

Ionic Liquids as Active Pharmaceutical Ingredients

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Ionic liquids (ILs) are ionic compounds that possess a melting temperature below 100 °C. Their physical and chemical properties are attractive for various applications. Several organic materials that are now classified as ionic liquids were described as far back as the mid-19th century. The search for new and different ILs has led to the progressive development and application of three generations of ILs: 1) The focus of the first generation was mainly on their unique intrinsic physical and chemical properties, such as density, viscosity, conductivity, solubility, and high thermal and chemical stability. 2) The second generation of ILs offered the potential to tune some of these physical and chemical properties, allowing the formation of “task-spe-

cific ionic liquids” which can have application as lubricants, energetic materials (in the case of selective separation and extraction processes), and as more environmentally friendly (*greener*) reaction solvents, among others. 3) The third and most recent generation of ILs involve active pharmaceutical ingredients (API), which are being used to produce ILs with biological activity. Herein we summarize recent developments in the area of third-generation ionic liquids that are being used as APIs, with a particular focus on efforts to overcome current hurdles encountered by APIs. We also offer some innovative solutions in new medical treatment and delivery options.

Introduction

Ionic liquids (ILs) have been a topic of great interest since the mid-1990s.^[1] They have attracted particularly high attention in recent years; approximately 1800 papers were published in the area of ILs in 2008 alone,^[2] documenting a variety of new IL applications. The range of IL uses had been broadened, and there was a significant increase in the scope of both physical and chemical IL properties.^[3,4]

ILs are generally defined as organic salts with melting points below 100 °C (some of them are liquid at room temperature) and composed entirely of ions.^[2,4–6] Despite the fact that ILs were first reported in the mid-1800s, widespread interest in this compound class has occurred only recently. ILs have come under worldwide scrutiny mainly through their use as solvents.^[2,4,7,8] In particular, the room temperature ionic liquids (RTILs), also known as “designer solvents” (because it is possible to create an IL with a given required property), have served as greener alternatives to conventional toxic organic solvents.^[2,7,9] RTILs have been used for several other applications, and their development continues at a considerable rate owing to their peculiar physical and chemical properties such as high thermal and chemical stability, lack of inflammability, low volatility, and tunable solubility with several organic compounds. By taking advantage of their unique properties,^[2,10] several IL applications have been described, including reaction media for many organic transformations,^[2,11] in separations and extractions,^[2,12] as electrolytes for electrochemistry,^[2,13] in nanotechnology,^[2,14] in biotechnology,^[2,15] and in engineering processes,^[2,16] among others.

ILs can be grouped into three generations according to their properties and characteristics.^[17] The first generation includes ILs for which the accessible physical properties such as decreased vapor pressure and high thermal stability^[18] are often

unique (Figure 1, *1st Generation*). Second-generation ILs have potential use as functional materials such as energetic materials, lubricants, and metal ion complexing agents, (Figure 1, *2nd Generation*). By taking advantage of their tunable physical and chemical properties, ILs can produce a remarkable platform on which—at least potentially—the properties of both cation and anion can be independently modified and designed to enable the production of new useful materials while maintaining the main properties of an IL. Some RTILs have been used as reaction media to produce or improve the preparation of various pharmaceuticals.^[7,19,20] Recently, the third generation of ILs^[17] (Figure 1, *3rd Generation*) has been described using active pharmaceutical ingredients (APIs) to produce ILs with biological activity.

While a tremendous amount of research has focused on the physical and chemical properties of ILs, more recently the toxicity and biological behavior of ILs have been included as two

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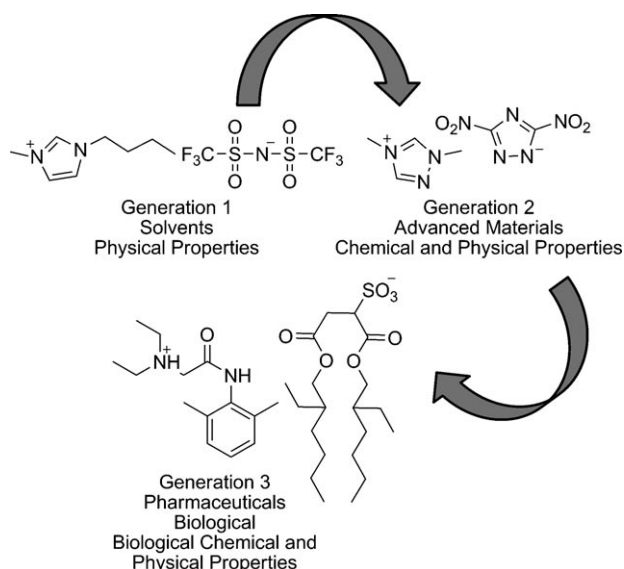


Figure 1. The scientific evolution of ILs, from unique physical properties (Generation 1) through the combination of chemical and physical properties (Generation 2), to the more recent studies of their biological and pharmaceutical activities (Generation 3) [adapted from Hough et al].^[17]

of the most highly debated topics in this field. Biologically active ions have been used to develop novel ILs; however, the primary drive behind the research into these materials has been focused on the use of well-known low-toxicity ions to obtain ILs with the desired set of properties.^[17,21,22]

Historical perspective

The first ionic liquid was described as “red oil” and was produced in the course of Friedel–Crafts reactions carried out in the mid-19th century. However, the composition of this red oil was only lately identified as a salt. For AlCl_3 -catalyzed reactions, the structure proposed for this liquid was the heptachlorodialuminate salt shown in Figure 2. This IL as red oil, along with

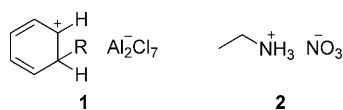


Figure 2. The structure proposed for the heptachlorodialuminate salt intermediate 1 in the Friedel–Crafts reactions. An example of alkylammonium nitrates: ethylammonium nitrate (2).

more complicated structures, were patented as useful materials, but no industrial application has been reported.^[7,23]

Modern ILs are quite different from those of the beginning of the 20th century, such as the alkylammonium nitrates 2, shown in Figure 2.^[23] The most common ILs containing quaternary heterocyclic cations (such as alkylpyridinium or dialkylimidazolium) and inorganic anions have an ancestry traceable to traditional high-temperature molten salts.^[23] The inorganic chloroaluminates are considered examples of salts between

the truly high-temperature molten salts (such as cryolite or LiCl–KCl) and the current ionic liquids.

The history behind the alkali chloroaluminate molten salts is a good example of fundamental research emerging rather quickly into practical application. In an example case, researchers at the United States Air Force Academy (Colorado Springs, CO, USA) picked up on work carried out by Frank Hurley and Thomas Wier^[24] on electro-deposition of aluminum using AlCl_3 -based molten salts. This led to the development of electrolytes for thermal batteries based on mixtures of AlCl_3 and 1-ethylpyridinium halides, mainly the bromide (Figure 3).

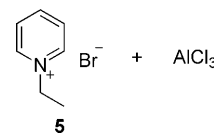


Figure 3. Mixture of AlCl_3 and 1-ethylpyridinium bromide (5).

One of most important breakthroughs in the history of ILs is related to the discovery of the 1-butylpyridinium chloride–aluminum chloride mixture (BPC– AlCl_3 , Figure 4).^[25] This all-chloride system represented a substantial improvement over the mixed bromide–chloride ionic liquids,^[25] but had some disadvantages; this led to new research and developments that brought forth the water-stable ionic liquids.^[23,26]

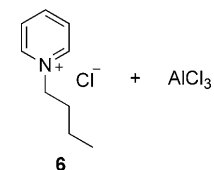


Figure 4. 1-Butylpyridinium chloride (6) and aluminum chloride mixture (BPC– AlCl_3).

