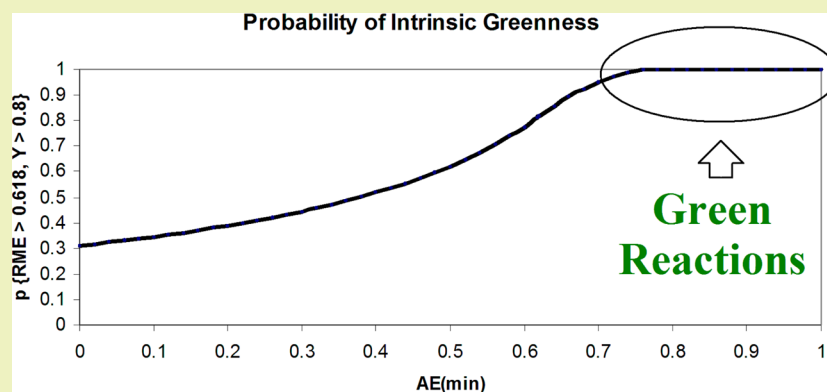# On the Probability That Ring-Forming Multicomponent Reactions Are Intrinsically Green: Setting Thresholds for Intrinsic Greenness Based on Design Strategy and Experimental Reaction Performance

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Ⓢ *Supporting Information*

ABSTRACT: This paper describes in detail the determination of the likelihood that a given generalized chemical reaction may be considered intrinsically "green" based on design strategy. Justification is given for setting threshold constraints on reaction yield and kernel reaction mass efficiency (RME) performances at greater than 80% and greater than 61.8%, respectively, for intrinsically green reactions. These criteria are applied to a survey of 60 named ring-forming multicomponent reactions (MCRs) and 2000+ such reactions reported in the literature from 2003 to 2011. Patterns among various ring construction motifs are discussed. Results show that 5- and 6-membered monocyclic rings are most commonly made by [2+2+1] and [3+2+1] cycloadditions where 57% and 76% of them, respectively, have a 100% chance of being intrinsically green from a design perspective. Similarly, the [4.3.0] and [4.4.0] skeletons are the most common fused bicyclic structures made by MCR strategies where 38% and 59% of them, respectively, have a 100% chance of being intrinsically green. The syntheses of various heterocyclic ring structures made by MCRs have also been surveyed using this new criterion. The application of this probability analysis is also demonstrated for the total synthesis of ring containing scaffold structures of praziquantel and frondosin B, two compounds of pharmaceutical interest made using MCRs. The direction of future research in MCR development is also briefly discussed.

KEYWORDS: *Atom economy, Cycloaddition, Green metrics, Heterocycles, Multicomponent reaction, Probability, Rings*

■ INTRODUCTION

Though there has been considerable progress made in recent years by various authors in quantifying the greenness of chemical reactions using various performance metrics,[1,2] only one report[3] has appeared suggesting that probabilities could be determined to gauge the likelihood that any given reaction is intrinsically green according to specified constraints. Such constraints are necessary because it is not possible to ascertain greenness for a given reaction in an absolute sense. It is now accepted that measures of greenness are valid only in a relative sense. The term "intrinsically green" in this article refers specifically to design strategy efficiency with respect to the synthesis of a given target molecule. For an individual reaction, design efficiency focuses on minimization of waste byproducts and maximization of reaction yield to a desired target product. For a synthesis plan, it refers to minimization of reaction steps and of overall production of waste byproducts and maximization

of overall yield. In both cases, minimization of auxiliary material consumption such as reaction solvents and other materials used in workup and purification, though important for attaining overall greenness, are excluded because minimization of these is not pertinent to how a given molecule is put together in a purely design sense. It was shown in prior[3] work that the key to achieving overall greenness is to first achieve intrinsic greenness at the design stage by deliberately choosing highly atom economical and high yielding reactions because this is the primary core optimization. Reduction of auxiliary material consumption was deemed a secondary level of optimization. The novel concept of quantifying associated probabilities for intrinsic greenness was briefly introduced and applied to
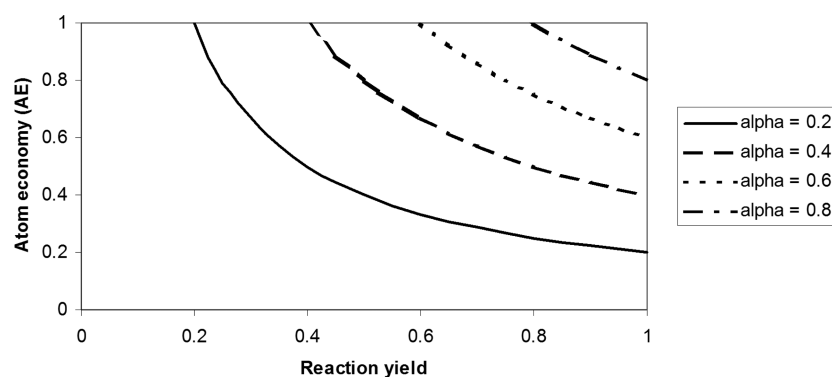
Figure 1. Plot of AE versus reaction yield for various values of α.

