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# Unconventional and Sustainable Syntheses of Polymethine Dyes. Critical Overview and Perspectives within the Framework of the Twelve Principles of Green Chemistry

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**Abstract:** Time, energy, and cost saving; waste reduction; health and safety preservation represent true milestones of green chemistry, as well as some of the most important aspects for the industrial synthesis of molecules having relevant technological applications. Herein, in the light of the non-conventional and sustainable approaches towards polymethine dyes that appeared in the literature in the last decade, the twelve principles of green chemistry serve as a guideline for a critical overview of such protocols. The *E* factor and the EcoScale score for the considered procedures are also assessed, to provide numerical parameters for the evaluation of their impact.

## 1. Introduction

Among the organic molecules having a synthetic relevance, and therefore deserving suitable protocols to be synthesized on an industrial scale, active pharmaceutical ingredients (APIs) and colorants play a major role, the latter class of compounds being the very first one to be explored by synthetic organic chemists since the pioneering discovery of mauveine by Sir William H. Perkin in 1856.<sup>[1]</sup> Apart from their classical use to stain tissue, some dyes found a plethora of different technological applications. This is the case of cyanine-type polymethine dyes (PMDs), introduced by Williams in 1856<sup>[2]</sup> and exploited by Vogel in 1873 as sensitizing agents for photographic plates.<sup>[3]</sup> The main features that made the fortune of PMDs are their highly tuneable absorption spectra, with absorption peaks that easily cover not only the whole visible spectrum, but also the near-infrared region, and their high molar extinction coefficients, in the order of  $10^4$ – $10^5$  L mol<sup>-1</sup> cm<sup>-1</sup>.<sup>[4]</sup> For these reasons, combined with the synthetic

flexibility, that allows the introduction of anchoring groups, as well as the modification of their physicochemical properties, the applications of PMDs range from photovoltaic devices, including organic photovoltaic and Grätzel cells,<sup>[4-5]</sup> to photodynamic and photothermal therapy,<sup>[5b, 6]</sup> and from molecular or ionic sensors and bioimaging<sup>[5b, 7]</sup> to nonlinear optics.<sup>[8]</sup>

In consideration of the constantly growing demand for green synthetic protocols, both from academia and industry, the development of sustainable procedures for the production of such widely employed compounds is highly desirable. The chromophore system in polymethine dyes is constituted by a conjugated polyene chain flanked by two terminal groups, usually aryl or heteroaryl rings (Figure 1). The nature of the polyene chain identifies the different classes of polymethine dyes. Indeed, part of the chain can be embedded into specific cyclic structures, namely that of squaric acid, giving rise to squaraines (Figure 1, a), and of croconic acid, as in the case of croconaines (Figure 1, b). On the other hand, an open polyene chain identifies cyanine dyes (Figure 1, c). The chain itself can be of different lengths, thus distinguishing between mono-, tri-, penta- or heptamethinic dyes. Roughly, each added double bond is able to red-shift the absorption peak by 100 nm. Another relevant distinction, from the structural point of view, is between symmetric polymethine dyes, in which the two terminal groups are identical, and non-symmetric ones. The first case is defined as the “ideal polymethine state”,<sup>[9]</sup> as the two resonance structures of the molecule are equivalent and possess the same energy, with all bonds in the polyene chain being of intermediate length between single and double bonds. This highly symmetric electron density determines an absorption peak at longer wavelengths compared with homologous unsymmetrical dyes, which on the other hand may display improved features in terms of polarity and solubility, functional groups to graft on polymers or biomolecules, or fine-tuning of the absorption spectrum.<sup>[10]</sup>

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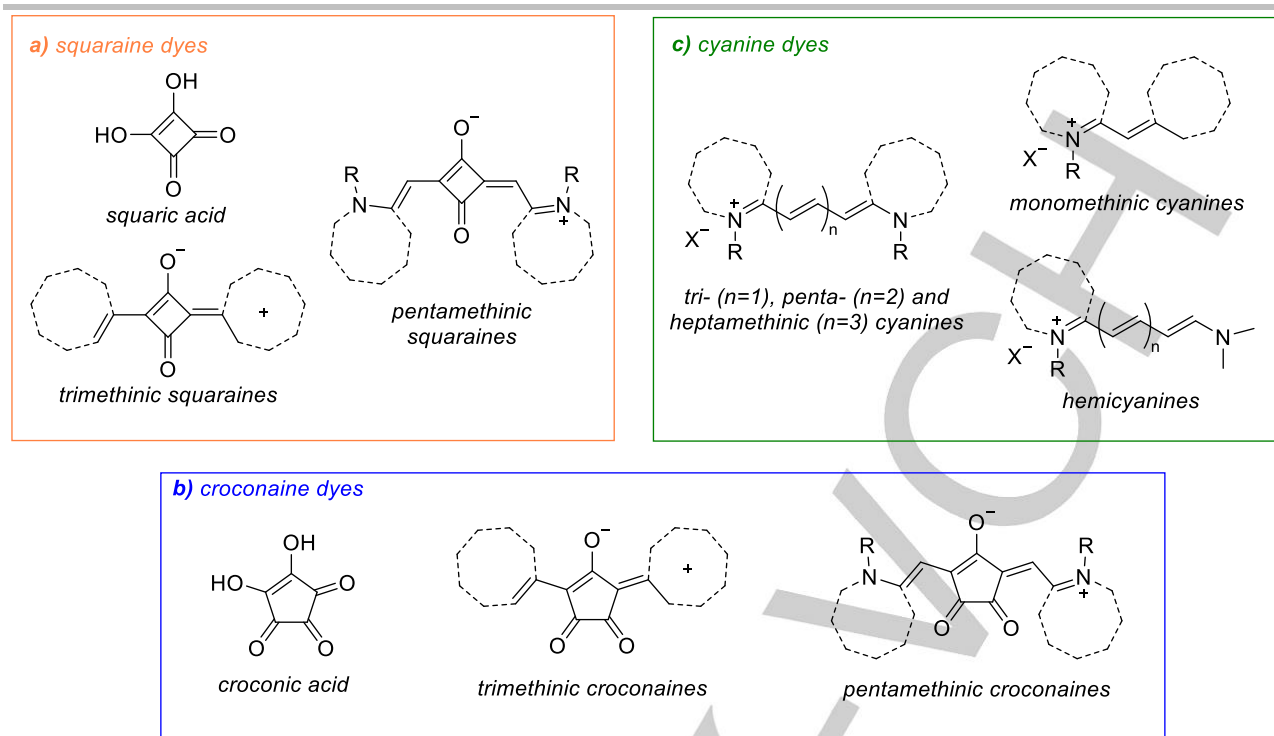


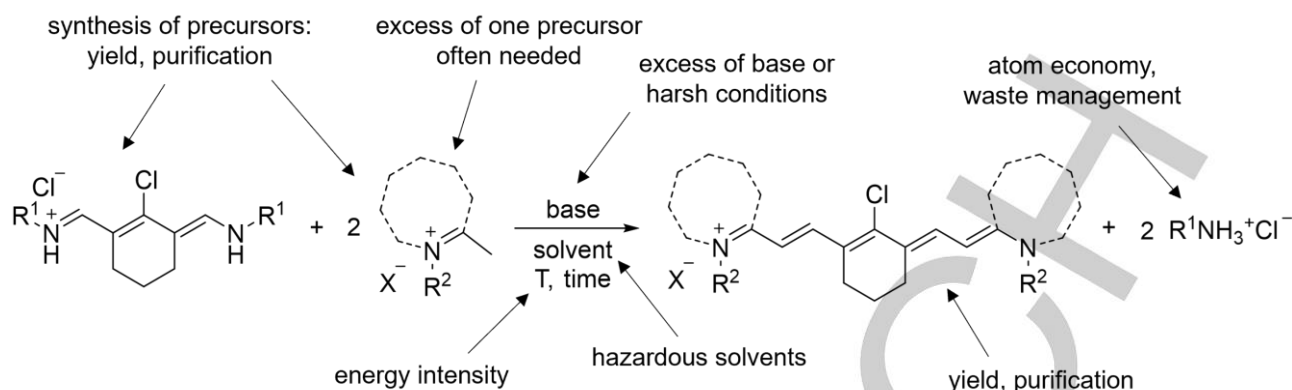
Figure 1. General structure of cyanine, squaraine, and croconaine dyes. The structures of squaric acid and croconic acid are reported as well. The (hetero)cyclic flanking groups can be identical or different.

Given the wide structural variability offered by cyanine, squaraine, and croconaine dyes, the synthetic pathways towards these compounds are impossible to be concisely summarized and have been subjected to several dedicated reviews.<sup>[11]</sup> However, the assembly of the chromogenic core is in most cases performed through a condensation reaction between an electrophilic polymethine bridge precursor and the nucleophilic flanking groups precursors, as exemplified by the representative synthesis of a heptamethinic cyanine reported in Scheme 1. If a non-symmetrical dye is required, the synthetic pathway generally involves an intermediate mono-functionalization of the polymethine bridge, as in the case of hemicyanines (Figure 1, c). In the case of squaraines and croconaines, the polymethine bridge precursor is usually squaric acid or croconic acid itself.

Looking at the wide body of literature on the synthesis of these classes of dyes, it is possible to highlight several common features that constitute drawbacks related to sustainability, which are summarized using the reaction in Scheme 1 as an exemplification. The procedures are generally carried out in volatile organic compounds (VOCs) as solvents, mostly aliphatic alcohols (ethanol, 2-propanol, butanol), often in a mixture with benzene or toluene in various ratios. The presence of an excess of a base (typically pyridine or quinoline), or even the use of acetic anhydride as the solvent, together with sodium or potassium acetate as base, is usually required to improve the reactivity. The reactions are often run for long times at high temperatures and little or even no attention is paid to green chemistry principles, such as the use of non-hazardous and renewable feedstock-derived materials, energy efficiency, and waste reduction. Furthermore, conversion or work-up procedures sometimes result inadequate, so that very low amounts of product are isolated, compared to the reaction scale and the amount of material (e.g.

stationary phases, solvents, base, excess reagent). Of course, some of the presented sustainability flaws appear very hard or impossible to solve, due to intrinsic features of the currently available synthetic pathways, as in the case of the low atom economy scores; however, there is room for improvement under some point of views, such as the choice of the solvent media, energy intensity, the efficiency of the synthesis, *i.e.* yield, selectivity, purifications (including the synthesis of the precursors).

In this framework, and given the aforementioned relevance of PMDs as components of advanced materials and devices, some attention has been recently devoted to the investigation of greener synthetic protocols for their production. The aim of this review is to analyse such studies under the lens of the twelve principles of green chemistry enunciated by Anastas and Warner,<sup>[12]</sup> by classifying them according to the principle they contribute to implement in the synthesis. Hence, each Section is dedicated to one of the considered principles: specifically, the contributions relevant to the 5<sup>th</sup>, 6<sup>th</sup> and 8<sup>th</sup> principle are discussed in Sections 2, 3 and 4, respectively. To address the topic in a more quantitative way, two green chemistry metrics are employed: the *E* factor and the EcoScale score, like recently done in other contexts of organic synthesis.<sup>[13]</sup> The *E* factor evaluates the amount of waste produced in a process *per* unit of mass of obtained product.<sup>[14]</sup> The EcoScale expresses the sustainability of a process, by assigning a score in the 0–100 range (75–100, “excellent”; 50–75, “acceptable”; 0–50, “inadequate”), which results from penalties given for each non-sustainable aspect of the process.<sup>[15]</sup> In all cases in which this metrics-based analysis is not possible, the matter is examined in a discursive way, as well as for the aspects that are not explicitly included in the two scores.<sup>[16]</sup>



**Scheme 1.** Summary of sustainability issues in the synthesis of PMDs, exemplified by the model synthesis of a heptamethinic cyanine.

