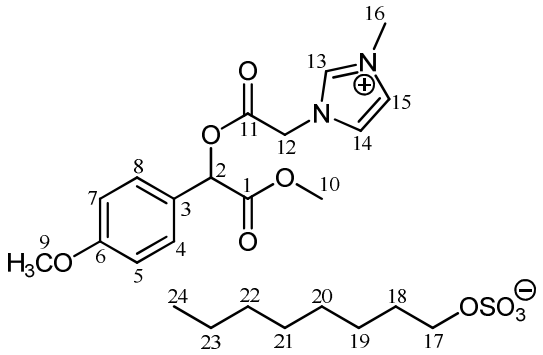
^{13}C NMR (100 Hz, CDCl$_3$) ppm: 168.45 (*C*OO, *C1*), 165.33 (*C*OO, *C14*), 149.28 (Ar*C*, *C5/C6*), 148.37 (Ar*C*, *C5/C6*), 146.67 (Ar*C*H, *C18*), 146.13 (2Ar*C*H, *C16, C20*), 129.08 (2Ar*CH*, *C17, C19*), 124.91 (Ar*C*, *C3*), 122.76 (Ar*CH*, *C8*), 108.78 (Ar*C*H, *C7*), 107.23

(Ar*C*H, *C4*), 101.61 (O*CH*$_2$O, *C9*), 76.29 (O*C*H, *C2*), 65.89 (O*CH*$_2$, *C21*), 65.17 (O*CH*$_2$, *C10*), 62.00 (*CH*$_2$, *C15*), 31.32 (*C*H$_2$), 30.33 (*C*H$_2$), 29.24 (*C*H$_2$), 28.66 (*C*H$_2$), 25.53 (*C*H$_2$), 22.48 (*C*H$_2$), 18.82 (*C*H$_2$), 18.51 (*C*H$_2$), 14.38 (*C*H$_3$), 13.16 (*C*H$_3$).

IR (neat, cm^{-1}): 3055, 2968, 1742, 1638, 1481, 1457, 1345, 1180, 1112, 1050, 1031, 922, 790.

MS (*m/z*): 372.10 [M-OctOSO$_3^-$]$^+$

1-{2-[2-Methoxy-1-(4-methoxyphenyl)-2-oxoethoxy]-2-oxoethyl}-3-methyl-1H-imidazol-3-ium octyl sulfate (132c)



The title compound (**132c**) was prepared using bromide salt (**132a**) (1.00 g, 2.5 mmol), sodium octyl sulphate (580 mg, 2.50 mmol) and distilled water (10 mL) according to the general procedure T to obtain a pale brown oil in 88 % yield (1.17 g, 2.2 mmol).

Molecular formula: $C_{24}H_{36}N_2O_9S$

Molecular weight : 528.62 g/mol

^{1}H NMR (400 Hz, $CDCl_3$) ppm: 9.32 (s, 1H, *H13*), 7.40 (t, *J* = 1.6 Hz, 1H, *H14/H15*), 7.31 (t, *J* = 1.6 Hz, 1H, *H14/H15*), 7.27 (d, *J* = 8.4 Hz, 2H, *H4, H8*), 6.83 (d, *J* = 8.4 Hz, 2H, *H5, H7*), 5.88 (s, 1H, *H2*), 5.31 (d part A of an AB system, *J* = 18.0 Hz, 1H, *H12*), 5.20 (d part B of an AB system, *J* = 18.0 Hz, 1H, *H12*), 3.90 (t, *J* = 6.8 Hz, 2H, *H17*), 3.88 (s, 3H, *H9*), 3.74 (s, 3H, *H16*), 3.64 (s, 3H, *H10*), 1.56-1.52 (m , 2H, *H18*), 1.26-1.14 (m, 10H, *H19-H23*), 0.80 (t, *J* = 7.2 Hz, 3H, *H24*).