Table 1. Summary of Probability Relationships Based on AE(min) and Minimum Reaction Yield Thresholds

equation	probability	threshold conditions
6	$p = \dfrac{1 - AE(\min) + \alpha\ln(AE)\min}{[1 - AE(\min)][1 - \varepsilon(\min)]}$	$(AE)\min \geq \alpha$ and $0 \leq \varepsilon(\min) \leq \alpha$
7	$p = \dfrac{1 - AE(\min) + \alpha - \varepsilon(\min) - \alpha\ln\left[\frac{\alpha}{(AE)\min\,\varepsilon(\min)}\right]}{[1 - AE(\min)][1 - \varepsilon(\min)]}$	$(AE)\min \geq \alpha$ and $\alpha \leq \varepsilon(\min) \leq \alpha/AE(\min)$
8	$p = 1$	$(AE)\min \geq \alpha$ and $\alpha/AE(\min) \leq \varepsilon(\min) \leq 1$
9	$p = \dfrac{1 - \alpha + \alpha\ln\alpha}{[1 - \alpha][1 - \varepsilon(\min)]}$	$(AE)\min = \alpha$ and $0 \leq \varepsilon(\min) \leq \alpha$
10	$p = \dfrac{1 - \varepsilon(\min) + \alpha\ln\varepsilon(\min)}{[1 - \alpha][1 - \varepsilon(\min)]}$	$(AE)\min = \alpha$ and $\alpha \leq \varepsilon(\min) \leq 1$
11	$p = \dfrac{1 - \alpha + \alpha\ln\alpha}{[1 - AE(\min)][1 - \varepsilon(\min)]}$	$(AE)\min \leq \alpha$ and $0 \leq \varepsilon(\min) \leq \alpha$
12	$p = \dfrac{1 - \varepsilon(\min) + \alpha\ln\varepsilon(\min)}{[1 - AE(\min)][1 - \varepsilon(\min)]}$	$(AE)\min \leq \alpha$ and $\alpha \leq \varepsilon(\min) \leq 1$

various well-known named organic reactions. It arose as a direct consequence of writing chemical transformations in general form using scaffold structures having various R groups and determining their associated minimum atom economies so that their worst case scenario reaction performances could be identified. Moreover, the notion of probabilities was a natural extension because it was realized that the key metrics reaction yield and atom economy were both fractional quantities ranging in value between 0 and 1 and were formally mutually exclusive variables. In this work, the probability of reaction greenness subject to specific and justifiable threshold constraints relevant to synthesis strategy and design using ring-forming multi-component reactions (MCRs) is described in detail. The mathematical formalism is fully presented and derivations are detailed in the Supporting Information, which also contains a template spreadsheet algorithm with embedded formulas to facilitate computations once a balanced chemical equation is written. After obtaining the key probability expressions as functions of minimum atom economy, AE(min), minimum reaction yield, $\varepsilon(\min)$, and kernel RME threshold, α, these are then applied to an extensive reaction database comprised of 60 named and more than 2000 ring-forming MCRs. The Supporting Information contains lists of fully balanced MCRs published in 2010 and 2011. Similar lists for prior years may be found elsewhere.[4] These kinds of reactions are widely considered to have the greatest potential of being intrinsically green because they generate the greatest number of target bonds in a single step and are thus used to make complex target

molecules quickly with a minimum of reaction byproducts. Hence, they are ideal candidate reactions to test the concept of probability of intrinsic greenness. They typically comprise at least three substrates that assemble to form a given molecule in a simultaneous one-pot or sequential one-pot reaction with minimal loss of atoms from those substrates. They are therefore attractive to synthetic and process chemists because they fulfill many of the optimization requirements that concatenation of steps in a telescoped sequence achieve such as reduced solvent demand as a direct result of reduced isolations of intermediates. Because the discovery of new MCRs is now a vigorous area of research particularly in the context of green chemistry, several reviews[5−66] and a book[67] have been written on these kinds of reactions. Ugi[65] has noted, however, that the invention of multicomponent reactions goes back to the 19th century. The ring motif in chemical structures is of specific and high interest to practicing synthetic organic chemists who are naturally attracted to target molecules with complex ring systems, particularly natural products, to test the utility and power of their synthesis methodologies. Furthermore, most commercially important fine chemicals and pharmaceuticals contain at least one ring in their structures. For these reasons, the database focuses on various documented MCR combinations for assembling 3-, 4-, 5-, 6-, 7-membered and higher monocyclic rings, as well as fused bicyclic rings, multiple disconnected rings, and other miscellaneous complex rings. For each reaction, the probability of intrinsic greenness is determined, and for a given combinatorial assembly, such as [3+2+1] for 6-membered rings,

its statistical distribution of probability ranges is given based on the kinds of reactions discovered so far. Syntheses of various heterocyclic ring structures made by MCRs and commonly found in pharmaceuticals were also examined with respect to the likelihood of achieving intrinsic greenness. On the basis of these surveys, it is found that (a) certain combinatorial motifs have a high number of literature examples and others not, (b) certain combinatorial motifs have a higher proportion of highly probable intrinsically green outcomes and others not, and (c) certain heterocyclic ring structures have been well optimized with respect to intrinsic greenness and others not. We also demonstrate how the described probability analysis may be applied to the total synthesis of ring scaffold structures using as examples derivatives of praziquantel,[68] a pharmaceutical used to treat schistosomiasis, and frondosin B,[69] a marine natural product containing four contiguous rings in a 4−5−7−6 assembly according to ring size. Both of these examples highlight how certain design elements and selection of key reactions can help to achieve intrinsic greenness in total synthesis when MCRs are incorporated in the synthesis plans.

