# Ionic Liquids: A New Strategy in Pharmaceutical Synthesis

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**Abstract:** The industrial synthesis of pharmaceutical compounds often involves the use of organic solvents. Unfortunately, these reaction media are responsible for organic contaminations in the final product. In recent years, ionic liquids (ILs) have become the "green alternatives" of volatile organic solvents. Thus, the application of ILs instead of conventional reagents offer a new opportunity to solve problems of environmentally harmful solvents. This mini-review discusses a new application of ILs in laboratory-scale pharmaceutical synthesis.

**Keywords:** Active pharmaceutical ingredient, biocatalytic reaction, green chemistry, ionic liquid.

## 1. INTRODUCTION

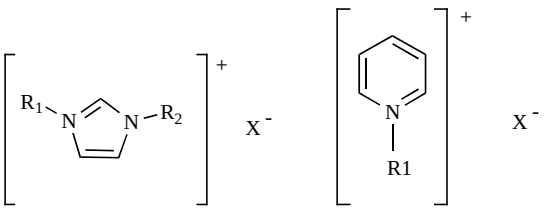
Industrial synthesis of pharmaceutical compounds often involves the use of organic solvents mainly for reasons of cost-effective procedure and ease of handling. Unfortunately, these reaction media are responsible for organic contamination of the final product and are therefore referred to as 'residual solvents' or 'organic volatile impurities'. The acceptable limits for contaminants resulting from the entire drug product manufacturing process have been specified in pharmacopoeias and the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use [1]. The ICH guideline distinguishes four classes of residual solvents in drug substances: solvents to be avoided, solvents to be limited, solvents with low toxic potential and solvents without adequate toxicological data. From the toxicological point of view, genotoxic impurities (GTIs) are the most dangerous contaminants for human health. Exposure to even low levels of such impurities present in the final active pharmaceutical ingredient (API) may induce genetic mutations and may potentially cause cancer in humans [2,3]. However, regardless of the solvent class, it is important to explore the possible opportunities to reduce or avoid the use of harmful solvents in the manufacturing process of pharmaceuticals.

The use of ionic liquids (ILs) as non-conventional media in chemical synthesis is increasing attention because of their physical and chemical properties. Their growing application in organic chemistry stems from their favourable physicochemical properties, such as the lack of vapour pressure, good thermal and chemical stability and very good dissolution properties of both organic and inorganic compounds. ILs are generally organic salts composed of various organic or inorganic cations and anions with a melting point at or near room temperature. They are therefore liquid at room temperature and are known by many synonyms, such as room-temperature ionic liquids (RTILs), liquid organic salts, low-temperature molten salts or ambient-temperature molten salts [4]. They are also referred to as neoteric solvents, meaning new types of solvent or materials that are finding new application as solvents.

ILs, being 'designer solvents', are convenient to use because of their combined cationic and anionic properties, which can be independently modified [5]. The ability to modify their properties, e.g. viscosity, density, solvent miscibility and melting point, results in their flexibility in the design of new functional materials [6-8]. ILs are also called 'environmentally friendly' and have been suggested as ideal replacements for volatile organic solvents [5,9]. The application of 'green' solvents, such as ionic liquids, in the pharmaceutical industry is currently being extensively investigated at the laboratory scale [10]. This mini-review discusses a new application of ILs in pharmacy.

## 2. THE APPLICATION OF IONIC LIQUIDS IN PHARMACEUTICAL SYNTHESIS

ILs have many desirable properties of interest to the pharmaceutical industry. Reactions in ILs are often faster and easier to carry out than those in conventional organic solvents and usually require no special apparatus or methodologies. It should, however, be emphasised that the thermodynamics and kinetics of the reactions carried out in ILs are different from those carried out in conventional solvents. Synthesis with the use of ILs mainly concerns liquid organic salts composed of the 1,3-dialkylimidazolium and *N*-alkylpyridinum cation and a non-coordinating anion (Fig. **1**) [11]. However, no universal catalytic system exists for all syntheses and each enzymatic process requires an individual solution [12].