The research for novel water-soluble ILs was described by Fuller et al.^[27] using a series of ILs from the traditional dialkylimidazolium cations combined with different anions (tetrafluoroborate, hexafluorophosphate, nitrate, acetate, and sulfate) along with the additional series of mostly larger anions (Figure 5). Over the years, new classes of cations and anions

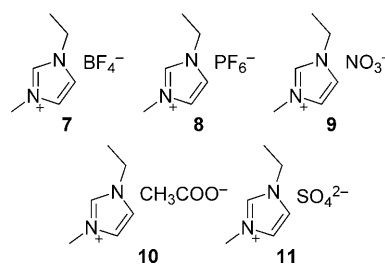


Figure 5. Tetrafluoroborate (7), hexafluorophosphate (8), nitrate (9), acetate salts (10), and sulfate (11) as anions combined with 1-ethyl-2-methylimidazolium cation ILs.

have been reported.^[2] Because ILs are intrinsically safer than highly volatile and flammable organic solvents, their use as solvents improves the safety margins and environmental performance in solution chemistry.^[4] Nowadays, the interest from disciplines outside chemistry and engineering is growing. Recent IL applications include use in sensors, solar cells, and solid-state photocells and batteries, as well as thermal fluids, lubricants, hydraulic fluids, and ionogels. ILs are indeed tunable, multipurpose materials for a variety of applications.^[6]

Finally, the particular interest in ILs from the biological and pharmaceutical sciences is not only for use as reaction media, but as pharmaceutical solvents or co-solvents for the delivery of drugs with poor water solubility.^[28] They are also applied in micro-emulsion systems, which can facilitate the dissolution of drugs that are insoluble or poorly soluble in water. Some IL micro-emulsions can be used as modern colloidal carriers for topical and transdermal delivery, while other IL systems have been used as entrapped/solubilized drug reservoirs for controlled release.^[29]

ILs as Active Pharmaceutical Ingredients (APIs)

Ionic pharmaceuticals and the polymorphism problem

The pharmaceutical industry is unquestionably facing a series of challenges. While many of these challenges are related to the features of this industry and present business models, there is also an urgent need for new scientific advances that yield innovative and effective drugs and therapies. The classical strategies currently being followed are reaching the point at which it is difficult to come up with effective and acceptable new chemical entities. Very few drugs (<10%) that are evaluated in clinical tests make it to the market, decreasing the accessibility of efficient therapies for the people who need them.^[30]

Roughly 50% of available drugs are administrated as salts. The physicochemical and biopharmaceutical properties of a given drug can be finely tuned by pairing with various counterions. From a pharmaceutical point of view, the melting temperature and solubility are relevant parameters because of their routine measurement and due to their potential influence on drug processing and bioavailability.^[31] This is an easy way to adjust the properties of a drug with ionizable functional groups to overcome undesirable features present in the parent drug.^[32] The quality, safety, and performance of a drug are related to the salt structure. The selected ion pair can significantly influence the pharmacokinetics of a drug candidate. This is one of the reasons why regulatory authorities have begun to classify novel salts of a registered drug as a new chemical entity.

The development of salts of the targeted active compounds is a suitable and well-known approach to overcome the limitations faced by the pharmaceutical industry. In spite of this, co-crystals, amorphous forms, and polymer-embedded pharmaceuticals have been tested in order to solve such classical problems as spontaneous polymorphic transformation of crystalline drug forms; this can pose significant problems for drug designers, and can convert an effective dose into a lethal dose by altering the solubility of the active ingredient.^[30] Pure compounds, salts, and all kinds of pharmaceuticals and drug candidates can suffer polymorphism (Figure 6), and there are no means to predict the emergence of polymorphism in any given compound despite recent efforts toward a better understanding of crystal polymorphism in pharmaceutical compounds.^[33–35]

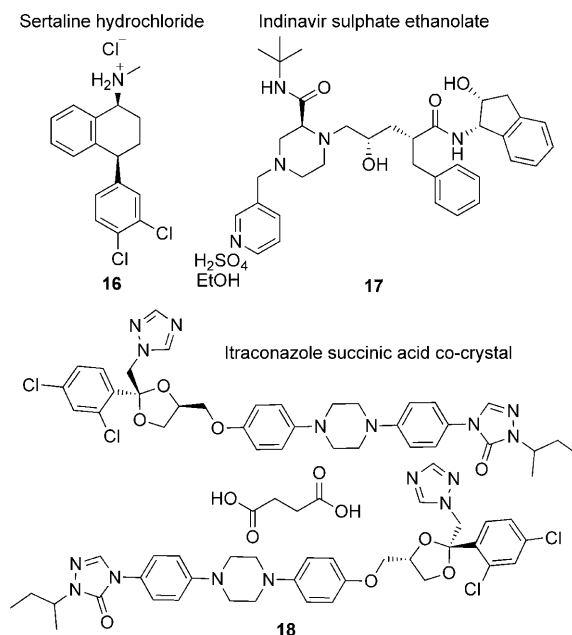


Figure 6. Examples of the types of crystal forms of pharmaceutical compounds that can have problems with polymorphism.

The cost of a pharmaceutical product depends directly on crystal polymorphism and solvation state. This situation has been illustrated by costly product failures and protracted patent litigation. For example, the case of the Norvir capsule product failure in 1998 was recounted and rationalized by solving the crystal structures of the Ritonavir polymorphs.^[36] In theory, all solid drugs are susceptible to unpredictable polymorph formation. An unexpected metastable form of 5-fluorouracil (a well-known drug) was described as a new polymorphic structure.^[33,37] The use of initial generic versions of some relevant drugs has been permitted based on patently different yet pharmaceutically equivalent polymorphs (or hydrates), which in some cases have led to legal disputes.^[33] Academic researchers are currently working with both experimental (engineering) and theoretical (prediction) insight into crystal forms.^[35]

The pharmaceutical industry should be open to the potential benefits that crystal engineering can offer, but it also has to be aware of other forms. Drug companies mainly rely on solid, primarily crystalline forms for the delivery of APIs for reasons of purity, thermal stability, manufacturability, and ease of handling. In contrast, liquid drug formulations are much less common, and are usually based on eutectic mixtures.^[38,39] However, problems associated with the solid form of many drugs have been consistently reported; issues include polymorphic conversion, low solubility, low bioavailability for crystalline solids, and the tendency of amorphous forms to spontaneously crystallize. For these reasons, and also due to considerable financial interests brought about by legal ramifications, screening for new drug forms, including salts, solvates, and co-crystals is a continuous pursuit.^[33,39] Therefore, the use of an active drug in liquid form can avoid some of polymorphism problems associated with solids. Other similar approaches

have been developed with liquid drug formulations prepared as eutectic mixtures,^[39,40] but these can dilute the APIs owing to large quantities of inactive ballast in the formulation. In this light, pure liquid-phase APIs would provide new perspectives for drug delivery and treatment approaches.