## 2. The 5<sup>th</sup> Principle: Safer Solvents and Auxiliaries

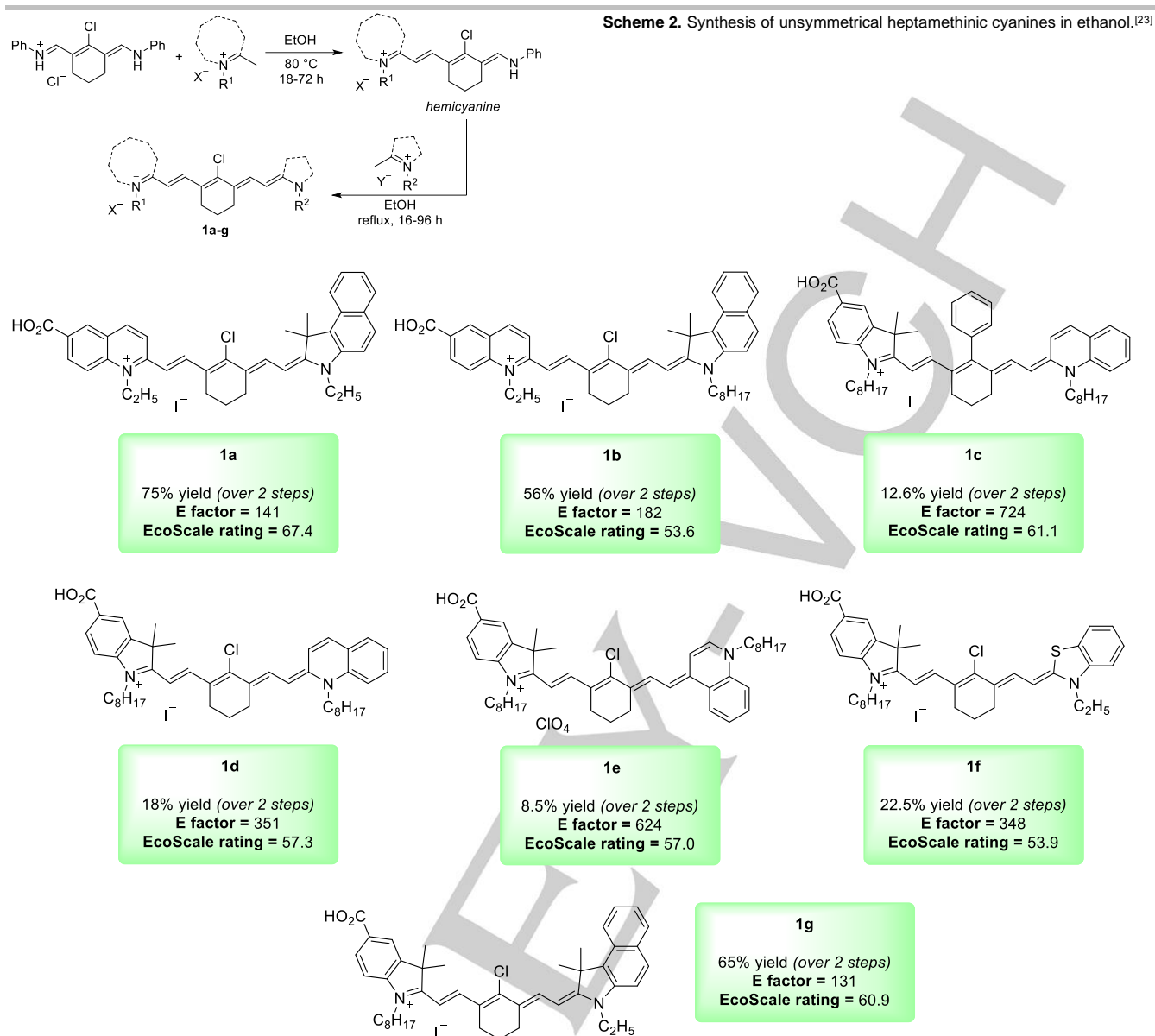
According to the 5<sup>th</sup> principle of green chemistry, the use of auxiliary substances, the term in this context mainly referring to solvents, should be possibly made unnecessary but, when used, shall result innocuous.<sup>[12]</sup> Pharmaceutical companies have dedicated efforts to establish guidelines for choosing the most suitable solvents, mainly under the point of view of safety.<sup>[17]</sup> The US Food & Drug Administration has drawn up recommendations based on the classification into three classes of solvents, being class 1 the most hazardous, while class 3 solvents may be regarded as less toxic and of lower risk to human health.<sup>[18]</sup> In this framework, solventless procedures for the synthesis of polymethine dyes should be priorly taken into consideration, followed from procedures involving the use of some proper class 3 solvents. Furthermore, the employment of new generation non-volatile reaction media, namely deep eutectic solvents,<sup>[19]</sup> will be taken into consideration. Despite class 3 includes solvents known as to be of little human health hazard at levels normally accepted in APIs, no long-term toxicity or carcinogenicity data have been provided yet for many of them. For this reason, only some selected class 3 solvents obtained from renewable feedstocks, in compliance with the 7<sup>th</sup> principle, will be taken into account. Indeed, while it is often not possible to fulfil all the 12 principles of green chemistry within the framework of a given process, one should at least try to find some mutual interconnections among them. For example, both ethanol and *n*-butanol are class 3 solvents and, as stated in the introduction, the latter is traditionally employed by most of the synthetic protocols towards polymethine dyes. Moreover, both of them can be classified as volatile solvents derived from renewable feedstocks, as ethanol can be obtained through alcoholic fermentation of yeasts belonging to the *Saccharomyces* family, bacteria such as *Zymomonas*, and other microorganisms; while *n*-butanol is the product of the fermentation of sugars and starch from *Clostridium acetobutylicum*.<sup>[20]</sup> However, despite *n*-butanol is significantly less volatile than ethanol (and this may represent an advantage if any product could be isolated by precipitation) and many symmetrical squarilium dyes are generally prepared in boiling butanol as the solvent,<sup>[21]</sup> the most typical situation is that, in order to improve yields, toluene (class 2 solvent) or even benzene (class 1 solvent)

is used as the co-solvent or, at least, added at the end of the reaction in order to perform azeotropic distillation, indispensable in getting rid of *n*-butanol.<sup>[22]</sup> For this reason, only ethanol will be herein treated as a green class 3 solvent for green approaches to the synthesis of polymethine dyes.

### 2.1 Synthesis of cyanines in ethanol

Ethanol has been employed by Geiger *et al.* as the solvent in the synthesis of heptamethinic cyanine dyes (Scheme 2) absorbing in the NIR region of the electromagnetic spectrum, thus being suitable as photosensitizers in Dye-Sensitized Solar Cells (DSSCs).<sup>[23]</sup> This work is considered for *E* factor and EcoScale calculation, and the results are reported in Figure 2. Due to the unsymmetrical structure of dyes **1a–g** presented, only a few common features can be found in their synthetic route, including a two-step route (quaternized heterocycle to hemicyanine intermediate, then reaction with a second quaternized heterocycle), inert atmosphere and purification by either filtration or crystallization. On the other side, affording the target compound seems to be a more or less difficult task, depending on each scaffold; thus, yields range from 8.5% to 75% and, consequently, the *E* factor values are in between 141 and 724 g of waste *per* g of final dye (Figure 2). However, all procedures seem to be moderately sustainable in general, with EcoScale ratings included in the range 50–75 (see the Supporting Information for detailed calculations). It must be stressed that, for this two-step synthetic protocol, EcoScale ratings have been calculated in relation to a total score of 200 points (100 points for each step) and finally normalized to a 100 points-scale, in order to obtain comparable values with EcoScale ratings from one-step procedures. Apart from intrinsic issues of the traditional preparation of polymethine dyes, the main critical point affecting the sustainability of the protocol from Geiger and co-workers is probably the low yield rather than the solvent consumption and the purification strategy, since column chromatography has not been employed to isolate the pure target compounds.

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**Figure 2.** E factor and EcoScale scores for the synthesis of unsymmetrical heptamethinic cyanines in ethanol.<sup>[23]</sup>

## 2.2 Solventless synthesis of cyanines

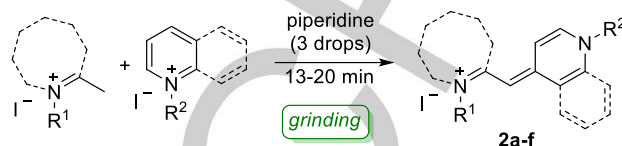
While the urgency for particular scaffolds, due to important structure-properties relationship, sometimes makes necessary to synthesize unsymmetrical polymethine dyes, the most advantageous syntheses are those referring to symmetrical polymethine dyes, either for the reduced amount of byproducts and for the fastness/easiness of performance and purification. Within this scenario, an exception is represented by some of the simplest unsymmetrical monomethinic cyanine dyes **2a–f**, for which a sustainable solventless and mild synthetic strategy, which takes advantage of grinding at room temperature, has been presented by Eissa in 2016 (Scheme 3).<sup>[24]</sup> The protocol takes the moves from previously published traditional solvent-based procedures,<sup>[25]</sup> compared to which the breakthrough is tangible not only in terms of sustainability (both related to the 5<sup>th</sup> and the 6<sup>th</sup> principle), but also in terms of greater-than-ever reaction yields

for such compounds. Curiously, the previous syntheses of the target monomethinic cyanines are performed in ethanol, thus being (nominally) moderately sustainable. Moreover, the comparison between traditional and innovative strategy is admittedly mentioned by Eissa and, consequently, it is interesting to perform an integrative quantitative comparison in terms of the E factor and the EcoScale score. The results of the calculations for the traditional (orange box) and the green protocol (green box) are summarized in Figure 3. Taking into account the EcoScale ratings, the sustainability upgrade is evident, as higher yields (from +11% up to +53%) are systematically obtained and the grinding at room temperature helps in getting rid of ethanol as the reaction solvent and to improve the overall energy efficiency. It must be stressed that no penalty points have been subtracted for the unconventional mechanochemical activation, since the grinding is rather performed by hand with mortar and pestle than in a ball mill. Comprehensively, remembering that the EcoScale

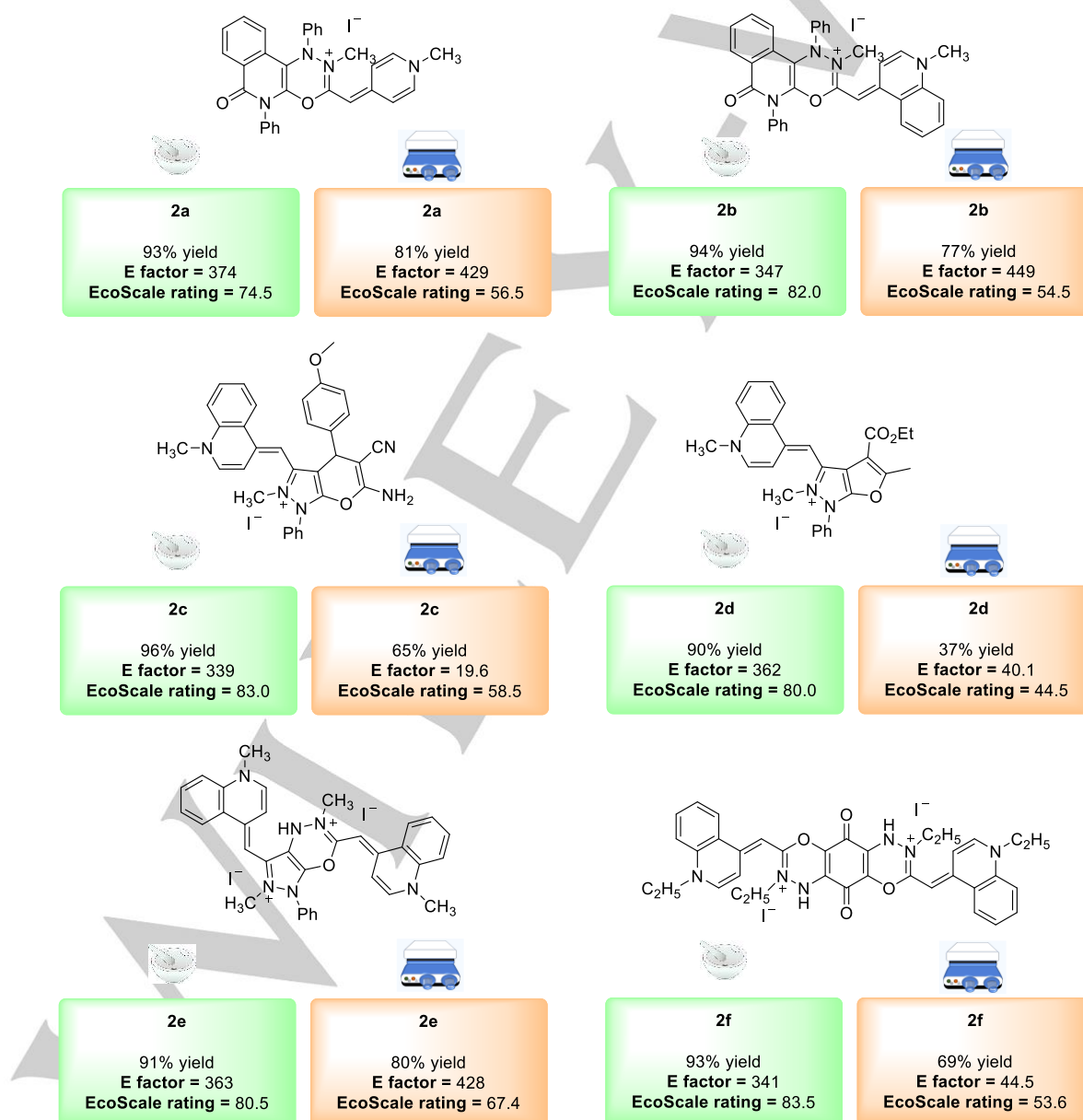
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rating allows for the sustainability classification of a given process as excellent (>75), acceptable (between 50 and 75) or inadequate (<50), almost all the compounds prepared through the novel green route can be isolated in an excellent sustainability fashion. The only outlier is **2a**, whose EcoScale score (74.5) is slightly below 75. This value is due to the necessity of refluxing the reaction crude for 30 minutes in ethanol after 13 minutes of room temperature solventless grinding, in order to push the reaction to completion. In any case, **2a** is obtained in overall higher yield (93% vs 81%) and with a reduced heating time, which considerably boosts sustainability, EcoScale score ranging from 56.5 to 74.5. With regard to the *E* factor, it can be noticed that the obtained values are, except for compounds **2a** and **2d**, systematically higher in the case of the green protocol. Indeed, in those cases, highly environmentally impacting (in terms of waste amount) column chromatography is the selected purification

method, rather than filtration or crystallization. Thus, it can be concluded that the only further improvement to be implemented to optimize the green protocol by Eissa is related to purification and reduction of the overall waste. Indeed, for those procedures for which column chromatography is the preferred purification method, most of the produced waste is just related to purification itself (see the Supporting Information for further details).