R1 , R2 - alkyl group
$X^-$ - anion (e.g. $BF_4^-$, $PF_6^-$, $CF_3SO_3^-$, $CF_3COO^-$)

**Fig. (1).** The most commonly used ILs in chemical synthesis: a) the 1,3-dialkylimidazolium cation and b) the *N*-alkylpyridinum cation.

In recent years, ILs have attracted an increasing attention as reaction media in enzymatic processes because of the very high enzymatic activity and stability in these 'green' solvents. Generally, there are three ways in which ILs can be involved in the biocatalytic process: (i) as pure solvents in monophasic systems, various water-immiscible ILs (e.g. 1-ethyl-3-methylimidazolium hexafluorophosphate ([bmim][$PF_6$]), (ii) as water-miscible ILs in monophasic systems—co-solvents in aqueous systems (e.g. *N*-ethylpyridinium trifluoroacetate), or (iii) as pure ILs in non-aqueous biphasic systems (used as liquid or solid enzyme immobilisation supports) [13-15]. However, 1,3-dialkylimidazolium- and *N*-alkylpyridinum-based ILs have also been considered in biocatalysis.

The properties of imidazolium-based ILs make it possible to use the solvents as a direct replacement for conventional solvents in multiphase bioprocess operations [16]. ILs containing the hexafluorophosphate anion ($PF_6$) may form triphasic mixtures with

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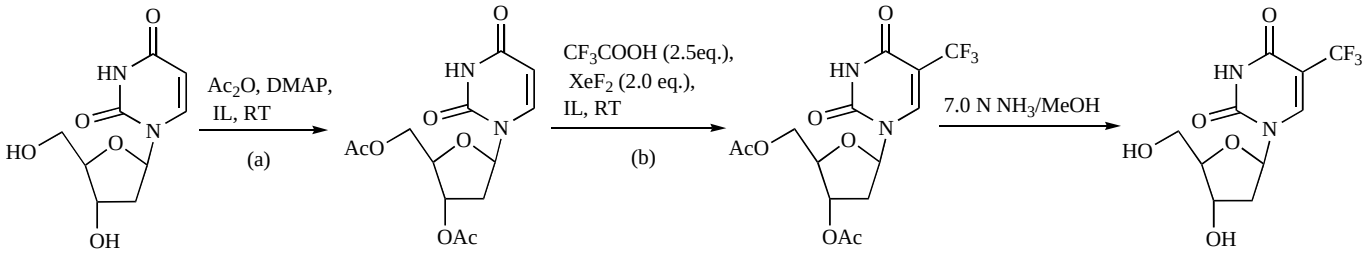
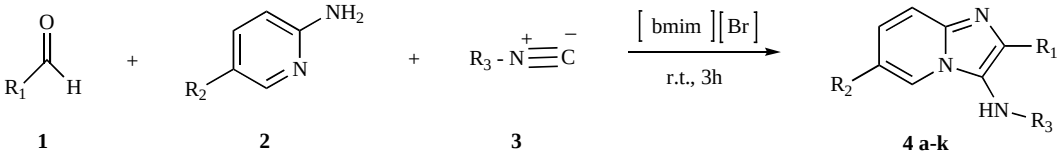



**1** **2** **3** **4**

| Solvents | Reaction (a) time (min.)/yield[1] (%) | Reaction (b) time (min.)/yield[1] (%) |
|---|---|---|
| [moemim][Ms] | 20/91 | 60/35 |
| [moemim][TFA] | 25/90 | 60/40 |
| [bmim][TFA] | 25/90 | 60/36 |