■ METHODOLOGY

We begin with the general expression for the global reaction mass efficiency (RME) for any single chemical reaction[70] given by eq 1

$$RME_{global} = (AE)(\varepsilon)\left(\frac{1}{SF}\right)(MRP) \tag{1}$$

where AE is atom economy, ε is reaction yield, 1/SF is the inverse of the stoichiometric factor that takes into account excess reagent consumption, and MRP is the material recovery parameter that takes into account all auxiliary material consumption (reaction solvent, workup, and purification materials). All of these parameters are fractions between 0 and 1.

Scheme 1. Generalized Biginelli Condensation Showing Markush Structures and Molecular Weights Underneath Structures[a]

r1 + r2 + 42   r3 + 29   60   r1 + r2 + r3 + 95   36
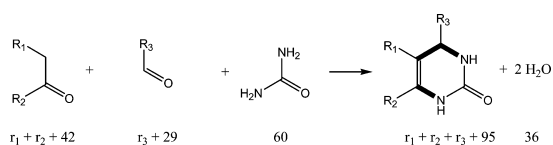
[a]Target bonds are shown in bold.

Note that the inverse of global RME is identical to the process mass intensity (PMI),[71−73] which has now been adopted by the pharmaceutical industry as a key green metric. When dealing with synthesis strategy performance as discussed in the Introduction, eq 1 reduces to the simplified expression given by eq 2, for the kernel RME, which involves only the variables that govern intrinsic chemical performance.

$$RME_{kernel} = (AE)(\varepsilon) \tag{2a}$$

Under these conditions, eq 2a implies that all auxiliary materials are eliminated or recovered and the reaction is run under stoichiometric conditions. The corresponding expression for kernel E-factor is given by eq 2b.

$$E_{kernel} = \frac{1}{RME_{kernel}} - 1 \tag{2b}$$

We now impose a threshold value, α, for the kernel RME such that the condition given by eq 3 is satisfied.

$$RME_{kernel} = (AE)(\varepsilon) \geq \alpha \tag{3}$$

Equation 3 may be rewritten as shown in eq 4, so that a plot can be made of AE versus reaction yield as given in Figure 1 for various values of α.

$$AE \geq \alpha/\varepsilon \tag{4}$$

We note from Figure 1 that as the full spectrum of values of AE and reaction yield are considered for a given reaction, any combination of these two variables must lie somewhere in the domain of the square bounded by the points (0,0), (0,1), (1,0), and (1,1). In order to satisfy the inequalities given by eq 3 or eq 4, such a combination of AE and reaction yield values must fall above the line given by the equality relationship. Also, we note that as the threshold value decreases, the area of the domain above the line increases. Because the parameters AE and reaction yield are independent variables and they each range in value between 0 and 1, we may directly interpret the area of the domain above the equality relationship given by eq 4 as the probability that the combination of AE and reaction yield for a given reaction will yield a kernel RME value that exceeds the threshold value, α.

For any given threshold, α, and without imposing any restriction on values for AE and reaction yield other than $0 \leq \varepsilon \leq 1$ and $0 \leq AE \leq 1$, such a probability is given by eq 5.
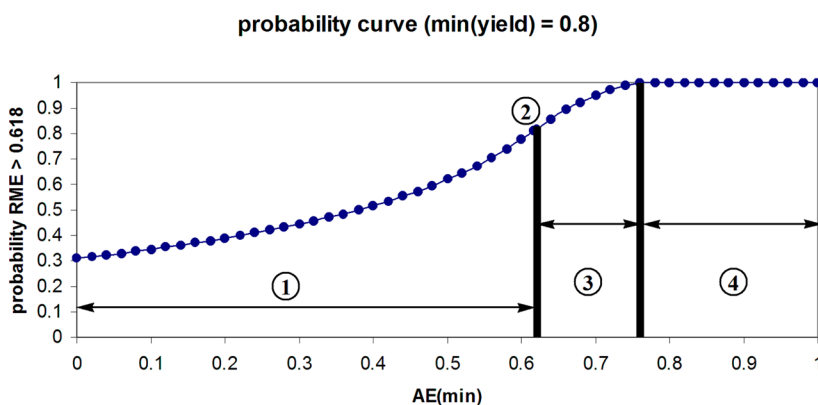
probability curve (min(yield) = 0.8)

