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An intelligent approach to solvent substitution resulting in the identification of a new class of levoglucosenone derivatives

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Response to Reviewers:	Reviewer 2: However, the paper new results are two: a computational work aimed to classify a vast amount of derivatives and one test reaction on the best solvent found. I

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	think that, with this data, the article seems like a technical company report instead of a journal article. Moreover, there is no critical discussion on the cost of this solvent considering that it should be used in large amount. I suggest to add a section with a second reaction test and a paragraph with the economic consideration. Our response: We have successfully carried out an additional test of Cygnet 0.0 as a reaction solvent and have included the new data along with additional text, and we have added a paragraph about the economic aspects of the work, highlighting the new manufacturing process and making an estimation of price. Reviewer 3: It would also be interesting to learn about the economic aspect of these solvents. That would be very interesting to the readers in order to understand the scope of this study. Our response: We have added a paragraph about the economic aspects of the work, highlighting the new manufacturing process and making an estimation of price.
Section/Category:	
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Has there been a previous version?	No
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An intelligent approach to solvent substitution resulting in the identification of a new class of levoglucosenone derivatives

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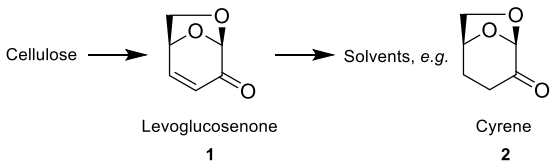
Abstract: With the increasing restriction and control of hazardous solvents safer alternatives need to be identified. Here a contemporary approach to solvent selection and substitution is presented, offering a more scientific alternative to a simple 'like-for-like' exchange. A new family of levoglucosenone-derived compounds are proposed, modelled to determine their solvent properties, synthesised, and tested. These novel molecules show promise as replacements for polar aprotic solvents with chronic toxicity issues such as dichloromethane, nitrobenzene, and *N*-methylpyrrolidinone. The success of this approach makes it possible for academia and industry to make calculated, intelligent choices for solvent substitution in the future.

Introduction

The substitution of hazardous chemicals is a priority worldwide with the European Union (EU) leading on the identification of Substances of Very High Concern (SVHC).[1] While organisations such as the European Chemicals Agency process the toxicity and other data of thousands of chemicals, large corporations are anticipating the inevitable consequences of new legislation and declaring their intention to stop using all SVHC.[2] Ultimately EU regulation concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) will prevent widespread use of SVHC.[3] One class of compounds that is severely impacted by SVHC categorisation is solvents. Some of the most widely used types of solvent, including halogenated compounds and amides, are among the solvents under threat. The challenge for the research community is to design new, safer and more sustainable alternatives that can match (or exceed) the often complex combinations of properties needed for various applications. There are few off-the-shelf candidates in this respect. In the case of amides, some alternative polar aprotic solvents do exist, notably sulphoxides and sulphones, although these are not without safety concerns and are not renewable.[4] Finding replacements for halogenated compounds (including solvents) is notoriously difficult, largely because of the quite apparent unique properties that halogens can confer on organic molecules.[5] As the evidence of environmental and health problems of such compounds accumulates many industry sectors face a very uncertain future.[6] It seems clear that rather than hoping better candidates are eventually identified through serendipity, we need a more intelligent approach to solvent substitution based on the fundamental understanding of key solvent properties.

There has been some very recent but limited progress in seeking greener polar aprotic solvents without the functionalities associated with human toxicity,[7-9] but because each substitute falls into a specific niche more alternatives are required. Bio-based solvents have begun to generate significant interest in academic studies and across a number of chemical industries.[10,11] However they are often derived from potential foodstuffs, namely sugars and vegetable oils. By contrast cellulosic biomass, a renewable and low cost feedstock, is widely available from a range of waste streams generated by the forestry, agriculture and food processing sectors.[12] This makes it a satisfactory sustainable feedstock for the production of bio-based solvents. We recently reported the use of levoglucosenone (**1**), obtained in one step from cellulose, to make the solvent dihydrolevoglucosenone (Cyrene, **2**) (Scheme 1).[7] Cyrene has been demonstrated to be an effective substitute for popular dipolar aprotic solvents, *e.g.* *N*-methylpyrrolidinone (NMP). This class of solvents are under enormous pressure from REACH due to their chronic toxicity and other end-of-life problems (*e.g.* NO_x formation upon incineration).[1,3] Levoglucosenone, given its straightforward preparation from abundant cellulosic biomass and its synthetic versatility, offers a useful template for the preparation of further compounds that might have properties suitable for use as solvents (among other applications). The preparation of bio-based levoglucosenone has been demonstrated at a commercially significant scale for a platform molecule,[13] therefore providing the potential to open up new fields of chemistry to industry.



Scheme 1. The synthetic steps to make Cyrene.

This work presents an evaluation of potential solvents made from levoglucosenone. The approach is based on comparisons to existing solvents, especially those with known hazards. Solvent selection is usually performed on a 'like-for-like' substitution basis,[14] but history tells us such a simple

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approach is never likely to allow users to completely escape the toxicity, safety issues or environmental impact of one type of solvent. For example toluene was once embraced as a replacement for benzene, but it too is now subject to restrictions because of its reproductive toxicity and capacity for chronic organ damage.[3] Similarly, at one time NMP was claimed to be non-toxic,[15] but it is now recognised to be reprotoxic and therefore a SVHC.[1]

The polarity of multifunctional solvents can be difficult to predict intuitively, and so computer generated models are a focused means by which to identify promising solvents from a large number of possible candidates. Herein three approaches to solvent polarity modelling have been performed and evaluated for levoglucosenone derivatives. Firstly, computed Hansen solubility parameters, and secondly, the "COnductor like Screening MOdel for Realistic Solvation" (COSMO-RS) were used to guide the design of new solvents. This combination of techniques was previously used by Moity *et al.* to describe four glycerol derivatives.[16] This informative study of commercial products characterised the solvents but did not seek a specific application. By contrast the present work has identified a novel class of solvent from a screening of more than 100 candidates, and found a relevant application for them based on the strength of their properties. Furthermore, this work substantially extends the basis of the prior art as it also incorporates a third approach to solvent modelling. Experimental solvatochromic parameters were used to populate a solvent polarity map and identify a suitable application for the most promising levoglucosenone derived solvent.