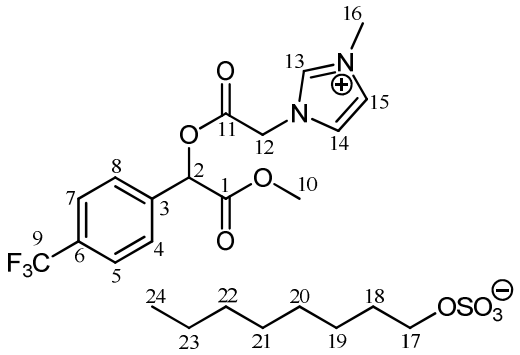
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 167.81 (*C*OO, *C1*), 166.04 (*C*OO, *C11*), 159.80 (Ar*C*, *C6*), 138.06 (Ar*CH*, *C13*), 130.53 (Ar*C*, *C3*), 127.91 (2Ar*CH*, *C4, C8*), 123.98 (Ar*C*H, *C14/C15*), 123.11 (Ar*C*H, *C14/C15*), 114.25 (2Ar*CH*, *C5, C7*), 76.13 (O*C*H, *C2*), 68.36 (O*C*H$_2$, *C17*), 55.34 (O*CH*$_3$, *C9*), 52.89 (O*C*H$_3$, *C10*), 49.88 (*C*H$_2$, *C12*), 36.37 (*C*H$_3$, *C16*),

31.80 (CH_2, *C18*), 29.38 (CH_2, *C19*), 29.29 (CH_2, *C20*), 29.08 (CH_2, *C21*), 25.78 (CH_2, *C22*), 22.63 (CH_2, *C23*), 14.07 (CH_3, *C24*).

IR (neat, cm^{-1}): 2928, 1746, 1611, 1514, 1439, 1211, 1171, 1026, 974.

MS (*m/z*): 319.10 $[M\text{-}OctOSO_3^-]^+$

1-(2-{2-Methoxy-2-oxo-1-[4-(trifluoromethyl)phenyl]ethoxy}-2-oxoethyl)-3-methyl-1H-imidazol-3-ium octyl sulfate (133c)



The title compound (**133c**) was prepared using bromide salt (**133a**) (1.04 g, 2.38 mmol), sodium octyl sulphate (540 mg, 2.33 mmol) and distilled water (10 mL) according to the general procedure T to obtain a white solid in 87 % yield (1.14 g, 2.03 mmol).

Molecular formula: $C_{24}H_{33}F_3N_2O_8S$

Molecular weight: 566.59 g/mol

Melting Point: 60-61°C

^{1}H NMR (400 Hz, $CDCl_3$) ppm: 9.31 (s, 1H, *H13*), 7.63 (d, *J* = 8.4 Hz, 2H, *H4, H8*), 7.57 (d, *J* = 8.4 Hz, 2H, *H5, H7*), 7.50 (t, *J* = 1.6 Hz, 1H, *H14/H15*), 7.36 (t, *J* = 1.6 Hz, 1H, *H14/H15*), 6.08 (s, 1H, *H2*), 5.47 (d part A of an AB system, *J* = 18.0 Hz, 1H, *H12*), 5.32 (d part B of an AB system, *J* = 18.0 Hz, 1H, *H12*), 3.93 (t, *J* = 6.8 Hz, 2H, *H17*), 3.92 (s, 3H, *H16*), 3.76 (s, 3H, *H10*), 1.60-1.53 (m , 2H, *H18*), 1.36-1.17 (m, 10H, *H19-H23*), 0.85 (t, *J* = 6.8 Hz, 3H, *H24*).

^{13}C NMR (100 Hz, $CDCl_3$) ppm: 169.27 (*C*OO, *C1*), 165.97 (*C*OO, *C11*), 137.70 (Ar*C*, *C13*), 136.34 (Ar*C*, *C3*), 128.83 (q, *J* = 32.0 Hz, Ar*CH*, *C6*), 127.56 (2Ar*CH*, *C4, C8*), 125.67 (q, *J* = 270.5 Hz, *C*F_3, *C9*), 123.51 (q, *J* = 3.8 Hz, 2Ar*C*H, *C5, C7*), 120.66 (Ar*CH, C14/C15*), 116.43 (Ar*C*H, *C14/C15*), 74.55 (O*C*H, *C2*), 67.78 (O*C*H_2, *C17*), 53.76 (O*C*H_3, *C10*), 49.89

(CH_2, *C12*), 35.46 (CH_3, *C16*), 31.71 (CH_2), 29.65 (CH_2), 29.19 (CH_2), 29.68 (CH_2), 25.88 (CH_2), 22.13 (CH_2), 14.50 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -62.09 (3*F*)

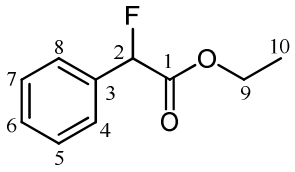
IR (neat, cm^{-1}): 3119, 2929, 1736, 1620, 1579, 1416, 1325, 1165, 1124, 1066, 1017, 832.