1) isolated yields

**Diagram 1.** Synthesis of TFT with the use of ionic liquids as the reaction medium [20].




**1** **2** **3** **4 a-k** 70-99%

| Entry | $R_1$ | $R_2$ | $R_3$ | Product | Yield (%) |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | Br | $C_6H_{11}$ | 4a | 98 |
| 2 | $C_6H_5$ | $CH_3$ | $C_6H_{11}$ | 4b | 98 |
| 3 | 4-$CH_3C_6H_4$ | $CH_3$ | $C_6H_{11}$ | 4c | 99 |
| 4 | 4-$ClC_6H_4$ | $CH_3$ | $C_6H_{11}$ | 4d | 92 |
| 5 | 3-$O_2NC_6H_4$ | $CH_3$ | $C_6H_{11}$ | 4e | 99 |
| 6 | 4-$C_5H_4N$ | $CH_3$ | $C_6H_{11}$ | 4f | 97 |
| 7 | $C_6H_5$ | $CH_3$ | $(CH_3)_3C$ | 4g | 99 |
| 8 | $C_6H_5$ | $CH_3$ | $(CH_3)_3C$ | 4h | 90 |
| 9 | 4-$CH_3C_6H_4$ | $CH_3$ | $(CH_3)_3C$ | 4i | 86 |
| 10 | $C_6H_5$ | $CH_3$ | 2,6-$(CH_3)_2C_6H_3$ | 4j | 72 |
| 11 | 4-$CH_3C_6H_4$ | $CH_3$ | 2,6-$(CH_3)_2C_6H_3$ | 4k | 70 |

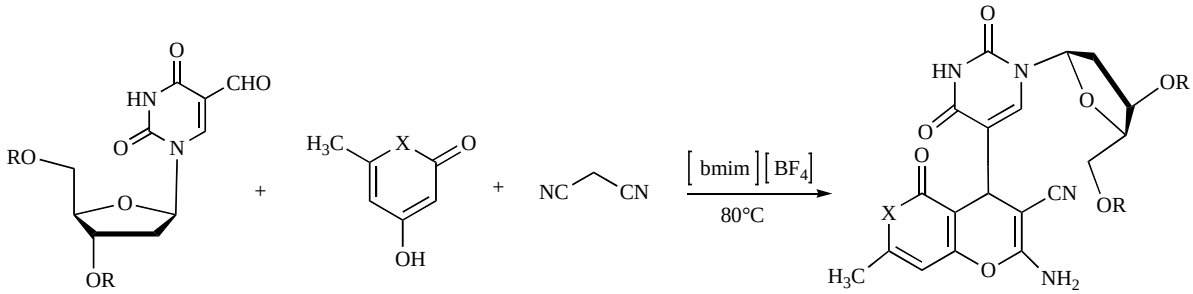
**Diagram 2.** Synthesis of 3-aminoimidazo[1,2-α]pyridines by three-component condensation with the use of [bmim][Br] as the reaction media [22].

alkanes, alkylated aromatic compounds and water. The successful use of [bmim] [$PF_6$] in liquid-liquid extraction of the antibiotic erythromycin-A and in *Rhodococcus* R312 catalysed biotransformation of 1,3-dicyanobenzene (1,3-DCB) in a liquid-liquid, two-phase system have been described [17]. The advantage of multiphasic behaviour of ILs over multiphase processes employing conventional mixtures has been demonstrated and the issues associated with the toxicity and flammability of other organic solvents emphasised. However, further research is required for a rational selection or design of ILs to improve their efficacy in particular transformation processes.

## ILs in the Synthesis of Antiviral, Antileishmanial and Antiparasitic Drugs

The search for novel antiviral nucleoside analogues has resulted in the design of ILs which provide high solubility to nucleosides and have been found to be an efficient reaction medium giving high yields under ambient conditions [18,19]. Syntheses of nucleoside-based antiviral drugs (Brivudine, Stavudine, Trifluridine) using such ionic liquids, as 1-methoxyethyl-3-methylimidazolium methanesulfonate ([moemim][Ms]), 1-methoxyethyl-3-methylimidazolium trifluoroacetate ([moemim][TFA]) and 1-butyl-3-methylimidazolium trifluoroacetate ([bmim][TFA]) as the reaction media have successfully been performed. For instance, selected ILs as reaction media for the synthesis of trifluridine (5-trifluoromethyl-2'-deoxyuridine, TFT) have given the final product in 90-91% yields as a single product with the reaction time in the range of 20-25 min (Diagram **1**) [20]. All the ILs made it possible to obtain TFT with high purity and a 10-fold decrease in solvent consumption compared to the standard reaction media, pyridine/DMAP or acetonitrile/$Et_3N$/DMAP.