Although the synthesis and application of a new solvent has been achieved, it is not the primary focus of this work. The multifaceted methodology of *in silico* solvent evaluation (and the identification of suitable applications) is the reason for reporting these results. The syntheses required here are intentionally limited to routine procedures (so that the product can be considered as a cost effective solvent), and the representative application (the Heck reaction) has strong literature precedent. For these reasons much of this information is presented separately as Electronic Supporting Information.

Results and Discussion

Main solvent candidate shortlist

Candidate molecules derived from levoglucosenone were extracted from research articles published between 1995 and 2015.‡ Potential solvents were identified from this literature search of recently reported levoglucosenone derivatives if the melting point (where available) did not exceed 100 °C. This lenient cut-off is consistent with the (somewhat arbitrary) definition of an ionic liquid.[17] Obvious derivatives were also considered to introduce novel compounds to the shortlist. To do this unsaturated carbon-carbon bonds were also listed as the saturated analogue, and alcohols also listed as the corresponding acetate ester, methyl ether, and ethyl ether where deemed appropriate. For solvents especially, removal of alkenes through hydrogenation provides valuable stability. There is an abundance of green alcohol solvents (most importantly bio-ethanol) and so the conversion of alcohols to ethers and esters leads to more valuable aprotic solvents.

Inspection of the selected literature compounds suggested that the functional group interconversion of a ketone into the corresponding ketal could be useful for developing solvents from levoglucosenone.[18,19] Not only is a different functionality introduced relatively easily, but removing the reactive ketone group is also advantageous. Therefore ketal derivatives were also considered as solvent candidates, primarily through the reaction of ethylene glycol with the ketone functionality of levoglucosenone. This completed the list of solvent candidates (featuring 96 literature compounds and 68 of their novel derivatives), which is presented in full as Electronic Supporting Information (Table S1).

Model 1: Hansen solubility parameters

The Hansen solubility parameters are regularly used to characterise the polarity of solvents in terms of their dispersion forces (δ_D), the degree of polarity arising from any dipoles (δ_P), and capacity for hydrogen bonding (δ_H).[20] The experimental procedures required to directly determine the Hansen solubility parameters are tedious, and so experiments are now generally done by observing the solubility of reference substances in different solvents.[21] Even so, calculation methods are now quite accurate and extremely fast to compute, allowing for rapid *in silico* screening of large numbers of compounds. This has been taken advantage of in this work for the quick identification of potential solvents without needing to synthesise and test them all. Hansen solubility parameters were calculated using HSPiP (version 4.1.04, 2013).

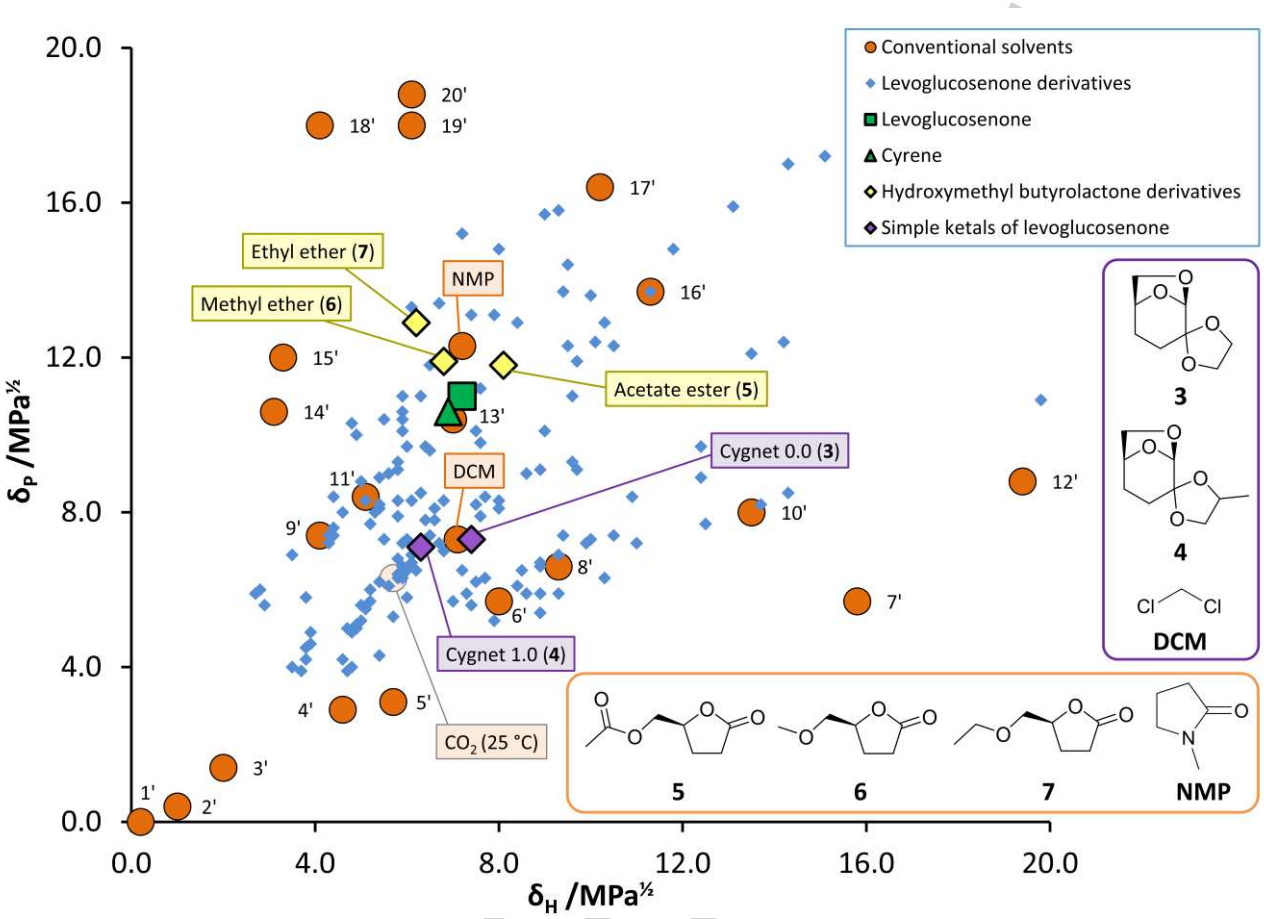


Figure 1. A two-dimensional Hansen solubility parameter map. Key: 1', cyclohexane; 2', triethylamine; 3', toluene; 4', diethyl ether; 5', chloroform; 6', tetrahydrofuran; 7', 1-butanol; 8', 1,3-dioxolane; 9', 1,2-dichloroethane; 10', acetic acid; 11', cyclohexanone; 12', ethanol; 13', acetone; 14', nitrobenzene; 15', benzonitrile; 16', DMF; 17', dimethyl sulphoxide; 18', propylene carbonate; 19', acetonitrile; 20' nitromethane. Data is tabulated in the Electronic Supporting Information (Table S5).

