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PERSPECTIVE

Perspectives on the replacement of harmful organic solvents in analytical methodologies: A framework toward the implementation of a novel generation of eco-friendly alternatives

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Volatile organic solvents derived from non-renewable fossil feedstocks are commonplace in analytical laboratories. In spite of their convenient performance in countless unit operations, their environmental, health and safety issues represent a major area of concern. The progressive replacement of organic solvents obtained from fossil resources by eco-friendly alternatives would involve remarkable advances within the framework of green analytical chemistry, while avoiding future uncertainties regarding forthcoming regulations. This perspective tackles the problem of organic solvent use in analytical methodologies, providing relevant information for solvent selection and identifying a range of solvents derived from natural and/or renewable resources, namely bio-based molecular solvents, ionic liquids composed wholly of biomaterials, and natural deep eutectic mixtures, that could potentially be exploited toward advanced, more benign, analytical methodologies. In addition, physicochemical properties are provided, and a number of challenging aspects to be considered on the implementation of eco-friendly alternatives are evaluated.

Introduction

Millions of litres of organic solvents are used each year in analytical laboratories, which poses potential risk to human health and significantly contribute to the generation of hazardous wastes, constituting an important source of volatile organic compounds (VOCs) emission.[1] The solvent consumption depends to a high extent on a set of parameters, namely the type and concentration levels of the analytes to be determined, the sample composition, the sample preparation technique (whenever required) and the analytical instrumentation employed. A rapid glance over recommended methods of analysis shows that several environmentally unfriendly organic solvents are frequently required in the determination of a wide range of target compounds. Some examples are summarized on **Table 1**. This has been precisely pinpointed by Anastas, who considers that "it is an unfortunate irony that environmental analytical methods often contribute to further environmental problems through the chemicals used in the analysis".[2] In this regard, the use of harmful solvents in analytical methodologies can represent an issue of environmental, health and safety concern.

The search for safer solvents is identified as a clear priority toward sustainable chemical processes. In fact, several principles of green chemistry[3–6] and green analytical chemistry[7–9] (**Figure 1)** directly or indirectly refer to this problematic issue. Thus, the 5th principle of green chemistry specifically refers to the removal of solvents from chemical laboratories whenever possible or their replacement by safer alternatives. In addition, other green chemistry principles can also be of relevance when considering solvents, such as waste prevention (1st), use and generation of substances that possess little or no toxicity (3rd), design of safer, non-persistent and biodegradable chemicals (4th and 10th), use of innocuous auxiliary substances and renewable feedstocks (5th and 7th), and inherently safer chemistry for accident prevention (12th).

A large variety of solvents, mainly derived from fossil fuels, are routinely used in different steps of the analytical process. Preparation of solutions, extraction and enrichment of target compounds, sample clean up, solvent exchange, sample preservation, dilution, glassware cleaning, liquid desorption, derivatisation, and analytical separation and detection are among the operations in which solvents are exploited in analytical chemistry. A progressive replacement of petroleum-based solvents by efficient and more sustainable alternatives would importantly reduce the current dependence on conventional organic solvents in analytical laboratories.

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Table 1 Solvents used in some approved analytical methodologies

Method ID	Solvents[a]	Sample preparation	Analytical technique	Target analytes	Samples
EPA Method 550	acetonitrile and methylene chloride	LLE	HPLC-UV/FLD	PAHs	drinking water
EPA Method 550.1	acetonitrile, methanol and methylene chloride	SPE	HPLC-UV/FLD	PAHs	drinking water
EPA Method 1668A	acetone, cyclohexane, hexane, isooctane, methanol, methylene chloride, nonane and toluene	SPE/LLE/CLLE/Soxhlet extraction	GC-MS	chlorinated biphenyl congeners	water, soil, sediment and tissue
EPA Method 1698	acetone, hexane, methanol, methylene chloride, pyridine and toluene	LLE/CLLE/Soxhlet extraction-clean up-derivatisation	GC-MS	steroids and hormones	water, soil, sediment and bio-solids
EPA Method 8032A	acetone, benzene, ethyl acetate, ethyl ether, methanol and methylene chloride	derivatisation-LLE-clean up	GC-ECD	acrylamide	water
EPA Method 8141B	acetone, acetonitrile, cyclohexane, ethyl acetate, hexane, isooctane, isopropanol, methanol, methyl tert-butyl-ether, methylene chloride, isopropanol, tetrahydrofuran and toluene	LLE/CLLE/SPE/Soxhlet extraction/PLE/MAE/UAE-clean up	GC-FPD/NPD	organophosphorus compounds	liquid and solid samples
APPA/AWWA /WEF 4500	benzene, glycerol, isobutanol and methanol	LLE	UV-vis	phosphorus	water
APPA/AWWA /WEF 5530	chloroform or methylene chloride	LLE	UV-vis	phenols	water
APPA/AWWA /WEF 5540	benzene, chloroform and methanol	LLE	UV-vis	anionic surfactants	water
APPA/AWWA /WEF 3110	methyl isobutyl ketone	LLE	FAAS	metals	water

[a] Note that not all the solvents listed may be needed for a single analysis as the list includes all the solvents required to carry out the different sample preparation techniques.

CLLE, continuous liquid-liquid extraction; ECD, electron capture detection; FLD, fluorescence detection; FAAS, flame atomic absorption spectrometry; FPD, flame photometric detection; GC, gas chromatography; HPLC, high performance liquid chromatography; LLE, liquid-liquid extraction; MAE, microwave-assisted extraction; MS, mass spectrometry; NPD, nitrogen-phosphorus detection; PAHs, polyaromatic hydrocarbons; PLE, pressurised liquid extraction; SPE, solid-phase extraction; UAE, ultrasound-assisted extraction; UV, ultraviolet detection

Francisco Pena-Pereira (born 1981) received his PhD (2009) in Chemistry from the University of Vigo (Spain). He then joined the Centre for Environmental and Marine Studies (CESAM) & University of Aveiro (Portugal) as a post-doctoral fellow (2011–2013). At present, he is focused on the development and application of environmentally sustainable analytical methodologies at the Gdańsk University of Technology (Poland).

Adam Kloskowski (born 1974) graduated from the Gdańsk University of Technology with an MSc in Chemical Technology in 2000. In 2002 obtained licentiate degree at Royal University of Technology (KTH) in Stockholm. He obtained his PhD in 2005. His major research interests include the development of new analytical procedures for determining polar organic compounds in various matrixes, electroanalytical methods as well as physicochemical properties of ionic liquids.

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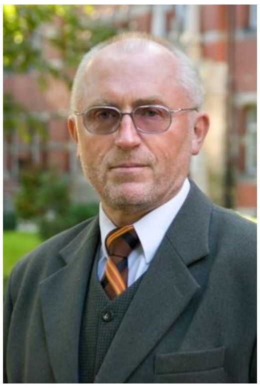
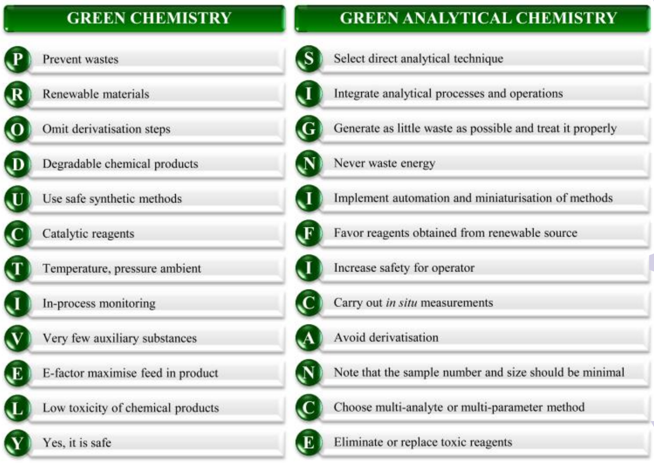
Regarding the use of organic solvents in the analytical process, sample preparation and analytical separation are of special importance due to the type and volumes of solvents used, which highly contribute to the generation of hazardous waste. Sample preparation is commonly the most polluting step of the analytical process. Conventional sample preparation techniques such as liquid-liquid extraction, Soxhlet extraction, accelerated solvent extraction and solid-phase extraction, among others, involve the use of significant volumes of volatile organic solvents. The introduction of solvent-free sample preparation techniques is a key step toward greener analytical methodologies. The well-established solid-phase microextraction, introduced by Pawliszyn and co-workers in the early 1990's,[10] represents a paradigmatic example of solventless enrichment technique, especially when combined with thermal desorption. Some other sample preparation approaches can be operated without making use of solvents, including open tubular traps,[11] needle trap devices,[12,13] inside needle capillary adsorption trap,[14,15] solid phase dynamic extraction[16] and single- and multi-bed adsorption systems, or with minimum solvent consumption, such as liquid-phase microextraction approaches.[17] However, the full phase-out of solvents is not always feasible and solvent reduction and replacement represents the 'least bad' approach in these cases. Moreover, solvents can also be needed even with essentially solvent-free techniques to improve the extraction efficiency (as modifiers), as well as to carry out derivatisation and/or liquid desorption.



Jacek Namieśnik (born 1949) obtained his PhD in 1978 and has been a professor since 1996. He was Dean of the Chemical Faculty, Gdańsk University of Technology, from 1996 to 2002 and since 2005 has been Head of the Department of Analytical Chemistry. He has also been Chairman of the Committee on Analytical Chemistry, Polish Academy of Sciences (PAS), since 2007. His major research interests include the development of new analytical procedures, the design and testing of customized analytical units and measuring devices, and the production of new types of matrix-free reference materials.