Shaabani *et al.* [21,22] studied drugs based on acyclic nucleoside analogues, which have a potential antiviral activity and reported an efficient and 'environmentally friendly' approach for the synthesis of 3-amino-imidazo[1,2-α]pyridines with high antiviral activity using the 1-butyl-3-methylimidazolium bromide ([bmim][Br]) ionic liquid. Replacing the commonly used organic solvents by the readily available imidazolium bromide improves the synthesis of the side-chain-modified imidazo[1,2-α]pyridinic derivative. The derivative was synthesized by three-component condensation of an aldehyde **1**, 2-amino-5-methylpyridine or 2-amino-5-bromopyridine **2** and isocyanide **3** in ([bmim][Br]) at room temperature with very high yields in the range of 70–99% (Diagram **2**). In addition, the removal of [bmim][Br] from the reaction media

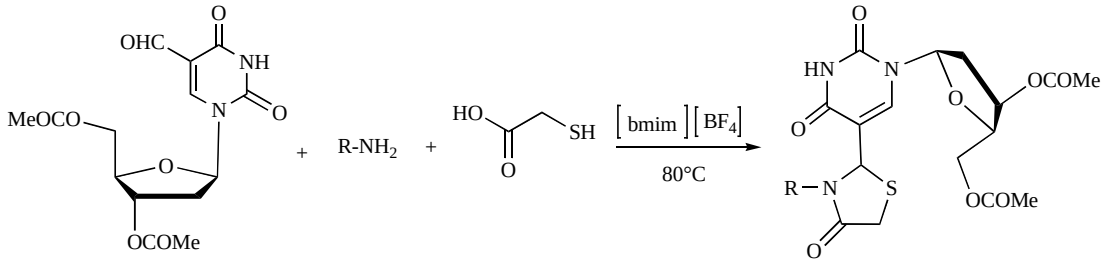



**1** **2** **3** **4**

| Entry | R | X | Product | Time (h) | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 | $COCH_3$ | N-$CH_3$ | 4a | 3 | 85 |
| 2 | $COCH_3$ | N-H | 4b | 3 | 80 |
| 3 | $COCH_3$ | N-$C_2H_5$ | 4c | 3 | 82 |
| 4 | $COCH_3$ | O | 4d | 4 | 79 |
| 5 | H | N-$CH_3$ | 4e | 2 | 86 |
| 6 | H | N-H | 4f | 3 | 82 |
| 7 | H | N-$C_2H_5$ | 4g | 3 | 80 |
| 8 | H | O | 4h | 4 | 78 |

a) isolated yields

**Diagram 3.** Synthesis of hybrids of pyrimidine nucleoside-pyrano[3,2-c]pyridone and pyrano[4,3-b]pyran. Reaction conditions: 1mmol of 1, 2, 3 and 1.5 g [bmim][$BF_4$], 80°C [23].




**1** **2** **3** **4**

| Entry | R | Product | Time (h) | Yielda (%) |
|---|---|---|---|---|
| 1 | Ph | 4a | 6 | 70 |
| 2 | p-$MeC_6H_4$ | 4b | 5 | 75 |
| 3 | p-$BrC_6H_4$ | 4c | 6 | 58 |
| 4 | p-$ClC_6H_4$ | 4d | 6 | 62 |
| 5 | p-$FC_6H_4$ | 4e | 6 | 65 |
| 6 | m-$NO_2C_6H_4$ | 4f | 6 | 60 |
| 7 | 2-$C_5H_4N$ | 4g | 8 | 53 |
| 8 | 6-Br-2-$C_5H_4$ | 4h | 8 | 50 |

a) isolated yields

**Diagram 4.** Synthesis of pyrimidine nucleoside-thiazolini-4-one hybrids using [bmim][$PF_6$] as the reaction medium. Reaction conditions: 1 mmol of 1, 2, 3 and 1.5 g of [bmim][$PF_6$], 80°C [24].