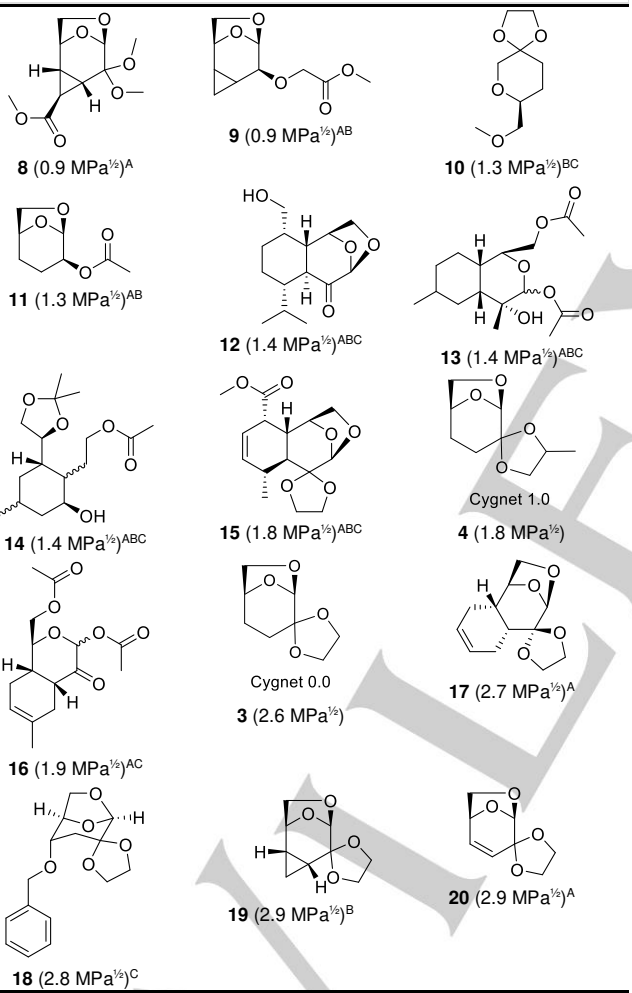
The Hansen dispersion forces (δ_D) expressed by solvents tend to be reasonably similar, and so for a simpler representation of the Hansen solubility parameters δ_P can be plotted against δ_H to represent different types of solvent in a two-dimensional graph (Figure 1). The full shortlist of levoglucosenone derived solvent candidates covers a large area of the so-called Hansen space. This permits selective targeting of a number of solvents, including those most in need of substitution. High polarity aprotic solvent classes were prioritised because of the inherent properties of the levoglucosenone template lends itself to creating polar solvents. Halogenated solvents and nitrohydrocarbons, *e.g.* dichloromethane (DCM) and nitrobenzene,[1] are known to cause cancer and are therefore worthy targets for substitution. Similarly, many dipolar aprotic amides including NMP and *N*,*N*-dimethyl formamide (DMF) are reprotoxic.[1]

Areas of the Hansen map not well represented by levoglucosenone derivatives are the regions occupied by hydrocarbon (including aromatic) solvents, and strongly hydrogen bonding compounds (represented by water, and low molecular weight alcohols including polyols). Finding replacements for the latter is not necessary from a green chemistry perspective.[4,14] Hydrocarbons are useful for extractions, but strongly associated with safety concerns caused because of their flammability, but also sometimes toxicity (*e.g. n*-hexane and toluene). Although levoglucosenone is not particularly suited as a platform molecule for renewable hydrocarbons, other bio-based feedstocks can be used for this purpose,[22] or in some instances replaced by carbon dioxide (Figure 1).[23]

Two solvents, DCM and NMP, were picked as appropriate targets for substitution. These are solvents that are very widely used, *e.g.* for polymer processing,[24] and are major targets for substitution, representative of the situation for halogenated solvents and dipolar aprotics generally. All the solvent candidates within 3 $MPa^{½}$ of DCM or NMP in terms of the three-dimensional Hansen space were identified. This led to 53 possible DCM replacements and 21 possible alternatives to

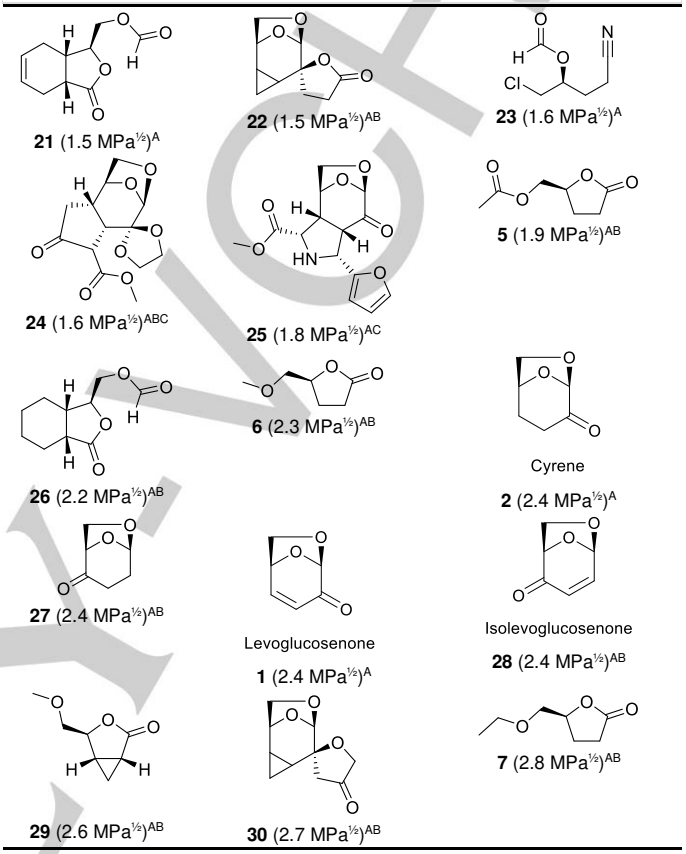
NMP made from the levoglucoseone platform molecule. To further reduce the candidates in the solvent screening, the more important δ_P and δ_H parameters of DCM and NMP were used as target values, with a radius in this two-dimensional Hansen space restricted to within 1.2 $MPa^{½}$ for DCM and 2.4 $MPa^{½}$ for NMP in order to limit the number of solvent candidates down to a more reasonable number of 15 in each case (Table 1 and Table 2). To further explain why DCM and NMP replacements have been prioritised, it is because fewer solvent candidates could be matched to alternative targets. Although chloroform (22 polarity matches) and DMF (8 matches) offered some promise, there were no suitable matches for toluene or nitrobenzene within the permitted 3 $MPa^{½}$ radius.