The use of large volumes of harmful solvents in analytical separations is also a matter of concern, especially in the case of liquid chromatography. It has been estimated that a continuously operated analytical liquid chromatograph would result in an annual waste generation of around 500 litres working under typical conditions.[18] Keeping in mind that the number of liquid chromatographs used in analytical laboratories worldwide is about 300000,[19] the real magnitude of using harmful solvents in liquid chromatography is considerable. Several strategies have been developed and reviewed, which address novel technologies devoted to carry out efficient separations with reduced organic solvent consumption and subsequent waste generation.[18,20,21]



GREEN CHEMISTRY	GREEN ANALYTICAL CHEMISTRY
P Prevent wastes	**S** Select direct analytical technique
R Renewable materials	**I** Integrate analytical processes and operations
O Omit derivatisation steps	**G** Generate as little waste as possible and treat it properly
D Degradable chemical products	**N** Never waste energy
U Use safe synthetic methods	**I** Implement automation and miniaturisation of methods
C Catalytic reagents	**F** Favor reagents obtained from renewable source
T Temperature, pressure ambient	**I** Increase safety for operator
I In-process monitoring	**C** Carry out *in situ* measurements
V Very few auxiliary substances	**A** Avoid derivatisation
E E-factor maximise feed in product	**N** Note that the sample number and size should be minimal
L Low toxicity of chemical products	**C** Choose multi-analyte or multi-parameter method
Y Yes, it is safe	**E** Eliminate or replace toxic reagents

Fig. 1 Twelve principles of green chemistry and green analytical chemistry expressed as the mnemonics PRODUCTIVELY[155] and SIGNIFICANCE,[9] respectively.

The term 'green solvent' has been referred to those solvents that enable minimizing the environmental impact that results from their use in chemical processes.[22] Apart from their direct impact on the environment, some other aspects are assessed to consider a solvent as green, namely, health and safety issues, but also indirect impacts derived from their production, use and disposal including, for instance, depletion of non-renewable sources, potential solvent recycling and energy consumption in their synthesis, recycling and waste treatment.[23] In this respect, it is striking that a wide number of publications devoted to the development of analytical methods includes the term 'green solvent' even when the evaluated solvents show certain important issues.

Two natural and renewable solvents are well established in analytical laboratories, namely water and carbon dioxide. Water is undoubtedly the most widely used solvent in every single step of the analytical process. Remarkably, the tunability of the physicochemical properties of water with temperature and pressure has expanded even more the applications of water in analytical chemistry, for example in subcritical extraction processes of less polar compounds[24] or as mobile phase in superheated water chromatography.[25] On the other hand, carbon dioxide is commonly used under supercritical conditions in extraction and separation processes.[26,27] The convenience of using carbon dioxide as supercritical fluid lies in its economy, environmental friendliness and advantageous supercritical temperature and pressure conditions (31 °C and 73.8 bar) when compared with alternative solvents.[28] Several comprehensive reviews can be consulted for detailed information regarding the use of water[29–32] and carbon dioxide[32–36] in analytical methodologies. In our paper, however, we would like to explore and discuss other recent eco-friendly solvents.

The development of novel solvents with advantageous physicochemical properties and minimal environmental and toxicological risks represents a challenging and exciting area of research. Specifically, the search of alternatives to solvents derived from non-renewable fossil resources represents an area of particular promise.[37–41] In this sense, it is encouraging to see the many efforts made in different scientific and technological fields for solvent replacement. For example, a recent European Cost Action has been focused on the scientific and technological transition from a fossil resources-based to a sustainable bio-based economy.[42] Many recent publications highlight the benefits of using solvents derived from natural and/or renewable resources. However, in spite of the increasing number of alternatives to conventional solvents, it is apparent that only a limited number have been evaluated in analytical chemistry.

The goal of this perspective is to address the problematic of harmful organic solvent usage in analytical laboratories and provide a framework for their replacement by safer alternative solvents. Possible ways of addressing this issue will be outlined, including the evaluation of appropriate alternatives *via* solvent selection guides and, as an advanced approach, the use of a novel generation of solvents derived from natural and/or renewable resources. Challenges and opportunities that could arise as a result of their implementation in analytical methods will also be identified and discussed.

Issues and restrictions on the use of conventional solvents in analytical laboratories

According to recent estimations, the worldwide solvent consumption approaches 30 million metric tons per year, and this value is expected to increase over the subsequent years.[43] Admittedly, solvent consumption in analytical laboratories represents a small fraction of the total, but their impact should not be considered negligible. In fact, organic solvents are used in a wide variety of unit steps of the analytical process, even though a significant number of them are considered hazardous air pollutants, and/or carcinogenic/mutagenic/reprotoxic substances.

Several solvents typically used in analytical laboratories have been included in the substance priority list elaborated by the Agency for Toxic Substances & Disease Registry (ASTDR) on the basis of their frequency on the National Priorities List (USA), toxicity and potential for human exposure.[44] **Figure 2** shows the rank position trends observed in this list over a 20 year-period for commonplace solvents. The US Environmental Protection Agency (EPA) 33/50 Program, aimed at reducing releases and transfers of chemicals of special environmental concern, targeted 11 solvents among the 17 priority chemicals.[45] Specifically, benzene, carbon tetrachloride, chloroform, dichloromethane, methyl ethyl ketone, methyl isobutyl ketone, tetrachloroethylene, toluene, 1,1,1-trichloroethane, trichloroethylene and xylenes were identified as target organic chemicals. On the other hand, a number of common organic solvents have been identified in the European candidate list of substances of very high concern,[46] and included on the list of priority substances and other certain pollutants by the European Commission,[47] respectively. Besides, indicative occupational exposure limit values have been established for the protection of the health and safety of workers exposed to hazardous substances at work. The European Union has also established, in 2006, a regulation concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) toward sustainable development, which pursues the production and use of chemicals that lead to the minimisation of significant adverse effects on human health and the environment by 2020.[48] Remarkably, the replacement of substances of high concern by safer substances or technologies has been identified as an important specific objective of this Regulation. This legislative initiative is aimed to contribute to fulfilment of the Strategic Approach to International Chemical Management (SAICM) adopted in Dubai in 2006.[49]

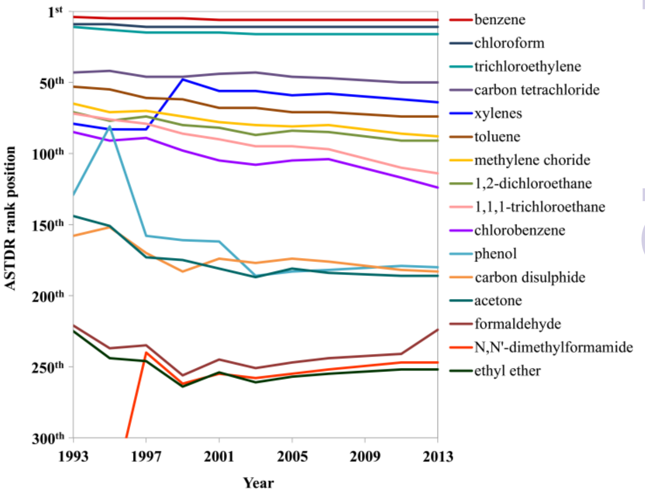


Fig. 2 Rank position trends observed in the ATSDR Substance Priority List for organic solvents commonly used in analytical methodologies.

A crucial event aimed at reducing the production and usage of ozone depleting substances was the Montreal Protocol on Substances that Deplete the Ozone Layer, which was agreed on 1987 and entered into force on 1989.[50] The list of controlled substances included organic solvents typically used in analytical laboratories, such as carbon tetrachloride, 1,1,1-trichloroethane and 1,1,2-trichloro-1,2,2-trifluoroethane (Freon 113). In spite of the restrictions initially established by the Montreal Protocol and the uncertainty that surrounded analytical laboratories before their implementation,[51–54] a global exemption for laboratory and analytical purposes was approved in 1997, which has been extended in successive years in the Meetings of the Parties to the Montreal Protocol. Although certain uses have been excluded from the global exemption for laboratory and analytical uses, the search for alternatives has not been as intense as could be expected almost two decades ago due to the expected phase out of chlorinated solvents. In fact, the relaxation of the regulatory restrictions has presumably contributed to the slower rate of adaptation of analytical methods by replacement of ozone depleting substances.

Nevertheless, advances have been made in the area toward greener analytical methodologies by replacing conventional techniques with greener ones, solvent reduction and/or replacement of troublesome solvents in accordance with green analytical chemistry recommendations.[8,9,55,56] In addition, evaluation tools such as the National Environmental Methods Index (NEMI),[55] the analytical eco-scale,[56] and self-organizing maps[57] have been proposed for assessing the greenness of analytical methodologies. The usage of certain organic solvents with important issues, however, has not been discontinued in analytical laboratories as would be expected and desirable, being even recurring solvents in certain modern sample preparation techniques.[58,59] The search for benign solvents, which is a highly active area of cutting-edge research, and their implementation in analytical methodologies, thus represent an area of special importance for further advances in green analytical chemistry.