was possible by washing with water and evaporating the solvent under vacuum. Also, the advantage of ILs as reaction additives has been confirmed by the reaction of *p*-methylbenzaldehyde, 2-amino-5-methylpyridine and cyclohexyl isocyanide in the absence of [bmim][Br]. The yield of product was 25% at room temperature after 12 hours.

'Hybrids compounds' have also been applied in this drug class. Fan *et al.* [23] have developed a novel, green efficient synthesis of hybrid compounds: pyrimidine nucleosides combined with pyrano[3,2-c]pyridines and pyrimidine nucleosides combined with pyrano[4,3-c]pyranes, as potential antiviral and antileishmanial agents (Diagram **3**). As a reaction medium in this procedure, they used the IL [bmim][$BF_4$] without any catalyst, achieving high yields in compared to the methods reported in the literature and, additionally, the possibility of easy recovery and reuse of the solvent. A study investigating the use of 'hybrids compound' and ILs as reaction media has also been performed by Zhang *et al.* [24]. They reported a novel and efficient catalyst procedure that required

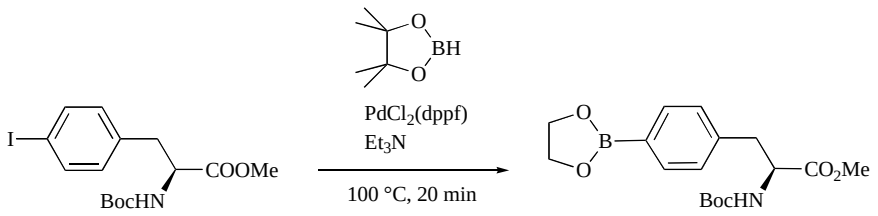
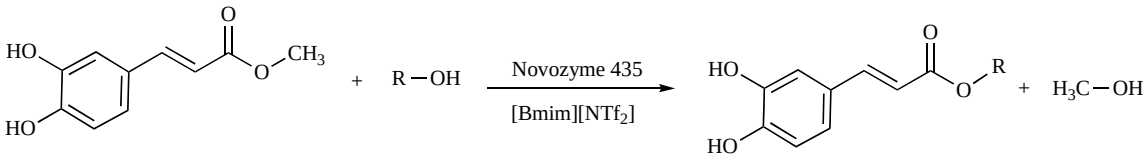



**Diagram 5.** Synthesis of *L*-BPA in imidazolium-type ILs [25].




| Compound | R | Conversion yields (%) |
|---|---|---|
| 1 | 2-cyclohexylethly | 97,6 |
| 2 | 3-cyclohexylpropyl | 93,8 |
| 3 | 4-phenylbutyl | 96,7 |
| 4 | 5-phenylpentyl | 84,0 |

**Diagram 6.** Production of CAPE analogues in the transesterification reaction of methyl caffeate with various alcohols using *Candida antarctica* lipase B (Novozyme 435) as the catalyst and [bmim][$NTf_2$] as the reaction medium [27].