Table 1. Top 15 levoglucosenone derived DCM replacements in order of best polarity match.



Key to identified solvent issues: A, reactive functionalities; B, synthesis requires more than 2 reactions from levoglucosenone; C, bio-based carbon content below 50%.§ Distance from target solvent in the 3D Hansen space given in brackets.

Table 2. Top 15 levoglucosenone derived NMP replacements in order of best polarity match.



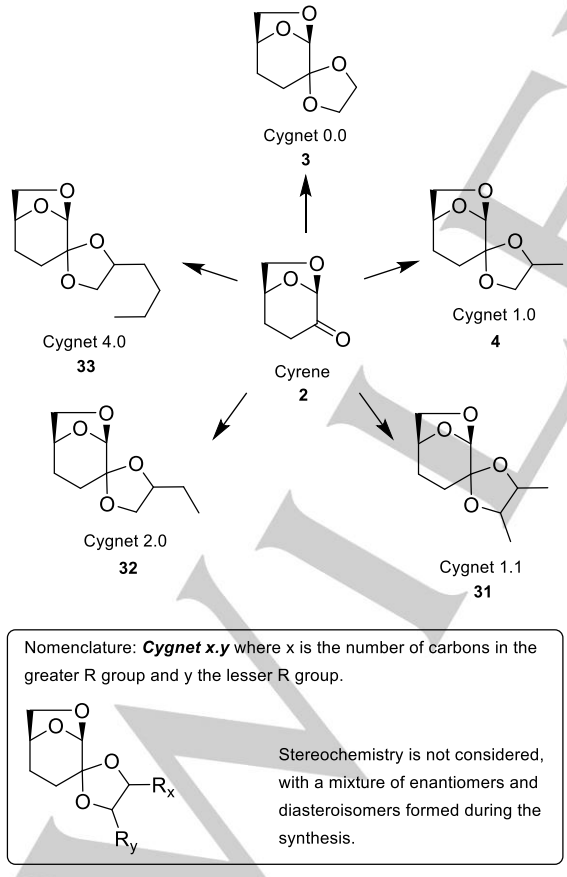
Key: See Table 1.

The 2 sets of solvent substitutes were scrutinised on the basis of unfavourable functionality (reactive alcohol, ketone, ester, and/or alkene groups), a synthesis requiring more than 2 reactions from levoglucosenone, and the incorporation of many new carbon atoms lowering the bio-based content below 50%.§ The synthesis of the additional reactants was not considered, although this can be significant in its own right. It can also be the case that the reactants are bio-based, although this too was not considered here. Greater detail describing the literature synthesis of each candidate can be found in the Electronic Supporting Information Table S3 and Table S4). The entries in Table 1 and Table 2 are labelled according to the aforementioned issues.

The Cygnets (an informal name for the ketals of Cyrene) are a new type of solvent, of which **3** and **4** occupy the same region of the Hansen space as the chlorinated solvent DCM (Figure 1). Some conventional ketones and ethers (*e.g.* cyclohexanone and tetrahydrofuran) are also found in this polarity region and so the distinction between the different types of solvent is not absolute. However, **3** and **4** are the only solvent

candidates to also meet all three structural and synthetic requirements (Table 1). These compounds were originally added to the list of solvent candidates because the literature compound **20** (also in Table 1),[18] the unsaturated equivalent of **3**, was identified to have potential following hydrogenation of the alkene.

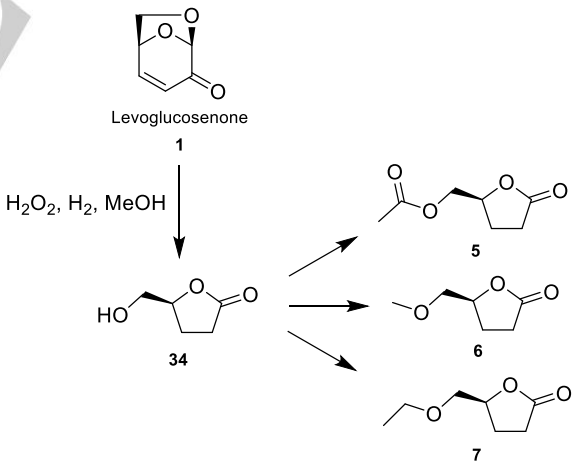
The Cygnets are named according to any substitution occurring at positions 4 and 5 on the dioxolane ring (Scheme 2). The principle is the same as that used for glycerol derivatives in the work of García *et al*.[25] The reaction of ethylene glycol with Cyrene to give Cygnet 0.0 (**3**) is straightforward (see the Electronic Supporting Information), and bio-based ethylene glycol can be obtained from commercial sources.[11] The resultant product is spiro[6,8-dioxabicyclo[3.2.1]octane-4,2'-[1,3]dioxolane] (**3**), the most hydrogen bonding (as an acceptor) and the most dipolar of the Cygnets. For these reasons **3** was selected to represent the new Cygnet family of solvents in this preliminary work. The synthesis of Cygnet 1.0 (**4**), Cygnet 1.1 (**31**), Cygnet 2.0 (**32**), and Cygnet 4.0 (**33**), will be reported in a subsequent publication, as will the incorporation of 1,3- and 1,4-substituted bio-derived diols. Estimations obtained from the ACD/I-lab service indicate the Cygnets are not expected to be genotoxic or mutagenic.[26] The only health effect predicted with high probability is to the lungs, which for a series of low-volatility compounds is less significant than many of the hazards known for conventional solvents.