Solvent selection guides: Helpful tools toward greener analytical methodologies

Solvent selection guides have been firstly introduced in the late 1990's with the aim of providing a highly relevant information and recommendations for the selection of greener solvents for chemical and engineering activities.[60] The development of these guides was initially based on the assessment of environmental waste, environmental impact, health and safety issues, and subsequently improved by substituting the general safety area with the reactivity and stability, and flammability and explosion areas,[61] and including the life cycle profile of solvents.[22,62] The latter one describes indirect environmental impacts over the full life cycle of a solvent, namely production, use, recycling and disposal.

The number of solvents evaluated has been increased from 35 in the first generation of the GlaxoSmithKline (GSK) solvent selection guide[60] to 110 in 2011,[61] and its updates with additional solvents are expected in a near future. Other pharmaceutical members of the American Chemical Society's Green Chemistry Institute such as Pfizer[63] and Astra Zeneca[64] have also developed solvent selection guides and, more recently, Sanofi developed a solvent selection guide devoted to scaling-up chemical processes.[65] Sanofi's guide included 96 commonly used solvents, which were evaluated and classified into four categories, namely recommended solvent, substitution advisable, substitution requested and banned solvent. The guide provided a complete ID card for each solvent in which the overall ranking, health, safety and environmental hazards, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) limits, cost, physical properties and substitution advice are all included. A comparison of the available guides has been recently published, showing an acceptable level of agreement in general, although a significant number of solvents (33%) could not be unequivocally classified within a single ranking category.[66] The overall ranking of conventional solvents obtained by comparison of the different solvent selection guides is provided in **Figure 3**. It is worth mentioning that these guides are not comprehensive but limited to organic solvents (also those which are derived from non-renewable resources), and the ranking green properties of the evaluated solvents is relative. Selection of a given solvent for analytical purposes should be made by considering both the required physicochemical properties for a specific task and the specific issues of solvents. Otherwise, when just the overall average score is used, serious issues could go unnoticed. Furthermore, certain parameters evaluated in the guides could be of less relevance or applicability in analytical laboratories depending on the specific purpose. In addition, the assumptions made to evaluate the life cycle of solvents in a chemical industry could be far from being representative in analytical laboratories.[67] Nevertheless, solvent selection guides allow the selection of better alternatives to highly hazardous solvents, and can be therefore considered valuable tools for the replacement of VOCs in different steps of the analytical process.

Alternative solvents derived from natural and/or renewable resources

The development of novel solvents from natural and/or renewable sources involves a challenging and ambitious strategy that pursues reducing the environmental, health and safety impact of organic solvents, providing new routes in different scientific and technological areas. The term "natural" is referred to resources existing in or caused by nature, whereas "renewable" refers to those resources capable of being renewed, and thus, theoretically inexhaustible. Keeping in mind the key role of solvents in analytical chemistry, the substitution of conventional solvents of environmental, health and safety concern used in analytical methodologies by alternatives obtained from natural and/or renewable feedstock have remarkable promise for developing sustainable analytical methods. Physicochemical properties of the solvents described below are shown on Tables 2-4.

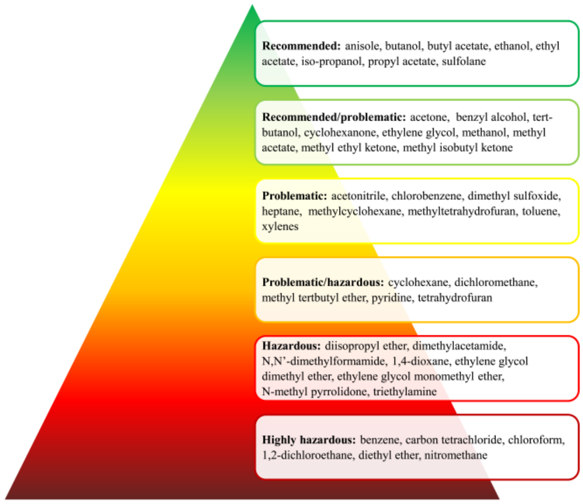


Fig. 3 Overall ranking of conventional solvents according to solvent selection guides.[66]

Bio-based molecular solvents

Production of chemicals derived from low value and widely available biomass feedstocks by means of low environmental impact chemical processes would enormously contribute to sustainability.[38,68,69] Several bio-based platform molecules, *i.e.*, base chemicals readily available from a renewable feedstock that can be chemically converted into value-added compounds, have been used in the preparation of bio-based molecular solvents, including lactic acid, levulinic acid, glycerol, sorbitol, furfural, 5-hydroxymethylfurfural, and γ-valerolactone. **Figure 4** shows some processing options reported in the literature to obtain bio-based solvent molecules. It should be noted that some of the platform molecules can also be used as solvents themselves. For example, glycerol has been applied as a green solvent and as precursor of valuable compounds, several of which have interesting properties for their use as solvents, including glycerol esters, and a large variety of alkyl glycerol alcohols and ethers,[70,71] which exhibit a rich structural diversity reflected in significant differences in polarity and up to three orders of magnitude lower viscosity than glycerol.[71] The remarkable increased interest in biodiesel fuel production, process in which glycerol is formed as by-product (10% in weight), has generated a large surplus of glycerol, so its application as both solvent and platform molecule can contribute to reduce the problem of waste glycerol generated in the biodiesel industry.[72,73] In fact, the worldwide glycerol production has recently surpassed 2 million metric tons, from which biodiesel production contributes two thirds of the total.[74] Another example of a platform chemical with promising solvent properties is γ-valerolactone, a colourless, biodegradable compound that occurs naturally in fruits and is used as food additive. It can be obtained from lignocellulosic biomass by hydrogenation of levulinic acid or ethyl levulinate.[75] Remarkably, non-dangerous, biodegradable intermediates such as glucose, levulinic acid, 5-hydroxymethylfurfural, or formic acid are mainly obtained in the synthesis of γ-valerolactone when starting from cellulose. γ-valerolactone is completely soluble in water, and has a high boiling point and low vapour pressure.

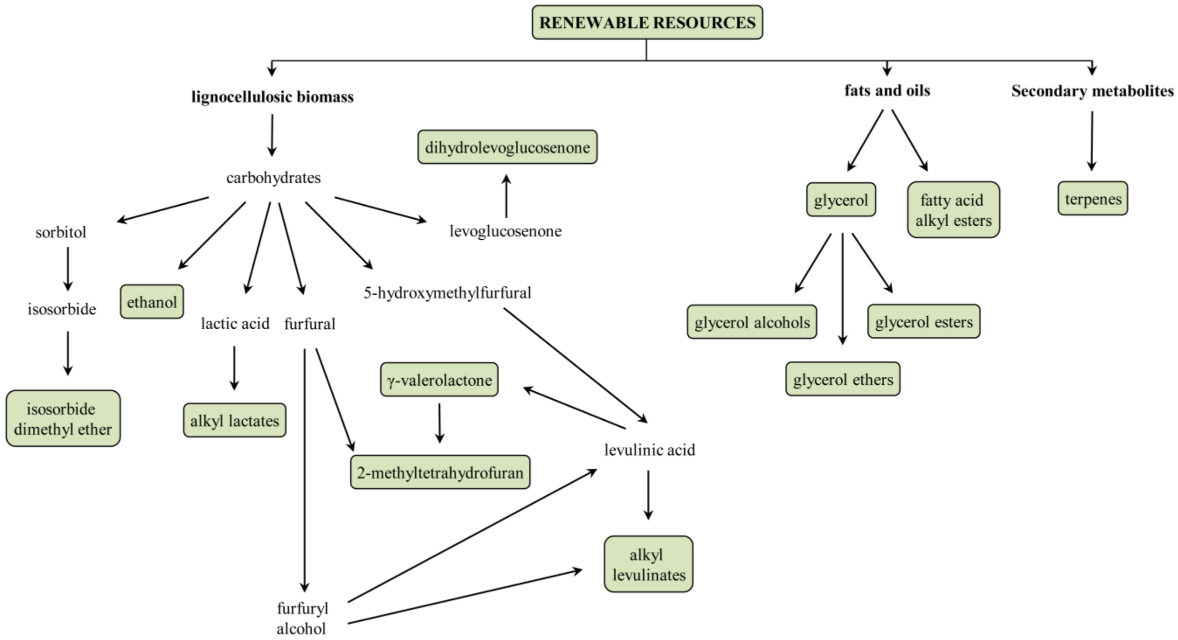


Fig. 4 Conversion of renewable resources into valuable bio-based molecular solvents.

In addition, certain compounds are naturally produced in high amounts and can be obtained by extraction and fractionation processes without further conversions. A variety of terpenes, which are diverse plant secondary metabolites derived from isoprene units, can be obtained in this way. For example, (R)-(+)-limonene, can be obtained from orange juicing wastes by steam distillation, supercritical fluid extraction or microwave assisted extraction. This represents an important application for the valorisation of this waste resource, which reaches 20 million metric tons per year.[76,77]

Valuable chemicals with promising properties as solvents can be obtained from a wide range of renewable starting compounds. In this sense, several alcohols,[74,78] ethers,[74,79,80] esters,[74,81–84] ketones,[85] and terpenes[86–88] derived from renewable feedstocks have been proposed as greener alternatives to harmful organic solvents, and recent works have demonstrated the potential of some bio-based solvents for their use in the analytical field.[89–91] The state of the art in this challenging area has been reviewed in detail,[23,69,92] so interested readers are referred to these publications for further information. The physicochemical properties of bio based solvents shown in **Figure 5** are summarized in **Table 2**.

