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Comparison of greenness and whiteness of selected mechanochemical and solution-based reactions using a new RGBsynt model†

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In analytical chemistry, the idea of assessing the "whiteness" of a method, which refers to the RGB model used in colour coding, has gained significant popularity in recent years. Whiteness represents the overall evaluation, which includes greenness (environmental impact) and functional features, represented by redness (analytical efficiency), and blueness (practicality). This work presents the first whiteness assessment model dedicated to chemical synthesis, called "RGBsynt", inspired by the metrics used in analytics. The assessment may be applied to a set of 2–10 methods, described by parameters such as yield, product purity, *E*-factor, ChlorTox, time-efficiency and energy demand, which refer to the three primary colours. The model is implemented in an easy-to-use Excel spreadsheet where users input the values of the mentioned parameters, and then data analysis, evaluation and results visualization are carried out fully automatically. The RGBsynt model was employed to compare 17 solution-based procedures for *O*- and *N*-alkylation, nucleophilic aromatic substitution, and *N*-sulfonylation of amines with their corresponding 17 mechanochemical alternatives. The selection of synthesis processes was preceded by a thorough literature review to ensure representative examples and reliable comparison of methods. The evaluation results clearly indicate the superiority of mechanochemistry, both in reducing environmental impact (greenness), and in overall potential (whiteness). The RGBsynt model might be considered as a simple and useful tool for evaluating synthesis methods, allowing comparison of various reactions based on empirical data.

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1. Introduction

1.1. Mechanochemistry

Reducing the risk associated with the use of chemical reagents that are hazardous to health and the environment is one of the main postulates of green chemistry.[1–3] Nevertheless, the use of organic solvents in synthesis processes to provide the appropriate reaction medium facilitating mass and heat transfer, ensuring high reaction yields, and reaction monitoring, but also enabling purification of obtained products is indispensable.

Various approaches have been proposed to reduce the amount of solvents in organic synthesis, among which mechanochemistry has been a focus of particular interest. In this approach chemical transformations occur upon direct absorption of mechanical energy supplied by grinding or milling substrates without or with a limited use of organic solvents.[4,5] In such procedures, conventional laboratory glassware and heaters are replaced by vibratory or planetary ball mills that facilitate surface interactions between reactants.

The application of mechanochemistry results in a drastic reduction in the volume of solvents used in a reaction setup, and facilitates the purification step, mainly by avoiding traditional solvent-consuming column chromatography. This method is increasingly acknowledged for its efficiency and safety. It also offers control over reaction selectivity and allows access to products that cannot be achieved using solution-based methods.[6] The contribution of mechanochemical methods to the preparation of active pharmaceutical ingredients (APIs) has resulted in the coining of the term "medicinal mechanochemistry".[7] Notably, this approach has expanded the medicinal chemistry toolbox for the generation of compound libraries.[8,9]

1.2. White chemistry and the RGB model

Currently, many indicators and models are known allowing the greenness of laboratory procedures to be assessed and

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compared.[10] Of note, most of the available models are limited to greenness itself, *i.e.* they consider only parameters related to environmental impact and safety, thus omitting other criteria determining the functionality of the method. As a result, positive verification of greenness does not necessarily mean that a given laboratory procedure is holistically better. This issue has been discussed more deeply in our recent article published in *Green Chemistry*, presenting the Unified Greenness Theory (UG-theory),[11] which is an attempt to comprehensively describe greenness from a theoretical perspective.

It is worth noting that a recent trend in analytical chemistry is the distinction between the greenness of a method and its "whiteness", which represents the overall picture comprising both its greenness and functionality (usefulness). In analogy to the red–green–blue (RGB) model used in electronics for colour coding, green is one of the three primary attributes (colours), with the other two being red and blue.[12] They refer to functional characteristics. Red indicates analytical parameters determined during method validation, *e.g.*, accuracy, precision and sensitivity, while blue indicates practical features and cost effectiveness. As a result, determining that a certain method is whiter means that it is overall better suited to a given application and its average score for all considered criteria is better. This approach is known as white analytical chemistry.[13] In our recent paper we also argue that "whiteness" is a more comprehensive and clear-cut term than "sustainability" – which is used in different contexts and does not embrace all functional aspects,[11] and that "whiteness" as a general term can be applied beyond analytics.

Obviously, the most desirable scenario is to find a method that is both greener and more functional. However, this may be impossible and may require us finding a "golden mean" represented by whiteness. Therefore, we need to use appropriate metrics to assess whiteness in an objective way, allowing us to establish the right compromise between green, red, and blue criteria.

One of the three available versions of the RGB model can be used for this purpose. The versions published in 2019,[12] and 2021,[13] provide some flexibility and assume that the assessment of a given criterion is made by the user by awarding an appropriate number of points based on available data. The latest version from 2024, called "RGBfast",[14] was designed to automate the assessment process and eliminate the need to award points, thus reducing the possibility of manipulation. In RGBfast, six main criteria are assessed, covered by all 3 colours: trueness, precision, limit of detection, ChlorTox (see section 2.2.),[15] energy demand and sample throughput. The reference point for the assessment of a given criterion is the average value of a given parameter obtained for the set of all compared methods (there must be at least 2 methods to apply this model).

This article aims at presenting a new whiteness assessment model, called "RGBsynt", which is used to address chemical synthesis methods (hence "synt"). Its structure has been adapted from the RGBfast model, which was originally developed for analysts. Our motivation for developing a new version of the RGB model aimed at chemical synthesis was the significant analogy of analytical and synthetic procedures, differing mainly in the red functional criteria, which allows the model, upon some modification, to be easily implemented in a totally new research domain. To illustrate and validate RGBsynt, we compared various mechanochemical and solution-based methods leading to analogous products.

2. Materials and methods

2.1 RGBsynt model

2.1.1 Criteria selection. Similarly to RGBfast, in the RGBsynt model the assessment is carried out on the basis of 6 criteria, but aligned with chemical synthesis procedures. Although the number of parameters that affect the overall usability and greenness of a synthesis method is much greater, not all of them are crucial. We have selected those that we believe are the most important and easy to quantify. Thanks to this, the model remains easy to use and user-friendly. Yield (criterion R1) and product purity (R2), both expressed in %, were selected as red criteria. These are key parameters that determine the effectiveness of a synthesis procedure, routinely calculated and provided in method descriptions. Another criterion is the *E*-factor, a popular green chemistry metric calculated as the ratio of the mass of all waste to the mass of the reaction product obtained.[16] This criterion was marked as simultaneously green and blue (G1/B1), because in fact it refers both to greenness – the less waste is produced, the lower the environmental burden, but also to the blue attribute indicating practicality – because a smaller mass of waste usually means lower costs and easier application of the procedure from the practical perspective. The next green criterion is the ChlorTox Scale (G2), a greenness indicator recently introduced in analytical chemistry,[15] which can also be successfully applied to synthetic chemistry. It indicates the overall risk associated with chemical reagents, taking into account their quantities and individual hazards described in safety data sheets (details are given in section 2.1.2.). Another blue criterion is time-efficiency (B2), *i.e.* the total time required to carry out all stages of a synthesis procedure (from setting-up reactions to isolation of pure products). The last criterion is the estimated energy consumption (G3/B3). Lower energy consumption means a smaller carbon footprint of the energetic requirements,[17] but also lower costs related to energy demand and less complicated laboratory equipment – which translates into the cost-effectiveness of the method. Therefore, this criterion also corresponds to two colours: green and blue. Despite accurate measurement of electricity consumption being possible, it is difficult to implement in practice and it is rarely reported. Therefore, the RGBsynt model is based on a simplified way of estimating energy consumption (see section 2.1.3 for details).