Scheme 2. Ketal derivatives of Cyrene.

Despite the suitable polarity match of Cygnet 0.0 with DCM, implementing replacements for chlorinated solvents is made difficult by the unique electronic structure and resulting properties of the halogenated hydrocarbons. It is important to note that the hydrogen bonding of oxygenated compounds is basic in character (*i.e.* electron donating), whereas it has been shown computationally using COSMO-RS theory that the δ_H value of chlorinated solvents is actually acidic in character.[27] The δ_H value of amphiprotic molecules is the combination of both modes of hydrogen bonding (hydrogen donating and accepting, as is the case for alcohols). Furthermore, low boiling chlorinated solvents such as DCM and chloroform are often employed in extractions because they can be removed easily after the process. The Cygnets are not suitable for this type of application, and substitutions need to be assessed on a case-by-case basis.

The acetate ester (**5**), methyl ether (**6**), and ethyl ether (**7**) of (S)-γ-hydroxymethyl-γ-butyrolactone (**34**), itself possible to produce bio-catalytically from levoglucoseonone,[28] meet the requirements of a suitable NMP substitute (Table 2). This family of solvents have a straightforward chemical synthesis (Scheme 3), and have notably larger δ_P values than the Cygnets (Figure 1). As reported elsewhere for the related compound γ-valerolactone, lactones are dipolar enough to substitute amide solvents in selected applications.[8] The ester functionality of the lactones can be considered as a weakness, but there is a similar problem with the potentially reactive ketone of Cyrene. The other possible NMP replacements in Table 2 are synthetically complex, including iso-levoglucosenone and the equivalent constitutional isomer of Cyrene.[29]



Scheme 3. Lactones produced by the Baeyer–Villiger oxidation of levoglucosenone.

None of the potential NMP replacements identified in Table 2 are without issues. The development of the hydroxylactones elsewhere,[28] and the prior discovery of Cyrene,[7] γ-valerolactone,[8] and cyclic carbonates,[9] as viable NMP replacements meant that after consideration only the Cygnet family of compounds was carried forward for further analysis.

Modelling with the Hansen solubility parameters is useful for qualitative solubility predictions only. The precise solubility of substrates, or the relationship between the solvent and observable phenomena in reaction chemistry, requires the use of further techniques in order to understand these processes. With the Hansen solubility parameters effectively being used to reduce the list of possible solvent candidates to a more manageable number of promising compounds, other modelling approaches were then pursued in a more focused manner.

Model 2: COSMO-RS

COSMO-RS theory can be used to calculate the chemical potential, μ(σ), of the surface of different solvent molecules in terms of their affinity towards a hypothetical solute with a polarisable charge density σ.[30,31] Graphical plots calculated with COSMOthermX (version C30_1501, 2015) use COSMO-RS theory to show repulsion or attraction at different regions of the molecular surface according to how the solvent interacts. At the simplest level of interpretation, the resulting chemical potential plots can be used to indicate the strength of electron pair donation and hydrogen bond donation of the solvent. This has obvious benefits over the description of hydrogen bonding provided by the Hansen solubility parameter δ_H, which does not distinguish between hydrogen bond donating and accepting ability.

Dipolar aprotic solvents have a distinctive 'S'-shaped chemical potential curve, indicating the electron rich portions of the solvent molecular surface provide an opportunity to accept hydrogen bonds, but do not donate hydrogen bonds (Figure 2).[31] The Cygnets in Scheme 2 are virtually indistinguishable using the COSMO-RS interpretation of solvent polarity and so only Cygnet 0.0 is shown in Figure 2 (an additional graph is provided in the Electronic Supporting Information, Figure S3). This analysis indicates that contrary to the Hansen solubility parameter assessment, the Cygnet family of solvents are not similar to DCM, and by the same measure Cyrene is not comparable to NMP (at least in terms of electron pair donation). Instead Cygnet 0.0 appears more similar to the typical oxygenated solvents such as acetone.

Clearly the Hansen solubility parameters, originally derived from empirical observations of solvent cohesive energy, and the computational COSMO-RS approach differ in how they represent solvent polarity. The Hansen solubility parameters are calculated independently of a solute, and are therefore based on solvent-solvent interactions only. Nevertheless they can provide an indication of any thermodynamic preference for a solute to dissolve (or not) in a solvent, through their proximity in the Hansen space. This approach does not provide quantitative estimates of solubility. The theoretical COSMO-RS calculations introduce a reference solute (only defined by its surface charge) and the data generated can be used to estimate the thermodynamic properties of liquids and to predict equilibria and relative solvation energies on a quantitative basis.[30]

The application of COSMO-RS resolves the ambiguity of the Hansen space, where chlorinated solvents occupy the same region as ethers. Differences in hydrogen bond character shown through COSMO-RS theory indicate possible limitations for Cyrene and the Cygnet solvents in applications currently dependent on either NMP or DCM respectively. However experimental studies using Cyrene as a solvent have shown it to be comparable to NMP in many respects. Missing from the representation of solvent polarity in Figure 2 is a clear account of the dipole interactions that can exist between solvent and solute. Some indication of solvent dipolarity can be derived from the COSMOthermX chemical potential plots, but this requires a principle component analysis in which the true physicochemical meaning of the solvent properties is lost.[31] Instead, the assessment was continued with alternative measures of solvent polarity to give greater significance to non-specific solvent-solute interactions (as obtained experimentally).