**Scheme 3.** Solventless synthesis of unsymmetrical monomethinic cyanines.<sup>[24]</sup>



**Figure 3.** Comparison of *E* factor and EcoScale scores for conventional (orange) and solventless (green) synthesis of unsymmetrical monomethinic cyanines.<sup>[24]</sup>

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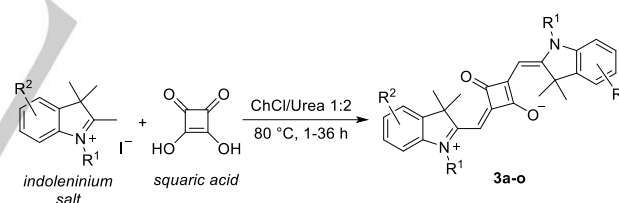
The mutual interconnection between mild and safer reaction conditions and the energy efficiency (6<sup>th</sup> principle) that often interests sustainable protocols for the synthesis of polymethine dyes is also the central core of the work by Farinola *et al.*, who proposed a comparison between different activation techniques for the solventless synthesis of indolenine-based squaraines and croconaines.<sup>[26]</sup> However, due to the centrality of the energy efficiency rather than the absence of any reaction solvent, this work will be more systematically reviewed in Section 3.1. Moreover, in Section 3.2 the use of MW irradiation for solvent-free reactions is presented.

### 2.3 Synthesis of squaraines in deep eutectic solvents

With more strict regard to the employment of more sustainable solvents, a special mention is deserved by alternative and new generation reaction media, such as Deep Eutectic Solvents (DESs). This class of eutectic mixtures, for which the discussion concerning their strict classification is still open,<sup>[27]</sup> has recently gained spotlights because of interesting properties such as nonvolatility, recyclability, durability, low polarity, easiness of preparation and naturally available cheap precursors<sup>[28]</sup> and has found widespread use in organic synthesis, including simple transformations,<sup>[29]</sup> reactions with harmful organometallic reagents<sup>[30]</sup> preparation of APIs,<sup>[31]</sup> and catalytic methodologies,<sup>[32]</sup> in some of which the DES plays an active role.<sup>[33]</sup>

In a work by Shankarling, a wide series of symmetrical squaraines **3a–o** is synthesized in one of the very first DESs to be prepared from quaternary ammonium salts, *i.e.* choline chloride/urea 1:2 by molar ratio.<sup>[34]</sup> The procedure, reported in Scheme 4, is extremely straightforward: stoichiometric amounts of the indoleninium salt (2.0 equivalents) and squaric acid (1.0 equivalent) are heated at 80 °C for the appropriate time, then the reaction mixture is rinsed with cold water, the product is filtered off and washed with diethyl ether. Accordingly, the calculated *E* factors are all below 1, except for **3l** (*E* factor = 1.04), for which the value is still very low (Figure 4). The only parameters susceptible to affect the overall environmental benignity of this procedure and, thus, the EcoScale score, are the use of highly flammable diethyl ether for the final washing and intrinsically low chemical yields of some of the products. Indeed, in the end the sustainability is excellent (EcoScale rating >75) for 9 of the 15 products and acceptable for

the remaining 6 products. Since all target squaraines are structurally related, the only differences residing in the substitution pattern of the indolenine and in the quaternizing chain, it is particularly interesting to highlight some trends of the guiding green metrics. First, the general tendency is the EcoScale score increasing and the simultaneous *E* factor decreasing upon increasing the length of the quaternizing chain in the order -H/-CH<sub>3</sub>/-CH<sub>2</sub>CH<sub>3</sub>, once the indolenine scaffold is established. This general tendency can be observed in the homologous series of squaraines obtained from simple indolenine (**3a** vs **3b** vs **3c**), benzindolenine (**3i** vs **3j** vs **3k**), 5-bromoindolenine (**3f** vs **3g** vs **3h**) and 5-nitroindolenine (**3m** vs **3n** vs **3o**). Since no particular waste is produced by purification and the DES can be recycled, the trend essentially reflects the increase in yield, which can be justified in terms of hyperconjugation of the alkyl quaternizing chain, which helps to stabilize the positive charge on the quaternary nitrogen atom, thus increasing the nucleophilicity of the methyl on the C2 atom of the indolenine ring. However, this effect is somehow compensated by the bulkiness of longer alkyl chains, for which the general tendency is, on the contrary, a yield and EcoScale rating decrease and *E* factor value increase upon increasing the length of the alkyl chain (**3c** vs **3d** vs **3e**). Moreover, it can be noticed that the presence of a carboxyl group on the quaternizing chain causes an important decrease of the yield: indeed, dye **3l** has the highest *E* factor value and the lowest yield and is, therefore, the very last in an ideal EcoScale ranking. Last but not least, the presence of strong electron withdrawing groups also has an important beneficial effect on yield increase and waste reduction (*e.g.*, **3a** vs **3f** vs **3i** vs **3m**), so that squaraines obtained from 5-nitroindolenine are at the top of the EcoScale ranking (lowest *E* factor values, highest yields).



**Scheme 4.** Synthesis of symmetrical squaraines in choline chloride/urea 1:2 as active reaction medium.<sup>[34]</sup>

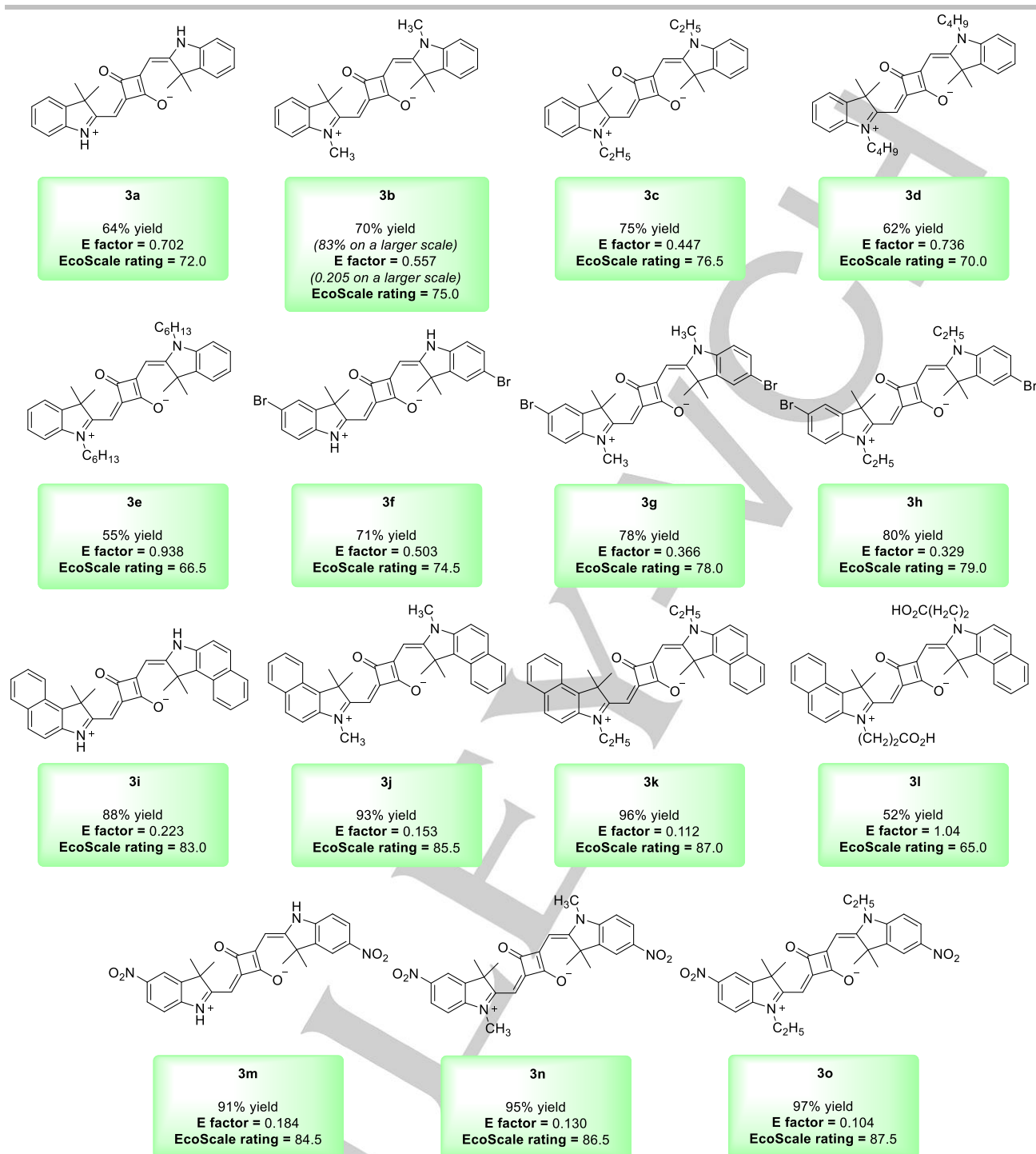


Figure 4. E factor and EcoScale scores for the synthesis of symmetrical squaraines in choline chloride/urea 1:2 as active reaction medium.<sup>[34]</sup>

Finally, within the scenario of the employment of sustainable solvents, the efforts made by Sleiman and Ladame to perform the synthesis of squaraine **3b** in water are appreciable.<sup>[35]</sup> However, the conversion is negligible, even in the presence of an electrophilic activator such as EDCI, and the green metrics have therefore not been calculated for this protocol.

### 3. The 6<sup>th</sup> Principle: Design for Energy Efficiency

The 6<sup>th</sup> principle of green chemistry states that energy requirements should be minimized for chemical processes, so that they can be ideally performed at room temperature and under atmospheric pressure.<sup>[12]</sup> Since each chemical transformation has



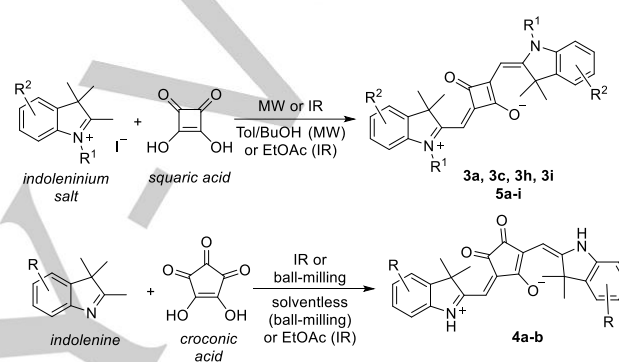
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its characteristic energy activation barrier, it is not surprising that, in the absence of any catalyst which can lower the activation barrier, the only way to pursue this challenge is to provide the system with the necessary energy amount. The most common conventional way to do that is to heat the reactor by contact with a high-temperature fluid, typically through an oil bath (at laboratory scale) or a heating jacket. Since such heating methods suffer from dispersive phenomena that lead to a waste in the power employed, techniques to transfer energy in a more efficient way have been developed in the last decades. These are mainly based on energy transfer through focused irradiation or mechanochemistry.