From the point of view of the pharmaceutical industry, the use of liquid salts is relevant, preferably those with melting points below room temperature. Some synthetic strategies that have been employed to decrease the melting point of the salts include selection of cations with a low tendency to crystallize, or ions with a more diffuse charge. For example, 3-ethyl-1-methylimidazolium chloride is an organic salt with a melting point of 77–79 °C that can be lowered to –21 °C by simple replacement of the chloride with a dicyanamide anion.^[39,41]

Pharmaceutical activity

The question of IL toxicity has delayed the entry of ILs into the biosciences. The toxicities observed toward microorganisms and cell cultures cover a wide range of biocidal potencies, from those of rather inactive molecular solvents such as ethanol or dimethyl sulfoxide, which are biocompatible to very high aqueous concentrations, to highly active biocides. The latter have even led to the proposal for the use of some ionic liquids as wood preservatives and in a variety of other pharmaceutical applications^[39,42] (Figure 7). The number of publications reporting antimicrobial activity for ILs is growing, and this could be very interesting for the development of new bioactive materi-

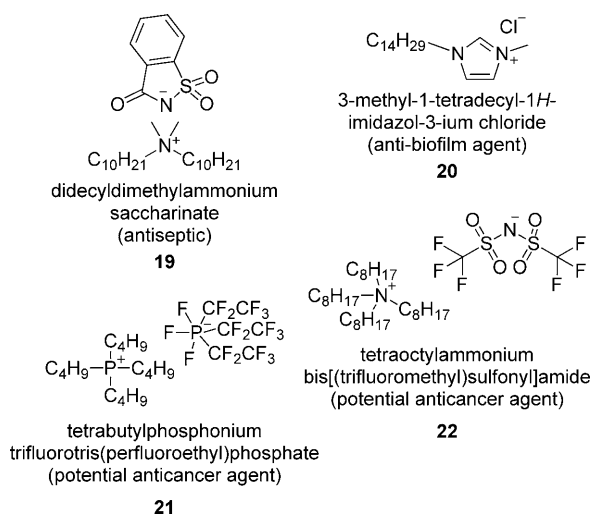


Figure 7. Some examples of ILs and their application.

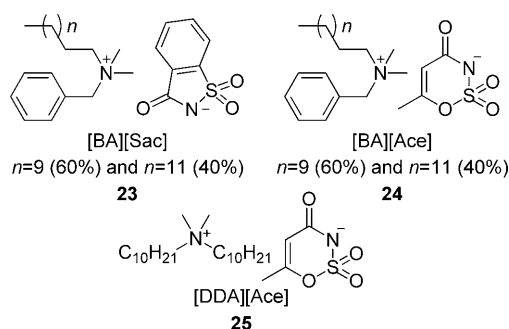


Figure 8. Examples of antibacterial agents.

als as antiseptics,^[39,43–45] for example (Figure 8). Table 1 and Table 2 list some examples of antimicrobial activity (minimum inhibitory concentration and minimum bactericidal or fungici-

Table 1. Minimum inhibitory concentrations for various ILs and starting salts.

Strain	MIC [ppm] ^[a]					
	[BA][Sac] (23) ^[b]	[DDA][Sac] (19) ^[c]	[BA][Ace] (24) ^[d]	[DDA][Ace] (25) ^[e]	[BA][Cl] ^[f]	[DDA][Cl] ^[f]
<i>S. aureus</i>	4	4	4	8	2	2
<i>S. aureus</i> (MRSA)	4	4	4	4	2	2
<i>E. faecium</i>	8	8	8	8	4	4
<i>E. coli</i>	16	16	31	16	8	8
<i>M. luteus</i>	8	4	8	8	4	2
<i>S. epidermidis</i>	4	4	4	4	2	2
<i>K. pneumoniae</i>	4	4	8	4	4	4
<i>C. albicans</i>	16	16	16	16	8	8
<i>R. rubra</i>	16	16	16	16	8	4
<i>S. mutans</i>	0.1	31	1	16	2	2

[a] Lowest compound concentration that inhibits visible growth of a microorganism after overnight incubation. [b] Benzalkonium saccharinate. [c] Didecyltrimethylammonium saccharinate. [d] Benzalkonium acesulfamate. [e] Didecyltrimethylammonium acesulfamate. [f] Starting salts: benzalkonium chloride ([BA][Cl]) and didecyltrimethylammonium chloride ([DDA][Cl]); data from Hough-Troutman et al.,^[43] listed for comparison.

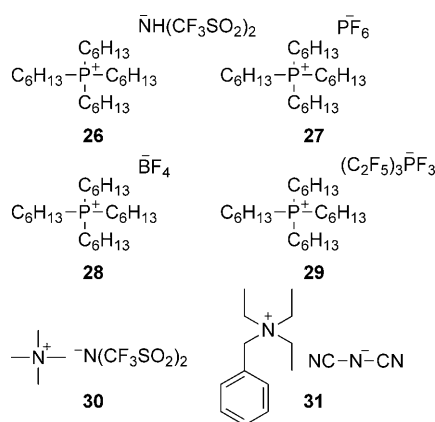
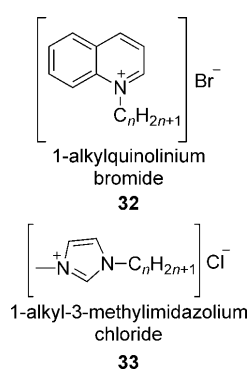
dal concentration, respectively) observed for ILs based on ammonium and benzalkonium cations combined with saccharinate and acesulfamate anions. These results demonstrate the potential use of ILs, in particular, against *Streptococcus mutans*. ILs could even be used as potential anticancer agents^[22,39,46,47] (Figure 9 and Table 3). Recently the anti-biofilm activity of some ILs and their reported potent, broad-spectrum activity against a variety of clinically significant microbial pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA),^[39] have been investigated^[45] (Figure 10 and Table 4).

Microbial biofilms are everywhere in nature and represent the dominant mode of microorganism growth. Various types of bacteria, such as MRSA, are observed in colonies adherent to material surfaces. These colonies often form coatings, known as biofilms. A common feature of biofilm communities is their tendency to exhibit significant tolerance and resistance to antibiotics and antimicrobial or biocidal challenge, relative to planktonic bacteria of the same species.^[45] One of the attractions of ionic liquids in this regard is the possibility to tailor their physical, chemical, and biological properties by building specific features into the chemical structures of the cation

Table 2. The minimum bactericidal or fungicidal concentrations for various ILs and starting salts.

Strain	MIC [ppm] ^[a]					
	[BA][Sac] (23) ^[b]	[DDA][Sac] (19) ^[c]	[BA][Ace] (24) ^[d]	[DDA][Ace] (25) ^[e]	[BA][Cl] ^[f]	[DDA][Cl] ^[f]
<i>S. aureus</i>	31.2	62.5	31.2	16	62.5	31.2
<i>S. aureus</i> (MRSA)	31.2	31.2	31.2	31.2	31.2	31.2
<i>E. faecium</i>	16	16	31.2	31.2	31.2	31.2
<i>E. coli</i>	62.5	16	125	62.5	62.5	31.2
<i>M. luteus</i>	62.5	31.2	62.5	62.5	31.2	31.2
<i>S. epidermidis</i>	31.2	16	62.5	31.2	16	31.2
<i>K. pneumoniae</i>	62.5	16	31.2	31.2	31.2	16
<i>C. albicans</i>	31.2	16	31.2	31.2	16	16
<i>R. rubra</i>	62.5	31.2	62.5	62.5	31.2	31.2
<i>S. mutans</i>	0.5	62.5	16	125	16	16

[a] Lowest compound concentration required to kill a microorganism. [b] Benzalkonium saccharinate. [c] Didecylmethylammonium saccharinate. [d] Benzalkonium acesulfamate. [e] Didecylmethylammonium acesulfamate. [f] Starting salts: benzalkonium chloride ([BA][Cl]) and didecylmethylammonium chloride ([DDA][Cl]); data from Hough-Troutman et al.,^[43] listed for comparison.