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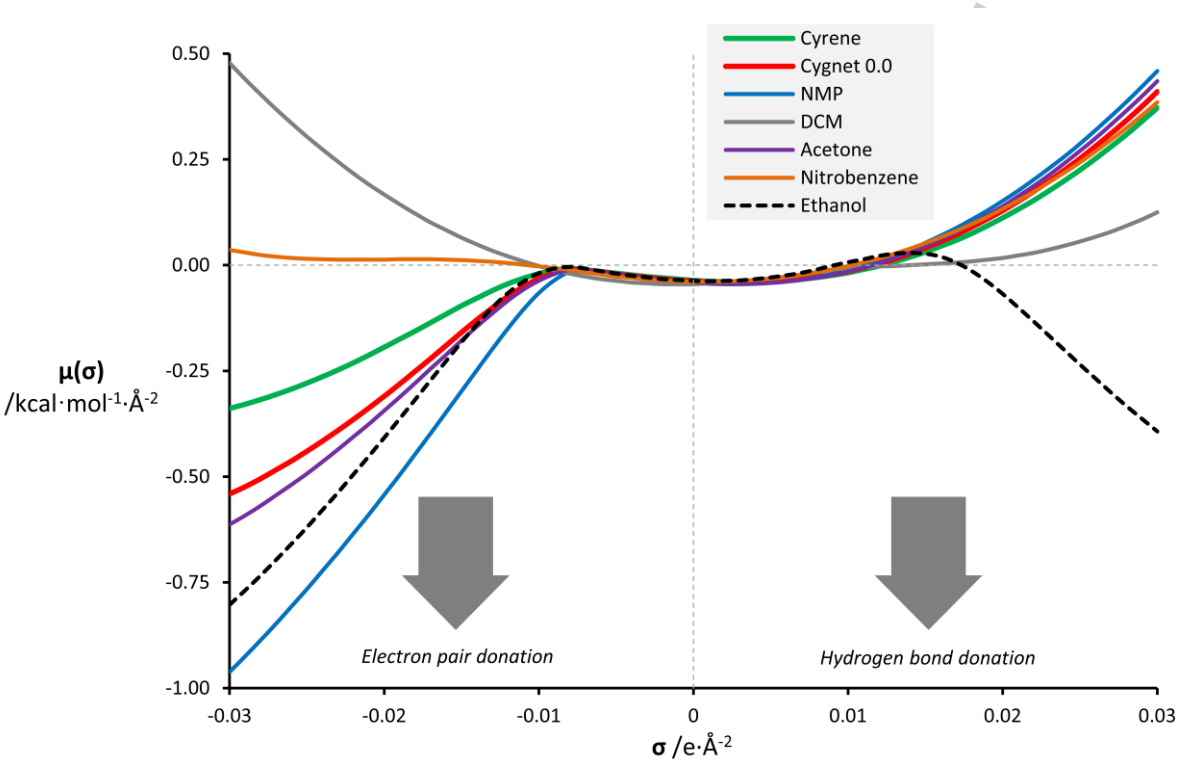

Figure 2. Chemical potentials of selected solvents (as a function of σ) in a comparison with Cygnet 0.0.

Model 3: Solvatochromic parameter mapping

Despite the different conclusions of the two models used thus far, both are providing a thermodynamic understanding of solvent effects. Only the experimental determination of solvent polarity, for example with the use of solvatochromic dyes, is able to provide a robust link between solvent polarity and observations in kinetic chemical systems (as well as thermodynamically controlled systems).[32] In reaction chemistry this is often much more preferable. The Kamlet-Abboud-Taft parameters are a reliable set of solvent polarity scales able to describe linear free energy relationships for chemical kinetics, product selectivities, reaction equilibria, partition coefficients, and a number of spectroscopic phenomena.[33]

The Kamlet-Abboud-Taft parameters are divided into three scales of solvent polarity (but not related to the Hansen solubility parameters). These are hydrogen bond donating ability (α), hydrogen bond accepting ability (β) and dipolarity and polarisability (π*). Each scale is unitless because it is normalised between 0.00 and 1.00. The Kamlet-Abboud-Taft parameters were obtained using Reichardt's dye, 4-nitroaniline, and *N,N*-diethyl-4-nitroaniline as previously described in the literature.[34] The separation of the two modes of hydrogen bonding (as α and β) has an obvious link to the chemical potential plots generated using COSMO-RS theory, but the introduction of a distinct measurement of permanent and induced dipoles (π*) is a key addition when attempting to understand the role of the solvent in a chemical process. For example, NMP and Cyrene have been found to accelerate reactions to a similar extent when the kinetics are dependent on solvent dipolarity, not hydrogen bonding.[7] Accordingly the Kamlet-Abboud-Taft π* parameter correlates to the reaction rate, which is not possible to achieve with the thermodynamic basis of the Hansen solubility parameters, or in COSMO-RS theory.

The solvatochromism of Cygnet 0.0 (**3**) demonstrates that this solvent is highly dipolar (Table 3). The value of π* obtained is typical of both conventional dipolar aprotic solvents and chlorinated solvents, including DCM. However the low hydrogen bond accepting ability (β) is consistent with the previous Hansen solubility parameter assessment which equated it to DCM. This is an interesting combination of solvent properties associated with chlorinated solvents, but considering the liquid range of Cygnet 0.0, nitrobenzene and benzonitrile are maybe more suitable targets when proposing a complete solvent replacement strategy.

Table 3. The polarity parameters of solvents.

Solvent	δ_D /MPa^{½}	δ_P /MPa^{½}	δ_H /MPa^{½}	β	π*
DCM[35]	17.0	7.3	7.1	0.10	0.82
Nitrobenzene[35]	20.0	10.6	3.1	0.30	1.01
NMP[7]	18.0	12.3	7.2	0.75	0.90
Cyrene[7]	18.8	10.6	6.9	0.61	0.93
Cygnet 0.0 (**3**)	18.3	7.3	7.4	0.17	1.09

α is zero in all instances except DCM (0.13).[35] DCM and nitrobenzene Kamlet-Abboud-Taft parameters are averages of different dye sets. Values of β and π* for **3** were obtained at 60 °C rather than room temperature.

It is important to note that the determination of the Kamlet-Abboud-Taft parameters was performed at an elevated temperature in the case of Cygnet 0.0 because of its high melting point. This can make the usual comparison between solvents biased by the thermosolvatochromic behaviour of the dyes.[36] However it should be appreciated that while the π* value for chlorinated solvents is quite temperature dependent,[36] the Kamlet-Abboud-Taft parameters of oxygenated solvents are much less so. For example literature data for ethanol shows that β decreases only slightly with each 25 °C increase in temperature, while π* falls even less significantly.[37] Therefore it interesting to note that Cygnet 0.0 has the Kamlet-Abboud-Taft parameter profile of a chlorinated solvent but at higher temperatures.