MS (*m/z*): 357.10 $[M\text{-}OctOSO_3^-]^+$

6.5 Miscellaneous:

6.5.1 Fluorinated compounds:

Ethyl 2-fluoro-2-phenylacetate (134)[16]



To a stirred solution of alcohol (510 mg, 2.83 mmol) in CH_2Cl_2 (10 mL) was added DAST (0.70 mL, 5.1 mmol) at 0 °C, and the resulting mixture was slowly warmed to rt and stirred for 14 h. The reaction was carefully quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (2 X 10 mL). The combined extracts were washed with 0.5 N HCl solution and dried over MgSO4. After evaporation of the solvent under reduced pressure, the resulting residue was chromatographed using silica gel (10:90 EtOAc/hexane) to obtain the title compound (**134**) as light yellow oil in 51 % yield (260 mg, 1.43 mmol).

Molecular formula: $C_{10}H_{11}FO_2$

Molecular weight: 182.19 g/mol

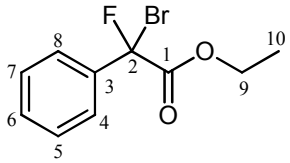
^{1}H NMR (600 MHz, $CDCl_3$) ppm: 7.48-7.46 (m, 2H, *H5, H7*) 7.42-7.39 (m, 3H, *H4, H6, H8*), 5.78 (d, J = 48.0 Hz, 1H), 4.26-4.13 (m, 2H, *H9*), 1.25 (t, J = 7.2 Hz, 3H, *H10*).

^{13}C NMR (150 MHz, $CDCl_3$) ppm: 168.60 (d, $^2J_{C\text{-}F}$ = 27.5 Hz, *C1*), 134.35 (Ar*C*, d, $^2J_{C\text{-}F}$ = 20.6 Hz, *C3*), 129.63 (Ar*C*H, *C6*), 128.81 (2Ar*C*H, *C5, C7*), 126.70 (2Ar*C*H, d, $^3J_{C\text{-}F}$ = 6.5 Hz, *C4, C8*), 89.4 (F*C*H, d, $^1J_{C\text{-}F}$ = 184.5 Hz, *C2*), 61.8 (O*C*H2, *C9*), 14.0 (C*C*H3, *C10*).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -179.68 (d, J = 48 MHz, 1F, HC*F*)

^{1}H and ^{13}C-NMR spectra are in agreement with literature data.[16]

Ethyl 2-bromo-2-fluoro-2-phenylacetate (135)



Fluoro ethyl ester (250 mg, 1.37 mmol) and NBS (240 mg, 1.37 mmol) were refluxed in CCl_4 (10 mL) under illumination from a 300-W mercury lamp. After 1 h an orange coloration appeared in the mixture which disappeared with additional 5 h. Filtration, evaporation of the solvent followed by column chromatography (SiO_2, EtOAc:Hexane; 10:90) afforded title compound (**135**) in 75 % yield (270 mg, 1.03 mmol).[17]

Molecular formula: $C_{10}H_{10}BrFO_2$

Molecular weight: 261.09 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 7.74-7.69 (m, 2H, *H5, H7*) 7.44-7.41 (m, 3H, *H4, H6, H8*), 4.33 (dt, *J* = 10.8, 7.2 Hz, 2H, *H9*), 1.33 (t, *J* = 7.2 Hz, 3H, *H10*).

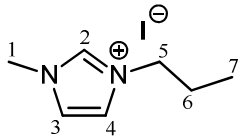
^{13}C NMR (100 MHz, $CDCl_3$) ppm: 165.77 (d, $^{2}J_{C\text{-}F}$ = 28.3 Hz, *C1*), 136.94 (Ar*C*, d, $^{2}J_{C\text{-}F}$ = 21.7 Hz, *C3*), 130.40 (Ar*C*H, *C6*), 128.55 (2Ar*C*H, *C5, C7*), 126.16 (2Ar*C*H, d, $^{3}J_{C\text{-}F}$ = 8.0 Hz, *C4, C8*), 96.80 (F*C*Br, d, $^{1}J_{C\text{-}F}$ = 262.3 Hz, *C2*), 63.76 (O*C*H2, *C9*), 13.94 (C*C*H3, *C10*).