**Figure 9.** Examples of potential anticancer agents.^[46]**Figure 10.** Some examples of anti-biofilm agents.^[45]

and/or anion components that could facilitate antibiotic entry into the biofilm.

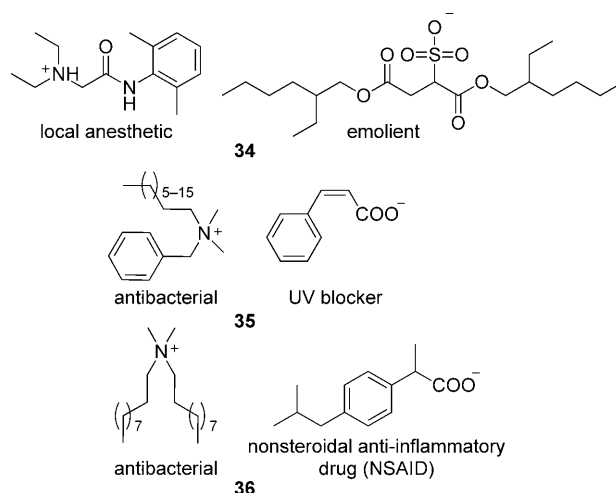
The pharmaceutical industry is currently paying more attention to ILs because they are customizable materials that can be specially tailored with selected characteristics by varying the combination of their cations and anions. This combination results in various ILs that can offer a wide range of hydrophobicity/hydrophilicity, acidity/basicity, viscosities, among other attributes.^[39,48]

The arrangement of cations and anions with few possibilities for strong attractive intermolecular hydrogen bonding interactions decreases the potential for crystallization and provides facile access to pharmaceutically active ILs.^[39,49] This will naturally lead to ILs or salts that otherwise would not be explored if crystallization is the primary goal. One such example is the combination of a didecylmethylammonium cation and saccharinate: the former is a cation with antimicrobial activity, and

the latter is an anion with a sweet taste (compound **19**, Figure 7). Indeed, the frequent designation of “designer solvents” for ILs might be easily adapted for IL “designer drugs,” as physical, chemical, and biological properties of a drug can be tuned by choice of counterion rather than by covalent modification.

Some compounds have difficulty penetrating biological membranes because they are very hydrophilic. The correct arrangement between an active ion with another more lipophilic character could offer a solution

for this problem. An elucidative example is the case of lidocaine docusate, which combines the local surface anesthetic lidocaine cation with the hydrophobic anion, docusate (an emollient) to create a novel hydrophobic IL salt. This IL demonstrates decreased or controlled water solubility, and thus should exhibit extended residence time on the skin^[17,39] (Figure 11). The counterions are chosen by their inactive nature in order to give the desired physicochemical properties of a

**Figure 11.** Examples of ILs with targeted biological properties combined with adequate selected physical and chemical properties.^[17]

neutral drug. Recently, a small number of so-called “combination salts” have been prepared, including two active units (APIs) (compound **36**, Figure 11) in the same singular compound coupled as a cation and an anion.^[39,50] In general this approach tends to be influenced by the need to obtain a crystalline material, or the fixed stoichiometry of active units found in such a crystalline salt. So called “dual functionality” has been explored as an important aspect of the IL field (for example, in dual acidic or double chiral ILs).^[39,51] In the context of APIs,

Table 3. Antitumor activity (GI_{50} [μM]^[a] and LC_{50} [μM]^[b] data) of compounds **26–30** (Figure 9) from five dose studies with the NCI 60-cell-line^[c] screen from Kumar and Malhotra.^[46]

	26		27		28		29		30	
	GI_{50}	LC_{50}	GI_{50}	LC_{50}	GI_{50}	LC_{50}	GI_{50}	LC_{50}	GI_{50}	LC_{50}
<i>Leukemia</i>										
CCRF-CEM	0.026	8.458	0.038	2.140	0.034	ND	4.410	> 100	0.190	2.440
HL-60(TB)	0.046	0.711	0.025	0.642	0.039	ND	2.420	> 100	0.173	1.230
K-562	0.041	> 100	0.087	> 100	0.038	> 100	1.680	> 100	0.186	4.859
MOLT-4	0.069	> 100	0.046	1.750	0.090	> 100	10.70	> 100	0.324	4.890
RPMI-8226	0.016	0.098	0.042	49.10	0.016	ND	1.640	> 100	0.046	0.951
SR	0.072	8.085	0.047	3.580	0.107	> 100	34.60	> 100	0.162	5.134
<i>Non-small-cell lung cancer</i>										
A549/ATCC	0.292	> 100	0.377	9.840	0.391	> 100	3.340	> 100	1.900	8.580
EKVX	0.123	> 100	0.069	4.600	0.206	ND	2.470	> 100	0.215	4.310
HOP-62	0.435	> 100	0.245	5.010	0.399	> 100	5.170	> 100	0.787	7.770
HOP-92	0.030	> 100	0.025	3.350	0.038	ND	4.790	> 100	0.206	4.470
NCI-H226	0.105	> 100	0.088	4.230	0.189	ND	3.910	> 100	0.478	4.410
NCI-H23	0.192	> 100	0.143	9.260	0.236	> 100	1.950	> 100	0.308	6.330
NCI-H322M	0.321	> 100	0.359	4.230	0.401	ND	6.120	> 100	1.810	6.120
NCI-H460	0.315	> 100	0.285	3.560	0.346	> 100	2.840	> 100	0.362	4.100
NCI-H522	0.105	> 100	0.069	4.260	0.158	> 100	3.420	> 100	0.287	5.400
<i>Colon cancer</i>										
COLO 205	0.182	> 100	1.730	> 100	0.243	> 100	1.700	9.160	0.292	> 100
HCC-2998	0.240	> 100	1.230	7.440	0.297	> 100	2.410	> 100	0.425	6.960
HCT-116	0.061	> 100	0.050	6.960	0.084	> 100	2.630	> 100	0.319	9.900
HCT-15	0.291	> 100	0.246	3.710	0.339	ND	2.880	> 100	0.993	5.230
HT29	0.053	> 100	0.057	6.490	0.061	> 100	3.800	> 100	0.305	5.170
KM12	0.049	> 100	0.045	0.080	0.059	> 100	2.890	> 100	0.310	5.310
SW-620	0.049	> 100	0.047	6.580	0.072	> 100	2.870	> 100	0.378	10.00
<i>CNS cancer</i>										
SF-268	0.072	> 100	0.066	6.270	0.088	> 100	7.440	> 100	0.493	5.500
SF-295	0.205	> 100	0.147	6.690	0.251	> 100	4.070	> 100	0.333	4.570
SF-539	0.174	> 100	0.100	3.450	0.234	ND	5.290	> 100	0.514	4.190
SNB-19	0.069	> 100	0.068	7.830	0.097	> 100	3.180	> 100	0.587	8.250
SNB-75	0.076	> 100	0.255	5.780	0.223	> 100	4.510	> 100	0.336	3.770
U251	0.041	5.620	0.037	3.610	0.037	ND	2.630	> 100	0.334	4.320
<i>Melanoma</i>										
LOX IMVI	0.058	0.592	0.037	0.418	0.050		4.240	> 100	0.192	1.080
MALME-3M	0.029	5.380	0.041	4.110	0.034	> 100	2.000	> 100	0.290	4.110
M14	0.052	> 100	0.044	5.490	0.087	> 100	3.050	> 100	0.453	9.190
SK-MEL-2	0.027	> 100	ND	ND	0.081	> 100	8.250	> 100	0.356	> 100
SK-MEL-28	0.207	6.590	0.178	6.060	0.376	> 100	1.800	> 100	0.710	7.180
SK-MEL-5	0.079	0.829	0.052	0.663	0.074	ND	2.470	> 100	0.177	0.677
UACC-257	0.103	> 100	0.112	4.810	0.272	ND	2.380	> 100	0.411	6.160
UACC-62	0.045	> 100	0.043	4.180	0.061	ND	3.440	> 100	0.335	4.100
<i>Ovarian cancer</i>										
IGROV1	0.071	> 100	ND	ND	0.316	> 100	7.460	> 100	0.388	> 100
OVCAR-3	0.051	6.760	0.036	3.100	0.118	> 100	2.620	> 100	0.315	4.180
OVCAR-4	0.073	> 100	0.096	8.690	0.125	> 100	4.340	> 100	0.309	5.800
OVCAR-5	0.318	> 100	0.279	7.590	0.337	ND	3.300	> 100	1.240	8.170
OVCAR-8	0.086	> 100	0.079	6.460	0.229	> 100	5.120	> 100	0.468	5.880
SK-OV-3	2.610	> 100	0.254	5.000	0.331	> 100	2.70	> 100	0.565	5.120
<i>Renal cancer</i>										
786-0	0.253	> 100	0.086	5.890	0.211	> 100	5.290	> 100	0.415	5.020
A498	0.310	> 100	0.451	6.080	0.472	ND	2.360	> 100	1.820	6.360
ACHN	0.260	> 100	0.212	3.390	0.244	ND	2.920	> 100	0.630	4.520
CAK-1	0.236	> 100	0.207	4.480	0.350	> 100	3.130	> 100	0.084	3.280
RXF 393	0.141	> 100	0.179	> 100	0.352	> 100	7.660	> 100	0.464	5.750
SN12C	0.042	4.440	0.043	3.560	0.062	ND	3.310	> 100	0.367	4.060
TK-10	0.341	> 100	0.145	4.490	0.234	ND	2.570	> 100	0.503	4.860
UO-31	0.350	> 100	0.298	5.410	0.398	> 100	4.330	> 100	0.686	5.950
<i>Prostate cancer</i>										
PC-3	0.045	5.900	0.035	0.779	0.044	> 100	3.780	> 100	0.282	3.990
DU-145	0.156	> 100	0.117	5.290	0.357	> 100	6.020	> 100	0.407	4.440
<i>Breast cancer</i>										
MCF7	0.144	> 100	0.082	3.910	0.253	> 100	3.050	> 100	0.317	4.020
NCI/ADR-RES	0.730	> 100	0.765	8.400	0.947	ND	3.080	> 100	1.680	8.130
MDA-MB-231ATCC	0.056	> 100	0.047	3.220	0.107	ND	6.980	> 100	0.345	3.630