To facilitate the use of RGBsynt, we designed a special Excel spreadsheet containing coded formulas, designated fields for data entry, and functions for visualization of the results. The

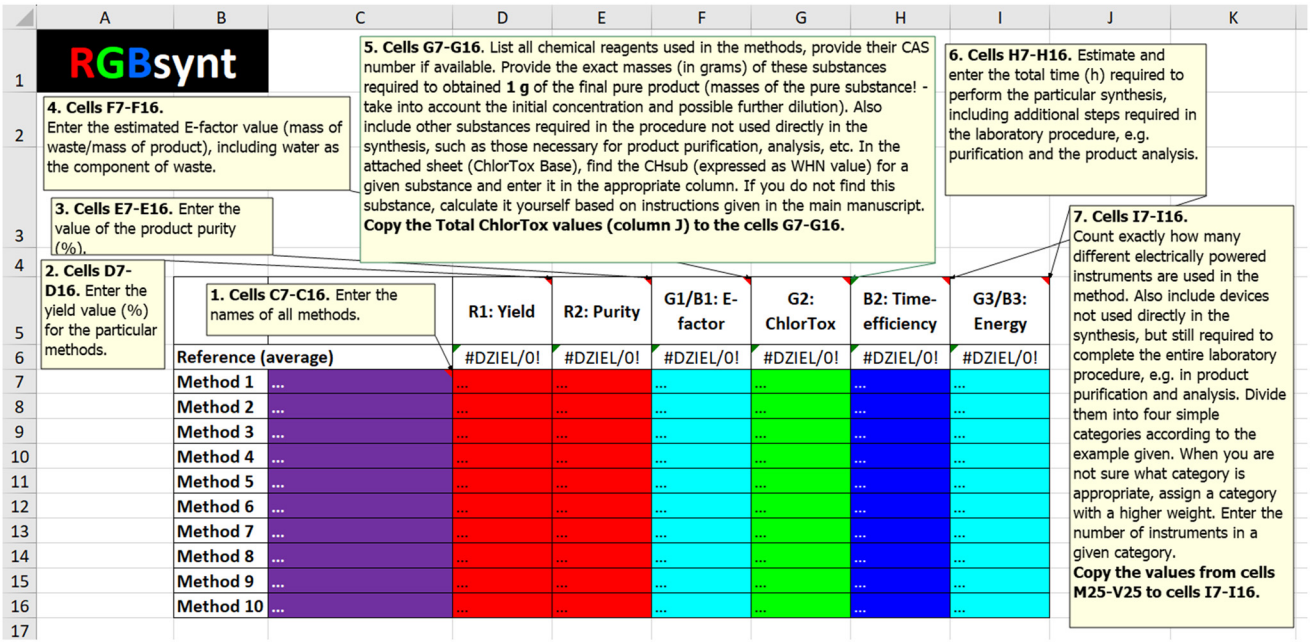

Fig. 1 A screenshot of the Excel spreadsheet with the RGBsynt model encoded showing the main table for data input. The assessment can be performed for 2–10 methods at the same time. To perform this, the values of six parameters only are needed. Guidelines for the individual criteria are described in the comments (1–7), and in the main text of the manuscript. After entering the data, everything is automated: the assessment results are presented in the form of automatically formatted tables/pictograms (see subsequent manuscript sections). Note that some parts of the spreadsheet are not shown in this figure, *e.g.* tables for calculating ChlorTox values and energy demands.

table containing the place for user input, including the six aforementioned parameters, is shown in Fig. 1. The Excel spreadsheet containing an empty template and completed sheets for all studied methods is attached as a supplement to this article.†

2.1.2. ChlorTox Scale. The Chloroform-oriented Toxicity Estimation Scale (ChlorTox Scale) is a greenness indicator aimed at estimating the chemical risk of a laboratory method/procedure in a comprehensive yet simple way.[15] To date, it has been used to assess analytical methods, but it is also suitable for evaluating synthesis procedures. In this article we present the first application of this metric in chemical synthesis, and therefore, this section provides its detailed description.

The basis of this approach is to refer hazards related to the substance of interest to the hazards identified for the standard substance – chloroform, and to consider the precisely known mass of the substance used in the method. The results are expressed as the equivalent mass of chloroform, indicating the degree of estimated chemical risk. This calculation is performed using the following simple equation:

$$\text{ChlorTox} = \frac{\text{CH}_{\text{sub}}}{\text{CH}_{\text{CHCl}_3}} \cdot m_{\text{sub}} \quad (1)$$

where the ChlorTox value, expressed in the mass of chloroform (g), reflects the degree of chemical risk associated with the substance of interest, considering its properties (hazards) and the amount used. $\text{CH}_{\text{sub}}/\text{CH}_{\text{CHCl}_3}$ represents the relative chemical hazard (CH) of using the assessed substance in relation to chloroform, while m_{sub} is the mass of the pure substance of interest required to obtain 1 g of the final product (any dilutions should be taken into account).

The ChlorTox values characterizing different substances can be combined to express the total chemical risk predicted for the entire method (Total ChlorTox). The ChlorTox value has a purely theoretical meaning; it is not directly reflected in reality, but it indicates the general scale of potential risk. For example, a method with a Total ChlorTox value of 10 g indicates a risk equivalent to a method using 10 g of pure chloroform as the sole hazardous chemical reagent. To facilitate rapid evaluation of the method using the ChlorTox Scale, a simple model for quantifying general chemical hazard, called the Weighted Hazards Number (WHN), was developed. This model involves gathering relevant information on the hazards posed by given chemical reagents from publicly available safety data sheets, presented in the commonly used Globally Harmonized System of Classification and Labelling of Chemicals (GHS) format. The GHS covers hazards associated with storage and transport, direct health hazards (*e.g.*, poisoning, chemical burns, irritation, carcinogenicity), and environmental hazards (*e.g.*, impact on model species of microorganisms, plants, and animals). In addition, the hazard categories are further classified by degree, ranging from 1 to 4, with category 1 indicating the highest hazard level (the greatest potential danger), and category 4 representing the lowest. This infor-

mation is always presented in Section 2 (Hazards identification) of these safety data sheets.

In the WHN approach, the overall hazard of the substance of interest (CH_{sub}) and chloroform (CH_{CHCl_3}) is expressed by its WHN value. The WHN is calculated as the sum of the hazards identified in Section 2 of the relevant safety data sheet (in its GHS format), with weights reflecting the degree of potential danger (hazard category): 1 for category 1, 0.75 for category 2, 0.5 for category 3 and 0.25 for category 4:

$$\mathrm{WHN}(CH_{sub}) = 1 \cdot N_{cat1} + 0.75 \cdot N_{cat2} + 0.5 \cdot N_{cat3} + 0.25 \cdot N_{cat4} \quad (2)$$

where N_{cat} is the number of hazards of a given category.