^{19}F NMR (376 MHz, $CDCl_3$) ppm: -114.36 (*F*CBr).

IR (neat, cm^{-1}): 2920, 2850, 1729, 1463, 1256, 727.

6.5.2 Commercial Ionic Liquids:

1-Methyl-3-propyl-1H-imidazol-3-ium iodide (138)[18]



To a stirred solution of iodopropane (21.93 g, 129.0 mmol) in diethyl ether (100 mL) at RT was added 1-methylimidazole (10.6 mL, 129 mmol) dropwise and the reaction mixture was stirred for 12 h. The viscous liquid which had settled at bottom, was washed with diethyl ether (5 x 50 mL) and dried under high vacuum to give the title compound as a pale yellow liquid in 81 % yield (26.41 g, 104.8 mmol).

Molecular formula: $C_7H_{13}IN_2$

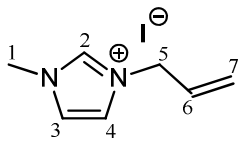
Molecular weight: 252.09 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 9.58 (s, 1H, *H2*), 7.45 (t, *J* = 1.6 Hz, 1H, *H3/H4*), 7.42 (t, *J* = 1.6 Hz, 1H, *H3/H4*), 4.06 (t, *J* = 7.2 Hz, 2H, *H5*), 1.72 (qt, *J* = 7.6, 7.2 Hz, 2H, *H6*), 3.86 (s, 3H, *H1*), 0.72 (t, J = 7.6 Hz, 3H, *H7*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 135.58 (Ar*C*H, *C2*), 123.18 (Ar*C*H, *C3/C4*), 121.92 (Ar*C*H, *C3/C4*), 50.76 (N*C*H_2, *C5*), 36.43 (N*C*H_3, *C1*), 23.02 (C*C*H_2, *C6*), 10.12 (C*C*H_3, *C7*).

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[18]

1-Methyl-3-(prop-2-en-1-yl)-1H-imidazol-3-ium iodide (139)[18]



To a stirred solution of allyl iodide (15.28 g, 91.0 mmol) in diethyl ether (100 mL) at RT was added 1-methylimidazole (7.5 mL, 91 mmol) dropwise and the reaction mixture was stirred for 12 h. Solid generated was washed with diethyl ether (5 x 50 mL) and dried under high vacuum to give the title compound as a pale yellow solid in 76 % yield (17.25 g, 67.0 mmol).

Molecular formula: $C_7H_{11}IN_2$

Molecular weight: 250.08 g/mol

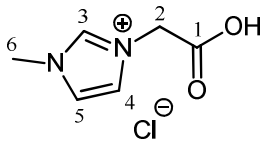
Melting point: 65-67 $^{\circ}$C

^{1}H NMR (600 MHz, $CDCl_3$) ppm: 9.76 (s, 1H, *H2*), 7.61 (t, *J* = 1.8 Hz, 1H, *H3/H4*), 7.48 (t, *J* = 1.8 Hz, 1H, *H3/H4*), 5.99 (m, 1H, *H6*), 5.47 (d, *J* = 16.8 Hz, 1H, *H7*), 5.40 (d, *J* = 10.2 Hz, 1H, *H7*), 4.95 (d, *J* = 6.6 Hz, 2H, *H5*), 4.05 (s, 3H, *H1*).

^{13}C NMR (150 MHz, $CDCl_3$) ppm: 136.39 (Ar*C*H, *C2*), 129.54 (Ar*C*H, *C3/C4*), 123.91 (Ar*C*H, *C3/C4*), 122.96 (C*C*H_2, *C7*), 122.17 (C*C*H, *C6*), 52.05 (C*C*H_2, *C5*), 37.19 (C*C*H_3, *C1*).

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[18]

3-(Carboxymethyl)-1-methyl-imidazolium chloride (140)[19]



Chloroacetic acid (18.2 g, 192.6 mmol) was added to 1-methylimidazole (15.5 mL, 193 mmol) over a period of an hour, and then the mixture was heated at 70 °C for 3.5 h. The solid thus obtained was cooled to RT, washed with acetonitrile (100 mL) and dried under high vacuum to obtain a white solid in 45 % yield (15.39 g, 87.2 mmol).