these kinds of studies open new avenues for exploration in pharmaceutical action.

Some examples of ILs composed of two biologically active ions were recently described in which both the cation and anion were selected based on the desired physical, chemical, and biological properties.^[43] Such ILs are frequently found as antimicrobials and disinfectants,^[54] for which the introduction of sweetness as a second functionality in the same formulation can be a desired factor for oral applications, such as mouthwashes.

In the context of APIs, a variety of approaches can be contemplated for which the two actives can be chosen. The counterions can be selected to synergistically enhance the desired effects or to neutralize unwanted side effects of the active entity. The counterion can also be chosen to pharmacologically act independently.^[39,50]

In 2007 Pernak and co-workers patented a method for the preparation of ILs containing active pharmaceutical, biological, nutritional, and energetic ingredients. When a pharmaceutical activity is a desired property of the IL, one or more of the ions in the disclosed IL composition can be a pharmaceutical ingredient^[55] (Figure 12).

Importantly, a co-formation of two separate solid actives in a solid dosage form is significantly different from IL formulation. The ions from an IL will dissolve in bodily fluids in exactly the same way, as one ion cannot dissolve without the other. This is not true of separate solid forms administered at the same time, as each may dissolve at quite different rates.^[39]

Table 3. (Continued)

	26		27		28		29		30	
	GI ₅₀	LC ₅₀	GI ₅₀	LC ₅₀	GI ₅₀	LC ₅₀	GI ₅₀	LC ₅₀	GI ₅₀	LC ₅₀
HS 578T	0.053	> 100	0.077	9.390	0.084	> 100	1.760	> 100	0.417	> 100
MDA-MB-435	0.045	19.80	0.038	8.460	0.050	> 100	3.560	> 100	0.335	5.700
BT-549	0.066	> 100	0.061	4.370	0.094	> 100	3.100	> 100	0.421	4.420
T-47D	0.073	> 100	0.068	20.40	0.089	> 100	1.150	> 100	0.428	> 100
MDA-MB-468	0.036	2.560	0.044	4.240	0.053	> 100	2.220	> 100	0.119	2.110

[a] Drug concentration that results in a 50% decrease in net protein increase relative to control cells and toxicity. [b] Drug concentration lethal to 50% of cells; ND: not determined. [c] A 60-cell-line panel used as an in vitro substitute for the use of transplantable animal tumors in anticancer drug screening.^[52]

and Drug Administration (FDA) is a major step forward in classifying the biopharmaceutical properties of drugs and drug products. Based on mechanistic approaches to the drug absorption and dissolution processes and intestinal permeability, the BCS enables regulatory bodies to simplify and improve the drug approval process. The knowledge of the BCS characteristics of a drug in a formula-

Table 4. MIC and minimum biofilm eradication concentration (MBEC)^[a] values (in mM) of 1-alkyl-3-methylimidazolium chlorides ([C_nmim]Cl) (**33**) from Carson et al.^[45]

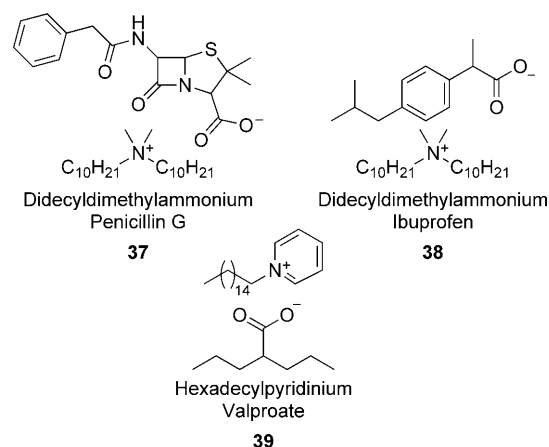
Organism	[mM]	n			
		8	10	12	14
<i>S. aureus</i>	MIC	722	40	18	16
ATCC 29213	MBEC	2708	2415	272	124
E-MRSA 15	MIC	722	40	18	16
	MBEC	2708	1207	272	248
MRSA	MIC	1444	160	36	16
	MBEC	21 666	4829	545	124
<i>S. epidermidis</i>	MIC	722	40	36	7.75
ATCC 35984	MBEC	10833	4829	272	124
<i>E. coli</i>	MIC	722	321	73	33
NCTC 8196	MBEC	21 666	9659	1089	124
<i>P. aeruginosa</i>	MIC	5416 ^[b]	2415 ^[b]	580	264
PA01	MBEC	21 666	2415	1089	496
<i>K. aerogenes</i>	MIC	1444	643	73	33
NCTC 7427	MBEC	43 331	19 318	2179	248
<i>B. cenocepacia</i>	MIC	> 1444	1287	290	132
J2315	MBEC	43 331	19 318	2179	496
<i>P. mirabilis</i>	MIC	1444	1287	580	264
NCTC 12442	MBEC	43 331	9659	4357	1984
<i>C. tropicalis</i>	MIC	1444	321	73	66
NCTC 7393	MBEC	> 43 331	19 318	8714	248