Figure 2. Relationship between probability of intrinsic greenness and AE(min) given a kernel RME threshold of $\alpha = 0.618$ and a reaction yield threshold of $\varepsilon(min) = 0.8$. The four regions are defined by eqs 16−19.
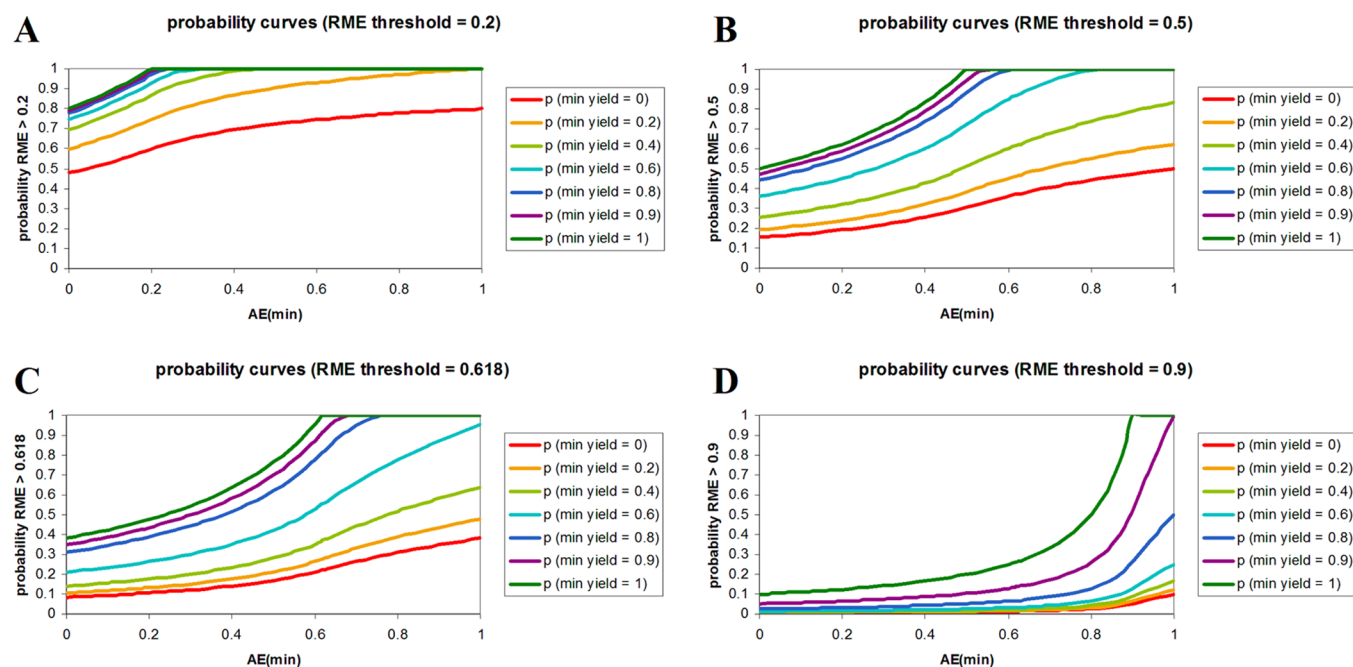
Figure 3. Plots of probability of intrinsic greenness as a function AE(min) for various kernel RME thresholds and ε(min) thresholds ($0 \le \varepsilon$(min) ≤ 1): (A) $\alpha = 0.2$; (B) $\alpha = 0.5$; (C) $\alpha = 0.618$; and (D) $\alpha = 0.9$.
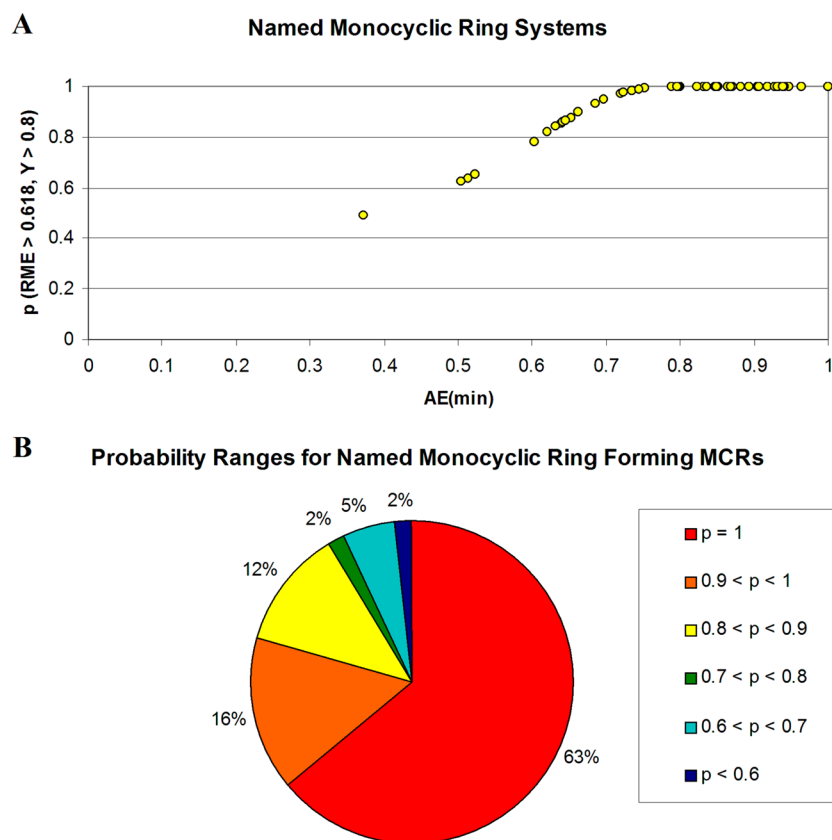

Figure 4. (A) Relationship between probability of intrinsic greenness and minimum atom economy for named monocyclic ring-forming MCRs in database. (B) Pie chart showing distribution of probability ranges.

$$p = \frac{\text{area above hyperbola}}{\text{area of square}} = 1 - \alpha + \alpha \ln \alpha \qquad (5)$$