Molecular formula: $C_6H_9ClN_2O_2$

Molecular weight: 176.6 g/mol

Melting point: 140-142 °C

^{1}H NMR (400 MHz, D_2O) ppm: 8.73 (s, 1H, *H3*), 7.44-7.43 (m, 2H, *H4, H5*), 4.99 (s, 2H, *H2*), 3.89 (s, 3H, *H6*).

^{13}C NMR (100 MHz, D_2O) ppm: 170.63 (*C*OO, *C1*), 137.15 (Ar*C*H, *C3*), 123.37 (Ar*C*H, *C4/C5*), 123.31 (Ar*C*H, *C4/C5*), 50.37 (N*C*H2, *C2*), 35.78 (N*C*H3, *C6*).

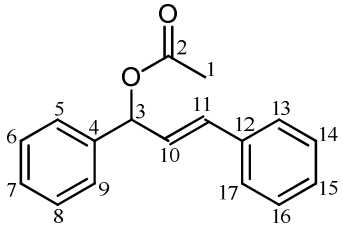
IR (neat, cm^{-1}): 3359, 3155, 3113, 3028, 1720, 1664, 1569, 1474, 1440, 1391, 1199, 1164, 979, 777.

MS (*m/z*): 141.10 $[M\text{-}Cl^-]^+$

^{1}H and ^{13}C-NMR spectra are in agreement with literature data.[19]

6.5.3 Tsuji-Trost Reaction Products:

(*2E*)-1,3-Diphenylprop-2-en-1-yl acetate (161)[20]



To a solution of *(E)*-1,3-diphenyl allyl alcohol (5.87 g, 27.9 mmol) triethylamine (7.80 mL, 56 mmol) and DMAP (3.41 g, 27.9 mmol) in diethyl ether (100 mL) acetic anhydride (3.96 mL, 41.88 mmol) was slowly added at 0-5 °C. The reaction was allowed to stir overnight at room temperature. The organic layer was extracted with saturated $NaHCO_3$ (1 x100 mL), water (1 x 100 mL), brine (1 x 100 mL), dried (Na_2SO_4) and concentrated to yield a dark yellow oil that was purified by column chromatography (SiO_2, 9:1 hexanes/EtOAc) to afford a colourless liquid in 93 % yield (6.54 g, 25.9 mmol).

Molecular formula: $C_{17}H_{16}O_2$

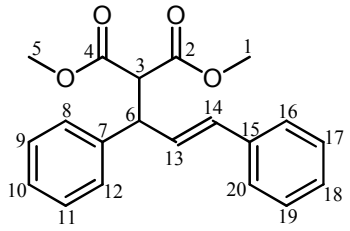
Molecular weight: 252.31 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 7.32-7.12 (m, 10H, *H5-H9, H13-17*), 6.53 (d, *J* = 15.6 Hz, 1H, *H11*), 6.34 (d, *J* = 7.0 Hz, 1H, *H3*), 6.24 (dd, *J* = 15.6, 7.0 Hz, 1H, *H10*), 2.02 (s, 3H, *H1*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 170.10 (*C*OO, *C2*), 139.28 (Ar*C*), 136.17 (Ar*C*), 132.63 (Ar*C*H), 128.70 (2Ar*C*H), 128.65 (2Ar*C*H), 128.25 (Ar*C*H), 128.14 (Ar*C*H), 127.52 (Ar*C*H), 127.11 (2Ar*C*H), 126.76 (2Ar*C*H), 76.21 (*C*H, *C3*), 21.43 (*C*H$_3$, *C1*).

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[20]

1,3-Dimethyl 2-[(2E)-1,3-diphenylprop-2-en-1-yl]propanedioate (**162**)[21]



To a mixture of 1,3-diphenyl allyl acetate (96 mg, 0.38 mmol), $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) and potassium carbonate (105 mg, 0.76 mmol) in dry THF (2 mL) dimethylmalonate (75 mg, 0.06 mmol) was added at rt under nitorgen and reaction was stirred at rt for 6 h. The volatiles were removed under reduced pressure, and residual crude product was purified by column chromatography (EtOAc:Hexane, 10:90) to afford colourless liquid in 55 % yield (67 mg, 0.21 mmol).