[a] Antimicrobial agent concentration required to kill a microbial biofilm.^[53] [b] MIC values determined by the chemical bath deposition (CBD) method as per manufacturer's protocol, and defined as the lowest concentration of antibiotic at which a planktonic population could not be established by shedding of bacteria from a biofilm;^[53] the NCCLS [now the Clinical and Laboratory Standards Institute (CLSI)] method was not used; data are included for clarification and comparison only.

Biopharmaceutics drug classification system (BCS)

The development of drugs is always associated with standards and directives that also aid in drug classification. Biopharmaceutics is defined by the physical and chemical properties of a biologically active compound as well as the formulation and physiology of the route of administration. Nowadays, numerous molecules are classified through screening processes, and promising candidates are selected for additional in vitro and in vivo tests. At the end of the process, regulatory agencies make the ultimate authorization.^[56]

The introduction of the biopharmaceutics drug classification system (BCS)^[57] (Table 5) into the guidelines of the US Food

**Figure 12.** Examples of an antibiotic (**37**), nonsteroidal anti-inflammatory agents/analgesics (**38**), and an antiepileptic agent (**39**) as ILs.^[55]**Table 5.** BCS^[a] classification of drugs and in vitro/in vivo correlation (IVVC) expectations for immediate-release products based on the biopharmaceutics class, from Löbenberg and Amidon.^[56]

Class	Solubility	Permeability	IVVC Expectation
I	High	High	IVVC if the dissolution rate is slower than the gastric emptying rate; otherwise, limited or no correlation.
II	Low	High	IVVC expected if the in vitro dissolution rate is similar to the in vivo dissolution rate, unless the dose is very high.
III	High	Low	Absorption (permeability) is rate-determining and limited or no IVVC with dissolution rate.
IV	Low	Low	Limited or no IVVC expected.

[a] Biopharmaceutics drug classification system.

tion can also be used by formulation scientists to develop a more optimized dosage form based on fundamental mechanistic, rather than empirical, information. In this context the combination of the appropriate anion or cation with a drug could be a simple method to a pharmaceutical ingredient change in the BCS.

Some examples of ionic APIs

There are numerous published examples in which pharmaceutically active compounds are salts of an active ion in combination with a relatively simple and inert counterion, or that can be easily transformed into cationic or anionic species. Table 6 illustrates some examples of drugs (or their APIs) that could be used for preparation of novel and pharmaceutically active ILs. The examples selected herein were listed in the 2009 Top-200 generic drug list by retail dollars.^[58] From the IL point of view, it is possible to use some examples from Table 6 as the cation unit, such as Omeprazole (rank 2), a drug used to treat gastroesophageal reflux disease, or the anion unit, such as the amoxicillin antibiotic (rank 9 and 28). Some of these possess dual functionalities, so they can be used as cation or anion, such as the antiepileptic Gabapentin (rank 8), or the angiotensin-converting enzyme inhibitor Lisinopril (rank 13), which is used for hypertension.

There are also numerous published examples of APIs in which both cation and anion are active pharmaceutical ingredients (Table 7).^[50] Following dissociation in solution, the cation and anion will each follow their independent kinetic and metabolic pathways.

Conclusions and Future Perspectives

The development of new synthetic strategies in organic chemistry using "eco-friendly" conditions is an issue of increasing interest. This leads to ILs, and has attracted the attention of the pharmaceutical industry. Naturally, further studies must be carried out in order to discover the full potential of their biomedical applications. The in-

Table 6. Examples of drugs (or their APIs) that could be used in ILs that are listed in the 2009 Top-200 generic drugs by retail dollars.^[58]

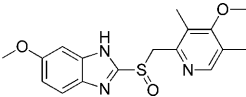
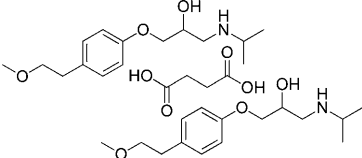
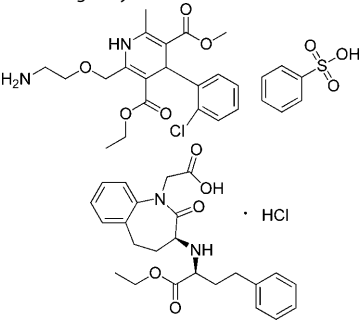
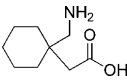
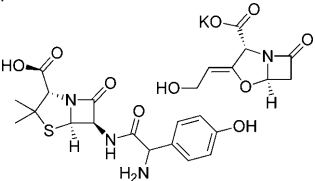
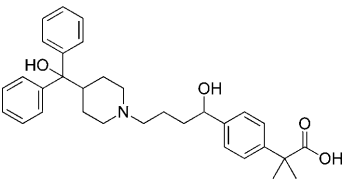
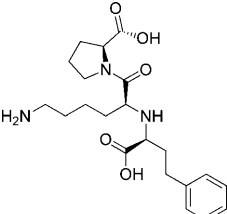
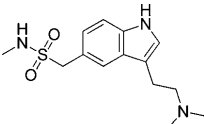
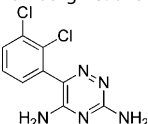
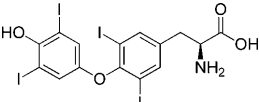
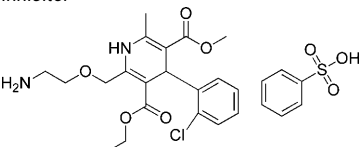
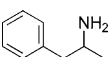
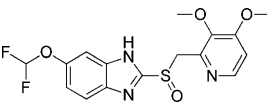
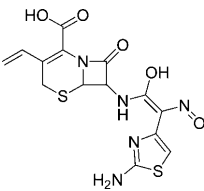
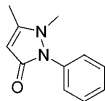
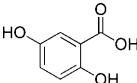
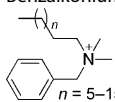
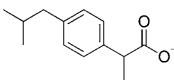
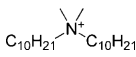
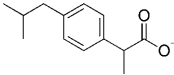
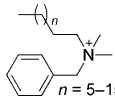
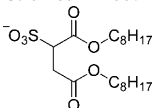
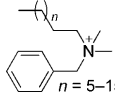
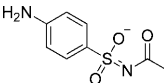
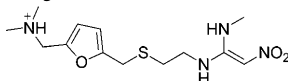
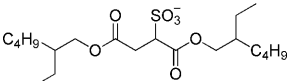
Rank	Drug ^[a]	Rank	Drug ^[a]
2	Omeprazole: <i>gastroesophageal reflux disease symptom treatment</i>	3	Metoprolol succinate: <i>angiotensin-converting enzyme inhibitor</i>
			