Noticeably, hazard data provided by different reagent manufacturers may vary quite considerably. There are two ways to ensure the consistency of the assessment. The first is to choose one preferred data supplier. Another approach, which seems more rigorous and objective, is to take into account data published for a given substance by different suppliers, and then calculate the average WHN value. Safety data sheets for a given substance can be easily searched using freely available tools, *e.g.*, the search engine on chemicalsafety.com.[18] In addition, comprehensive data for nearly 700 different reagents, including ready-to-use averaged WHN values, have been collected and published in a specially designed database – ChlorTox Base.[19]

The Excel file containing ChlorTox Base has been integrated (as one of the sheets) into RGBsynt, allowing users to quickly access information on commonly used reagents. If a reagent is not included in the database, it is recommended that one independently calculates its WHN value (eqn (2)). It is then recommended to average the values obtained from the data sheets of different manufacturers. If this is not possible, *e.g.* when a given reagent has not yet been characterized, it is recommended that the value of WHN = 5.83, corresponding to chloroform, is used. Since chloroform is a highly toxic reference reagent, using this value helps prevent underestimation of chemical risk. RGBsynt users may also adopt an alternative method of determining relative chemical hazard ($CH_{sub}/CHCl_3$), different from WHN, as long as it is reasonable and well described.

2.1.3. Estimation of energy demand. The energy demand in the RGBsynt model is calculated in a straightforward and user-friendly manner. Calculation of Estimated Energy Demand (EED) requires counting how many electrically powered instruments are used in total at all stages of the synthesis procedure. Then, these instruments are divided into 4 categories, which are assigned different weights: low-power instruments – weight 1, medium-power instruments – weight 2, high-power instruments – weight 3, and very high-power instruments – weight 4. The examples of instruments, which can be classified into these particular categories, are provided in the attached Excel template and in Table 11 of the ESI†). Additionally, the formula includes the square root of total time of the synthesis procedure, since the longer it is, the greater the amount of energy that is likely to be consumed by the instruments used (see eqn (3)):

$$\mathrm{EED} = (1 \cdot N_{cat1} + 2 \cdot N_{cat2} + 3 \cdot N_{cat3} + 4 \cdot N_{cat4}) \cdot \sqrt{t_{tot}} \quad (3)$$

where N_{cat} is the number of instruments classified in a given category, and t_{tot} is the total procedure time (h). The use of the square root means that the weighted number of instruments is more important than the time of the procedure. This is justified by the fact that the most energy-intensive instruments, *e.g.* advanced spectrometers, are not used all the time, so the real energy consumption is usually not linearly dependent on the duration of the whole procedure.

It should be emphasized that this approach does not require estimating the operating time of each individual device, because, first, it would significantly complicate the evaluation process, and second, some instruments require being placed in stand-by mode, which could introduce some inconsistency. The adopted formula (eqn (3)) seems to us to be a good compromise between simplicity and reliability of the assessment.

2.1.4. Data analysis and visualization. The basic assumption of the RGBsynt model is that at least two methods are assessed against each other. The values of the relevant criteria (input table shown in Fig. 1) are compared to the arithmetic average obtained for all compared methods, which depends on the specificity of the methods. There is an appropriate mathematical rule allowing the assessment results (score values) to be narrowed down to 0–100 in each case (eqn (4)):

$$\mathrm{Score} = 100 \times \frac{1}{1 + \frac{\mathrm{result}}{\mathrm{average\ result}}} \quad (4)$$

where result is the value of a given criterion for the assessed method, and average result is the arithmetic mean for all methods. In the case of yield and product purity (R1 and R2), result is automatically calculated as the difference between 100 and the percentage values of these parameters (*e.g.*, for yield = 80% the result is 100–80 = 20). For that reason, for all six criteria, the higher the result value, the worse the characteristics of the method.

Adopting this formula allows for a simple interpretation of the score. When the criterion is rated as being close to ideal and the result value is extremely low in comparison with the average result, the score is close to 100; when the result and average result show the same value, the score is 50; when the result is worse (higher) than the average result, the score is <50 (note that score = 0 is unattainable in practice, as it would require the method to perform infinitely poorly).

The saturation of a given primary colour and the overall whiteness are calculated as the geometric average of the corresponding score values (eqn (5)–(8)). The outcomes are presented by the model in the tables/pictograms shown in Fig. 2, as well as in the bar chart shown in Fig. 3. The G1/B1 and G3/B3 criteria (which are assigned to two colours simultaneously), have the same importance for the final result (whiteness) as

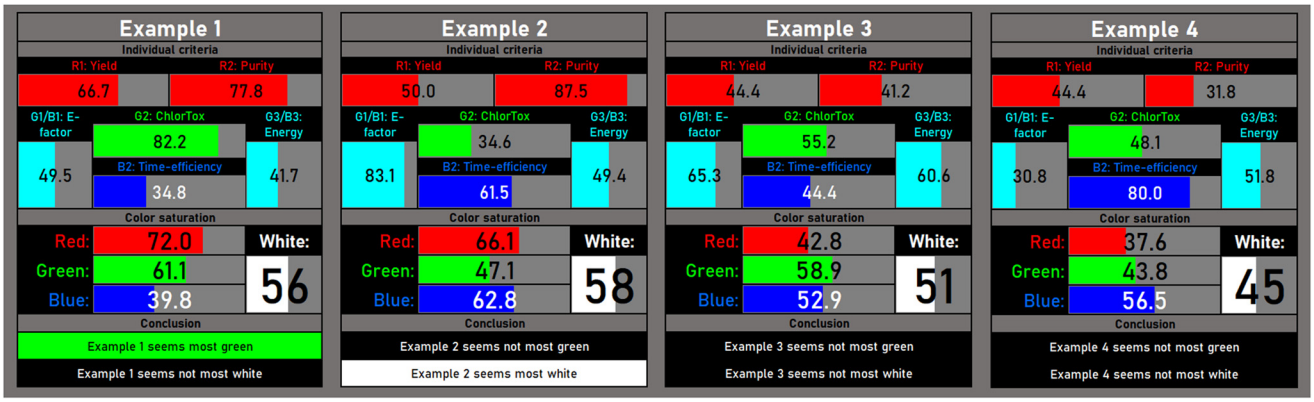

Fig. 2 Results from evaluating 4 examples of methods using RGBsynt, presented in automatically formatted tables/pictograms, copied from the Excel spreadsheet. The assessment of a particular criterion is given as a number from 0–100 and is additionally reflected by the length of the coloured bar filling the cell. The middle part shows the average results of the assessment of red, green and blue criteria, as well as the overall assessment, *i.e.* whiteness. In the lower part, the model automatically indicates the methods that turned out to be the greenest and whitest in the comparison.