Molecular formula: $C_{20}H_{20}O_4$

Molecular weight: 324.37 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) ppm: 7.18-7.14 (m, 10H, *H8-H12, H16-20*), 6.44 (d, *J* = 15.6 Hz, 1H, *H14*), 6.28 (dd, *J* = 15.6, 8.8 Hz, 1H, *H13*),4.22 (dd, *J* = 10.8, 8.8 Hz, 1H, *H6*), 3.91 (d, *J* = 10.8 Hz, 1H, *H3*), 3.66 (s, 3H, *H1/H5*), 3.48 (s, 3H, *H1/H5*).

^{13}C NMR (100 MHz, $CDCl_3$) ppm: 168.35 (*C*OO, *C2/C4*), 167.93 (*C*OO, *C2/C4*), 140.27 (Ar*C*), 136.92 (Ar*C*), 131.96 (2Ar*C*H), 129.21 (Ar*C*H), 128.88 (2Ar*C*H), 128.62 (2Ar*C*H), 128.00 (2Ar*C*H), 127.72 (Ar*C*H), 127.32 (Ar*C*H), 126.53 (Ar*C*H), 57.77 (*C*H, *C3*), 52.81 (O*C*H_3, *C1/C5*), 52.63 (O*C*H_3, *C1/C5*), 49.34 (*C*H, *C6*).

^{1}H and ^{13}C-NMR spectra are in agreement with the literature data.[21]

6.6 Procedures for Toxicity and Biodegradation Tests and Applications:

6.6.1 Antibacterial Toxicity Screening at Charles University (Czech Republic)

In vitro antibacterial activities of the compounds were evaluated on a panel of three CCM strains (*Staphylococcus aureus* CCM 4516, *Escherichia coli* CCM 4517, *Pseudomonas aeruginosa* CCM 1961) and five clinical isolates (*Staphylococcus aureus* MRSA H 5996/08, *Staphylococcus epidermidis* H 6966/08, *Enterococcus sp.* H 14365/08, *Klebsiella pneumoniae* D 11750/08, *Klebsiella pneumoniae* ESBL H 14368/08) from the collection of fungal strains deposited at the Department of Biological and Medical Sciences, Faculty of Pharmacy, Charles University, Hradec Králové, Czech Republic. The abovementioned ATCC strains also served as the quality control strains. All the isolates were maintained on Mueller-Hinton dextrose agar prior to being tested.

Dimethyl sulfoxide (100 %) served as a diluent for all compounds; the final concentration did not exceed 2 %. Mueller-Hinton agar (MH, HiMedia, adersky-Envitek, Czech Republic) buffered to pH 7.4 (±0.2) was used as the test medium. The wells of the microdilution tray contained 200 µL of the Mueller-Hinton medium with 2-fold serial dilutions of the compounds (2000 or 1000 to 0.48 µmol/l) and 10 µL of inoculum suspension. Inoculum in MH medium was prepared to give a final concentration of 0.5 McFarland scale (1.5×10^8 cfu.mL^{-1}). The trays were incubated at 36°C and MICs were read visually after 24 h and 48 h. The MICs were defined as 95 % inhibition of the growth of control. MICs were determined twice and in duplicate. The deviations from the usually obtained values were no higher than the nearest concentration value up and down the dilution scale.

6.6.2 Antifungal Toxicity Screening at Charles University (Czech Republic)

In vitro antifungal activities of the compounds were evaluated on a panel of four ATCC strains (*Candida albicans* ATCC 44859, *Candida albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 6258) and eight clinical isolates of yeasts (*Candida krusei* E28, *Candida tropicalis* 156, *Candida glabrata* 20/I, *Candida lusitaniae* 2446/I, *Trichosporon asahii* 1188) and filamentous fungi (*Aspergillus fumigatus* 231, *Absidia corymbifera* 272, *Trichophyton mentagrophytes* 445) from the collection of fungal strains deposited at the Department of Biological and Medical Sciences, Faculty of Pharmacy, Charles University, Hradec Králové, Czech Republic. Three of the above ATCC strains (*Candida albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 6258) also served as the quality control strains. All the isolates were maintained on Sabouraud dextrose agar prior to being tested. Minimum inhibitory concentrations (MICs) were determined by the microdilution format of the NCCLS M27-A guidelines.[22]