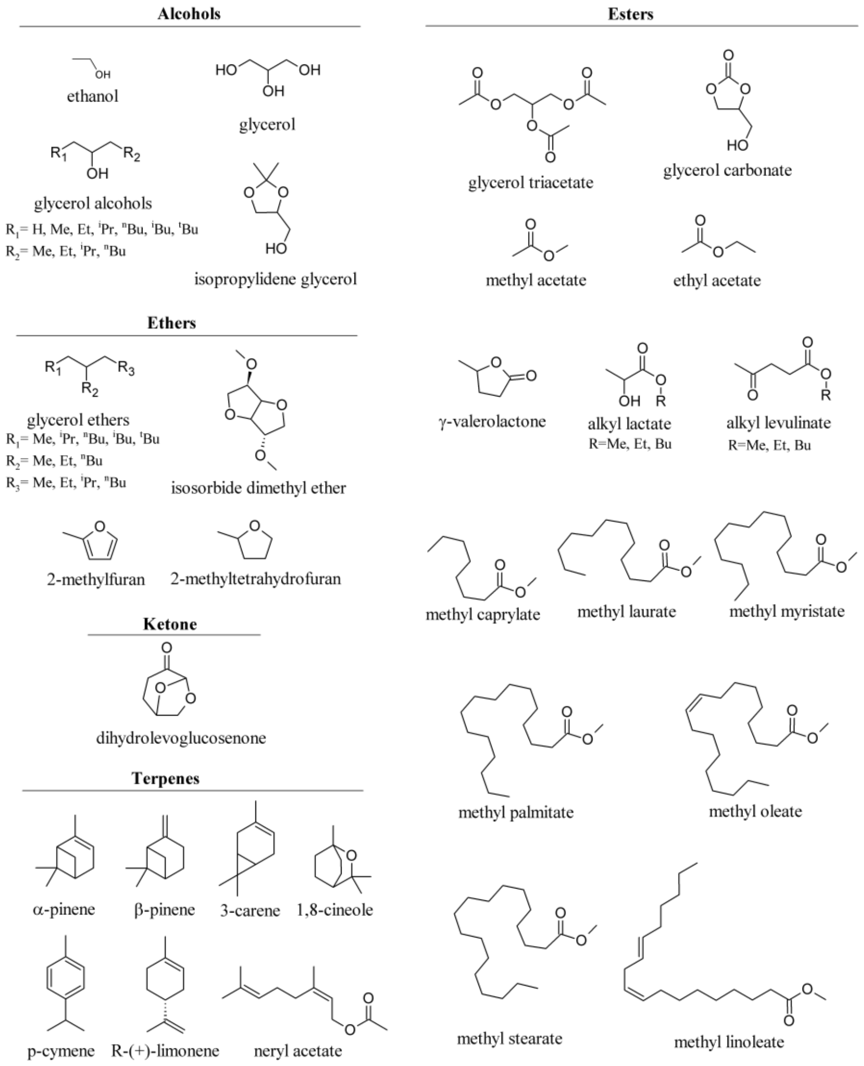


Fig. 5 Chemical structures of selected molecular solvents derived from renewable resources.

Table 2 Physicochemical properties and solvatochromic parameters of selected bio-based solvents[a]

Solvent	Boiling point (°C)	Melting point (°C)	Density (g cm^{-3})	Viscosity (cP)	Log P[b]	Kamlet-Taft parameters			Refs.
						α	β	π*	
ethanol	78	-114	0.79	1.1	-0.19	0.96	0.83	0.51	156
1,3-di-iso-propoxy-2-propanol	202		0.9		0.86				71
1,3-dimethoxypropan-2-ol	170		1.01 (20 °C)	3.4 (20 °C)	-0.59	0.72		0.73	71
1,3-di-n-butoxy-2-propanol	248		0.91 (20 °C)	5.5 (20 °C)	2.07	0.10		1.09	71
1-ethoxy-3-iso-propoxy-2-propanol	187		0.93 (20 °C)		1.42	0.36		0.75	71
1-iso-butoxy-3-ethoxy-2-propanol	214		0.91 (20 °C)		0.95	0.40		0.71	71
1-iso-butoxy-3-iso-propoxy-2-propanol	215		0.92		1.33	0.47		0.57	71
1-iso-butoxy-3-methoxy-2-propanol	200		0.93 (20 °C)		0.60	0.55		0.62	71
1-methoxy-3-(propan-2-yloxy)propan-2-ol	188		0.95 (20 °C)	3.4 (20 °C)	0.13	0.47		0.71	71
1-n-butoxy-3-ethoxy-2-propanol	220		0.93 (20 °C)		1.42	0.21		0.96	71
1-n-butoxy-3-iso-propoxy-2-propanol	223		0.91 (20 °C)	4.6 (20 °C)	1.46	0.77		0.16	71
1-n-butoxy-3-methoxy-2-propanol	208		0.94 (20 °C)		0.74	0.27		0.96	71
1-tert-butoxy-3-ethoxy-2-propanol	204		0.92 (20 °C)		0.69	0.36		0.62	71
1-tert-butoxy-3-iso-propoxy-2-propanol	202		0.93		1.07	0.29		0.62	71
1-tert-butoxy-3-methoxy-2-propanol	195		0.93 (20 °C)		0.34	0.36		0.71	71
3-buthoxypropane-1,2-diol	249		1.00 (20 °C)	42.0 (20 °C)	0.33	0.91		0.68	71
3-ethoxypropane-1,2-diol	221		1.06 (20 °C)	35.2 (20 °C)	-0.65	0.86		0.77	71
3-methoxypropane-1,2-diol	222		1.11 (20 °C)	37.7 (20 °C)	-1.00	0.83		0.86	71
3-n-butoxy-1-iso-butoxy-2-propanol	229		0.90 (20 °C)		1.93	0.50		0.57	71
3-n-butoxy-1-tert-butoxy-2-propanol	230		0.90 (20 °C)		1.67	0.22		0.75	71
glycerol	290	18	1.26	1200 (20 °C)	-2.32	0.93	0.67	1.04	73,156
isopropylidene glycerol	188-189	-26	1.06	11 (20 °C)	0.03	0.59	0.63	0.86	157
butyl lactate	185-187	-28	0.98	3.3	0.88				158
butyl levulinate	106-108		0.97	2.5	1.46				
ethyl lactate	154	-26	1.03	2.4	-0.19	0.64	0.63	0.69	156,159
ethyl levulinate	93-94		1.02	1.9	0.40				
glycerol triacetate	258	3	1.16	23 (20 °C)	-0.24			0.63	156
methyl caprylate	194-195	-40	0.87	1.3	3.37	0.00	0.45	0.60	160,161
methyl lactate	144-145	-66	1.09	2.6	-0.72				158
methyl laurate	262	4	0.87	2.8	5.49			0.37	156,161
methyl levulinate	193-195	-24	1.04	1.9	-0.13				
methyl linoleate	192	-35	0.88	4.4	7.64				161
methyl myristate	323	18	0.86	4.0	6.55				161
methyl oleate	218		0.87	5.6	8.16	0.00		0.43	156
methyl palmitate	185	32-35	0.85 (35 °C)	4.2 (35 °C)	7.62				161
methyl stearate	181-182	37-41	0.85 (45 °C)	4.4 (45 °C)	8.68				161
γ-valerolactone	207-208	-31	1.05		-0.27	0.00	0.60	0.83	156
1,2,3-trimethoxypropane	150		0.94 (20 °C)		0.18				71
1,2,3-tri-n-butoxypropane	270		0.86 (20 °C)	2.7 (20 °C)	3.8			1.12	71
1,2-di-n-butoxy-3-methoxypropane	234		0.89		2.47				71
1,3-di-n-butoxy-2-methoxypropane	244		0.88 (20 °C)	3.8 (20 °C)	2.47	0.10		0.24	71
1-iso-butoxy-2,3-diethoxypropane	210		0.89		1.71			0.41	71
1-iso-butoxy-2,3-dimethoxypropane	193		0.89		1.01				71
1-iso-butoxy-2-ethoxy-3-methoxypropane	198		0.89		1.36				71
1-iso-butoxy-3-ethoxy-2-methoxypropane	201		0.89		1.36	0.07		0.32	71
1-iso-propoxy-2,3-dimethoxypropane	170		1.40 (20 °C)	1.0 (20 °C)	0.54				71
1-n-butoxy-2,3-diethoxypropane	217		0.89		1.84	0.21		0.25	71
1-n-butoxy-2,3-dimethoxypropane	199		0.90		1.14				71
1-n-butoxy-2-ethoxy-3-iso-propoxypropane	222		0.89		2.22				71
1-n-butoxy-2-ethoxy-3-methoxypropane	209		0.89		1.68	0.23		0.16	71
1-n-butoxy-2-methoxy-3-iso-propoxypropane	218		0.89 (20 °C)	1.7 (20 °C)	1.87	0.07		0.31	71
1-n-butoxy-3-ethoxy-2-methoxypropane	209		0.89		1.49	0.21		0.16	71
1-tert-butoxy-2,3-diethoxypropane	199		0.89		1.44	0.44		-0.17	71
1-tert-butoxy-2,3-dimethoxypropane	180		0.90		1.80	0.02		0.53	71
1-tert-butoxy-2-ethoxy-3-methoxypropane	190		0.89		1.10				71
2,3-diethoxy-1-iso-propoxypropane	192		0.89		1.24				71