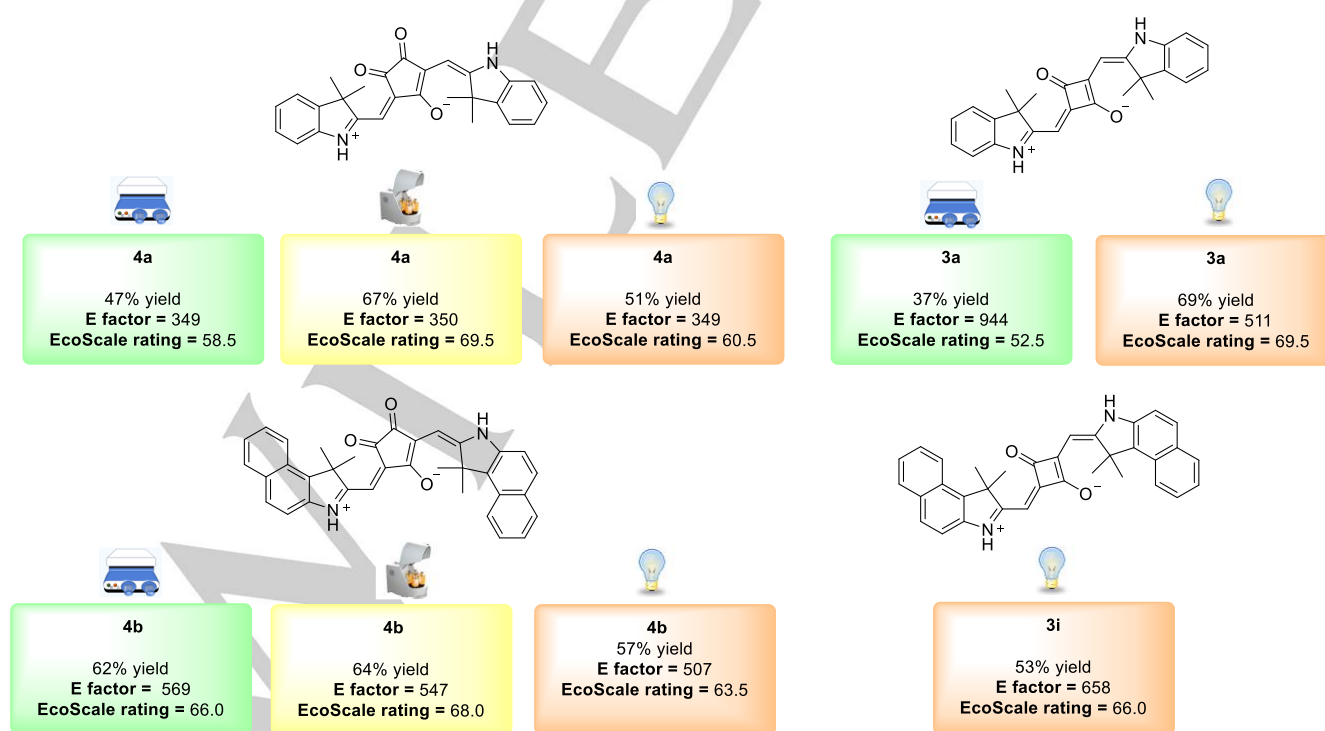
### 3.1 Mechanochemical and IR irradiation-assisted synthesis of squaraines and croconaines

The use of non-conventional energy sources is a valid alternative to thermal heating. However, some of these methods (e.g., microwave irradiation, ultrasound sonication, and mechanical milling) often require specific and expensive instruments. In this context, infrared (IR) irradiation has been recently demonstrated to be a highly efficient form of heating, emitted from inexpensive lamps (i.e., a tungsten filament sealed in a quartz envelope with a halogen gas). It represents a promising tool for fast, cheap, and green organic synthesis by respecting the 6<sup>th</sup> principle. IR irradiation, able to excite the molecular vibrational levels, has been used as a convenient thermal activation method for various chemical processes, such as selective extraction of natural products and condensation reactions. IR irradiation allows to minimize reaction time, get higher product yields, and reduce undesired by-products.<sup>[36]</sup> Within this scenario, the aforementioned work by Farinola *et al.* (see Section 2.2) is

precisely aimed at exploring different unconventional activation modes, moreover being in all cases respectful of the 5<sup>th</sup> principle of green chemistry (all of the activation modes are performed on a solventless system).<sup>[26]</sup> The benchmark dyes on which the comparison is performed, shown in Figure 5, are the two symmetrical croconaines **4a–b** and the two symmetrical squaraines **3a** and **3i**, whose synthesis is reported in Scheme 5. An unsymmetrical croconaine was also studied, but it will not be taken into account in this review, due to the lack of experimental details on the synthesis of hemicroconaine intermediate. In any case, the disadvantages in terms of sustainability of unsymmetrical dyes have already been previously pointed out (see Sections 1 and 2). The results of the green metrics calculations for thermal heating (green box), mechanochemical approach (yellow box) and radiative activation in the IR region (orange box) are summarized in Figure 5.



**Scheme 5.** Synthesis of symmetrical squaraines and croconaines with different energy sources.<sup>[26, 41]</sup>



**Figure 5.** Comparison of *E* factor and EcoScale scores for the thermal (green), mechanochemical (yellow) and IR irradiation (orange) synthesis of symmetrical croconaines and squaraines.<sup>[26]</sup>

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First of all, it is important to stress that, when approaching an alternative technology with sustainability aims, the purification strategy is not less important than the synthetic strategy itself. Indeed, in this case the *E* factor values reflect the strong dependence of the overall waste amount from highly impacting column chromatography, making difficult any other observation related to this parameter. On the other side, it should not be forgotten that chromatography itself has a 10% weight on the EcoScale ranking, and despite the appreciable effort to provide an alternative activation mode to work under mild reaction conditions, no one of the proposed protocols affords the target polymethine dye in excellent sustainability. All EcoScale scores are included in the range 50-75 (namely, overall acceptable sustainability), a result which could have room for improvement by attempting an alternative purification strategy. In the case of symmetrical croconaines **4a–b**, similar results are obtained, in terms of yield and overall sustainability, by the thermal approach and the IR activation, while a significance sustainability boost is offered by the mechanochemical approach (EcoScale score 69.5 vs 58.5 and 60.5 for compound **4a**; 68.0 vs 66.0 and 63.5 for **4b**, respectively), even if one penalty point has been subtracted for the use of ball mill as the reaction equipment. However, going deeper into the perspective of energy consumption, it is worth stressing the remarkably lower energy consumption of the IR irradiation (0.06 kWh/mmol for **4a**; 2.1 kWh/mmol for **4b**) compared to heating (8.3 kWh/mmol for **4a**; 6.3 kWh/mmol for **4b**) and mechanochemistry itself (10.6 kWh/mmol for **4a**; 16.6 kWh/mmol for **4b**). On the other side, for what concerns squaraines, it is remarkable how the IR activation can incredibly boost the transformation to afford the target dye, when the other activation techniques obtain a far worse result or even fail. Indeed, while any result is reported neither for dye **3a**, nor for dye **3i**, regarding the mechanochemical approach, the first is obtained only in 37% yield through thermal heating (EcoScale score 52.5) against 69% by IR irradiation (EcoScale score 69.5) and the latter can be isolated in 53% yield (EcoScale score 66.0) only by IR irradiation, while only traces of the product can be observed after heating benzindolenine and squaric acid in neat conditions.

### 3.2 Microwave-assisted synthesis of cyanines and squaraines

Talking about radiative activation, it is worth mentioning microwaves, for which proper reactors, namely laboratory microwave ovens, have been developed. The employment of microwaves in organic synthesis dates back to 1986<sup>[37]</sup> and proved, across the years, to be effective in reducing reaction times, while increasing yield and selectivity towards the desired reaction product, thus minimizing the formation of undesired byproducts<sup>[38]</sup> in a plethora of organic transformations.<sup>[39]</sup>

The concept of microwave-assisted organic synthesis as an energy-saving method is widely recognized in the research community, however, surprisingly, there it has been addressed from a quantitative point of view only in a few publications.<sup>[40]</sup> In a representative example by Kappe,<sup>[40c]</sup> the energy consumed in different organic transformations, carried out under microwave and conventional heating, was compared. Besides reducing reaction time from hours to minutes, significant savings in energy were observed when taking advantage of sealed-vessel microwave processing at high temperatures.

Within this framework, our group has disclosed a microwave-assisted strategy for the synthesis of a broad scope of variously functionalized indolenine-based squaraines **5a–l** (Figure 6, synthesis in Scheme 5), as well as **3a**, **3c** and **3h**, already reported in Section 2.3.<sup>[41]</sup> No column chromatography is necessary in most cases, while crystallization from *n*-butanol, followed by washing with diethyl ether, is sufficient to afford the products in high purity. Since the reactions are carried out in a classical mixture *n*-butanol/toluene 1:1 as the solvent system, perhaps the weak point of this protocol is represented by the massive use of class 2 and 3 volatile organic solvents, always being flammable or toxic. Indeed, the EcoScale ratings are heavily affected by the employment of such compounds throughout the reaction or the purification (16 total penalty points), and the reaction yield is decisive in moving the needle of the scale towards a bad (EcoScale score <50) or an acceptable (EcoScale score 50–75) sustainability outcome. Among the selected representative squaraine dyes (Figure 6), only **5a** (yield 99%) has an EcoScale rating above 75, and can therefore be considered sustainable.

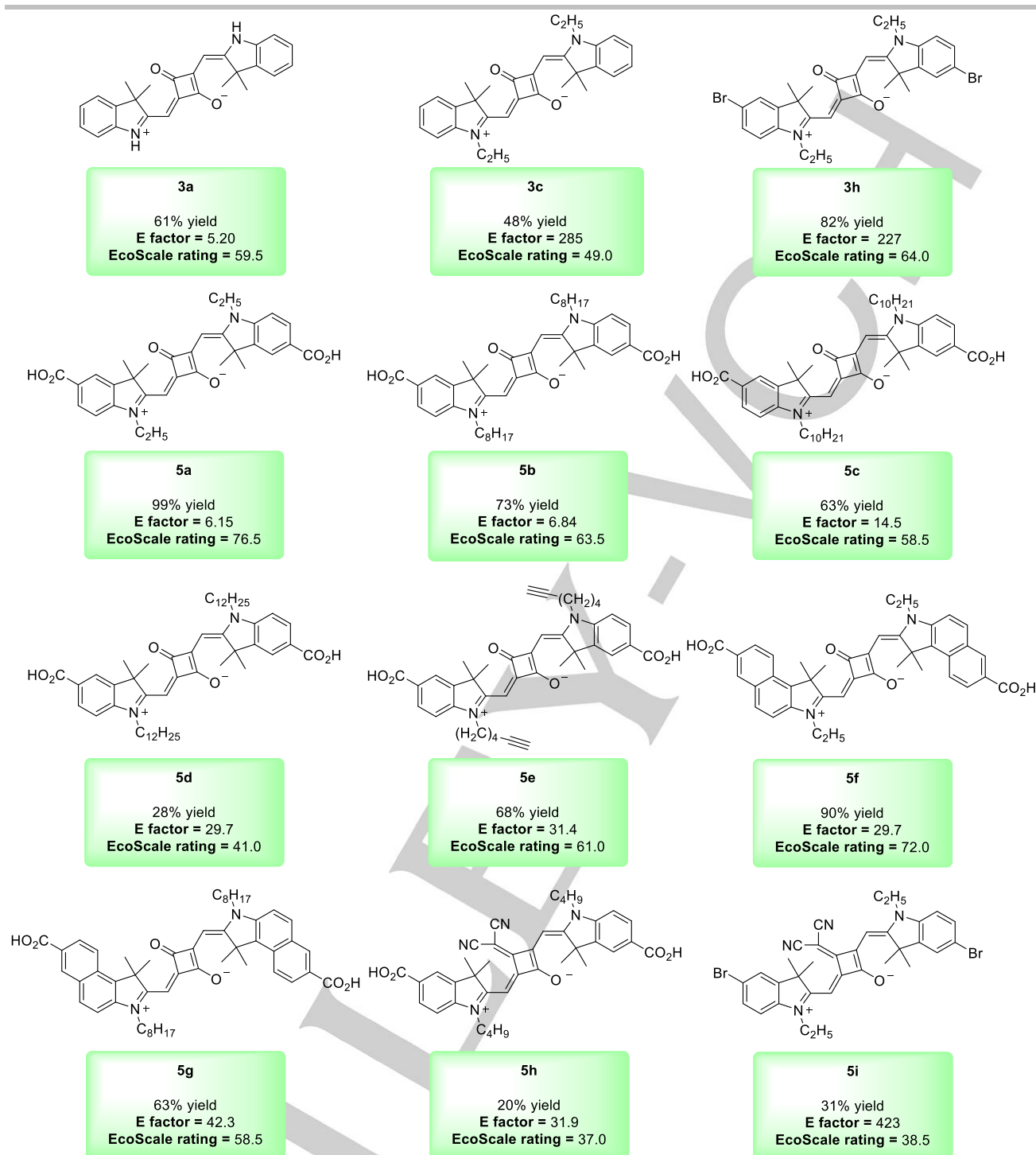


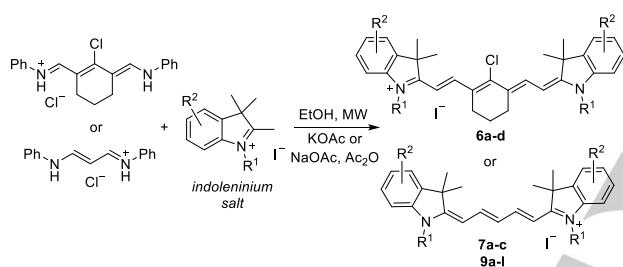
Figure 6. E factor and EcoScale scores for the synthesis of symmetrical squaraines using microwaves as the energy source.<sup>[41]</sup>

For what concerns the *E* factor, it is worth stressing the remarkable higher value obtained for **3h** and **5i**: the two dyes, which share the presence of a bromine atom substituent, require in fact a chromatography column. From the perspective of the *E* factor, it is remarkable the higher values obtained for squaraine **3c** and for bromine-substituted dyes **3h** and **5i**, for which column chromatography was employed. At first sight, and only having a look at the calculated green metrics, one could argue that the use of microwaves and VOCs requires a different and higher