Dimethyl sulfoxide (100 %) served as a diluent for all compounds; the final concentration did not exceed 2 %. RPMI 1640 (Sevapharma, Prague) medium supplemented with L-glutamine and buffered with 0.165 M morpholinepropanesulfonic acid (Serva) to pH 7.0 by 10 N NaOH was used as the test medium. The wells of the microdilution tray contained 100 µL of the RPMI 1640 medium with 2-fold serial dilutions of the compounds (2000 or 1000 to 0.48 µmol/L) and 100 µL of inoculum suspension. Fungal inoculum in RPMI 1640 was prepared to give a final concentration of $5 \times 10^3 \pm 0.2$ cfu.mL^{-1}. The trays were incubated at 35°C and MICs were read visually for filamentous fungi and photometrically for yeasts as an absorbance at 540 nm after 24 h and 48 h. The MIC/IC_{50} values for the dermatophytic strain (*T. mentagrophytes*) were determined after 72 h and 120 h and for *A. fumigatus*, *A. corymbifera* after 24 and 48 h. For all other strains MIC/IC_{80} values were evaluated. The MICs were defined as 50 % or 80 % inhibition of the growth of control. MICs were determined twice and in duplicate. The deviations from the usually obtained values were no higher than the nearest concentration value up and down the dilution scale.

6.6.3 Antibacterial Toxicity Screening at Higher Concentration (Dept. of Biotechnology, DCU)

Mueller-Hinton broth was purchased from Oxoid. Five bacteria strains were used in this study: the Gram-positive bacterium *Bacillus subtilis* DSMZ 10 (*B. subtilis*) and the Gram-negative bacteria *Escherichia coli* DSMZ 498 *(E. coli)*, *Pseudomonas fluorescens* DSMZ

50090 (*P. fluorescence)*, *Pseudomonas putida* CP1 (*P. putida* CP1) and *Pseudomonas putida* KT2440 (*P. putida* KT2440). All strains were purchased at DSMZ (German Collection of Microorganisms and Cell Cultures).

IC_{50} values for the compounds were determined using a modification of the broth microdilution method described by Amsterdam.[23] Strains were grown in nutrient broth overnight, washed with 0.01M sodium phosphate buffer (pH 7) and the cell number adjusted to give an optical density reading of 0.07 at 660 nm. The antimicrobial activity of the ILs was tested in 96 well round bottom microplates. 180 µL of Mueller-Hinton broth was pipetted into **column** 1 of the wells and 100 µL into the other wells. 20 µL of the chemical solution was transferred into **column** 1 giving a concentration of 200 mM. 100 µL of the solution from **column** 1 was then transferred to the next **column** and mixed. The procedure was repeated to give a series of two-fold dilutions. Each well was inoculated with 5 µL of bacterial culture. Wells containing medium only were used as blanks and wells containing medium and culture only were used as positive controls. All the toxicity tests were carried out in triplicate. The microplates were incubated overnight at 30°C. The presence or absence of growth was determined by measuring the optical density of the wells at a wavelength of 405nm using a plate reader. The IC_{50} values were determined as the concentration or range of concentrations that caused a 50% reduction in growth.

6.6.4 Toxicity Study using Fresh water Green Algae (Aveiro, Portugal)

The growth inhibition of the ILs towards the green microalgae *P. subcapitata* and *C. vulgaris* was assessed using a static bioassay conducted according to adequate growth inhibition testing procedures[24] guidelines, with adaptation to 24-well microplate.[25] The algae were exposed during 72 h under continuous illumination to serial dilutions of the IL in MBL medium: 0 (control), 6.25, 12.5, 25, 50, 75 and 100 %. Peripheral wells of the microplates were excluded from the assay given that as an "edge-effect" the evaporation is greater in these wells, which would introduce unnecessary variability among replicates. Each microplate held two test treatments with three 3 replicates plus 2 replicates of a blank control. Each well was filled with 990 µL test solution plus 10 µL microalgae inoculum; this was prepared based on microscopic cell counting in a Neubauer haemocytometer by dilution of the exponential-growing batch culture to achieve a cell density of 10^6 cells.mL^{-1} so that the final nominal cell density at the beginning of the test could be set at 10^4 cells.mL^{-1}. The test microplates were incubated as described above for algal cultures and the contents of each well were thoroughly

mixed twice daily by repetitive pipetting to promote active gas exchange and prevent cell clumping. At the end of the bioassay, cell density was determined by microscopic cell counting in a Neubauer haemocytometer of a well-mixed aliquot collected from each replicate. Yield and the daily growth rate were calculated from the cell density measurements. EC_{50} parameters and their 95% confidence limits were estimated on the basis of non-linear regression with former fitting of the data to the logistic equation through the least squares statistical method.