When a low threshold value is set for the kernel RME, the probability of achieving it is high. Conversely, when a high threshold is set, the likelihood of achieving it diminishes. In other words, if we aim for mediocrity, we are more likely to achieve it, whereas if we aim for excellence, we are less likely to achieve it. A plot of eq 5 is given in Figure S1 of the Supporting Information.
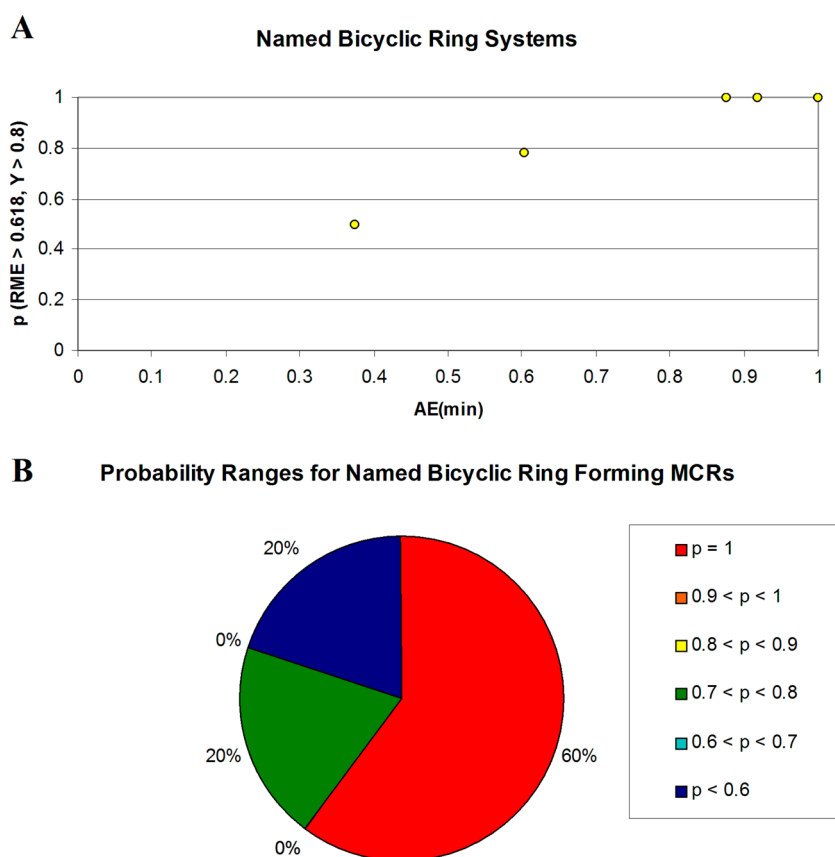
A

Named Bicyclic Ring Systems

B

Probability Ranges for Named Bicyclic Ring Forming MCRs

Legend:
- $p = 1$
- $0.9 < p < 1$
- $0.8 < p < 0.9$
- $0.7 < p < 0.8$
- $0.6 < p < 0.7$
- $p < 0.6$

Figure 5. (A) Relationship between probability of intrinsic greenness and minimum atom economy for named fused bicyclic ring forming MCRs in database. (B) Pie chart showing distribution of probability ranges.
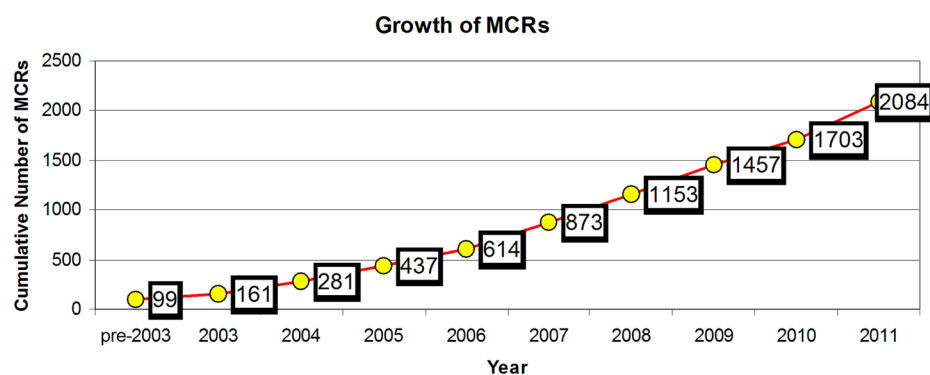
Growth of MCRs

Figure 6. Cumulative growth of MCRs reported in the chemistry literature.

When dealing with a specific reaction where a minimum atom economy may be determined for a generalized structure of the intended target product, and a minimum reaction yield is imposed, the probability of achieving a kernel RME exceeding α is given by expressions listed in Table 1. Full derivations are given in the Supporting Information. There are seven cases to consider depending on where the AE(min) and ε(min) values fall in the square in relation to α.

Using the Biginelli reaction[74−76] as an example because it is the most studied of all MCRs with currently over 950 examples documented in the literature to date, we first write out a generalized Markush-type balanced equation as shown in Scheme 1.