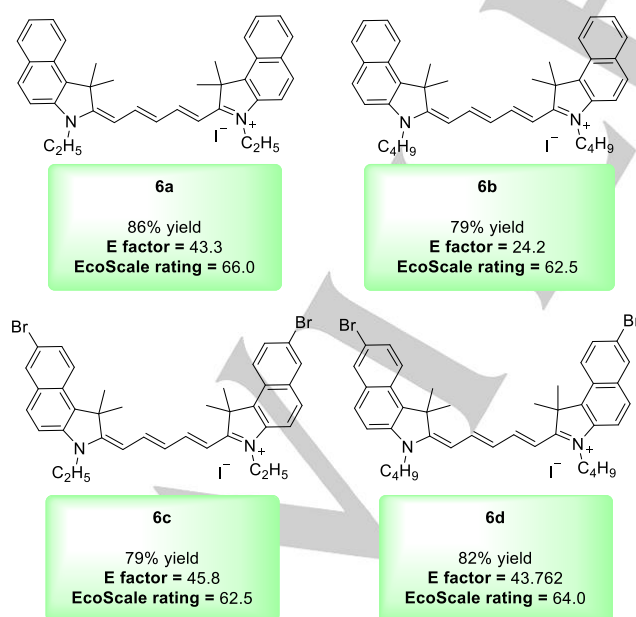
environmentally impacting purification strategy than using conventional heating with DESs (see Figure 4), in the case of the above mentioned three dyes, especially those bearing a bromine substituent. Actually, in other works from our group, the same dyes<sup>[42]</sup> or strictly related scaffolds<sup>[43]</sup> were obtained without the need for column chromatography. It can be concluded that, within the framework of green chemistry, a strong experience of the operator in the purification of such compounds and a more goal-oriented perspective towards sustainability are highly desirable to

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achieve the best possible results. In the other cases, quite homogeneous trends can be individuated, where higher length of the quaternizing chain is associated with a lower yield and, thus, a higher *E* factor and lower EcoScale rating. As a matter of fact, such trends can be observed in the case of indolenine (**3a** vs **3c**), 7-carboxybenzoindolenine (**5f** vs **5g**) and 5-carboxyindolenine (**5a** vs **5b** vs **5c** vs **5d**) as the flanking groups. In the latter trend, at least for what concerns the waste amount, squaraine **6e**, having a terminal triple bond on the quaternizing chain, is excluded because of the higher dilution of the reagents in the solvent mixture, which determines a relatively high *E* factor value (31.4), compared to the acceptable yield (68%). Finally, higher yields, lower *E* factors and higher EcoScale scores can be obtained upon increasing the strength of the electron withdrawing substituent on an indolenine moiety, given a fixed length of the quaternizing chain (**3c** vs **3h** vs **5f** vs **5d**). The same lower energetically impacting protocol has furthermore been demonstrated by our group to be efficient, even if on a reduced substrate scope, also in the synthesis of some benzoindolenine-based pentamethinic cyanine dyes (Figure 7, synthesis in Scheme 6).<sup>[44]</sup>

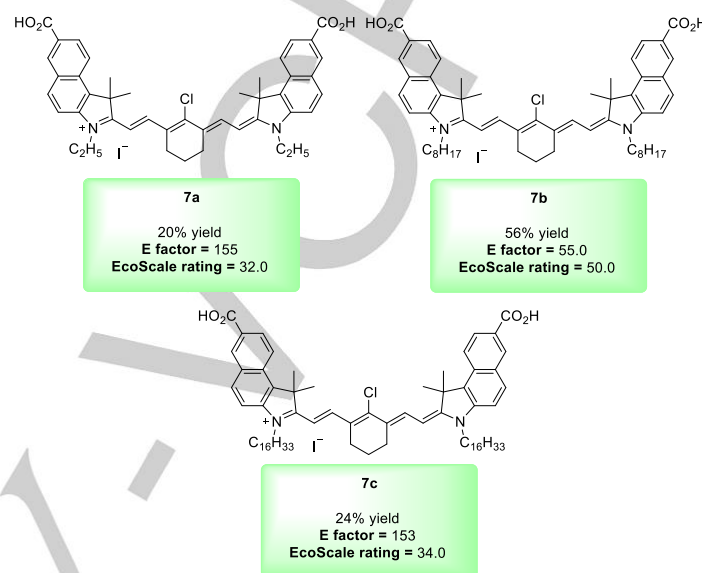


**Scheme 6.** Synthesis of pentamethinic cyanines using microwaves as the energy source.<sup>[44, 45]</sup>



**Figure 7** *E* factor and EcoScale scores for the synthesis of pentamethinic cyanines using microwaves as the energy source.<sup>[44]</sup>

However, one of the latest successful applications of the employment of microwaves as the energy sources for the synthetic approach to cyanine dyes, is represented by highly engineered symmetrical heptamethinic cyanines **7a–c**, obtained from 7-carboxybenzoindolenine and central chlorine-substituted Vilsmeier-Haack reagent, recently presented by Sauvage (Figure 8, synthesis in Scheme 6).<sup>[45]</sup>

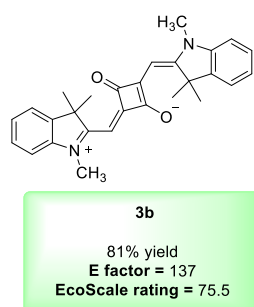


**Figure 8.** *E* factor and EcoScale scores for the synthesis of heptamethinic cyanines using microwaves as the energy source.<sup>[45]</sup>

The high degree of molecular engineering is tied hand in glove to its performance, when integrated in a DSSC but, disappointingly, also to a lower sustainability. Indeed, while the presence of the carboxyl substituent is necessary for an efficient anchoring of the scaffold to the TiO<sub>2</sub> support and the higher degree of conjugation of benzoindolenine is required for the proper absorption wavelength of the final dye (in this case, in the NIR region of the electromagnetic spectrum), these structural features are also responsible for the high cost of the starting material (*i.e.*, 7-carboxybenzoindolenine), which is not commercially available and whose preparation by a classical Fischer indole synthesis protocol requires, on average, an overall reaction time of five days. It is however remarkable that the MW activation strategy is suitable for both the quaternized heterocycle and the final dye, and that for none of them column chromatography is necessary for the purification. The high consumption of volatile organic solvents during washing, filtration (diethyl ether recycled after washing) and crystallization is responsible for the high (albeit not excessively) values of *E* factor, which strongly depend upon the reaction yield. For what concerns the length of the quaternizing chain, from the three examples presented in the paper by Sauvage, it seems that the yield of this kind of heptamethinic cyanines follows a bell-shaped curve, with a maximum of 56% yield in the case of *N*-octyl chains, which diminishes to 24% in the case of *N*-hexadecyl chains, similarly to the case of *N*-ethyl chains (20% yield). However, the overall sustainability is practically never acceptable, as suggested by the low EcoScale scores, the only one on the border (50) being that of compound **7b**. General considerations which can be made about this point,

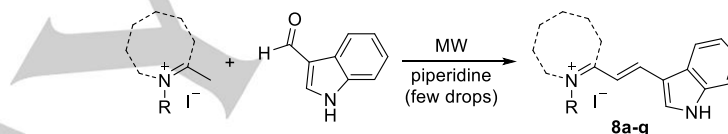
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then, regard the necessity of: finding a compromise between in-cell performances (e.g., the length of the quaternizing chain has an important influence in preventing the self-aggregation of the molecules of the dye) and a sustainable preparation of the dye; to reduce the amount and the number of employed solvents, as well as to optimize the purification (e.g., may washing and filtration with diethyl ether be avoided after crystallization from acetonitrile?). It is quite superfluous to underline once again that among the limits of the above-described microwave-assisted syntheses of polymethine dyes is the employment of volatile organic compounds, both from the point of view of the waste amount and, especially, from that of the ecosustainability. For this reason, in 2018, a new microwave-assisted protocol in ethyl lactate as a more sustainable reaction medium has been proposed by Minkovska *et al.* for squaraine **3b** (Figure 9, synthesis analogous to the one reported in Scheme 5).<sup>[46]</sup> Even if the EcoScale score is very good (75.5) and comparable to those (75.0) obtained in DES (Figure 4), purification may be quite impacting from an environmental point of view (*E* factor = 137) if water and solvent recycling is not taken into consideration (no comment on this purpose could be found in the paper). Furthermore, the generality of the protocol has not been demonstrated on other substrates.

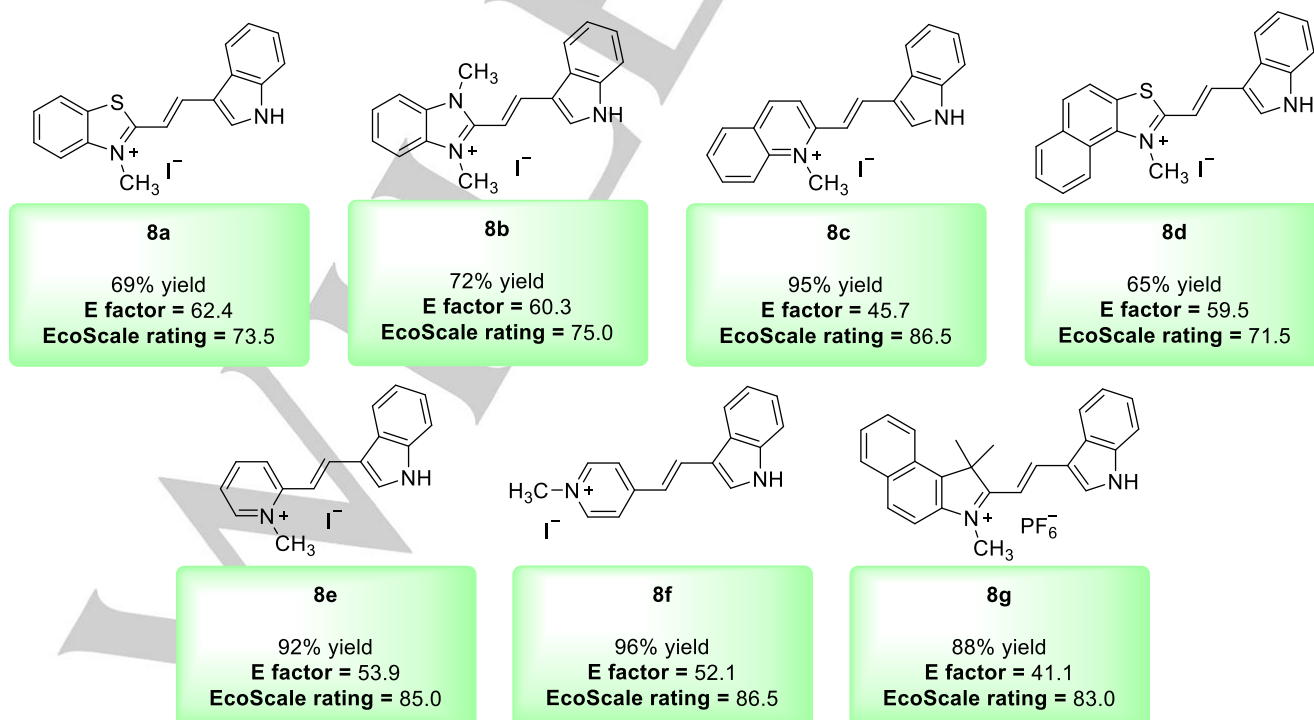


**Figure 9.** *E* factor and EcoScale scores for the synthesis of squaraine **3b** using microwaves as the energy source, in ethyl lactate as more sustainable solvent.<sup>[46]</sup>

As introduced in Section 2.2, an important upgrade, related also to the compliance to the 5<sup>th</sup> principle of green chemistry, within the scenario of microwave irradiation as the activation strategy has been instead reached by Wang, with a MW-assisted solventless strategy for the synthesis of dimethinic cyanines **7a–g** (Figure 10, synthesis in Scheme 7).<sup>[47]</sup> In this case, yields range from a minimum of 65% to a maximum of 96%. EcoScale ratings goes from acceptable to excellent but, besides calculated values, it must be stressed that *E* factors, whose values range from 45.7 to 62.4, do not take into account any solvent recycling, albeit the authors highlight the particular attention in minimizing solvent waste, even if they do not provide any other numerical detail to include that in the calculations. A further interesting information, in this perspective, is represented by really short reaction times (2 to 10 minutes), with an irradiation power ranging from 173 to 700 watts. Since 3-indolecarboxaldehyde is the electrophilic reaction partner in any case, the numerical parameters (*i.e.*, yields, *E* factors, EcoScale scores) can be taken as reference values in hypothetical relative reactivity/sustainability scales, since they reflect the properties of the employed heterocycles acting as the flanking groups of the final dyes.