Solvent	Boiling point (°C)	Melting point (°C)	Density (g cm^{-3})	Viscosity (cP)	Log P^b	Kamlet-Taft parameters			Refs.
						α	β	π*	
2-ethoxy-3-methoxy-1-iso-propoxypropane	161		0.89		0.89	0.35		-0.02	71
2-methylfuran	63-66	-89	0.91	4	1.84				
2-methyltetrahydrofuran	78-80	-136	0.86	0.6	0.82	0.00	0.58	0.53	156
2-n-butoxy-1-iso-butoxy-3-methoxypropane	227		0.88		2.34				71
2-n-butoxy-1-tert-butoxy-3-methoxypropane	219		0.89		2.08				71
2-n-butoxy-3-methoxy-1-iso-propoxypropane	215		0.89		1.87	0.03		-0.06	71
3-ethoxy-2-methoxy-1-iso-propoxypropane	183		0.89		0.89	0.22		0.15	71
3-n-butoxy-1-iso-butoxy-2-ethoxypropane	241		0.88		2.69				71
3-n-butoxy-1-iso-butoxy-2-methoxypropane	226		0.88		2.34	0.00		0.39	71
3-n-butoxy-1-tert-butoxy-2-ethoxypropane	211		0.88		2.43				71
3-n-butoxy-1-tert-butoxy-2-methoxypropane	234		0.89		2.08	-0.04		0.42	71
isosorbide dimethyl ether	93-95		1.15		-0.65				
dihydrolevoglucosenone	203		1.25		-0.71	0.00	0.61	0.93	85
(R)-(+)-limonene	178	-74	0.84	0.8	4.45	0.00	0.00	0.16	86,16
1,8-cineole	176	1.5	0.92	2.6	2.82	0.00	0.61	0.36	156,163
3-carene	170-172		0.86		4.37				
neryl acetate	134		0.88		4.10				
p-cymene	177	-68	0.86	0.8	4.02	0.00	0.13	0.39	86,162
α-pinene	155	-64	0.88	1.3	4.37	0.00	0.00	0.11	86
β-pinene	165-167	-61	0.87	1.6	4.37				

[a] Data were obtained from listed references, as well as from ChemSpider and commercial materials safety data sheets.

[b] When not available, density and log P were calculated *in silico* by ACD/ADME software.

A comparison of Hansen solubility parameters of bio-based molecular solvents with the ones corresponding to organic solvents typically used in analytical methods is shown on **Figure 6**, where the three parameters δ_d, δ_p and δ_h refers to dispersion (nonpolar) interactions, polar cohesive (permanent dipole-permanent dipole) interactions and hydrogen bond donating ability, respectively.[93] Hansen solubility parameters (despite the absence of a hydrogen bond accepting descriptor) are very useful tools for solvent selection in extraction processes and chromatographic separations, among other applications. Potential bio-based substitutes for certain conventional solvents can be deduced from **Figure 6** by checking the relative positions of a given alternative bio-solvent to the classical solvent to be replaced. It can also be observed that several conventional solvents (**Figure 6 C** and **D**) appear in unpopulated areas of the diagram corresponding to the bio-based solvents (**Figure 6 A** and **B**), which means that the replacement of these harmful organic solvents by a bio-based substitute would presumably give rise to a decline of analytical performance.

Very recently, a computer-assisted tool named as GRASS (GeneratoR of Agro-based Sustainable Solvents) has been developed to help in the design of novel solvents by using platform molecules of the biomass feedstock under acceptable experimental conditions.[94] The GRASS program generates a list of both existing and potential solvents that could be prepared by using a given building block. The discovery of novel bio-based solvents is thus expected to be boosted by using this program.

Ionic liquids derived from natural compounds

Ionic liquids (ILs) are referred to solvents composed entirely by ions, with melting points below 100 °C.[95] Firstly introduced by Walden a century ago,[96] ILs gained enormous interest in the last decades due to the introduction of air- and moisture-stable imidazolium ILs.[97] ILs are generally characterised by their high thermal and chemical stability, negligible vapour pressure, non-flammability and outstanding solvation capacity for a variety of materials. Remarkably, these properties are highly tunable as a huge number of combinations of cationic and anionic constituents can be performed to meet specific requirements. Owing to their unique physicochemical properties, ILs have attracted much interest in different scientific and technological fields[98–104] and, more specifically, they have been extensively applied in several areas of analytical chemistry, namely sample preparation, chromatographic and electrophoretic separations and detection systems.[105–111] The ILs of choice in analytical methods are, however, mainly derived from petroleum-based constituents, such as imidazolium- and pyridinium-based ILs. Furthermore, they can display high toxicity and poor levels of biodegradation, and hazardous decomposition products can be released under certain conditions.[112–114] The 'green label' generally assigned to every single IL is, therefore, somewhat questionable. As a matter of fact, a comparison of the cradle-to-gate life cycle of a typically used IL (1-butyl-3-methylimidazolium tetrafluoroborate) with conventional organic solvents showed that the evaluated IL displayed the most significant impacts per unit of mass in most categories, mainly due to the large number of chemical steps in the synthesis tree and the purification steps required to separate the IL from unreacted materials, by-products and solvents, which involved the use of several harmful solvents.[115] A comprehensive assessment of environmental performance as well as safety and health issues of a given IL would therefore be required to consider its greenness.[112]

The use of anionic and cationic constituents of natural origin offered the chance to obtain a new generation of ILs with greener characteristics and advantageous physicochemical properties.[116–118] Several works have been devoted to the preparation of ILs based on natural compounds, which can be included in the structure of ILs, or even used as a source of different ILs when not capable of being converted into ions.[117]

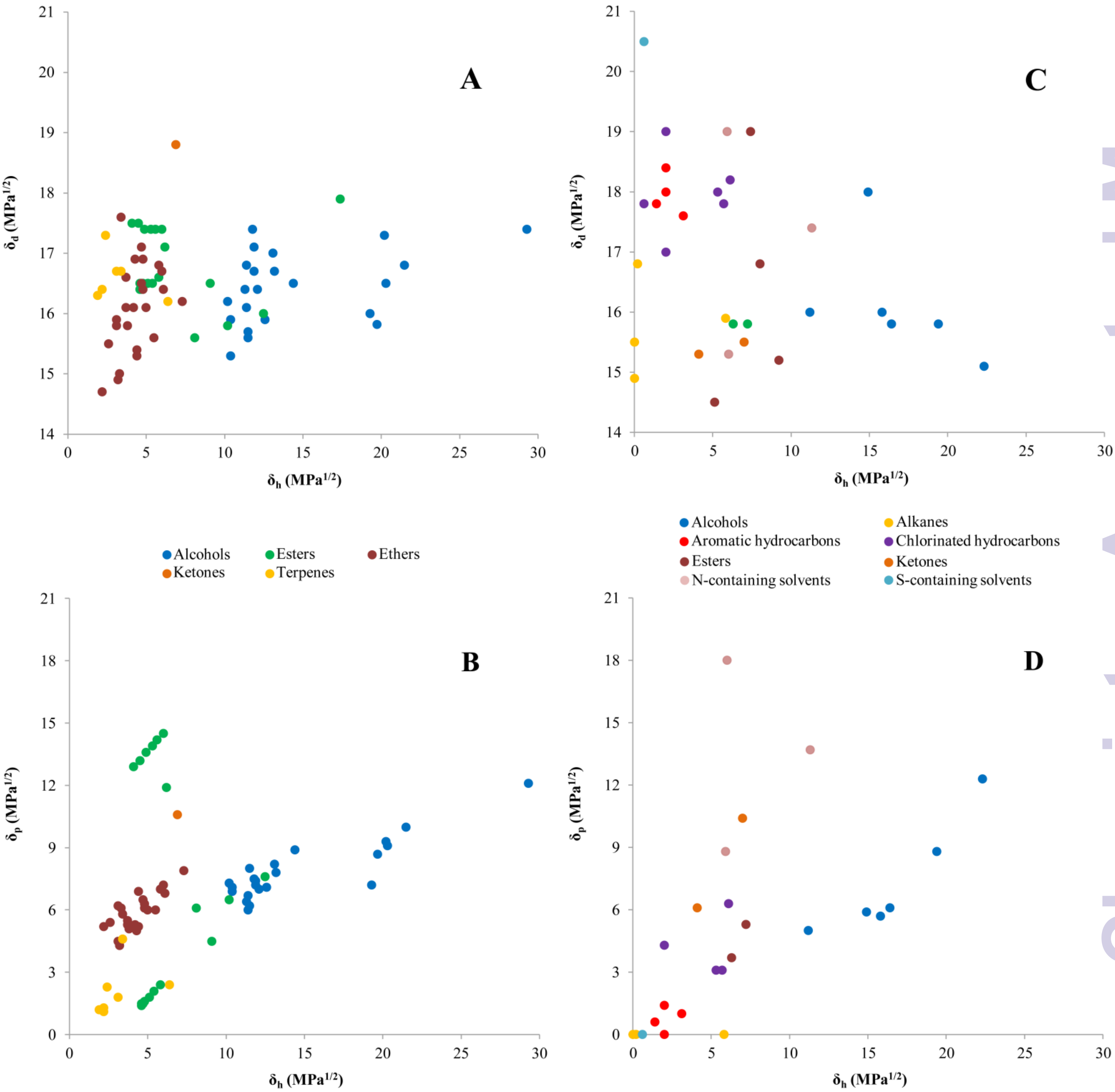


Fig. 6 Hansen solubility parameters of molecular solvents derived from renewable resources (A and B) and conventional organic solvents (C and D).