As with the Hansen solubility parameters, it is convenient to represent solvent polarity as a map using just two of the three scales. In the case of the Kamlet-Abboud-Taft solvatochromic parameters, α is sacrificed because the solvents of interest here are aprotic (Figure 3). The polarity of Cygnet 0.0 occupies an area of the solvent map not yet currently populated by any known bio-based solvents and no green solvents (as explained further in the Electronic Supporting Information, Figure S5).[38,39] This means Cygnet 0.0 could be an incredibly useful addition to the existing catalogue of bio-based solvents. In particular there are many examples of high temperature reaction chemistry that could benefit from the use of the Cygnet solvents in place of nitrobenzene for example.[40]

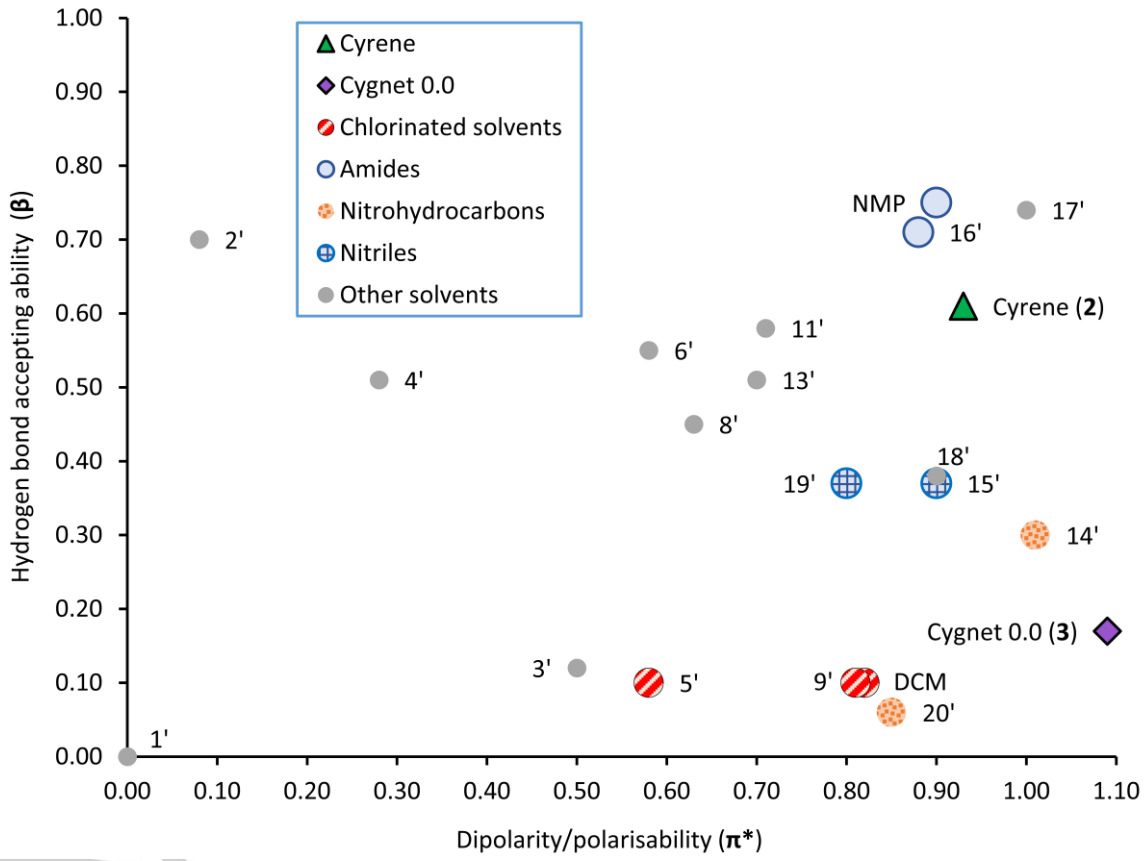

Figure 3. A Kamlet-Abboud-Taft polarity map. Key: See Figure 1. Data is tabulated in the Electronic Supporting Information (Table S5).

Test applications: Heck reaction and fluorination

The high dipolarity of Cygnet 0.0 could be used advantageously in a number of chemical transformations where polarised activated complexes must be stabilised by the solvent to provide acceptable reaction kinetics. The Heck reaction between methyl acrylate and iodobenzene to give methyl cinnamate is one example. Cross couplings are an important reaction in the pharmaceutical industry due to the high synthetic potential they provide.[41]

A linear solvation energy relationship (LSER) correlating the kinetics of this Heck reaction with π* is available from the literature,[9] vindicating the typical choice of highly polar solvents for cross coupling reactions. If π* is known the rate of reaction in a solvent can be estimated. To represent this, the horizontal axes in Figure 4 are scaled to be equivalent. Validation of the reaction confirmed the experimental initial rates of reaction (vertical axis, Figure 4) in Cyrene and Cygnet 0.0 (**3**) to be comparable to NMP and dimethyl sulphoxide, slightly below the estimations. Dichloromethane could not be added to the dataset because the reaction is conducted at 100 °C, whereas Cygnet 0.0 is capable of application under such conditions.

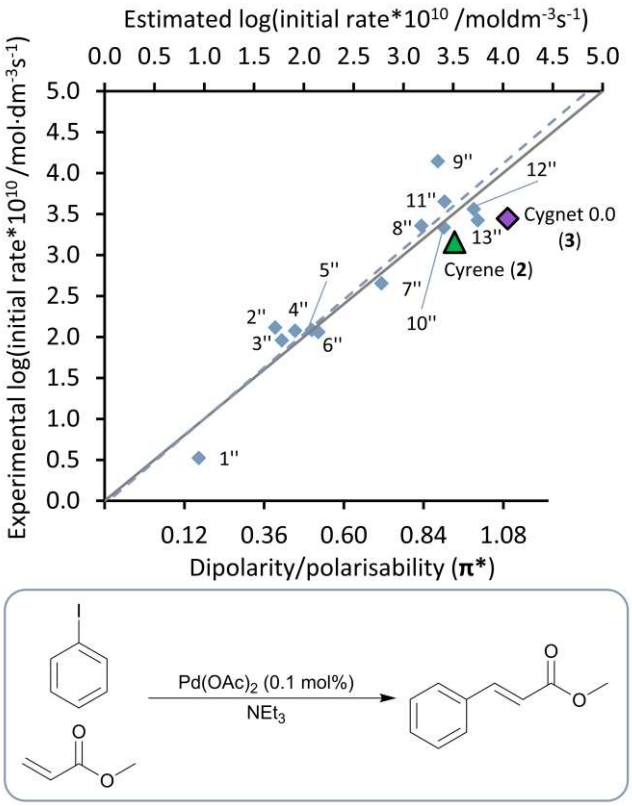

Figure 4. A LSER of the kinetics of the model Heck reaction (as shown) correlated with solvent dipolarity. An equivalence line between experimental and estimated reaction rates is drawn in grey. The actual data trend is given by the dashed line. Key: 1'', limonene; 2'', p-cymene; 3'', cyclopentyl methyl ether; 4'', diethyl carbonate; 5'', toluene; 6'', 1,4-dioxane; 7'', cyclohexanone; 8'', γ-valerolactone; 9'', DMF; 10'', propylene carbonate; 11'', NMP; 12'', ethylene carbonate; 13'', dimethyl sulphoxide.