**Scheme 7.** Synthesis of unsymmetrical dimethinic cyanines using microwaves as the energy source, under solventless conditions.<sup>[47]</sup>

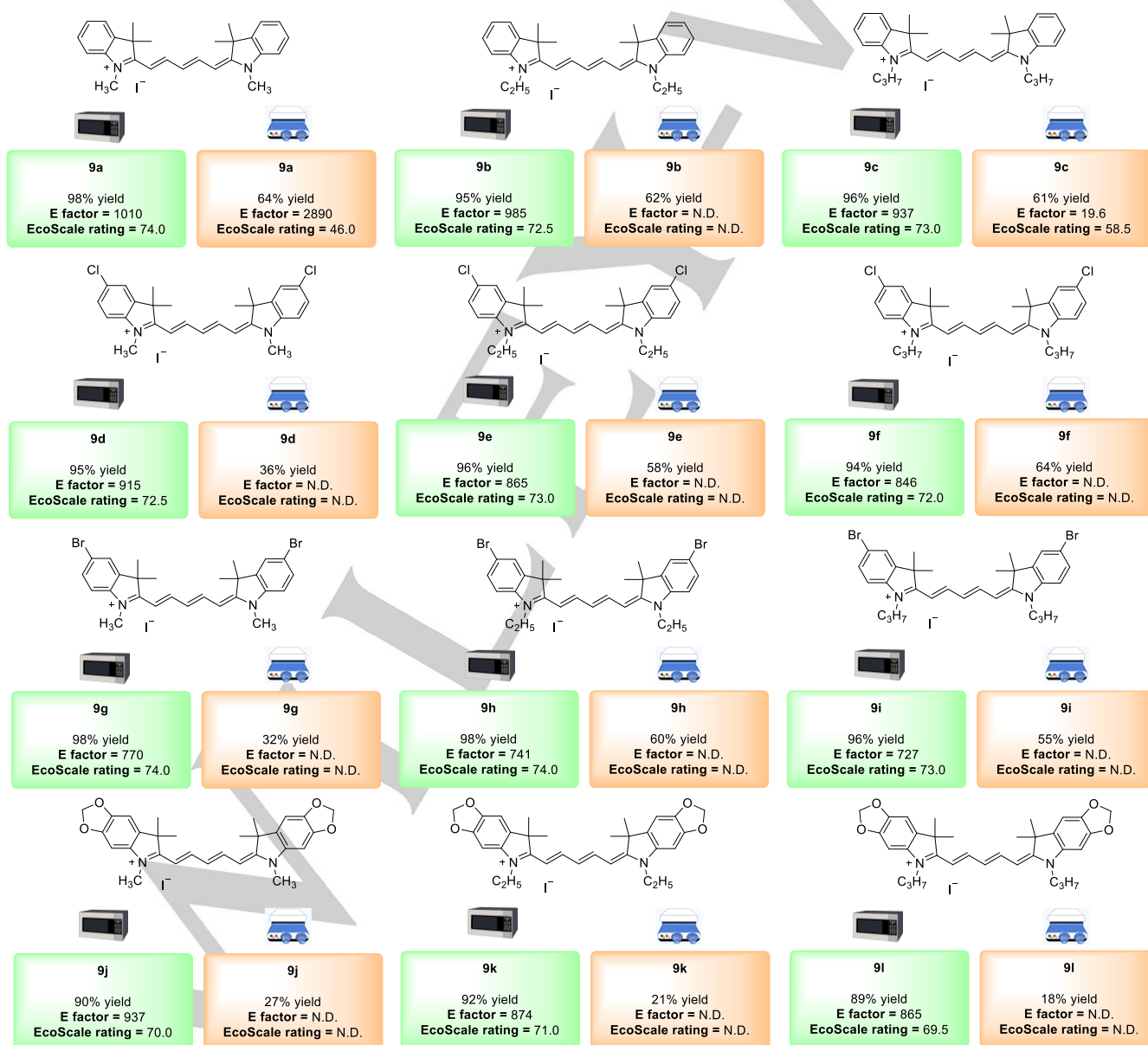


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**Figure 10** *E* factor and EcoScale scores for the synthesis of unsymmetrical dimethinic cyanines using microwaves as the energy source, under solventless conditions.<sup>[47]</sup>

The microwave irradiation activation and the absence of any reaction solvents are also the main features of a green synthetic route to pentamethinic cyanines proposed by Henary in 2015 (Figure 11, synthesis analogous to the one reported in Scheme 6).<sup>[48]</sup> It is interesting to notice the comparison between traditional thermal activation and the new MW-assisted strategy, proposed by the authors and quantified by us, at least for dye **9a** as the representative compound, in terms of the *E* factor and the EcoScale. In all cases, an important sustainability boost can be remarked, both in terms of yield (up to +71%, **9i**) and EcoScale, that for compound **9a** has a value almost three times lower for the MW-assisted procedure compared to classical thermal procedure in acetonitrile. The proposed MW-assisted protocol reveals an almost overall acceptable sustainability; indeed, all of the

EcoScale values range in between 69.5 and 74.0, the main weak point being the massive use of volatile organic solvents in the purification of the target colorants. On this purpose, it is worth highlighting the futility of the calculated *E* factors, which strongly depend on the purification strategy, the obtained values even differing in magnitudes when comparing traditional thermal heating (for which column chromatography is the preferred purification strategy) to MW irradiation. This is the reason why, except for a representative example, the calculation of the two guiding parameters has not been systematically carried out. Finally, another significant advancement in the MW-assisted synthesis of PMDs is represented by the combination with polymer-supported synthetic techniques, which is presented in Section 4.3.



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**Figure 11.** Comparison of the synthesis of pentamethinic cyanines using, as the energy source, microwave in a solventless system (green) or conventional heating in acetonitrile (orange).<sup>[48]</sup>

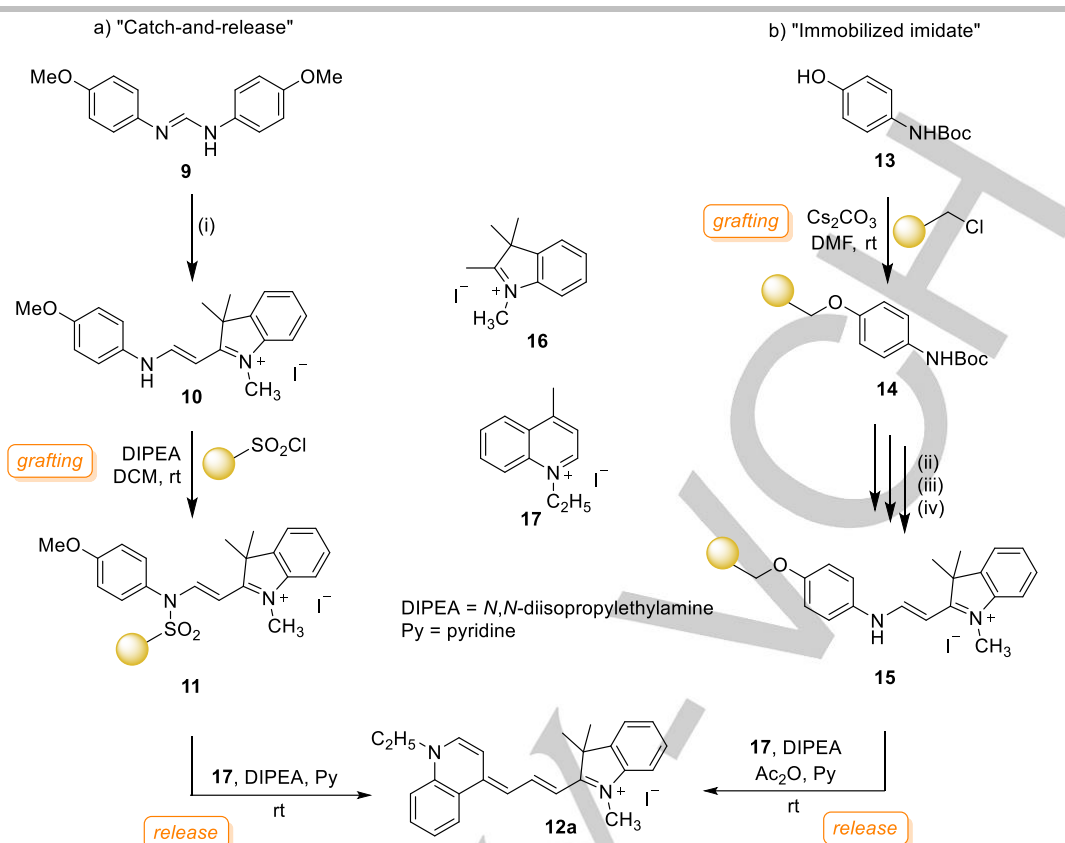
#### 4. The 8<sup>th</sup> Principle: Reduce Derivatives

The 8<sup>th</sup> principle of Green Chemistry states as a fundamental goal to “minimize or even avoid if possible the use of derivatives and blocking/protecting groups in the synthesis of target molecules; since such measures require additional reagents and may generate waste”.<sup>[12]</sup> Under this point of view, the synthetic pathways towards PMDs do not present much room for improvement, since usually they do not include many steps, and the insertion/removal of protecting groups is not needed. On this topic, however, a recurring weak point is constituted by the low yields and heavy purifications required in the synthesis of PMDs precursors. This is particularly true for the synthesis of asymmetric dyes, due to the need of passing through a hemicyanine or hemisquaraine intermediate, which implies a delicate balance between low reactivity, leading to incomplete conversions, and over-functionalization, which would afford the undesired symmetrical dye. To address this issue, two main strategies are possible: a) solid-state synthesis applying resin-based methodology, which takes advantage of solid-phase techniques to generate compounds in high purity with minimal purification; b) biocatalysis, exploiting tailor-made enzymes with high selectivity.<sup>[49]</sup> To the best of our knowledge, biocatalytic reactions have not been applied for the synthesis of PMDs yet, so this Section will focus on solid-phase synthetic methodologies. First introduced for the synthesis of peptides,<sup>[50]</sup> solid-phase organic techniques have been as well employed for the synthesis of drug-like molecules, and during the last two decades it has found broader applications in areas such as material science or catalysis. In particular there are a number of recent examples of solid-phase synthetic routes to dyes: styryl dyes, BODIPYs, phthalocyanines and cyanines.<sup>[51]</sup> The first solid-phase synthesis of asymmetric cyanine dyes dates back to 2001.<sup>[21]</sup> The application of solid-phase chemistry is particularly interesting for the synthesis of asymmetric cyanines. To the best of our knowledge, solid-phase methods have not been applied to the synthesis of squaraine and croconaine dyes. In this Section, differently from the previous two ones, we do not systematically include all the studies on the supported synthesis of cyanines, but only those works which are more relevant under the point of view of sustainability. The topic in its entirety has recently been subject to a comprehensive review,<sup>[52]</sup> in which it is highlighted that two main methodologies have been developed based on the solid-phase approach, called the “catch-and-release” and the “immobilized imidate” method. In the first one, the hemicyanine scaffold (that is, with only one flanking groups, see Figure 1, c) is synthesized by classical in-solution methodology, then it is loaded onto the resin. The bond with the polymeric support is formed on

the side of the polymethinic bridge opposite to the flanking group. In this way, reaction with the second flanking group determines the formation of the final dye concurrently to the cleavage/release from the resin. On the other hand, the “immobilized imidate” method involves the formation of the hemicyanine by reaction with a precursor already grafted to the resin; then, similarly to the “catch-and-release”, the final unsymmetrical dye is released from the support by reaction of the bounded hemicyanine.

##### 4.1 “Catch-and-release” vs “immobilized imidate”

An interesting case to compare the two strategies is represented by two papers by the group of Balasubramanian. In the first one,<sup>[53]</sup> a new strategy to obtain unsymmetrical trimethinic dyes with limited need for purification, employing a sulfonyl chloride resin, was described (exemplified by the synthesis of dye **12a** in Scheme 8, a). The hemicyanine intermediate **11** is first prepared in solution by amidine chemistry; then, the immobilization on the resin through *N*-sulfonylation activates the hemicyanine carbon towards a second nucleophilic attack, affording the final product **13a**. Activation through *N*-sulfonylation had already been applied in solution, and it takes advantage of the higher electron-withdrawing character of the -SO<sub>2</sub>R group, compared to more classical *N*-acylations.<sup>[54]</sup> Apart from that, the use of the resin improved the synthesis from the point of view of the purification steps. Indeed, the selective immobilization of the hemicyanine allows to get rid of contamination from symmetrical dye, possibly formed as byproduct in the condensation of **9** with **16**. Moreover, the reaction of bound hemicyanine **11** with a second heterocyclic nucleophile leads to simultaneous and automatic release of pure cyanine product into solution, leaving the unreacted hemicyanine attached to the resin (being removed by filtration). This approach was successfully exploited for the synthesis of nine unsymmetrical trimethinic cyanines, three of which are presented in Figure 12. Lately, the same research group further improved the methodology by taking advantage of the immobilized imidate strategy.<sup>[55]</sup> In this case, a Merrifield resin (DVB cross-linked chloromethyl polystyrene) was used. The polymer-bound imidate **15** (Scheme 8, b) was reacted with heterocycle **16**, leading to intermediate **15**, which was subsequently reacted with **17**, resulting in the cleavage of pure unsymmetrical product **12a** into solution, and allowing its facile purification by filtration. In this way, the hemicyanine-formation step, which is particularly sensitive because of selectivity and purification issues, was avoided. The authors expanded the scope to all dyes synthesized in the “catch-and-release” previous study, and compared the two strategies, highlighting higher chemical purities for the “immobilized imidate” strategy.<sup>[55]</sup>