The general expression for the atom economy is given by eq 13.

$$AE = \frac{r_1 + r_2 + r_3 + 95}{r_1 + r_2 + r_3 + 131} \tag{13}$$

The minimum atom economy is found by setting minimum values for the molecular weights of the R groups. Using methyl groups for all substituents, $r_1 = r_2 = r_3 = 15$, so that AE(min) = 0.795. If, for example, a minimum reaction yield of 80% (ε(min) = 0.80) is imposed for this reaction and a target kernel RME threshold of $\alpha = 0.6$ is set, then the relevant domains are (AE)min $\geq \alpha$ and α/AE(min) = 0.777 $\leq \varepsilon$(min) ≤ 1. This implies that eq 8 in Table 1 applies so that the probability of achieving the threshold kernel RME is 100%. However, if the minimum reaction yield is lowered to 50% and the kernel RME
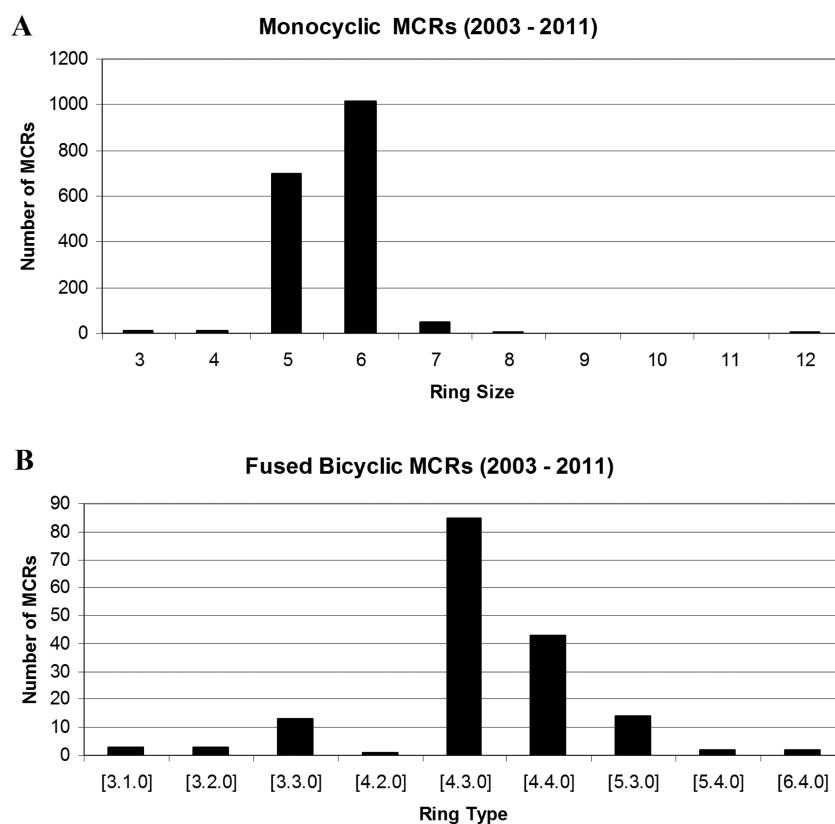
Figure 7. Histograms showing distribution of ring-forming MCRs: (A) by ring size for monocyclic rings, and (B) by ring type for fused bicyclic rings.

threshold set higher at $\alpha = 0.8$, then the relevant domains are now $(AE)\text{min} \leq \alpha$ and $0 \leq \varepsilon(\text{min}) \leq \alpha$. This implies that eq 11 in Table 1 applies so that the required probability drops down significantly to 21%.

For designating a reaction as intrinsically green, we need to set reasonable lower limit bounds on both $\varepsilon(\text{min})$ and α. The minimum reaction yield may be set to 80%, which is generally agreed to describe a "good" yield. At this point, it needs to be emphasized that the choice for this threshold is purely subjective, open to debate, and can never be made rigorous; however, a cutoff needs to be made nonetheless. In deciding a kernel RME threshold value, α, the universal connecting relationship between RME and E-factor[70] given by eq 14 may be used. In this case, the basis of the choice of cutoff is rational as illustrated.

$$RME = \frac{1}{1 + E} \tag{14}$$

A graph of the hyperbolic relation given by eq 14 clearly shows two domains for the function: one domain applies to the case when RME > E and the other when RME < E. Setting RME = E = x, allows determination of where the boundary between these domains exists. Thus, we obtain a quadratic $x^2 + x - 1 = 0$, whose positive real solution is given by eq 15.

$$x = \frac{1}{2}(\sqrt{5} - 1) = 0.618 \tag{15}$$

The net result is that imposing a threshold value such that RME > $\alpha = 0.618$ guarantees that the magnitude of kernel RME exceeds that of the corresponding kernel E-factor. Put another way, the kernel process mass intensity (i.e., molar mass of reagents required per molar mass of target product) is

guaranteed to be less than the inverse of the kernel E-factor (molar mass of target product per molar mass of byproduct and unreacted reagent waste). The magnitude of the threshold value given in eq 15 is recognizable as the "golden ratio". It should be emphasized that this observation is a direct consequence of the functional form given by eq 14 and not a fanciful attempt to impose the "golden ratio" criterion in the context of achieving reactions that satisfy principles of green chemistry. Another algebraic form connecting RME to E would have obviously lead to a different threshold value upon equating these variables. Moreover, this threshold is rather modest in magnitude and is achievable by over half of the known named organic chemical reactions.[3] The upshot is that reactions satisfying this threshold may be correctly interpreted as intrinsically green reactions on the basis of "designing in" the minimum reaction byproducts possible for chemical transformations.