The development of ILs composed solely of biomaterials involved a step further toward sustainability.[119,120] Thus, several ILs composed mainly by 2-hydroxyethyltrimethylammonium chloride, a natural essential micronutrient commonly known as choline chloride,[121] as the cation, and a variety of natural carboxylate salts and amino acids as the anions have been reported in the literature, showing advantageous properties for the pretreatment of lignocellulosic materials,[122–124] extraction and separation,[125–127] and solubilisation and stabilisation of biopolymers.[128,129]

Very recently, Socha and co-workers described the application in biomass pretreatment of three novel ILs prepared by reductive amination of three aromatic aldehydes derived from lignocellulosic biomass, namely furfural, vanillin and p-anisaldehyde, opening the door to the use of monomers obtained from lignin and/or hemicellulose for obtaining greener ILs.[130] The physicochemical properties of ILs derived from natural and/or renewable compounds, as well as the chemical structure of the corresponding cationic and anionic components are provided on **Table 3** and **Figure 7**, respectively.

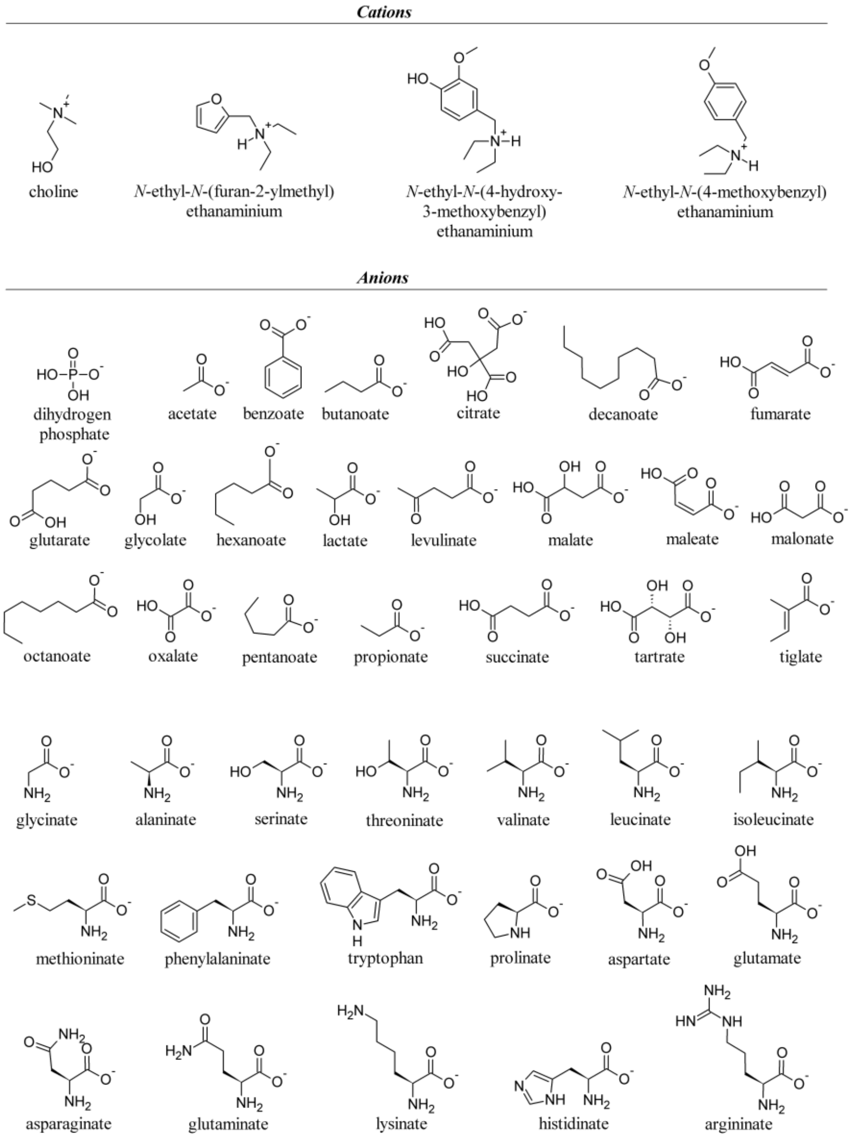


Fig. 7 Chemical structures of cationic and anionic components of IL_S derived from natural and/or renewable compounds.

Table 3 Physicochemical properties and solvatochromic parameters of selected ILs derived from natural and/or renewable compounds

IL	T_{decom} ^{a} (°C)	T_g ^{b} (°C)	Melting point (°C)	Density (g cm^{-3})	Viscosity (cP)	Kamlet-Taft parameters			Refs.
						α	β	π^*	
Choline acetate	189; 210	--	51; 72; 80			0.68 (90 °C)	1.22 (90 °C)	0.76 (90 °C)	119,125,164–166
Choline benzoate	202	-51	47						119
Choline butyrate	166; 209		45	1.05	631				125,165,166
Choline citrate	215		72; 103						125,167
Choline decanoate	168		50						166
Choline fumarate	219; 235	-62	78; 80						119,167
Choline glutarate	242	-67							167
Choline glycolate	220	-67	38; 49	1.19	2149				119,125,127
Choline hexanoate	169; 204		52	1.02	711				165,166
Choline lactate		-52	<-80	1.14	2310	0.59	0.80	1.12	125,127,168
Choline levulinate			<-80	1.12	1589				127
Choline malate	210; 239	-40; -35	99; 106						119,167
Choline maleate	223	-72	25	1.20	650	0.75	0.58	1.08	119,169
Choline malonate	198	-65	<-80	1.21	7426				127,167
Choline octanoate	166		26						166
Choline oxalate	230		57; 99						125,167
Choline pentanoate	203; 204		31	1.02	711				165,166
Choline propionate	172; 184; 212	-74	--	1.07; 1.08	290	0.52	0.98	1.05	119,125,165,166,169
Choline succinate	212; 233	-56; -52	48						119,167
Choline tartrate	203	-6	131						119
Choline tiglate	192	-62	--	1.06		0.59	0.95	1.04	119,169
Choline alaninate	152; 159; 189	-59; -56	RT^c	1.11	163; 386				122,170,171
Choline argininate	163	-10	RT^c		1002				122
Choline asparaginate	187	-14	RT^c		1903				122
Choline aspartate	202	-22	RT^c		2060				122
Choline histidinate	128; 171	-40	RT^c		980				122,170
Choline glutamate	202	-18	RT^c		2308				122
Choline glutaminate	203	-40	RT^c		2589				122
Choline glycinate	148; 150; 175	-61; -59	RT^c	1.14	121; 182				122,170,171
Choline isoleucinate	175	-47	RT^c		480				122
Choline leucinate	175	-47	RT^c		476				122
Choline lysinate	165	-48	RT^c		460		1.30	0.67	122,164
Choline methionine	178	-61	RT^c		330				122
Choline phenylalaninate	160; 166	-60	RT^c		520				122,170
Choline serinate	182; 190	-55; -49	RT^c	1.19	402; 11544				122,171
Choline threoninate	172	-39	RT^c		454				122
Choline tryptophanate	174	-12	RT^c		5640				122
Choline prolinate	163; 195	-52; -44	RT^c	1.12	500; 10644				122,171
Choline valinate	177	-74	RT^c		372				122
N-ethyl-N-(furan-2-ylmethyl)ethanaminium dihydrogen phosphate						2.14 eV	3.53 eV		130
N-ethyl-N-(4-hydroxy-3-methoxybenzyl)ethanaminium dihydrogen phosphate			155-157			2.35 eV	2.99 eV		130
N-ethyl-N-(4-methoxybenzyl)ethanaminium dihydrogen phosphate						2.28 eV	3.37 eV		130

$^a T_{decom}$: decomposition temperature

$^b T_g$: glass transition temperature

^{c}RT: liquid at room temperature (numerical value not available)

Natural deep eutectic solvents

Deep eutectic solvents (DES) were firstly introduced by Abbott and co-workers in 2003.[131] This pioneer work demonstrated that mixtures of urea and a range of quaternary ammonium salts resulted in the formation of homogeneous liquids with unusual physicochemical properties. DES consist on the association of at least two molecules, which act as hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD), respectively, *via* hydrogen bond interactions. DES are characterised by a marked reduction of the freezing point, showing melting points significantly lower than that of each compound involved. Homogeneous DES can be easily obtained by mixing suitable HBA-HBD combinations. Interestingly, the DES formation does not involve any chemical reaction but intermolecular interactions, so the atom economy is 100% and the purity of the obtained DES depends solely on the purity of the individual components. Thus, purification is generally not required, which is an important advantage with regards to ILs. DES with different physicochemical properties can be obtained by modifying the nature and molar ratio of the compounds involved. Due to their promising properties, DES have been used as solvents in a variety of scientific and technological applications, including chemical synthesis and catalysis, electrochemistry, extraction processes, nanomaterials preparation or materials solubilisation. Some recent review articles can be consulted for further details on different aspects of DES.[132–136]