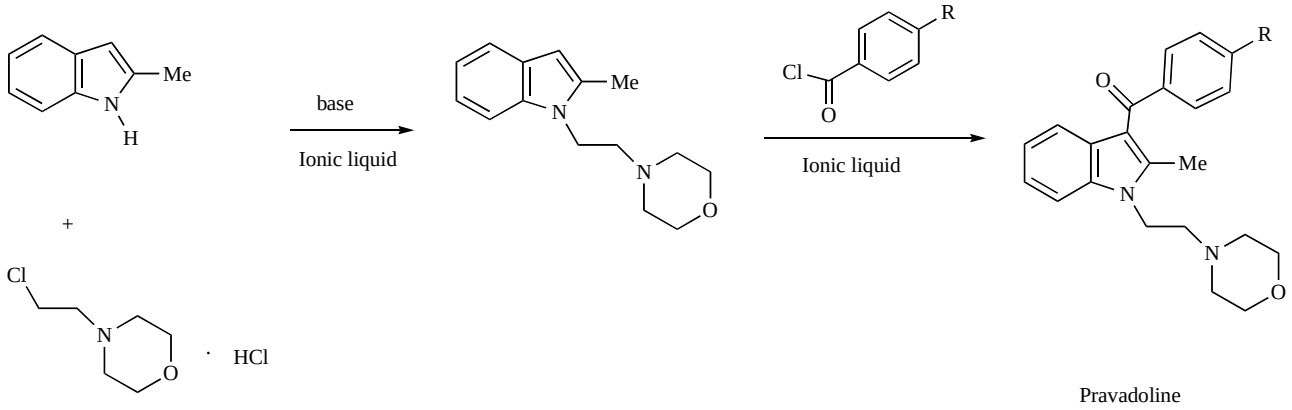



**Diagram 7.** Synthesis of pravadoline in [bmim][$PF_6$] with solid potassium hydroxide (as the base in 90-94% overall isolated yield [28]. (R = $OCH_3$)

no catalyst for the development of potentially antiparasitic drugs. They synthesised a series of pyrimidine nucleoside-thiazolini-4-one hybrids using 1-butyl-3-methyl-imidazolium hexafluorophosphate [bmim][$PF_6$] as the reaction medium (Diagram **4**). The procedure is simple and straightforward and makes it possible to avoid the use of volatile and poisonous conventional organic solvents.

## ILs in Synthesis of Anticancer Drugs

ILs have also been used in the synthesis of drugs with a promising antitumour potential. Zaidlewicz *et al.* [25,26] used ionic liquids [bmim][X] (bmim= 1–butyl-3-methylimidazole, X=$BF_4$, $PF_6$) in the synthesis of *L*-4-boronophenylalanine (*L*-BPA), a clinically approved drug in boron neutron capture therapy (BNCT) (Diagram **5**). BNCT is based on boron-containing compounds that target tumour tissue using a suitable boron carrier. Cross-coupling with pinacolborane with the use of protected *p*-iodophenylalanine was performed in an $BF_4$ ionic liquid as part of the search for new alternative protocols of efficient synthesis of boron compounds that might offer therapeutic advantage. The use of "non-volatile" solvents enabled the synthesis of BPA and its analogues with a good yield (82–89%) after 20 min.

There is also a report of another synthesis of compounds with antitumor activities that used ILs as the reaction medium. Kurata *et al.* [27] developed a novel, efficient biocatalytic procedure providing various caffeic acid phenethyl ester (CAPE) analogues exerting potential antiproliferative effects on human tumour cells by using *Candida antarctica* lipase B (Novozyme 435) in 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([bmim][$NTf_2$]) as the solvent (Diagram **6**). A comparable conversion yield was obtained for CAPE analogues produced with the use of ([bmim][$NTf_2$]) and CAPE synthesised in isooctane (yield of 91,65%).

## ILs in the Synthesis of Non-steroidal Anti-inflammatory Drugs (NSAIDs)

The application of ILs offers an alternative in the synthesis of all the conventional non-steroidal anti-inflammatory drugs (NSAIDs). The synthesis of pravadoline has already been per-