Now, setting $\alpha = 0.618$ and $\varepsilon(\text{min}) = 0.8$ as the desired threshold parameters for intrinsic greenness, so that $\alpha \leq \varepsilon(\text{min}) \leq 1$ is satisfied, yields expressions for the corresponding probability of intrinsic greenness as a function of $AE(\text{min})$ only as given by eqs 16−19. These may be obtained by direct substitution in eqs 12, 10, 7, and 8, respectively, found in Table 1. Each equation is associated with its own valid domain range along the $AE(\text{min})$ axis. This means that a plot of p versus $AE(\text{min})$ is a smooth continuous piecewise function comprising four regions as shown in Figure 2.

For region 1, $AE(\text{min}) \leq 0.618$ and eq 12 reduces to

$$p = \frac{0.31}{1 - AE(\text{min})} \tag{16}$$
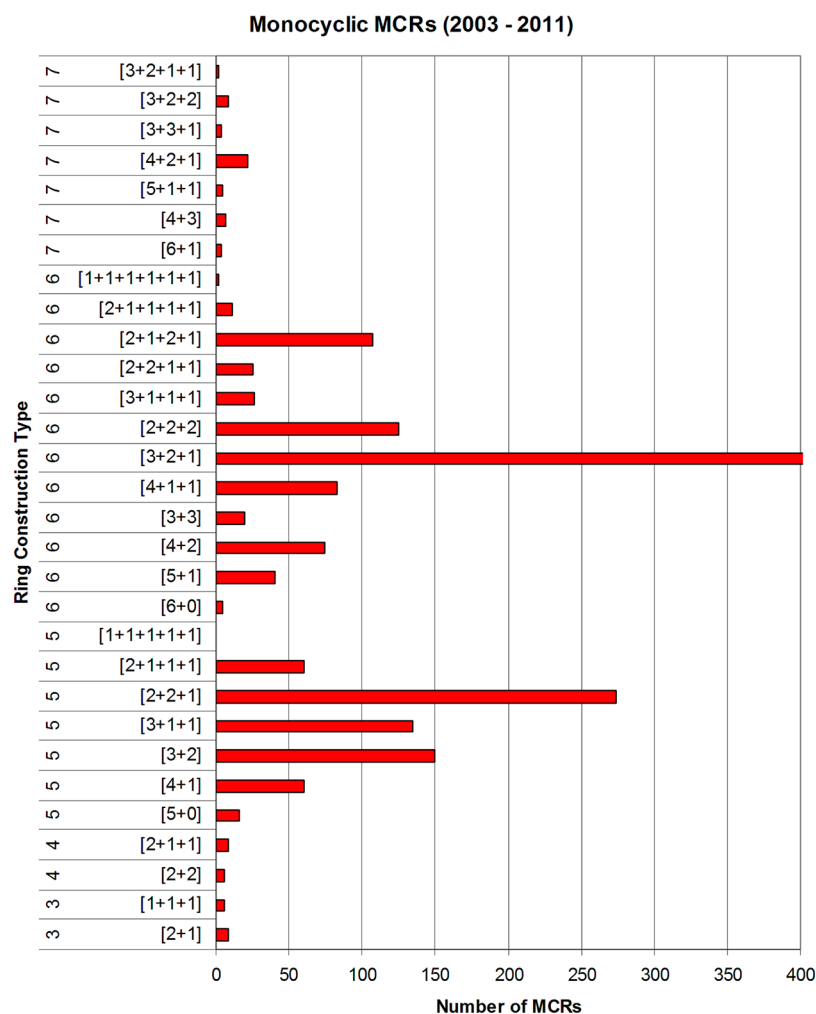
Monocyclic MCRs (2003 - 2011)

Figure 8. Histogram showing distribution of monocyclic ring-forming MCRs in database by ring size and ring construction type up to 7-membered rings.

For region 2, AE(min) = 0.618 and eq 10 reduces to

$$p = 0.813 \tag{17}$$

For region 3, $0.618 \leq AE(min) \leq 0.773$ and eq 7 reduces to

$$p = \frac{0.818 - AE(min) - 0.618\ln\left[\frac{0.773}{AE(min)}\right]}{0.2[1 - AE(min)]} \tag{18}$$

For region 4, $AE(min) \geq 0.773$ and

$$p = 1 \tag{19}$$

Armed with a relationship between p and AE(min), it is possible to explore various trends of this function as both α and $\varepsilon(min)$ are changed. Figure 3 summarizes the effect of changing $\varepsilon(min)$ at fixed α and the effect of changing α at fixed $\varepsilon(min)$. The dark blue curve in Figure 3C corresponds to the graph shown in Figure 2. From Figure 3A with $\alpha = 0.2$, we observe that as we increase $\varepsilon(min)$ we compress and shift the curves toward the upper left-hand corner of the plot so that the range of AE(min) values corresponding to a 100% probability increases (compare red curve ($\varepsilon(min) = 0$) with green curve ($\varepsilon(min) = 1$)). The same trend is found in Figure 3B–D. In other words, for a given kernel RME threshold value, the probability of achieving it increases as we increase the lower limit on reaction yield. On the other hand, when we compare