7	Amlodipine besylate and benazepril: <i>angiotensin-converting enzyme inhibitor</i>	8	Gabapentin: <i>antiepileptic and major depressive disorder treatment</i>
			
9	Amoxicillin with potassium clavunate: <i>antibiotic with β-lactamase inhibitor</i>	10	Fexofenadine: <i>antihistaminic</i>
			
13	Lisinopril: <i>angiotensin-converting enzyme inhibitor</i>	14	Sumatriptan oral: <i>antimigraine</i>
			
15	Lamotrigine: <i>antiepileptic</i>	16	Levothyroxine: <i>hypothyroidism treatment</i>
			
17	Amlodipine besylate: <i>angiotensin-converting enzyme inhibitor</i>	18	Amphetamine: <i>CNS stimulant</i>
			
21	Pantoprazole: <i>gastroesophageal reflux disease symptom treatment</i>	22	Cefdinir: <i>antibiotic</i>
			

Table 7. Examples of ionic liquid salt pairs with both cation and anion as active components; data from Kumar and Malhotra.^[50]

Cation	Anion	Salt Pair
Phenazone: (mp: 113 °C) <i>analgesic, anti-inflammatory, antipyretic</i>	Gentisic acid: (mp: 200–205 °C) <i>analgesic, anti-inflammatory, antipyretic</i>	Phenazone gentisate (mp: 87–88 °C) <i>analgesic, anti-inflammatory, antipyretic</i> ^[59]
		
Benzalkonium: <i>antibacterial</i>	Ibuprofenate: <i>anti-inflammatory</i>	Benzalkonium ibuprofenate: (mp: −41 °C ^[60])
 $n = 5-15$		
Didecyldimethylammonium: <i>antibacterial</i>	Ibuprofenate: <i>anti-inflammatory</i>	Didecyldimethyl ammonium ibuprofenate: (mp: liquid at RT ^[17])
 $C_{10}H_{21}$		
Benzalkonium: <i>antibacterial</i>	Colawet MA-80: <i>wetting agent</i>	Benzalkonium colawet MA-80: (mp: liquid at RT ^[60])
 $n = 5-15$		
Benzalkonium: <i>antibacterial</i>	Sulfacetamide: <i>anti-acne</i>	Benzalkonium sulfacetamide: (mp: liquid at RT ^[60])
 $n = 5-15$		
Ranitidine: <i>histamine H2 receptor antagonist</i>	Docusate: <i>emollient</i>	Ranitidine docusate ^[17]
		

- [24] a) F. H. Hurley, T. P. Wier, *J. Electrochem. Soc.* **1951**, *98*, 203–206; b) F. H. Hurley, T. P. Wier, *J. Electrochem. Soc.* **1951**, *98*, 207–212.
- [25] R. J. Gale, B. Gilbert, R. A. Osteryoung, *Inorg. Chem.* **1978**, *17*, 2728–2729.
- [26] a) S. Christie, R. H. Dubois, R. D. Rogers, P. S. White, M. J. Zaworotko, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1991**, *11*, 103–114; b) J. M. Martell, M. J. Zaworotko, *J. Chem. Soc. Dalton Trans.* **1991**, 1495–1498; c) J. S. Wilkes, M. J. Zaworotko, *J. Chem. Soc. Chem. Commun.* **1992**, 965–967.
- [27] a) J. Fuller, R. T. Carlin, *J. Chem. Crystallogr.* **1994**, *24*, 489–493; b) J. Fuller, R. T. Carlin, H. C. Delong, D. Haworth, *J. Chem. Soc. Chem. Commun.* **1994**, 299–300.
- [28] H. Mizuuchi, V. Jaitely, S. Murdan, A. T. Florence, *Eur. J. Pharm. Sci.* **2008**, *33*, 326–331.
- [29] a) V. Jaitely, A. Karatas, A. T. Florence, *Int. J. Pharm.* **2008**, *354*, 168–173; b) M. Moniruzzaman, N. Kamiya, M. Goto, *J. Colloid Interface Sci.* **2010**, *352*, 136–142; c) M. Moniruzzaman, M. Tamura, Y. Tahara, N. Kamiya, M. Goto, *Int. J. Pharm.* **2010**, *400*, 243–250; d) L. Viau, C. Tourné-Péteilh, J.-M. Devoisselle, A. Vieux, *Chem. Commun.* **2010**, 46, 228–230.
- [30] H. Rodriguez, K. Bica, R. D. Rogers, *Trop. J. Pharm. Res.* **2008**, *7*, 1011–1012.
- [31] S. N. Black, E. A. Collier, R. J. Davey, R. J. Roberts, *J. Pharm. Sci.* **2007**, *96*, 1053–1068.
- Pharm. Sci.* **1985**, *74*, 815–820.
- M. J. Zaworotko, O. Almarsson, *J. Pharm.*
- ton, M. L. Peterson, J. F. Remenar, M. J. J. Cima, C. R. Gardner, *Adv. Drug Delivery*
- Singhal, W. Curatolo, *Adv. Drug Delivery*
- Drug Discovery* **2004**, *3*, 42–57.
- J. Quick, W. Dziki, W. Porter, J. Morris,
- cher, *J. Am. Chem. Soc.* **2005**, *127*, 1116–
- T. Wadsten, B. Forslund, F. Broberg, *J.*
- Jane, K. Bica, R. D. Rogers, *Pharm. Res.*
- K. B. Vigour, T. D. Morgan, G. A. Broker, **2006**, 4767–4779.
- J. Golding, G. B. Deacon, *Green Chem.*
- nn, J. Arning, B. Jastorff, *Chem. Rev.* **2007**,
- s, L. Perez, F. Comelles, I. Ribosa, A. Man-
terface Sci. **2011**, *355*, 164–171; c) S. M.
- F. H. M. Abu Shawish, *Ecotoxicol. Environ.*
- glak, S. Griffin, W. M. Reichert, I. Mirska, J.
- Nawrot, M. Stasiewicz, R. D. Rogers, *J.*
- 26–33.
- S. J. Choi, S. Y. Park, H. Lee, C. J. Kim, I. D.
- J.* **2012**, 853–857.