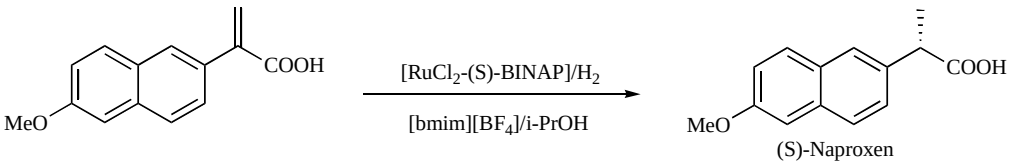
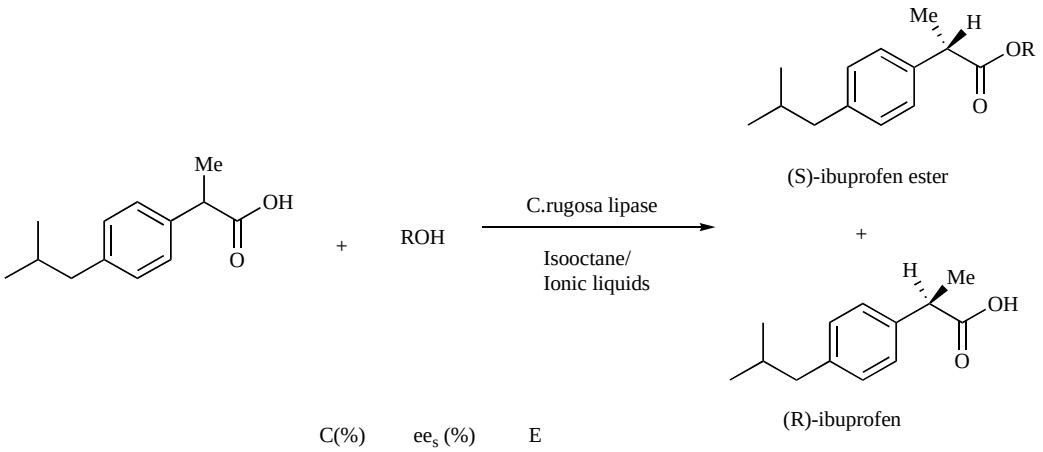



**Diagram 8.** Hydrogenation of 2-arylacrylic acid. Reaction conditions: 75atm., RT, 20h; Enantiomeric excess of (S)-Naproxen equal 80% [29].




| | C(%) | $ee_s$ (%) | E |
|---|---|---|---|
| Isooctane | 29 | 33 | 13.0 |
| [bmim][$PF_6$] | 30 | 38 | 24.1 |

**Diagram 9.** Kinetic resolution of (R,S)-ibuprofen with an enzyme. Experimental results for 24h (conversion (c), enantiomeric excess of the remaining substrat ($ee_S$), enantioselectivity (E)) [31].

formed in an ionic liquid by combined Friedel-Crafts reaction and nucleophilic displacement reaction (Diagram **7**). Numerous imidazolium-based ILs have been tested to improve the efficiency of the reaction. The best yield (99%) of alkylation of 2-methylindole with 1-(*N*-morpholino)-2-chloroethane has been achieved in 1-butyl-2,3-dimethylimidazolium hexafluorophosphate ([bmim][$PF_6$]), while the best yield of Friedel-Crafts acylation of the product from the nucleophilic displacement reaction has been obtained in [bmim][$PF_6$] at 150˚C. It is interesting to note that no catalyst or strictly anhydrous conditions are required when using the ILs as the reaction media [16, 28].

The synthesis of another NSAID, (*S*)-naproxen, can be performed in the presence of *in situ* or performed Ru-BINAP catalyst precursors immobilised in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate IL phase with similar optical yields in comparison with the homogeneous reaction (Diagram **8**). One of the advantages of the ILs involves the possibility of using and recycling a homogenous transition-metal catalyst without significant changes in activity or selectivity [29]. A further study on optimisation and extension to other chiral pharmaceutical compounds is ongoing [16].

Ibuprofen, commercially available as a racemate, is one of the most popular NSAIDs. However, the (*S*)-(+)-enantiomer has been proved to be 160 times more active than the *(R)*-(–)-enantiomer [30]. Numerous alternative biosyntheses with the use of ILs have therefore been designed to obtain a more enantioselective product compared to the conventional solvent systems.