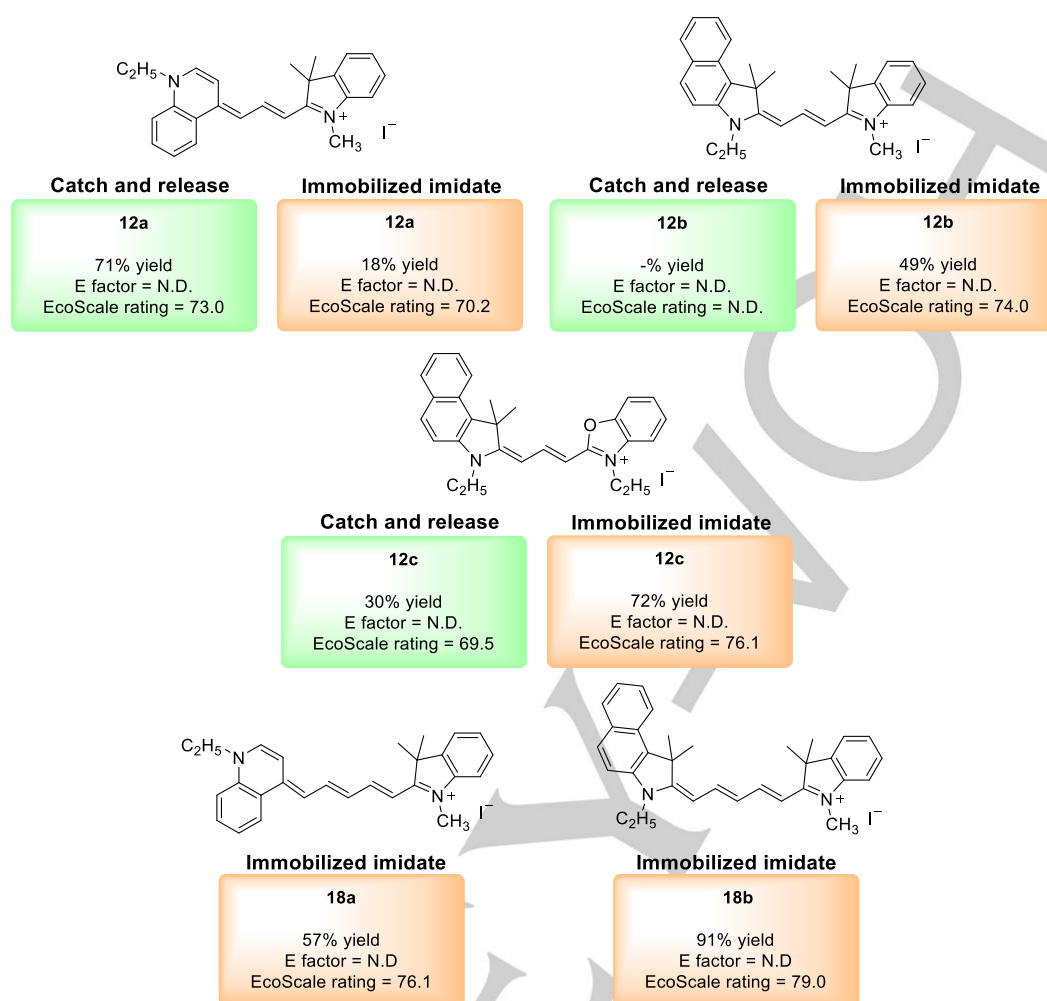


**Scheme 8.** Synthesis of unsymmetrical trimethinic cyanine dye by a) "catch-and-release" and b) "immobilized imidate" strategy. (i) **16**,  $(\text{EtO})_3\text{CH}$ , EtOH, reflux; (ii) DCM, TFA; (iii) DCM,  $\text{BF}_3\cdot\text{OEt}_2$ ,  $(\text{EtO})_3\text{CH}$ ; (iv) **16**, DMF, 80 °C.<sup>[53, 55]</sup>

On this basis, we deemed it worthwhile to extend the comparison to the EcoScale green metric: the results are reported in Figure 12 (see the Supporting Information for more details). Compounds for the "catch-and-release" and the "immobilized imidate" methods come from the first<sup>[53]</sup> and the second publication<sup>[55]</sup>, respectively, by the same group. For example, cyanine **12a** was obtained with 79% yield and 89% purity when synthesized by "catch-and-release", and 19% yield and > 95% purity when obtained by "immobilized imidate". In both cases, the EcoScale values are comparable, 73.0 and 70.2 respectively. Thus, it seems that the introduction of three additional synthetic steps and the dramatic drop in the final yield do not justify a small increase in the purity. On the other hand, in the case of dye **12b** the second strategy leads to 49% yield of the isolated compound with an acceptable EcoScale score (74.0), while the "catch-and-release" did not allow to afford the product, and it required the addition of a strong base in the last step.<sup>[53]</sup> Regarding **12c**, the yield again

increased significantly in the "immobilized imidate" strategy and the process can be defined as "excellent" by its EcoScale score (76.1). Apart from trimethinic cyanines, the "immobilized imidate" strategy was applied by the authors also for the synthesis of pentamethinic derivatives. Two of these, cyanines **18a** and **18b**, are reported in Figure 12 to make a comparison with analogue trimethinic dyes **12a** and **12b**: it appears that the longer is the length of the polymethinic bridge, the higher are the isolated yield and the EcoScale score. The *E* factor could not be calculated due to the lack of information about the synthetic procedures and individual yields in every synthetic step. As shown, the sustainability of a process merges several factors and consequently, it should be carefully analysed from different points of view. The same process/synthetic step could depict opposite results depending on the parameter that is considered as a measurement of the "greenness" of the process.





**Figure 12.** Comparison of the *E* factor and EcoScale scores for the synthesis of trimethinic and pentamethinic dyes by solid-phase chemistry. Yields refer to the final step only.<sup>[53, 55]</sup>

The solid-phase chemistry has also been applied to the synthesis of unsymmetrical water-soluble cyanines. The first report on such dyes dates back to 1993<sup>[56]</sup> and they have been found in numerous applications in the field of biomedicine. On this ground, the group of Balasubramanian expanded the scope of the pentamethinic cyanines to four water-soluble dyes (two trimethinic and two pentamethinic cyanines), bearing alkyl or aryl sulfonic acid salts. However, the results showed that the sulfonated moiety was not suitable to be loaded onto the resin (playing the role of **16** in Scheme 8, b), and it was only possible to use it as the heterocycle in the last step (similarly to **17** in Scheme 8, b). Therefore, the methodology was limited to dyes with only one hydrophilic group, reducing the number of possible applications.

#### 4.2 Use of soluble polymer as support

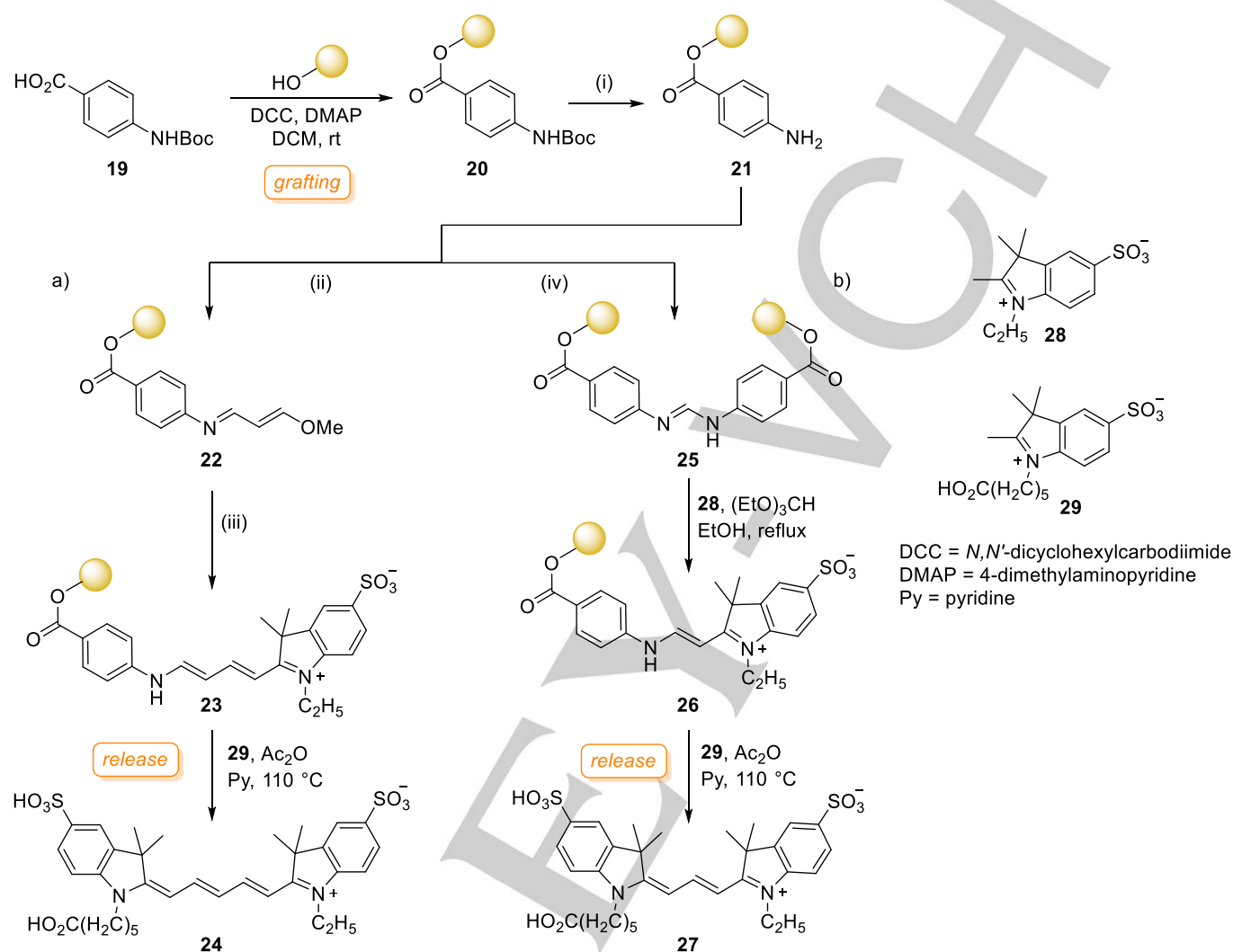
To overcome these limitations, Li *et al.*<sup>[57]</sup> in 2007 described an efficient synthetic approach to obtain unsymmetrical water-soluble cyanine dyes, which exploited soluble polymers as supports. The technique takes advantage of the strengths of both solid-phase synthesis methods (easy work-up and purification of

products) and homogeneous reactions (high reactivity). The support chosen in this case was polyethylene glycol (PEG, MW2000), which is soluble in dichloromethane or ethyl acetate but not in Et<sub>2</sub>O, thus making the reaction homogeneous, but the separation heterogeneous. The synthesis is described in Scheme 9. In this case, it was not possible to calculate the *E* factor and EcoScale scores, due to a lack of information in every synthetic step; the methodology will then be analyzed only in a discursive manner, by taking into account the yield and the purity of the products. The synthetic pathway involves the grafting of intermediate **19** through formation of an ester bond with the -OH groups of the polymeric support, affording **20**, in which the aniline is deprotected to **21**. This intermediate can then undergo two different synthetic routes, a) or b), to finally afford trimethinic cyanine **24** or pentamethinic cyanine **27**, respectively. In both cases, it was possible to generate polymer-bounded hemicyanines (**23** and **26**) with a sulfonyl functional group, which was impossible with the procedure of Balasubramanian.<sup>[55]</sup> Thus, the methodology enabled the synthesis of unsymmetrical water-soluble dyes **24** and **27**, decorated with two hydrophilic groups. Notably, none of the steps required a purification through column chromatography (not even for the synthesis of precursors **19**, **28**,

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and **29**), which is remarkable for a multi-step synthesis. Furthermore, the yields were  $\geq 70\%$  for all steps, apart from the last steps, which afforded **24** in 24% yield and **27** in 22% yield,

which are anyway significantly higher than those of similar compounds, synthesized by traditional solution method.<sup>[56, 58]</sup>