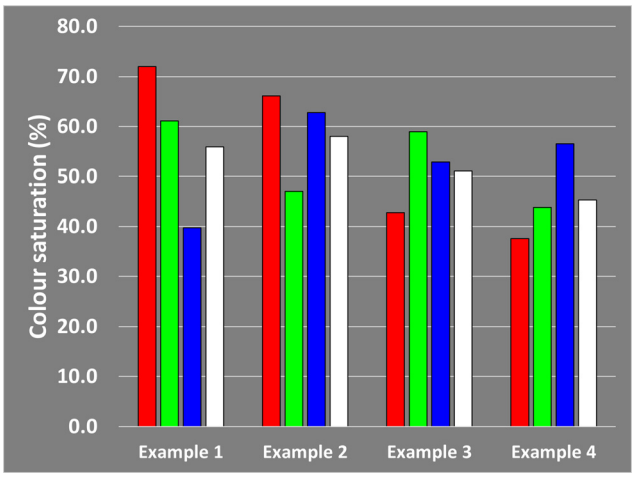

Fig. 3 The results of the evaluation of individual colours (red, green, blue, and white, respectively) for 4 examples of methods shown in a bar chart (created automatically in the Excel spreadsheet).

all other criteria. Concurrently, G2 and B2 are twice as important from the point of view of greenness and blueness considered individually (eqn (6) and (7)). Thanks to this, the share of each parameter in the model is equal, and the tables/pictograms (Fig. 2) reflect well the model's structure:

$$\text{Redness} = \sqrt[2]{\text{score}_{R1} \cdot \text{score}_{R2}} \quad (5)$$

where R1 is yield, and R2 is product purity;

$$\text{Greenness} = \sqrt[4]{\text{score}_{\text{G1/B1}} \cdot \text{score}_{\text{G2}}{}^2 \cdot \text{score}_{\text{G3/B3}}} \quad (6)$$

where G1/B1 is *E*-factor, G2 is ChlorTox, and G3/B3 is estimated energy demand;

$$\text{Blueness} = \sqrt[4]{\text{score}_{\text{G1/B1}} \cdot \text{score}_{\text{B2}}{}^2 \cdot \text{score}_{\text{G3/B3}}} \quad (7)$$

where G1/B1 is *E*-factor, B2 is time-efficiency (total time of the procedure), and G3/B3 is estimated energy demand; and

$$\text{Whiteness} = \sqrt[6]{\text{score}_{\text{R1}} \cdot \text{score}_{\text{R2}} \cdot \text{score}_{\text{G1/B1}} \cdot \text{score}_{\text{G2}} \cdot \text{score}_{\text{B2}} \cdot \text{score}_{\text{G3/B3}}} \quad (8)$$

Of note, the use of the geometric average guarantees consistency and balances the method's potential without introducing significant bias. For example, while the arithmetic mean of the sets (1,4,10) and (5,5,5) is the same, *i.e.* 5, the geometric mean for the first set is approximately 3.4, while for the second it remains 5. A better result was obtained for the second set, where the values show less variation. In the first set, the value "1" may constitute a significant bottleneck of the method, excluding its use. The adopted model therefore rewards the search for the reasonable compromise between individual criteria and primary colours.

Another issue is the use of appropriate terminology. In a recently published article about UG-theory,[11] we devoted significant attention to the theoretical analysis of the "greenness" concept, pointing out three different interpretations of the "state of being green": purist, pragmatic, and formal. Now it is only worth mentioning that there is no universal correct interpretation, with each of them having its own advantages and disadvantages. The RGBsynt model clearly indicates which method appears more/less green or white, or which method appears to be the best of all (the greenest or whitest), but does not assume any specific interpretation of the "state of being green or white". In other words, the RGBsynt model does not explicitly state that "some method appears generally green or white" as this would require certain assumptions that were deliberately avoided to provide the user with a freedom of choice in how they want to see greenness and whiteness as a state.

2.1.5. Decision making and cut-off thresholds. Questions arise regarding the practical application of the RGBsynt model – What should we focus on when making decisions? Should whiteness be the universal criterion for choosing a synthesis method? Should whiteness be always more important than greenness? In our opinion, in decision making the model should not be treated as an oracle. According to our primary assumption, each criterion is of equal importance, but in practice, depending on what is the assessed object and how its planned application looks, some criteria may be more important than others. What is worth emphasizing is that from the point of view of green chemistry and promoted initiatives such as the EU's "safe and sustainable by design" framework, green criteria should be considered with a priority allowing the developed procedures to be "benign by design". Therefore, we recommend adjusting a decision key to the given problem each time. This can take into account not only whiteness (as a measure of the total potential) and greenness, but also the values of individual parameters. For example, such a key could include an initial pre-selection of available synthesis procedures, assuming a certain ChlorTox Scale cut-off value indicating the total chemical risk, *e.g.* 100 g (equivalent to 100 grams of chloroform), and then selecting the best option from those meeting this criterion in terms of whiteness. There are many possibilities; our goal is not to impose any specific option.

2.2. Generation of source data for the RGBsynt model

As in the case of RGBfast, source data are critical for the objective method evaluation with the aid of RGBsynt. Owing to the vast landscape of known organic reactions used in drug discovery, we selected processes that can be performed using both mechanochemical and solution-based approaches to enable their direct comparison and verify mechanochemistry's merits as presented in the newest literature.[20] We chose *O*- and *N*-alkylation, nucleophilic aromatic substitution (S_NAr) and sulfonylation of amines, which represent the most frequently used chemical transformations performed by medicinal chemists for generation of biologically active compounds (Fig. 4, Stage 1).[21]

The limited number of available mechanochemical methods for medicinal chemistry purposes restricted our data source to our in-house reported protocols (Fig. 5).[9,22,23] To assess the representativeness of our routinely used solution-based protocols (alternatives to mechanochemical methods), we gathered data from 80 solution-based procedures reported in the literature and patents (Fig. 4, Stage 2A). To ensure unbiased comparison, we selected only in-batch methods that provided the same derivatives or, in the absence of reports, their structurally related analogues. Then, solution-based protocols for each selected reaction were systematically compiled (Tables 1–4 in the ESI†), using conventional parameters employed by synthetic chemists, such as type of reagents and solvents, reaction conditions (time, temperature), work-up and purification procedures, as well as yields, purity and scale. Assuming the isolated yield as a reliable parameter to assess the quality of a synthesis protocol, we then calculated the average value for each type of in-batch chemical transformations from the literature review and compared it to isolated yields obtained accordingly to in-house solution-based procedures (Fig. 4, Stage 2B).[24–26] The results confirmed that our routinely used in-solution protocols are representative and consistent with those reported by other research groups (Tables 1–4 in the ESI†).

In parallel, to expand the set of evaluated methods for RGBsynt assessment (Fig. 4, Stage 3A), we adapted the reported *O*- and *N*-alkylation mechanochemical procedures for the synthesis of propranolol (a first-in-class β-blocker) and brexpiprazole (a third-generation antipsychotic; see structures in Fig. 5). Additionally, we optimized S_NAr and sulfonylation reactions in the ball mill for key intermediates of the antidepressant vortioxetine and the anti-inflammatory agent sulfasalazine, respectively (Fig. 5). To meet the objective criteria, we selected in-solution methods for synthesis of the abovementioned drugs and drug intermediates from the literature review (Tables 5–9 in the ESI†). Due to the limitation in finding detailed and reliable experimental procedures reporting on amounts of reagents and solvents used, reaction condition work-up/purification step protocols and yields, patents were excluded from the analysis. The selection was based on the following criteria: (i) laboratory scale (up to 20 g), (ii) the use of the least toxic reagents and solvents; (iii) cost-effective and commercially available substrates (excluding explosives and highly flammable reagents), (iv) the shortest reaction time and lowest reaction temperature and (v) smooth work-up procedures (*e.g.*, extraction and/or crystallization) for purification, excluding column chromatography methods where possible. This enabled the identification of high-quality in-batch methods suitable for the comparison with the newly developed mechanochemical procedures (Fig. 4, Stage 3B).[27–31]