*Candida rugosa* lipase was shown to posses a comparable or higher activity and enantioselectivity in some ILs compared to those in isooctane (Diagram **9**) [31]. It was concluded that [bmim][$PF_6$] could be applied to substitute the conventional organic solvent. Contesini *et al*. [32] described the effect of commercially available lipases and two native lipases from *Aspergillus niger* and *Aspergillus terrus* on the kinetic resolution of (*R,S*)-ibuprofen in systems containing [bmim][$PF_6$] and [bmim][$BF_4$]. The results indicated that the commercial *Candida rugosa* and native *Aspergillus niger* lipases exhibited the highest enantioselectivity and esterification activity in a two-phase system containing isooctane and [bmim][$PF_6$] (1:1) compared with a system in pure isooctane.

### ILs in the Synthesis of Antidepressant Drugs

(*S*)-3-chloro-1-phenyl-1-propanone ((*S*)-CPPO) obtained from enantiopure (*S*)-3-chloro-1-phenyl-1-propanol (3-CPP), is often used as a substrate in the synthesis of the most popular drugs employed in the treatment of depressive disorders (fluoxetine, atomoxetine) (Fig. **2**). Enantioselective enzymatic reduction using a variety of reductases and dehydrogenases enables asymmetric synthesis of pure chiral compounds. However, the problem in this system is the low solubility of 3-CPP in the aqueous phase resulting in a low yield of (*S*)-CPPO.

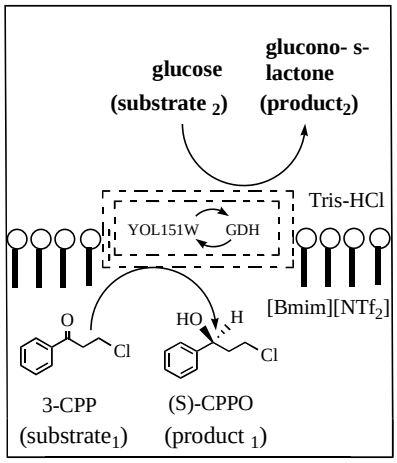



**Fig. (2).** A model of a biphasic reaction system used in the manufacture of (*S*)-CPPO. Enantiomeric excess of product ($ee_P$) >99% [33].

The entire cell-ionic liquid biphasic system enables the synthesis of water-insoluble chiral compounds. A system based on recombinant *Escherichia coli* cells co-expressing reductase and glucose dehydrogenase in a biphasic medium was used for the synthesis of (*S*)-CPPO. A variety of ILs were tested in aqueous two-phase systems to increase the solubility of 3-CPP. Finally, ([bmim][$NTf_2$]) was selected as the optimal modifier which dramatically increased the concentration of the substrate and the yield of the target compound ((*S*)-CPPO) with an enantiomeric excess of >99% [33].

## 3. CONCLUSIONS

In recent years, ILs have become 'green alternatives' of the volatile organic solvents. Because of their properties ILs have a great potential as reaction media in a wide range of biocatalytic and conventional syntheses. The reaction yields with the use of ILs are generally comparable or higher than those obtained in conventional organic solvents. Sometimes the use of ILs as a component of a multiphasic system makes it possible for a reaction to occur that would not have occurred in the absence of the ILs in a conventional reaction environment. Also, thermal stability in mono- and multiphase IL based systems and regio- or enantioselectivities have been observed [11]. Additionally, products and by-products can be separated from such liquids by distillation or solvent extraction with either an aqueous or an organic phase [28]. Furthermore, the use of ILs leads to a cost reduction because these solvents can often be recycled and reused [15].

The rapid growth of interest in the application of ILs in most areas of chemistry is reasonable in view of their unique properties. The use of ILs as 'green chemistry' instead of the conventional environmentally harmful agents offers new opportunities to solve the problems of difficult chemical synthesis of different substances. These solvents are currently employed in laboratory-scale pharmaceutical synthesis. Only time will show the real potential of ILs. Further research will definitely be required to verify the feasibility of developing the laboratory procedures in the pharmaceutical industry.

## ACKNOWLEDGEMENT

None declared.

## CONFLICT OF INTEREST

None declared.

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