A specific group of DES, introduced as natural deep eutectic solvents (NADES) by Verpoorte and coworkers,[137] can be obtained from a wide range of naturally occurring compounds. NADES presumably play a paramount role as alternative media to water in living cells and organisms for solubilising, storing and transporting water immiscible metabolites.[137,138] A large number of combinations of natural compounds has been reported in the literature for the preparation of NADES, including amines, amino acids, alcohols, carbohydrates and carboxylic acids (**Figure 8** and **Table 4**). Choline chloride is by far the most commonly used HBA in the publications devoted to the preparation of NADES. Importantly, some NADES are commercially available, including the eutectic mixtures of choline chloride with urea, glycerol, malonic acid and oxalic acid. It must be taken into consideration, however, that a large number of the NADES reported in the literature are not liquid at room temperature, as can be inferred from the data shown in **Table 4**. Furthermore, the viscosity of some NADES is excessively high to be implemented in certain analytical applications. For example, a viscosity as high as 34400 cP has been attributed to the eutectic mixture choline chloride:glucose (molar ratio 1:1) at 50 °C.[139] Even though these facts represent an important limitation to the application of certain NADES in analytical methodologies, the addition of small amounts of modifiers can significantly modify the properties of the original NADES. Water has been mainly used with this aim. Thus, water, commonly in the range 5-10%, yields liquid NADES at room temperature with lower viscosity than the original NADES and tunable solubilizing capability.[138] Glycerol has also shown remarkable results as a modifier of eutectic mixtures formed between choline chloride and carbohydrates, yielding NADES with decreased melting points and reduced viscosities.[139] Remarkably, choline chloride:glycerol NADES are characterised for showing lower viscosities than pure glycerol. For example, the eutectic mixture obtained by mixing choline chloride and glycerol (molar ratio 1:2) shows a viscosity three times lower than that of bulk glycerol.[140] Addition of modifiers can also be exploited to tune the polarity of NADES. For instance, several mixtures of sugars, sugar alcohols or citric acid with urea and inorganic salts showed polarity values above the ones corresponding to 2-propanol, and in most of cases much higher than water.[141] Interestingly, NADES showed excellent solubilising capabilities for a range of both polar and non-polar small molecules and macromolecules.[138,142–144]

Few works have been recently reported involving NADES, which show the promising characteristics of these novel solvents in the analytical field, including the solubilisation and extraction of organic compounds,[138,143–145] as well as the ultrafast microwave-assisted digestion of solid samples.[146,147] Further improvements in analytical methodologies are envisaged in the near future by the implementation of NADES.

Challenges and concluding remarks

The recent efforts performed in the preparation of solvents from natural and/or renewable resources can offer novel solutions that could potentially boost the development of sustainable analytical methodologies. Several obstacles, however, could arise when substituting harmful solvents used in analytical methods by alternative solvents, including deficient sensitivity, inadequate accuracy and precision and increased implementation costs.[148]

The applicability of solvents derived from natural and/or renewable resources in analytical methodologies could be specially challenging in certain cases. First of all, adequate solvent purity is of paramount importance in analytical methods, as problems of contamination and artefact formation could be produced. This is of especial relevance in analytical methodologies devoted to trace and ultra-trace analysis. In this sense, harmful solvents and/or high energy consumption processes could be required to obtain highly pure alternative solvents, which could compromise to a certain extent their eco-efficiency. Solvent stability is also a major issue. Thus, the applicability of some solvents is restricted to those experimental conditions in which the solvent is not subjected to thermal or chemical degradation. In addition, their commercial availability at reasonable prices would be of high importance, especially for those solvents with potential application in analytical operations that require relatively large solvent volumes per sample.

Solvent replacement could also be difficult to carry out in analytical procedures involving method-defined parameters, *i.e.*, “measurands that can be obtained only by using a well-established and detailed (bio)chemical measurement process, which has been designed to fulfil a well-defined purpose when dealing with a specific type of sample in a particular field”,[149] as the chemistry of the method could be changed. Nevertheless, some of these methods have been revised in the past to avoid the use of hazardous solvents, and future solvent replacements could presumably be carried out. This is the case, for instance, of the method for oil and grease determination in water samples (USEPA Method 1664), based on a solvent extraction process and subsequent gravimetric analysis.[150] Remarkably, the original method, based on the use of Freon-113, a Class I chlorofluorocarbon banned by the Montreal Protocol, has been modified by replacing the formerly employed solvent by n-hexane. Importantly, the term “oil and grease” has been replaced by “n-hexane extractable material”, as the solvent used could extract materials other than oils and greases.

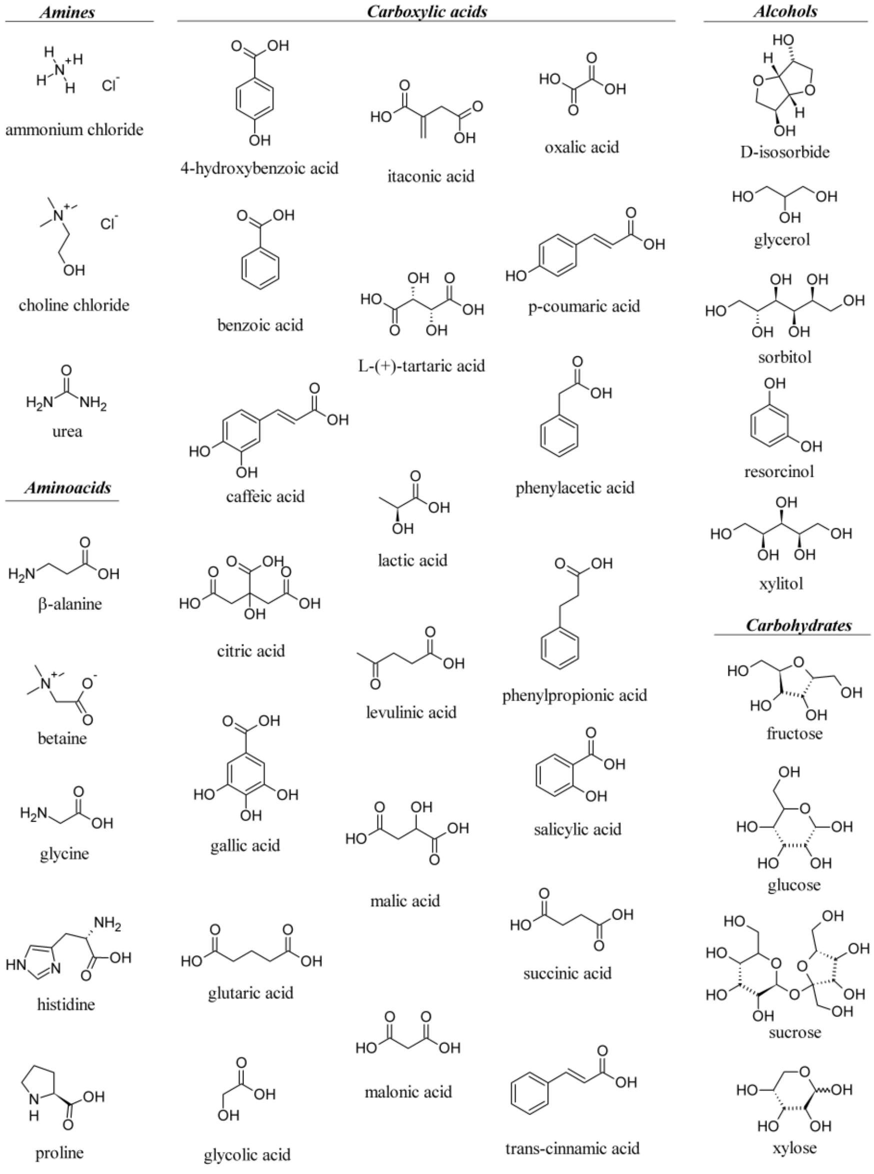


Fig. 8 Chemical structures of natural compounds used in the preparation of NADES.

Table 4 Physicochemical properties of selected NADES.