Finally, the 17 known and newly developed mechanochemical reactions were compared with the 17 solution-based alternatives in terms of their greenness and whiteness, using

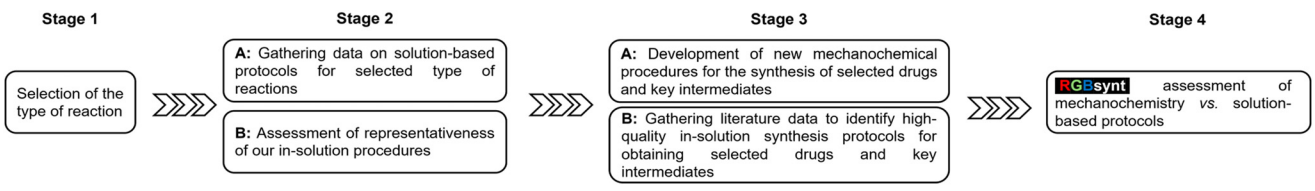

Fig. 4 Graphic representation of RGBsynt model source data: from the selection of synthetic protocols to the assessment of synthesis methods using the RGBsynt model.

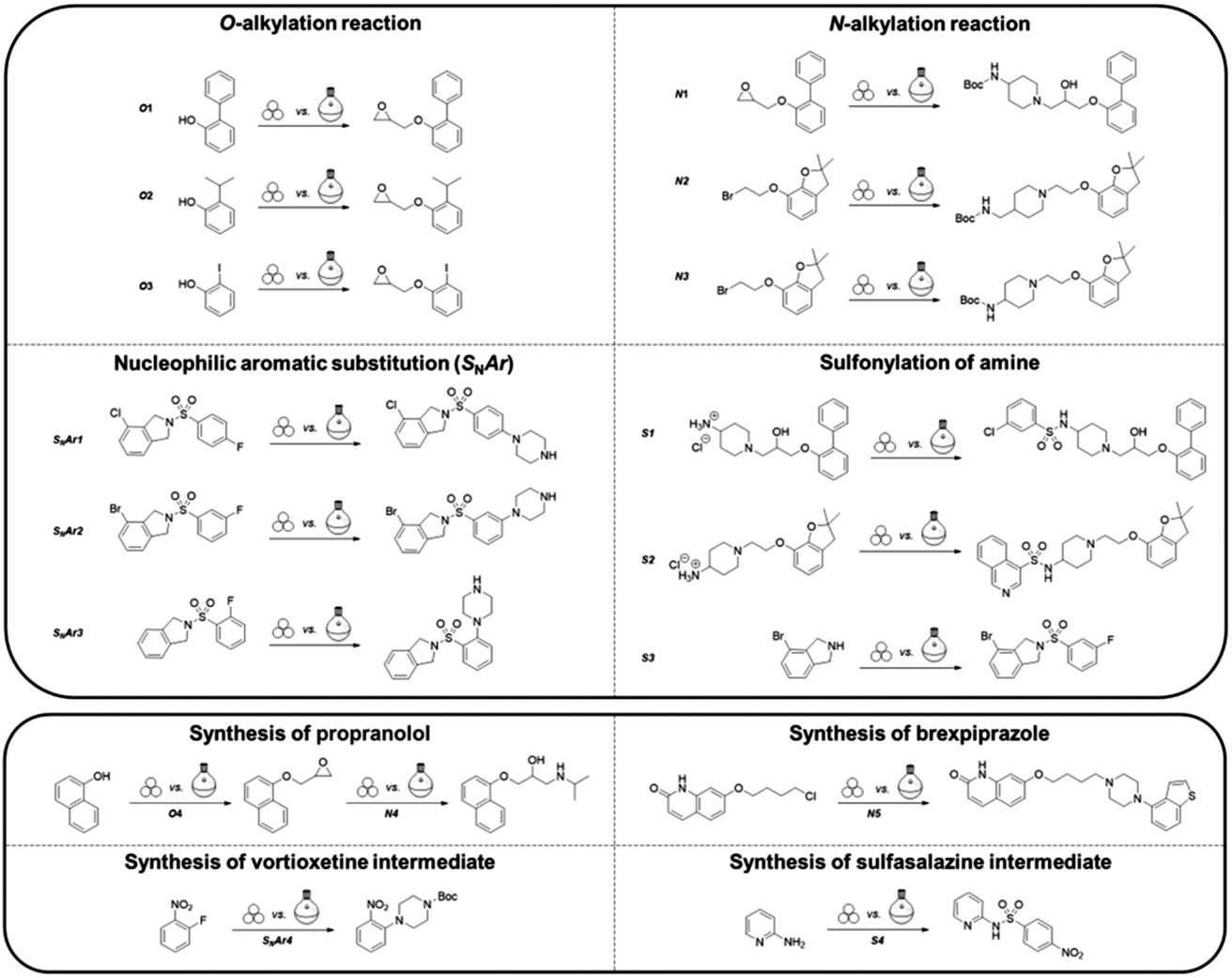

Fig. 5 Selected reactions for verifying the greenness and whiteness of the mechanochemical and solvent-based methods using the RGBsynt model. Experimental conditions for the presented mechanochemical *O*-alkylation (*O*1–3), *N*-alkylation (*N*1–3), nucleophile aromatic substitutions (S_NAr1–3), and sulfonylation (*S*1–3) reactions were taken from our previously reported data.[9,22,23] Newly developed synthetic procedures for obtaining selected drugs – propranolol and brexipiprazole as well as intermediates of vortioxetine and sulfasalazine – are presented in detail in the ESI.† Solvent-based chemical transformations are in accordance with in-house protocols,[23–26] and the literature data.[27–31]

the RGBsynt model (Fig. 4, Stage 4). The experimental details referring to all the reactions disclosed herein are shown in the ESI.†

2.3. Experimental section

All mechanochemical reactions were carried out in a Retsch Mixer Mill MM 400 vibratory ball-mill (Retsch GmbH, Haan, Germany) operated at 30 Hz. Reactions were conducted in stainless steel or PTFE jars with a volume of either 10 mL or 35 mL, containing one stainless steel ball (φ_{ball} = 1.5 cm). Milling load is defined as the sum of the mass of the reactants per free volume in the jar and was equal to 15, 45 or 90 mg mL^{-1}. Total mass of reagents used was 125 mg (10 mL jar) or alternatively 500 mg, 1.5 g or 3 g (in the 35 mL jar). All reactions carried out using the vibratory ball-mill were performed under air and at ambient temperature.

HPLC analyses were performed by using an Arc Waters System (Waters Corporation, Milford, MA, USA) equipped with a UV/Vis PDA spectrophotometric detector. Spectra were analysed in the 200–800 nm range with 1.2 nm resolution. Chromatographic separations were carried out using a Chromolith SpeedROD RP 18 column with dimensions of 4.6 × 50 mm and particle size of 1.7 μm. The column was maintained at 40 °C, and eluted under gradient conditions from 95% to 0% with eluent A over 3 min, at a flow rate of 3 mL min^{-1}. Eluent A was water/formic acid (0.1%, v/v); eluent B was acetonitrile/formic acid (0.1%, v/v).