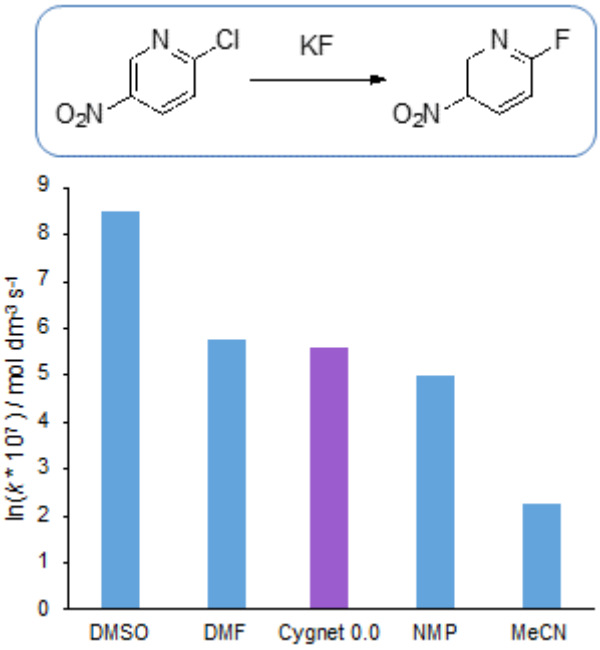

Figure 5. Reaction rates for the model fluorination reaction (as shown) for conventional dipolar aprotic solvents as well as Cygnet 0.0. Fluorination was performed at 85°C.

Another important application of dipolar aprotic solvents can be found in fluorination reactions, which are commonly used in the pharmaceutical industry. Greener methods of performing fluorination are in high demand, having been identified as a key green chemistry research area by the ACS GCI Pharmaceutical Roundtable.[42] Fluorine can most easily be introduced into an aromatic molecule via an S_NAr reaction in which the charged Meisenheimer intermediate must be stabilized by a dipolar aprotic solvent.[43]

To further test the suitability of Cygnet 0.0 in practical chemical transformation, its ability to promote an S_NAr fluorination reaction was compared against conventional dipolar aprotic solvents (Figure 5). Cygnet 0.0 was found to be a suitable solvent, providing kinetics comparable to those of DMF and performing better than NMP. This is an improvement over the performance of Cyrene in the same reaction, and shows the applicability of Cygnet 0.0 as a replacement solvent under standard reaction conditions.[7]

Economic considerations

While Cygnet 0.0 is not currently commercially available, its precursors, levoglucosenone and Cyrene, are now being manufactured by Circa Group Pty in the world's first scalable continuous process for making levoglucosenone from waste sawdust.[13] At the low production volumes expected in 2017, Cygnet 0.0 will sell at speciality chemical prices, but if the manufacture of levoglucosenone substantially increases and it becomes a platform molecule, then the price of this compound will drop significantly, possibly lower than €10/kg.

Conclusions

While there is rapidly increasing demand for safer and more sustainable solvents, the properties of commercially available bio-based solvents currently fill a limited proportion of the solvent space. Bio-based molecules such as Cygnet 0.0 and Cyrene are helping to cover the full range of solvent polarity through their unique properties. The variety of solvent properties expressed by levoglucosenone derivatives is potentially quite substantial, and our future studies will look to take advantage of this.

The use of different approaches to represent solvent polarity in this work has emphasised the importance of context. After all, it is the performance of the application that matters, be it a reaction, extraction, formulation, or cleaning product, not the identity of the solvent itself. When developing solvent replacements, not all the properties of the solvent to be substituted will be relevant. How these properties are defined and represented will change the conclusion. With this in mind it is essential to understand the role of the solvent in an application and the limitations of each interpretation of solvent polarity.

The primary disadvantage of Cygnet 0.0 is that (like ethylene carbonate for example) it is solid at room temperature. It is also miscible in water which is a concern for aqueous separations following reaction chemistry and other processes. However, it is a problem equally faced by many conventional solvents such as NMP.

The application of Cygnet 0.0 in two pharmaceutically relevant syntheses has again demonstrated the levoglucosenone platform is capable of producing valuable solvents, as was shown by the prior discovery of Cyrene.[7] Other possible applications for the Cygnet compounds include their use as chelators, fuel additives, and viscosity modifiers, all options that will be explored in subsequent studies.

Experimental Section

Experimental Details and computational methods are presented separately as Electronic Supporting Information.

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Keywords: Green chemistry • Solvents • Molecular modelling • Levoglucosenone • Solvatochromism

‡ The literature search (17/11/2015) was conducted using the Scopus® database for articles containing 'levoglucosenone' in the title, abstract, or as a keyword.

§ Bio-based content can be measured analytically by ^{14}C isotopic analysis, and is reported on the basis of carbon mass. A European standard technical report describing the procedure is available (CEN/TS 16640:2014), as is the ASTM standard D6866-12.

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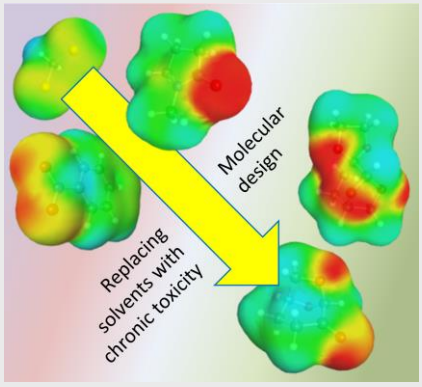

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