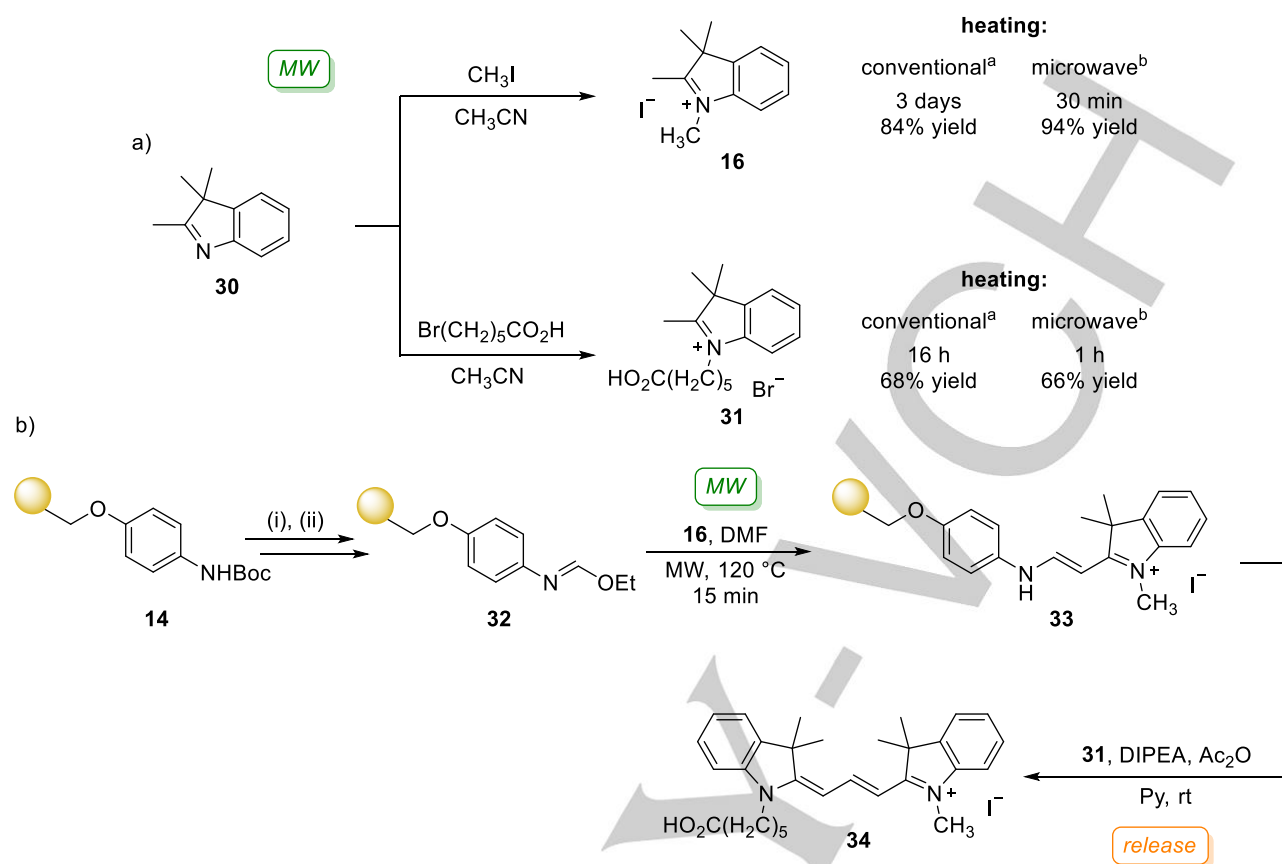


**Scheme 9.** Synthesis of unsymmetrical water-soluble cyanines by using PEG as polymeric support. Route a) for trimethinic dye **24**, route b) for pentamethinic dye **27**. (i) trifluoroacetic acid, DCM, reflux; (ii) 1,1,3,3-tetramethoxy-propane, acetic acid, 55 °C; (iii) **28**, acetic acid, 80 °C; (iv) (EtO)<sub>3</sub>CH, acetic acid, 55 °C.<sup>[57]</sup>

#### 4.3 Microwave-assisted supported synthesis

It is of course possible to combine solid-phase techniques with microwave (MW) irradiation heating, as reported in 2009 by Bradley *et al.*<sup>[59]</sup> The support used was the Merrifield resin (see also Scheme 8, b). Through the use of MW, it was possible to improve both the preparation of the precursors and the supported synthesis of the final dye. Indeed, as exemplified by the synthesis of trimethinic cyanine **34** in Scheme 4, the first simplification of the synthetic pathway was the time shortening in the formation of quaternary ammonium salts **16** and **31**, from hours, or even days, to just minutes (Scheme 10, a). Then, MW heating was again employed in the condensation of **16** with the resin-bound imine **32**. Subsequent condensation with the second precursor **31** finally produced the desired dye **34** (Scheme 10, b). The protocol was

successfully extended to pentamethinic dyes, while for heptamethinic cyanines it was necessary to include a modification in the synthetic pathway, due to undesired cleavage of the hemicyanine from the support during the hemicyanine formation step itself.<sup>[59]</sup> Eventually, the methodology enabled the efficient synthesis of a small library of unsymmetrical dyes, including water-soluble ones, with moderate to high yields (49–94%) and high purities (85–100% by HPLC-ELSD), again without the need of column chromatography.<sup>[59]</sup> The same advantages, increase in yields and chemical purities, together with the avoided column purification, were observed in the final steps of the synthesis of a wide library (80 products) of heptamethinic cyanines with increased photostability,<sup>[60]</sup> which had presented issues with purification in the conventional synthesis.<sup>[61]</sup>



**Scheme 10.** Combination of solid-phase synthesis and MW heating in the synthesis. a) Preparation of the quaternary ammonium salts. b) Synthesis of the dye. (i) trifluoroacetic acid, DCM, rt; (ii) (EtO)<sub>3</sub>CH, BF<sub>3</sub>·Et<sub>2</sub>O, DCM, rt. <sup>a</sup> Reflux (bath set at 100–110 °C). <sup>b</sup> 150 °C.<sup>[59, 62]</sup>

In conclusion, the relation of PMDs' synthesis with the 8<sup>th</sup> principle of green chemistry is not as straightforward as it could be for other classes of compounds. Apparently, it is necessary to pay a price in terms of additional synthetic steps, thus contradicting the principle, to improve the quality of the synthetic steps themselves. In a broader sense, the elimination of column chromatography from one or more reactions (even from an entire synthesis, see for example Schemes 8 and 9) could be intended as the reduction of time-, solvent- and silica-consuming steps. This is particularly true for a medium- and large-scale production of the dye of interest. It should be noted that, as we have repeatedly highlighted in Sections 2 and 3, the sustainability is heavily affected by chromatography, to such extent that *E* factor values result leveled by its impact on the final figure. This is valid for the EcoScale too, even if to a minor extent. Furthermore, since the formation of the unsymmetrical dye, through condensation with the second flanking heterocycle, is coincident with the release of the dye itself from the support, only one synthetic step is actually added to the sequence, *i.e.* the grafting to the polymer. Finally, in the present Section, the use of the two green metrics has been limited due to the difficulty to apply them to longer synthetic pathways, in which it is necessary to introduce too many approximations, thus undermining the reliability of the final result. Hence, the evaluation of the sustainability of these solid-phase procedures is less accurate than for the 5<sup>th</sup> and 6<sup>th</sup> principles, and it is mainly based on yield and purity values.

## 5. Conclusion

A critical overview on the existing sustainable synthetic protocols for the synthesis of polymethine dyes, guided by quantitative (*E* factor) and semi-quantitative green metrics (EcoScale), has been carried out. Excluding some "physiological" limitations of the guiding parameters (*e.g.*, heavy influence of chromatographic purification on the *E* factor, flattening of penalty points in the case of more or less highly expensive reagents in the case of EcoScale), their evaluation has allowed to outline strengths, critical issues and room for improvement. Different synthetic approaches have been reviewed for both symmetric and asymmetric polymethine dyes. The 5<sup>th</sup> principle can be followed thanks to the use of ethanol or DES as solvents for the synthesis of heptamethine cyanines and squaraines, respectively. A solventless approach has also been proposed towards the synthesis of cyanine dyes. The combination of these green solvents or solventless protocols with the minimization of energy requirements (especially MW) was also proposed for both cyanine and squaraine dyes, meeting the requirements of the 6<sup>th</sup> principle of green chemistry.

Unfortunately, a systematic study considering all the possible ways of improving the synthetic approach (*i.e.* use of green solvents or solventless reactions, use of mechanochemical, IR or

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MW as a source of energy etc.), on the same dyes, is not present and it is therefore difficult to get a clear trend. We could only perform such a kind of comparison for compounds **3a**, **3b**, **3c** and **3h**. Among the different synthetic approaches (DES, thermal, IR, MW synthesis) to get **3a**, it is clear that the synthesis in DES is the more sustainable one, leading to a very low *E* factor value and an excellent EcoScale rating. If we consider **3b**, only the MW synthesis conducted in a greener solvent like ethyl lactate is comparable to the same synthesis in DES, which in any case leads to a lower *E* factor.

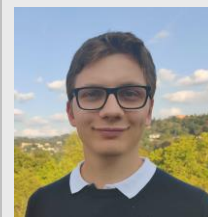
At present, we can conclude that, at least to some extent, the synthesis of polymethine dyes cannot be strictly defined as sustainable, the main issues concerning specific principles such as atom economy and design/use of safer chemicals. On the other hand, important efforts focused on the use of more sustainable reaction media and energy efficiency boosting paved the way for a future systematic tuning of routinely employable sustainable protocols for the synthesis of such compounds. Special attention should be dedicated to choosing the less waste-impacting purification technologies, in order to obtain quantitative metrics which could effectively help the evaluation of the produced waste amount (e.g. *E* factor) and to design overall sustainable protocols, as environmentally impacting purification strategies may even invalidate the sustainability of a well-designed synthetic route. In a certain measure, the latter goal has been pursued in terms of the 8<sup>th</sup> principle, when multi-step immobilization-based synthetic strategies have allowed to avoid chromatography and crystallization. Moreover, other green approaches could be followed: to the best of our knowledge, no examples of PMDs synthesis in micellar catalysis have been reported, while this could be a way to synthesize these dyes in water as solvent with the possibility to recycle the employed surfactant. Future perspectives of sustainability improvement in the synthesis of cyanines, squaraines and croconaines, then, include an extension of the reaction scope of sustainable protocols (possibly integrating the respectfulness towards more than one green chemistry principle at the same time) to as many compounds as possible, also considering the intermediates as well as the final compounds.

Achille Antenucci was born in Campobasso in 1991. He obtained his PhD from University of Roma "La Sapienza" in 2019, then moved to University of Torino, where he spent two years working as a post-doc fellow. In January 2022, he joined CRCF S.r.l. at Silvateam S.p.a. in San Michele Mondovì (CN), Italy, where he is working as R&D Product Developer, dealing with tannin chemistry. His research interests rely on sustainable synthesis and catalysis, with particular attention devoted to the exploitation of renewable feedstocks.



Stefano Nejrótti graduated in Chemistry at the University of Torino, in 2017, after spending a research period at the IRCOF in Rouen (France). He obtained his PhD at the University of Torino in 2021, working on gold-catalyzed synthetic methodologies, and on synthesis in unconventional solvents. In 2019, he spent a period as visiting PhD student in the group of

prof. A. M. Echavarren at the ICIQ in Tarragona (Spain). He is currently a post-doc fellow at the University of Torino.



María Jesús Morán Plata graduated in Chemistry at the University of Extremadura (Spain) in 2016. Afterwards she moved to the Department of Drug Science and Technology of the University of Torino (Italy), where she obtained her PhD in 2020, working on nanocopper-catalyzed transfer hydrogenation strategies for the synthesis of valuable target molecules. Her PhD was funded by the ETN Marie Skłodowska-Curie Program (COSMIC), giving her the possibility to have an effective trans-national mobility: KU Leuven (Belgium), MEAM (Belgium) and Arkema (France). In 2020 she joined the Department of Chemistry of the University of Torino as post-doc fellow, where she was involved in the H2020 ARTIBLED project. In 2021 she was granted with a MSCA-IF at the Donostia International Physics Center (Spain) within the project DELCAT (Catalysis toward platinum substrates for drug delivery).



Nicole Mariotti graduated *cum laude* at the University of Camerino, defending a thesis on green and sustainable approaches in the synthesis of nitro-compounds. She was then enrolled in the Erasmus Traineeship program developing green one-pot multicomponent reactions. After her master's degree, she joined the department of Chemistry at the University of Torino, where she continued her studies by attending an interdisciplinary PhD program in Innovation for the Circular Economy, working on sustainable and innovative materials for energy-related applications and sustainability assessment approaches. She is (co)author of 6 peer-reviewed publications.

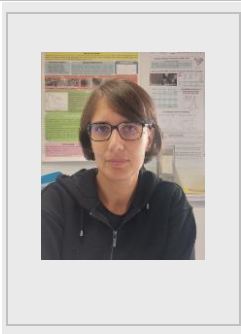


Nadia Barbero is Associate Professor of Organic Chemistry at the University of Turin and her research interests are the design and synthesis of organic and hybrid functional materials for non-conventional and technological applications. One of the main research focus is the development of NIR functional dyes, polymethine dyes in particular, as photosensitizers for Dye-Sensitized Solar Cells and Photodynamic Therapy. She is currently involved in two EU projects working on the synthesis of functional materials for the development of transparent dye-sensitized and perovskite solar cells (IMPRESSIVE, H2020 RIA project) and for the development of bio-based

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LEDs (ARTIBLED, H2020 FETOPEN

project). She is (co)author of 77 publications in international peer-reviewed journals (h-index = 26).

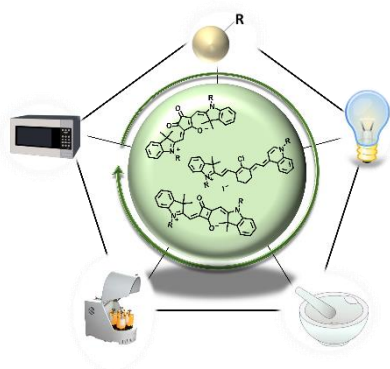


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**Keywords:** Polymethine dyes • Cyanines • Squaraines • Green Chemistry • Sustainability

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**Entry for the Table of Contents**

The aim of this review is to critically analyze the synthetic routes followed to prepare polymethine dyes, providing the reader a critical overview on the synthetic processes within the framework of the twelve principles of green chemistry. A detailed critical evaluation in terms of two complementary green chemistry metrics like the EcoScale and the *E* factor is provided.

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