- [10] M. J. Earle, K. R. Seddon, *Pure Appl. Chem.* **2000**, *72*, 1391–1398.
- [11] a) M. Haumann, A. Riisager, *Chem. Rev.* **2008**, *108*, 1474–1497; b) W. S. Miao, T. H. Chan, *Acc. Chem. Res.* **2006**, *39*, 897–908.
- [12] a) X. Han, D. W. Armstrong, *Acc. Chem. Res.* **2007**, *40*, 1079–1086; b) J. G. Huddleston, H. D. Willauer, R. P. Swatloski, A. E. Visser, R. D. Rogers, *Chem. Commun.* **1998**, 1765–1766.
- [13] a) P. Hapiot, C. Lagrost, *Chem. Rev.* **2008**, *108*, 2238–2264; b) D. R. Macfarlane, M. Forsyth, P. C. Howlett, J. M. Pringle, J. Sun, G. Annat, W. Neil, E. I. Izgorodina, *Acc. Chem. Res.* **2007**, *40*, 1165–1173.
- [14] a) T. Ichikawa, M. Yoshio, A. Hamasaki, T. Mukai, H. Ohno, T. Kato, *J. Am. Chem. Soc.* **2007**, *129*, 10662–10663; b) K. Biswas, C. N. R. Rao, *Chem. Eur. J.* **2007**, *13*, 6123–6129.
- [15] F. van Rantwijk, R. A. Sheldon, *Chem. Rev.* **2007**, *107*, 2757–2785.
- [16] a) T. L. Greaves, C. J. Drummond, *Chem. Rev.* **2008**, *108*, 206–237; b) S. Schneider, T. Hawkins, M. Rosander, G. Vaghjani, S. Chambreau, G. Drake, *Energy Fuels* **2008**, *22*, 2871–2872.
- [17] W. L. Hough, M. Smiglak, H. Rodriguez, R. P. Swatloski, S. K. Spear, D. T. Daly, J. Pernak, J. E. Grisel, R. D. Carliss, M. D. Soutullo, J. H. Davis, R. D. Rogers, *New J. Chem.* **2007**, *31*, 1429–1436.
- [18] M. Deetlefs, K. R. Seddon, M. Shara, *Phys. Chem. Chem. Phys.* **2006**, *8*, 642–649.
- [19] J. D. Holbrey, K. R. Seddon, *Clean Technol. Environ. Policy* **1999**, *1*, 223–236.
- [20] M. J. Earle, P. B. McCormac, K. R. Seddon, *Green Chem.* **2000**, *2*, 261–262.
- [21] E. B. Carter, S. L. Culver, P. A. Fox, R. D. Goode, I. Ntai, M. D. Tickell, R. K. Traylor, N. W. Hoffman, J. H. Davis, *Chem. Commun.* **2004**, 630–631.
- [22] J. Pernak, K. Sobaszekiewicz, I. Mirska, *Green Chem.* **2003**, *5*, 52–56.
- [23] J. S. Wilkes, *Green Chem.* **2002**, *4*, 73–80.

- [32] B. D. Anderson, R. A. Conradi, *J. Pharm. Sci.* **1985**, *74*, 815–820.
- [33] M. L. Peterson, M. B. Hickey, M. J. Zaworotko, O. Almarsson, *J. Pharm. Pharm. Sci.* **2006**, *9*, 317–326.
- [34] a) S. L. Morissette, Ö. Almarsson, M. L. Peterson, J. F. Remenar, M. J. Read, A. V. Lemmo, S. Ellis, M. J. Cima, C. R. Gardner, *Adv. Drug Delivery Rev.* **2004**, *56*, 275–300; b) D. Singhal, W. Curatolo, *Adv. Drug Delivery Rev.* **2004**, *56*, 335–347.
- [35] S. Datta, D. J. W. Grant, *Nat. Rev. Drug Discovery* **2004**, *3*, 42–57.
- [36] J. Bauer, S. Spanton, R. Henry, J. Quick, W. Dziki, W. Porter, J. Morris, *Pharm. Res.* **2001**, *18*, 859–866.
- [37] A. T. Hulme, S. L. Price, D. A. Tocher, *J. Am. Chem. Soc.* **2005**, *127*, 1116–1117.
- [38] A. Brodin, A. Nyqvistmayer, T. Wadsten, B. Forslund, F. Broberg, *J. Pharm. Sci.* **1984**, *73*, 481–484.
- [39] J. Stoimenovski, D. R. MacFarlane, K. Bica, R. D. Rogers, *Pharm. Res.* **2010**, *27*, 521–526.
- [40] W. M. Reichert, J. D. Holbrey, K. B. Vigour, T. D. Morgan, G. A. Broker, R. D. Rogers, *Chem. Commun.* **2006**, 4767–4779.
- [41] D. R. MacFarlane, S. A. Forsyth, J. Golding, G. B. Deacon, *Green Chem.* **2002**, *4*, 444–448.
- [42] a) J. Ranke, S. Stolte, R. Stormann, J. Arning, B. Jastorff, *Chem. Rev.* **2007**, *107*, 2183–2206; b) A. Cornellas, L. Perez, F. Comelles, I. Ribosa, A. Manresa, M. T. Garcia, *J. Colloid Interface Sci.* **2011**, *355*, 164–171; c) S. M. Saadeh, Z. Yasseen, F. A. Sharif, H. M. Abu Shawish, *Ecotoxicol. Environ. Saf.* **2009**, *72*, 1805–1809.
- [43] W. L. Hough-Troutman, M. Smiglak, S. Griffin, W. M. Reichert, I. Mirska, J. Jodynis-Liebert, T. Adamska, J. Nawrot, M. Stasiewicz, R. D. Rogers, J. Pernak, *New J. Chem.* **2009**, *33*, 26–33.
- [44] D. Demberelnyamba, K. S. Kim, S. J. Choi, S. Y. Park, H. Lee, C. J. Kim, I. D. Yoo, *Bioorg. Med. Chem.* **2004**, *12*, 853–857.

- [45] L. Carson, P. K. W. Chau, M. J. Earle, M. A. Gilea, B. F. Gilmore, S. P. Gorman, M. T. McCann, K. R. Seddon, *Green Chem.* **2009**, *11*, 492–497.
- [46] V. Kumar, S. V. Malhotra, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4643–4646.
- [47] J. Pernak, J. Feder-Kubis, *Chem. Eur. J.* **2005**, *11*, 4441–4449.
- [48] R. D. Rogers, K. R. Seddon, *Science* **2003**, *302*, 792–793.
- [49] P. M. Dean, J. Turanjanin, M. Yoshizawa-Fujita, D. R. MacFarlane, J. L. Scott, *Cryst. Growth Des.* **2009**, *9*, 1137–1145.
- [50] V. Kumar, S. V. Malhotra in *Ionic Liquid Applications: Pharmaceuticals, Therapeutics, and Biotechnology*, American Chemical Society, Washington DC, **2010**, pp. 1–12.
- [51] Z. F. Fei, T. J. Geldbach, D. B. Zhao, P. J. Dyson, *Chem. Eur. J.* **2006**, *12*, 2122–2130.
- [52] R. H. Shoemaker, *Nat. Rev. Cancer* **2006**, *6*, 813–823.
- [53] M. E. Olson, H. Ceri, D. W. Morck, A. G. Buret, R. R. Read, *Can. J. Vet. Res.* **2002**, *66*, 86–92.
- [54] L. S. C. Wan, *J. Pharm. Sci.* **1968**, *57*, 1903–1906.
- [55] a) R. Rogers, D. T. Daly, R. P. Swatloski, W. L. Hough, J. H. Davis, M. Smiglak, J. Pernak, S. K. Spear, WO2007044693, **2007**; b) R. Rogers, D. T. Daly, G. Gurau, D. MacFarlane, J. Turanjanin, P. Dean, J. L. Scott, K. Bica, K. Seddon, WO2010078300 (A1), **2010**; c) K. Bica, C. Rijksen, M. Nieuwenhuyzen, R. D. Rogers, *Phys. Chem. Chem. Phys.* **2010**, *12*, 2011–2017.
- [56] R. Löbenberg, G. L. Amidon, *Eur. J. Pharm. Biopharm.* **2000**, *50*, 3–12.
- [57] G. L. Amidon, H. Lennernäs, V. P. Shah, J. R. Crison, *Pharm. Res.* **1995**, *12*, 413–420.
- [58] Drug Topics: <http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/252010/674976/article.pdf> (accessed April 7, 2011).
- [59] M. Hoffer, N. J. Nutley, US 2541651, **1951**.
- [60] W. L. Hough, R. D. Rogers, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 2262–2269.

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