Mass spectra were recorded using a UPLC-MS/MS system comprising a Waters Acquity Premier instrument coupled to a Waters Xevo TQ-S Cronos mass spectrometer (electrospray ionization mode, ESI). The Analyses were carried out using an Acquity UPLC BEH (bridged ethylene hybrid) C18 column (2.1

× 100 mm, and 1.7 μm particle size), equipped with an Acquity UPLC BEH C18 VanGuard pre-column (2.1 × 5 mm, and 1.7 μm particle size). The column was maintained at 40 °C, and eluted under gradient conditions from 95% to 0% with eluent A over 10 min, at a flow rate of 0.3 mL min^{-1}. Eluent A was water/formic acid (0.1%, v/v); eluent B was acetonitrile/formic acid (0.1%, v/v). Chromatograms were recorded using a Waters eλ PDA detector. Spectra were analyzed in the 200–500 nm range with 1.2 nm resolution and sampling rate of 20 points per second. MS detection settings of the Waters Xevo TQ-S Cronos mass spectrometer were as follows: source temperature 150 °C, desolvation temperature 350 °C, desolvation gas flow rate 600 L h^{-1}, cone gas flow 100 L h^{-1}, capillary potential 3.00 kV, cone potential 30 V. Nitrogen was used as both the nebulizing and drying gas. The data were obtained in scan mode ranging from 50 to 1000 *m*/*z* in 0.5 s time intervals. Data acquisition software was MassLynx V 4.2 (Waters). ^{1}H-NMR spectra were respectively recorded using a JEOL JNM-ECZR500 RS1 instrument (ECZR version) at 500 MHz (JOEL Ltd, Tokyo, Japan), and reported in ppm using deuterated solvent for calibration ($CDCl_3$ or DMSO-d_6). The other experimental details are shown in the ESI.†

2.4. Optimization of mechanochemical protocols for the synthesis of selected drugs and intermediates

To demonstrate the usefulness of RGBsynt in the evaluation of new synthetic methods, previously reported mechanochemical protocols were adapted for the laboratory-scale synthesis of propranolol, brexpiprazole, and the key intermediates of vortioxetine and sulfasalazine. In general, all the newly developed procedures enabled us to obtain pure products in high yields (>85%) by simple and routine extraction or filtration from the milling jar mitigating the use of column chromatography purification.

2.4.1. Mechanosynthesis of propranolol. The first step involved the mechanochemical *O*-alkylation of α-naphthol (1 equiv.) with epichlorohydrin (2 equiv.) in the presence of potassium carbonate at room temperature. Surprisingly, application of a previously reported mechanochemical protocol resulted in the formation of a dimer (up to 30%), while the desired product was obtained in unsatisfactory yield. In contrast, full conversion was achieved by prior milling of α-naphthol with sodium *tert*-butoxide followed by alkylation of the corresponding phenolate in the presence of an excess of epichlorohydrin. In the next step, optimization of our previously reported *N*-alkylation protocol for the nucleophilic substitution of oxirane in a ball mill was required, due to the high volatility of isopropylamine at low temperature. This issue was resolved by the addition of an excess of nucleophile (3 × 4 equiv.) in three portions at 1 hour intervals, which ensured full conversion of the reagents (up to 97%) yielding propranolol with very high purity (>95%).

2.4.2. Mechanosynthesis of brexpiprazole. An increasing number of mechanochemical procedures for the *N*-alkylation of Boc-protected alicyclic diamines with various halogenoalkanes in the presence of a base and/or auxiliary reagents (*e.g.*, zeolite) have been reported so far.[32] In our case, milling of the 7-(4-chlorobutoxy)quinolin-2(1*H*)-one with a commercially available arylpiperazine derivative at room temperature for 90 minutes in a stoichiometric ratio, yielded pure brexpiprazole in high yield (94%). Of note, the use of nontoxic potassium carbonate was sufficient to improve the rheology of the reaction and facilitate the recovery of the product from the jar.

2.4.3. Mechanosynthesis of *tert*-butyl 4-(2-nitrophenyl) piperazine-1-carboxylate (vortioxetine intermediate). Among the widely used synthetic approaches for obtaining Boc-protected 4-(2-nitrophenyl)piperazine, an intermediate of the antidepressant vortioxetine, one of the most efficient methods involves nucleophilic aromatic substitution. In contrast to our recently described procedure, the desired compound was mechanochemically synthesized by milling 2-fluoro-nitrobenzene with an excess of Boc-piperazine (3 equiv.) at room temperature, without the need of liquid-assisted grinding (*e.g.*, acetonitrile or dimethyl sulfoxide as lubricants). After purification of the crude product by extraction with ethyl acetate, this key intermediate was obtained in high purity and yield (95%).

2.4.4. Mechanosynthesis of 4-nitro-*N*-(pyridin-2-yl)benzenesulfonamide (sulfasalazine intermediate). Previously reported mechanochemical procedures[33] for yielding sulfonamide moieties starting from primary or secondary aliphatic amines were adapted, for the first time, to the sulfonylation of an aniline derivative. Simple milling of 2-aminopyridine (1 equiv.), 4 nitrobenzenesulfonyl chloride (1.3 equiv.) and potassium carbonate (3 equiv.) for 15 minutes resulted in complete conversion of the substrates into a sulfasalazine intermediate. The desired compound was obtained in high yield (86%) and purity after simple precipitation upon addition of 5% aqueous solution of hydrochloric acid.

3. Results and discussion

The model and all assessment data were collected in the Excel and Word files, which are attached as ESI.† The first Excel spreadsheet serves as a legend for the other sheets. This section discusses the most significant of the differences between the solution-based methodology and mechanochemistry, along with explanations of their underlying causes.

The assessment results shown in Fig. 6 and 7 clearly indicate that the mechanochemical approach is both greener and whiter, *i.e.* better overall. Among the criteria divided into three attributes, the differences observed for the red parameters were relatively the smallest. In particular, product purity was usually similar in both reaction cases, although yield values were almost always higher for mechanochemical reactions. The largest differences were recorded for the remaining green and blue criteria.

The *E*-factor and ChlorTox values were significantly lower (*i.e.*, better) for the mechanochemical methods in each case. This improvement is primarily due to the elimination of column chromatography purification steps, which are typically