6.6.5. CO_2 Headspace test (Spain):

To evaluate the biodegradability of the test ionic liquids, the "CO_2 Headspace" test (ISO 14593) was applied.[23] There are several biodegradation study methods (Chapter 1) but the CO_2 Headspace test was chosen as it is particularly suited for charged, volatile and water soluble compounds. Also, this method allows for the evaluation of the ultimate aerobic biodegradability of an organic compound in an aqueous medium at a given concentration of microorganism, by analysis of the inorganic carbon produced. The test ionic liquid, as the only source of carbon and energy, was added to a buffer/mineral salts medium which had been inoculated with a mixed population of microorganisms derived from activated sludge collected from a sewage treatment plant located in Manresa (Barcelona), to give a final organic carbon concentration of 20 mg/L. These solutions were incubated in sealed vessels with a "headspace" of air, which provided a reservoir of oxygen for aerobic biodegradation. The volume of activated sludge used for inoculation was that which gave a concentration of 4 mg/L suspended solids in the final mixture. Based on experience, the use of this inoculum concentration in this test is suitable to give a population (102-105 colony-forming units in the final mixture) which offers adequate biodegradative activity and degrades the reference substance by the stipulated percentage.

Biodegradation (mineralization to carbon dioxide) was determined by measuring the net increase in total inorganic carbon (TIC) levels over time compared to unamended blanks. Sodium *n*-dodecyl sulfate (SDS) was used as a reference substance. The test ran for 28 days. The extent of biodegradation was expressed as a percentage of the theoretical amount of inorganic carbon (ThID) based on the amount of IL added initially. Assuming 100% mineralization of the test ionic liquid, the theoretical amount of inorganic carbon (ThID), in excess of that produced in the blank controls, equals the amount of total organic carbon (TOC) added as the test compound to each vessel at the start of the test, that is: (ThIC=TOC)

Percentage biodegradation D_t in each case is given by:

$$D_t = \frac{(\mathrm{TIC_t} - \mathrm{TIC_b})}{\mathrm{TOC_i}} \mathrm{x}100$$

where:

TIC_t is the TIC, in milligrams, in test vessel at time t,
TIC_b is the mean TIC, in milligrams, in blank control vessels at time t
TOC_i is the TOC, in milligrams, initially added to the test vessel

The measured data of the last day of the test (28 days) were used to calculate the mean biodegradation value and the precision with which the percentage of biodegradation was determined. To know the precision with which percentage of biodegradation was determined, four replicate test vessels and the same number of blanks control vessels on the 28th day were analysed:

- the mean total inorganic carbon in the blank vessels and the percentage of biodegradation for each individual vessel was calculated
- the mean of the separate degradation values and their standard deviation was calculated
- and finally the confidence limits for the mean value of biodegradation was evaluated as

  $$\pm \frac{t.s}{\sqrt{n}}$$

  where t is the Student's t value for (n-1) degrees of freedom at the 95% probability level, s is the standard deviation and n is the number of individual values used to determine the biodegradation percentage.

6.6.6 Procedure for Tsuji-Trost Reactions:[26]

$Pd_2(dba)_3 \cdot CHCl_3$ (4.58 mg, 0.005 mmol) and ferrocenylphosphine ligand (19.25 mg, 0.02 mmol) were added to pre-dried IL (0.50 mmol) and the resulting mixture was stirred at 80°C under Ar-atmosphere for 20 min. Substrate (126 mg, 0.50 mmol), dimethyl malonate (132 mg, 1.0 mmol) and K_2CO_3 (276 mg, 1.0 mmol) were added to the cooled reaction mixture. The reaction mixture was stirred at room temperature under Ar-atmosphere for 15 h. Toluene (2 mL) was added and mixture was vigorously stirred for 5 min, the separated toluene layer

was collected and this procedure was repeated until no product was detected in the toluene layer (*ca.*10 times). The combined toluene extracts were washed with water (5 mL), dried and solvent was evaporated. The residue was purified by chromatography on a SiO_2-column (30 g, 12.5% EtOAc–hexane). The product was obtained after evaporation of solvent as clear colourless oil.

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