NADES components	Mole ratio	T_{decom}[a] (°C)	T_g[b] (°C)	T_f[c] (°C)	Density (g cm^{-3})	Viscosity (cP)	Refs.
Choline chloride:benzoic acid	1:1			95			172
Choline chloride:caffeic acid	2:1			67			139
Choline chloride:caffeic acid:glycerol	2:2:1			RT[d]			139
Choline chloride:citric acid	1:1			69			172
Choline chloride:glutaric acid	1:1	239.0	-16.8	RT[d]	1.19	2015	173
Choline chloride:gallic acid	2:1			77			139
Choline chloride:gallic acid:glycerol	4:1:1			53			139
Choline chloride:glycolic acid	1:1	227.1	-16.1		1.19	547.9	173
Choline chloride:4-hydroxybenzoic acid	2:1			87			139
Choline chloride:4-hydroxybenzoic acid:glycerol	4:2:1			63			139
Choline chloride:itaconic acid	1:1			57			139
Choline chloride:itaconic acid:glycerol	2:1:1			RT[d]			139
Choline chloride:L-(+)-tartaric acid	2:1			47			139
Choline chloride:L-(+)-tartaric acid:glycerol	4:2:1			RT[d]			139
Choline chloride:lactic acid	1:1.3		-76.7				174
	1:2		-77.7				174
	1:5		-69.2				174
	1:10		-66.3				174
Choline chloride:levulinic acid	1:2	176.6	-11.9	RT[d]	1.14	226.8	139,173
Choline chloride:malic acid	1:1		-56.5				174
Choline chloride:malic acid:water	1:1:2	201	-71.3		1.23 (°40 C)		138
Choline chloride:malonic acid	1:1	124.7	-14.1	10	1.23	1389	172,173
Choline chloride:oxalic acid	1:1	159.9	-21.7	34	1.26	8953	172,173
Choline chloride:p-coumaric acid	2:1			67			139
Choline chloride:p-coumaric acid:glycerol	4:2:1			63			139
Choline chloride:phenylacetic acid	1:1			25			172
Choline chloride:phenylpropionic acid	1:1			20			172
Choline chloride:succinic acid	1:1			71			172
Choline chloride:trans-cinnamic acid	1:1			93			139
Choline chloride:trans-cinnamic acid:glycerol	2:2:1			87			139
Choline chloride:sorbitol	1:1			RT[d]		12730 (30 °C)	139
Choline chloride:sorbitol:glycerol	2:1:1			RT[d]		1710 (30 °C)	139
Choline chloride:D-isosorbide	1:2			RT[d]			139
Choline chloride:glycerol	1:2	205-216		-40	1.18	259	140,175,176
Choline chloride:glycerol:water	1:2:1	187	-101.6		1.17 (°40 C)		138
Choline chloride:resorcinol	4:1		-60.0			1883	177
Choline chloride:resorcinol	3.75:1		-64.0			1813	177
Choline chloride:resorcinol:urea	1:3.5:2		-48.5			2348	177
Choline chloride:resorcinol:urea	1:3:2		-53.0			2440	177
Choline chloride:sorbitol:water	2.5:1:3	>200	-89.6		1.18 (°40 C)		138
Choline chloride:xylitol	1:1			RT[d]		5230 (30 °C)	139
Choline chloride:xylitol:glycerol	2:1:1			RT[d]		1420 (30 °C)	139
Choline chloride:xylitol:water	2:1:3	>200	-93.3		1.18 (°40 C)		138
Choline chloride:fructose	1:1			20	1.34	14702	178
	1.5:1			13	1.30	14347	178
	2:1			10	1.28	12027	178
	2.5:1			37	1.26	17645	178
Choline chloride:fructose:water	2.5:1:2.5	160	-84.6		1.21 (°40 C)		138
Choline chloride:glucose	1:1			6	1.30	9037; 34400 (50 °C)	139,179
	1.5:1			-1	1.27	8000	179
	2:1			-10	1.24	8045	179
Choline chloride:glucose:glycerol	2:1:1					4430 (40 °C)	139
Choline chloride:glucose:water	2.5:1:2.5	170	-83.9		1.21 (°40 C)		138
Choline chloride:sucrose:water	4:1:4	>200	-83.0		1.23 (°40 C)		138

NADES components	Mole ratio	T_{decom}[a] (°C)	T_g[b] (°C)	T_f[c] (°C)	Density (g cm^{-3})	Viscosity (cP)	Refs.
Choline chloride:xylose:water	2:1:2	178	-81.8		1.21 (°40 C)		138
Choline chloride:urea	1:2	205-216		12	1.25	750	131,175,17
Choline chloride:urea:water	1:2:0.5				1.19	324	180
	1:2:0.9				1.18	114	180
	1:2:1.3				1.18	45	180
	1:2:1.7				1.17	21	180
Ammonium chloride:glucose:urea	1:3:7.4			75			181
Ammonium chloride:sorbitol:urea	1:2:1.8	220		67			181
Alanine:lactic acid	1:9		-59.3				174
Alanine:malic acid	1:1		-42.6				174
Alanine:malic acid:water	1:1:3	164	-70.9		1.35 (°40 C)		138
Betaine:benzoic acid	1:1.5			53	1.15 (°80 C)		182
Betaine:citric acid (monohydrate)	1:1.5			48			182
Betaine:glycolic acid	1:2			-36	1.27	937	182
Betaine:lactic acid	1:2		-46.9				174
Betaine:malic acid	1:1		-20.0				174
Betaine:oxalic acid (dihydrate)	1:1		-17.2				174
	1:2			33	1.27 (°50 C)	93	182
Betaine:phenylacetic acid	1:2			-7	1.16	523	182
Betaine:salicylic acid	1:1.5			63			182
Glycine:lactic acid	1:9		-54.5				174
Glycine:malic acid	1:1		-34.1				174
Histidine:lactic acid	1:9		-39.2				174
L-carnitine:urea	2:3			74			183
Proline:lactic acid	1:2		-36.7				174
Proline:malic acid	1:1		-13.6				174
Proline:malic acid:water	1:1:3	156	-61.3		1.32 (°40 C)		138
Proline:oxalic acid (anhydrous)	1:1		-14.4				174
Proline:oxalic acid (dihydrate)	1:1		-42.9				174
Fructose:glucose:sucrose:water	1:1:1:11	138	-50.77		1.37 (°40 C)		138
Fructose:urea	1:2			65			181
Fructose:urea:sodium chloride	7: 2:1			73			141
Glucose:lactic acid:water	1:5:3	135	-77.1		1.25 (°40 C)		138
Glucose:urea:sodium chloride	6:3:1			78			141

[a] T_{decom}: decomposition temperature

[b] T_g: glass transition temperature

cT_f: freezing point

[d] RT: liquid at room temperature (numerical value not available)

Attention should also be paid to the solvents used in the development of analytical systems. This is the case, for example, of solvents used in the preparation of novel materials with improved characteristics for their application in analytical procedures. Thus, even though the thus obtained materials can commonly be used repeatedly even under solventless conditions, the replacement of harmful organic solvents by greener alternatives in their preparation would have a non-negligible effect on their overall life cycle impact.

Suitable alternatives to conventional organic solvents with the required physicochemical properties are not always available, as recently pinpointed by Jessop.[151] In this vein, additional efforts on the design of novel sustainable solvents are especially welcomed. Besides, the search for alternative synthetic pathways from natural and/or renewable resources for the preparation of solvents that are typically produced from fossil resources and for which there are not efficient replacements could solve this limitation. This would also be highly desirable in the case of those conventional solvents classified as recommended in solvent selection guides. In fact, several conventional organic solvents with few health, environmental and safety hazards according to the above mentioned selection guides can be produced from renewable resources, including methanol, ethanol, isopropanol, acetone, methyl ethyl ketone and ethyl acetate.[66,152] Furthermore, mixtures of eco-solvents can also be exploited to replace conventional solvents with no direct substitute bearing in mind that the Hansen solubility parameters of the mixture depend directly on the relative amounts and solubility parameters of each solvent.[93]

It is important to remark that the fact of being obtained from natural and/or renewable resources does not necessarily mean that an alternative solvent is safe and benign. For example, methyltetrahydrofuran can be obtained from renewable feedstocks, such as furfural or levulinic acid,[153] although this ethereal solvent has been classified as problematic in solvent selection guides due to its flammability and explosion safety hazards.[61]

It is also important to highlight that some of the naturally occurring compounds used in the preparation of alternative solvents are obtained industrially from petrochemical sources. For instance, choline chloride is industrially prepared from trimethylamine and ethylene oxide, which in turn are products of the petrochemical industry. This is also true in the case of compounds and ions such as urea, malonic acid, vanillin, benzoate or propionate, among others. The preparation of those solvent constituents from renewable feedstocks would enable preparing alternative solvents in a more sustainable manner.

Finally, it must be aware that the implementation of solvents derived from renewable feedstock does not always lead to sustainable chemical processes.[1,154] Undoubtedly, this is also true in the specific case of analytical procedures. In fact, a life cycle assessment would be required to assess the impact in a holistic manner (from cradle to grave) and, therefore, clarify whether the alternative solvent is indeed greener for an analytical application. The availability of a comprehensive set of data that included different solvents and solvent mixtures would also be highly valuable for selecting benign solvents for analytical methods. In addition, a timely evaluation of environmental, health and safety issues of novel solvents would greatly contribute toward the development of more sustainable procedures. Analytical chemists are therefore encouraged to assess the applicability of alternative solvents derived from natural and renewable resources in different steps of the analytical process to go a step further toward fully sustainable practices in the area.

Acknowledgements

F. Pena-Pereira thanks Xunta de Galicia for financial support as a post-doctoral researcher of the I2C program.

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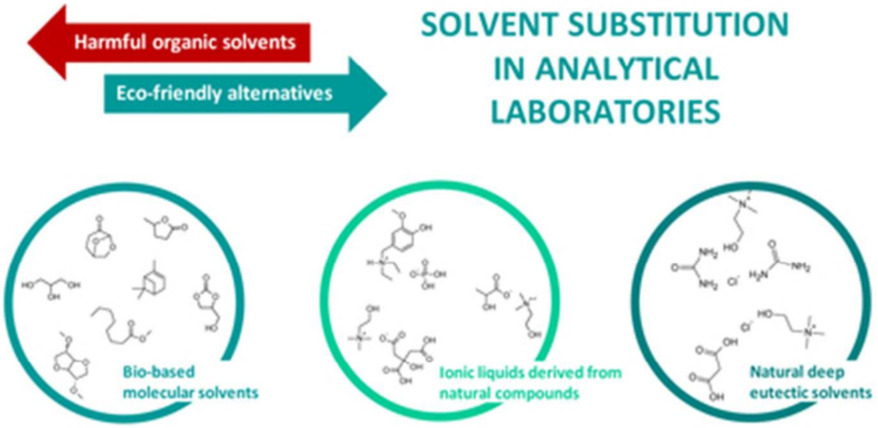

This perspective addresses the replacement of harmful organic solvents by a novel generation of promising alternatives toward sustainable analytical methodologies.
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