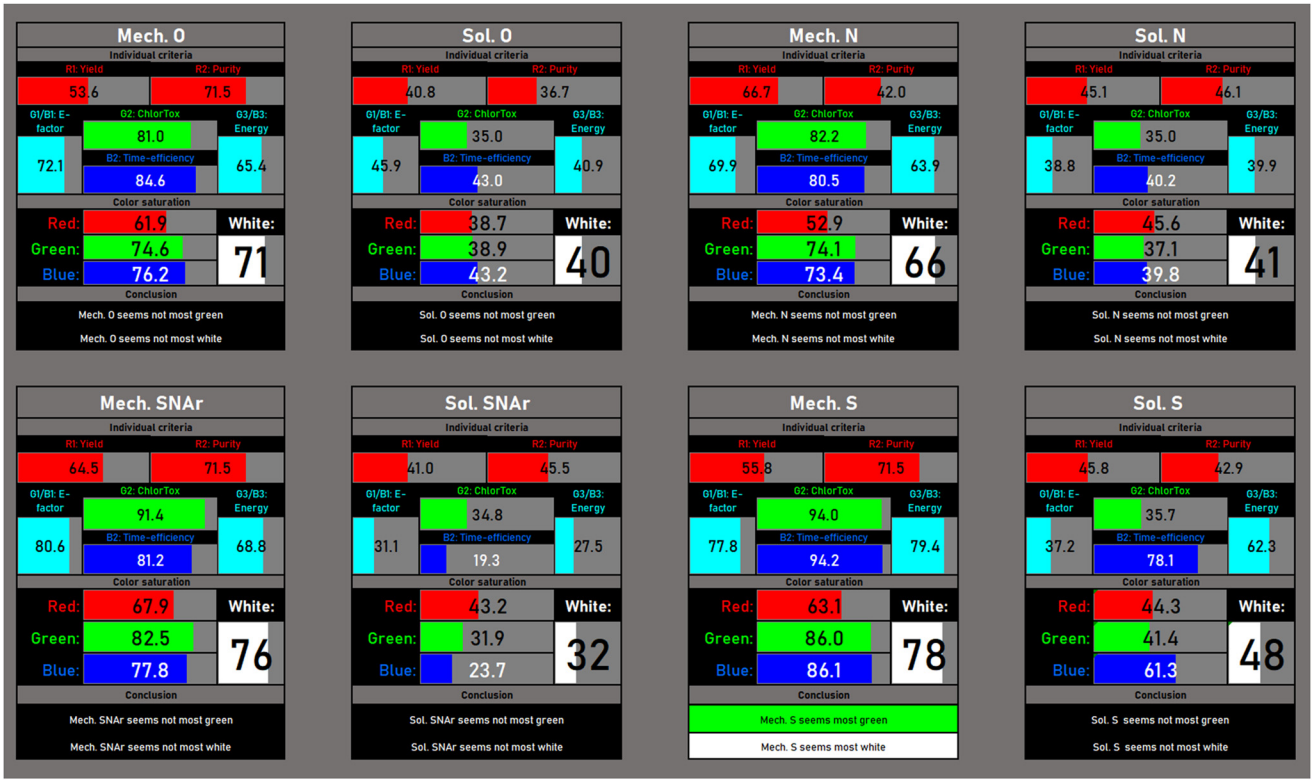

Fig. 6 Results of the assessment using the RGBsynt model for various types of synthesis carried out as mechanochemical (Mech.) and solution-based (Sol.) reactions, acquired as averaged values of the input data (each type of reaction included 4 or 5 unit procedures). The mechanochemical and solution-based procedures corresponded to the same products; O – *O*-alkylation, N – *N*-alkylation, SNAr – nucleophilic aromatic substitution, *S* – sulfonylation.

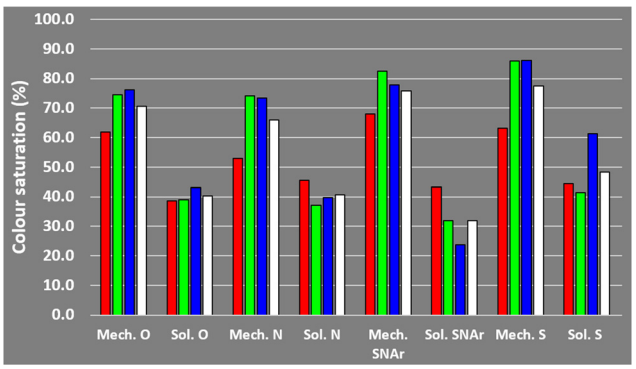

Fig. 7 Results of assessing various types of synthesis reactions in terms of the saturation of the corresponding colours of the RGB model.

required for solution-based reactions. Large volumes of reagents such as *n*-hexane, ethyl acetate, dichloromethane and methanol – used as components of the mobile phase – resulted in an unfavourable comparison of the *E*-factor value indicating increase in the waste production. Moreover, their high harmfulness reflected in WHN values (hazards presented in safety data sheets) contributed to the significant differences in the ChlorTox values. However, mechanochemical methods were not completely "pure". The extraction stage still involves the use of harmful solvents such as dichloromethane and ethyl acetate, albeit in much smaller amounts than in the case of the solution-based reaction. To illustrate how these two approaches compare to each other with respect to chemical risk, the ChlorTox values obtained for *O*-alkylation in-solution suggest a risk corresponding to approximately 276 grams of chloroform, whereas the respective mechanochemical reactions for obtaining the same product correspond to only 35 grams.

An important reason for the worse assessment of the whiteness of the traditional solution-based approach is also the time of the entire synthesis procedure, which due to the need for chromatographic purification, was several times longer. The energy demand estimation for this type of reaction also results in it having a worse performance since it also depends on the procedure time (eqn (3)). However, it is worth mentioning that the number of instruments powered by electricity and their overall power used in both methods were similar. An interesting example of an electrical device is the magnetic stirrer used in solution mixing, which displays higher overall energy consumption than the vibrational ball-mill used in the mechanochemical approach due to the prolonged heating and operation time required for solution-based procedures.

An interesting aspect is also the mutual comparison of *O*-alkylation, *N*-alkylation, nucleophilic aromatic substitution

and sulfonylation (Fig. 6 and 7), even though this was not the main goal of this study. It turns out that for both solution-based and mechanochemical reactions, the sulfonylation reaction was rated the highest in terms of greenness and whiteness. On the other hand, the aromatic substitution reaction scored the worst in the case of the solution-based approach, while *N*-alkylation had the lowest green and white score among reactions performed by mechanochemistry.

4. Conclusions

A transparent and simple RGBsynt model was developed and applied to assess the superior benefits of mechanochemistry over solvent-based methods for the synthesis of selected organic compounds.

To ensure unbiased comparisons, a comprehensive database was created, gathering data from the literature survey on in-batch procedures (*i.e.*, *O*- and *N*-alkylation, S_NAr, and sulfonylation reactions), followed by newly developed synthesis procedures for selected drugs (propranolol, brexpiprazole) and key drug intermediates for vortioxetine and sulfasalazine. This allowed us to establish that our already disclosed solution-based methods are representative and suitable for analysis. In parallel, the mechanochemical procedures already reported by our group were supplemented with new protocols adapted specifically for this study. In total, 34 methods were assessed, half of which were solution-based reactions and half that were their mechanochemical counterparts.

RGBsynt is the first whiteness metric applied to synthesis methods, taking into account their specificity and considering the most important parameters determining individual attributes represented by red, green and blue primary colours. The greenness assessment using the *E*-factor is enriched with the ChlorTox Scale – a chemical risk indicator that considers the hazards of each reagent independently enabling a quantitative comparison of methods. In addition, a simplified approach for estimating energy demand is used, which does not require direct electricity measurements for each device. By taking into account only the most important criteria, the model remains transparent, intuitive and user-friendly.

The assessment results demonstrate the superiority of mechanochemistry as an overall better synthetic strategy than traditional solution-based methods, as indicated by the higher whiteness and greenness scores. In particular, mechanochemistry offers several advantages such as improvement of yields, limitation of the use of organic solvents, and simplification of workup procedures while avoiding the need for chromatographic purification, which usually involves huge amounts of mobile phase components. This also ensures shorter duration times for the synthesis process and reduces the energy consumption. Importantly, our conclusions are consistent with the recent report by Sharma *et al.* on the greenness of mechanochemistry, which was analyzed with the DOZN 2.0 tool.[20] However, the obtained results cannot be easily extrapolated to other types of reactions.

In addition, although the calculated green metrics (*E*-factor and ChlorTox) may seem very favourable, the mechanochemical approach may not be considered an ideally green approach. In our case, the purification stage by extraction following a mechanochemical reaction still involves the use of harmful solvents (ethyl acetate and dichloromethane), albeit in much smaller quantities than those used in solution-based reactions.

Finally, we postulate that a novel RGBsynt model can be successfully used to compare other synthesis methods, where the attached Excel template† can be used for that purpose. We strongly believe that whiteness, as a measure of "how greenness is reconciled with functionality", might serve as a valuable parameter for identifying the overall best organic synthesis methods within the assessed group.

Author contributions

P. M. N.: conceptualization, validation, writing — original draft, writing — review & editing, visualization, funding acquisition. M. K.: investigation, data curation, preparation of the ESI,† visualization. W. T.: investigation, visualization. V. C.: conceptualization, validation, writing — original draft, writing — review & editing. P. Z.: conceptualization, supervision, writing – review & editing, funding acquisition.

Data availability

The data that support the findings of this study are available in the ESI† attached to this article (including Word and Excel files).

Conflicts of interest

The authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1 R. A. Sheldon, *Chem. Soc. Rev.*, 2012, **41**, 1437–1451.
2 A. D. Curzons, D. J. C. Constable, D. N. Mortimer and V. L. Cunningham, *Green Chem.*, 2001, **3**, 1–6.

3 M. Poliakoff, J. M. Fitzpatrick, T. R. Farren and P. T. Anastas, *Science*, 2002, **297**, 807–810.
4 T. Friščić, T. C. Mottillo and H. M. Titi, *Angew. Chem., Int. Ed.*, 2020, **59**, 1018–1029.
5 D. Tan and F. García, *Chem. Soc. Rev.*, 2019, **48**, 2274–2292.
6 K. T. Ardila-Fierro and J. G. Hernández, *ChemSusChem*, 2021, **14**, 2145–2162.
7 D. Tan, L. Loots and T. Friščić, *Chem. Commun.*, 2016, **52**, 7760–7781.
8 Z. Kudličková, M. Stahorský, R. Michalková, M. Vilková and M. Baláž, *Green Chem. Lett. Rev.*, 2022, **15**, 474–482.
9 V. Canale, W. Trybała, S. Chaumont-Dubel, P. Koczurkiewicz-Adamczyk, G. Satała, O. Bento, K. Blicharz-Futera, X. Bantreil, E. Pękala, A. J. Bojarski, F. Lamaty, P. Marin and P. Zajdel, *Biomolecules*, 2023, **13**, 12.
10 J. Martínez, J. F. Cortés and R. Miranda, *Processes*, 2022, **10**, 1274.
11 P. M. Nowak, *Green Chem.*, 2023, **25**, 4625–4640.
12 P. M. Nowak and P. Kościelniak, *Anal. Chem.*, 2019, **91**, 10343–10352.
13 P. M. Nowak, R. Wietecha-Posłuszny and J. Pawliszyn, *TrAC, Trends Anal. Chem.*, 2021, **138**, 116223.
14 P. M. Nowak and F. Arduini, *Green Anal. Chem.*, 2024, **10**, 100120.
15 P. M. Nowak, R. Wietecha-Posłuszny, J. Płotka-Wasylka and M. Tobiszewski, *Green Anal. Chem.*, 2023, **5**, 100056.
16 R. A. Sheldon, *Green Chem.*, 2023, **25**, 1704–1728.
17 ISO 14067:2018.
18 Chemical Safety Software, Safety Data Sheet search, **https://chemicalsafety.com/sds-search/**(accessed on 09-Oct-2024).
19 P. M. Nowak, A. Bis and A. Zima, *Green Anal. Chem.*, 2023, **6**, 100065.
20 P. Sharma, C. Vetter, E. Ponnusamy and E. Colacino, *ACS Sustainable Chem. Eng.*, 2022, **10**, 5110–5116.
21 D. G. Brown and J. Boström, *J. Med. Chem.*, 2016, **59**, 4443–4458.
22 V. Canale, M. Kotańska, A. Dziubina, M. Stefaniak, A. Siwek, G. Starowicz, K. Marciniec, P. Kasza, G. Satała, B. Duszyńska, X. Bantreil, F. Lamaty, M. Bednarski, J. Sapa and P. Zajdel, *Molecules*, 2021, **26**, 3828.
23 V. Canale, V. Frisi, X. Bantreil, F. Lamaty and P. Zajdel, *J. Org. Chem.*, 2020, **85**, 10958–10965.
24 V. Canale, A. Partyka, R. Kurczab, M. Krawczyk, T. Kos, G. Satała, B. Kubica, M. Jastrzębska-Więsek, A. Wesołowska, A. J. Bojarski, P. Popik and P. Zajdel, *Bioorg. Med. Chem.*, 2017, **25**, 2789–2799.
25 A. Rak, V. Canale, K. Marciniec, P. Żmudzki, M. Kotańska, J. Knutelska, A. Siwek, G. Stachowicz, M. Bednarski, L. Nowiński, M. Zygmunt, P. Zajdel and J. Sapa, *Bioorg. Med. Chem.*, 2016, **24**, 5582–5591.
26 R. Kurczab, V. Canale, G. Satała, P. Zajdel and A. J. Bojarski, *J. Med. Chem.*, 2018, **61**, 8717–8733.
27 A. Gharib, M. Jahangir, M. Roshani, N. N. Pesyan, J. W. Scheeren, S. Mohadesazadeh and S. Lagzian, *Synth. React. Inorg., Met.-Org., Nano-Met. Chem.*, 2015, **45**, 350–355.
28 V. A. Tran, N. H. T. Tran, L. G. Bach, T. D. Nguyen, T. T. Nguyen, T. T. Nguyen, T. A. N. Nguyen, T. K. Vo, T. T. T. Vo and V. T. Le, *J. Chem.*, 2020, 1–10.
29 R. Tyagi, H. Singh, J. Singh, H. Arora, V. Yelmeli, M. Jain, S. Girigani and P. Kumar, *Org. Process Res. Dev.*, 2018, **22**, 1471–1480.
30 T. Hermann, R. Wallner, J. Dolensky, W. Seebacher, E. M. Pferschy-Wenzig, M. Kaiser, P. Mäser and R. Weis, *Pharmaceuticals*, 2022, **15**, 1503.
31 X. Lu, H. Xu, X. Zhang, T. Sun, Y. Lin, Y. Zhang, H. Li, X. Li, X. Yang, H. Duan and Y. Ling, *Molecules*, 2022, **27**, 6133.
32 J. Jaśkowska, A. K. Drabczyk, P. Michorczyk, D. Kułaga, P. Zaręba, P. Jodłowski, Z. Majka, J. Jakubski and E. Pindelska, *Catalysts*, 2022, **12**, 464.
33 V. Canale, M. Kamiński, W. Trybała, M. Abram, K. Marciniec, X. Bantreil, F. Lamaty, J. R. Parkitna and P. Zajdel, *ACS Sustainable Chem. Eng.*, 2023, **11**, 16156–16164.