the red curves in all four graphs, where α is changed while maintaining $\varepsilon(min)$ fixed at 0, we observe that they are compressed and shifted toward the bottom right-hand corner as the kernel RME threshold is increased. This scenario illustrates that the probability of achieving a target kernel RME value diminishes rapidly as we set a higher threshold bar for α. The same trend is observed if we examine the green or any other colored curve in all four graphs. Intrinsically green reactions are those that fall anywhere along the upper right-hand plateaus of these curves. These plots nicely describe in a visual way the tension between setting lower bounds on both $\varepsilon(min)$ and α. If we set our kernel RME threshold too high, then the likelihood of achieving it is low resulting in a very few chemical reactions being considered intrinsically green. Similarly, if we set our minimum yield too low, then it too will reduce the probability. So, setting $\alpha = 0.618$ and $\varepsilon(min) = 0.8$ is a reasonable compromise.

■ RESULTS AND DISCUSSION

Having established a workable master p versus AE(min) curve as shown in Figure 2, this was then applied to 60 named MCRs to see how many of them would be categorized as intrinsically green. Tables S1 and S2 of the Supporting Information summarize data for those MCRs that produce monocyclic and bicyclic ring systems, respectively. The actual reactions along
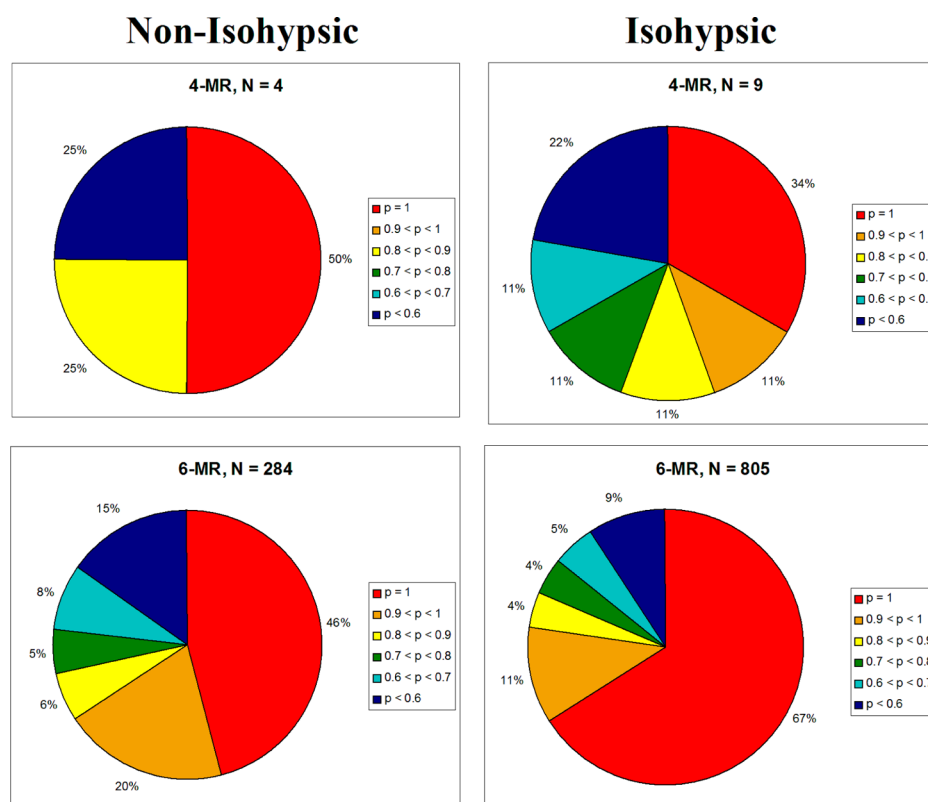
Figure 9. Pie charts showing distribution of probability ranges for nonisohypsic and isohypsic MCRs producing even numbered monocyclic ring sizes (*geraderings*). Note: 4-MR denotes a four-membered ring.

with their references are also given in the Supporting Information. Figures 4A and 5A show plots of *p* versus AE(min) according to eqs 16−19 and Figures 4B and 5B show pie charts depicting the distribution ranges of probabilities of intrinsic greenness found. Each range is color coded so that red sectors represent highly probable intrinsically green MCRs (*p* = 1), and blue sectors represent low probable reactions (*p* < 0.6). The pattern of clustering of points along the probability curves, particularly in the upper right-hand corners of each plot, indicates the population of highly probable "green" reactions in each category that have been discovered so far. Sixty-three percent of named monocyclic ring-forming MCRs have a 100% chance of being intrinsically green, whereas 60% of the named bicyclic MCRs fall into this category. The named bicyclic MCRs are 10 times more likely to fall into the lowest probability sector than the named monocyclic MCRs. This is consistent with the fact that reactions producing bicyclic ring systems are more challenging to achieve by multicomponent strategies.

The analysis was then widened to include MCRs published over the period from 2003 to 2011. Figure 6 shows the cumulative growth of publications announcing the discovery of such reactions over this time period, including those known before 2003 under the category of named MCRs. It is clear that the pace of discovery is vigorous. Figure 7 shows histograms of the kinds of reactions discovered by ring construction type. Figure 8 shows a more detailed breakdown of ring construction motifs for monocyclic rings according to ring size. From these diagrams, we observe that most of the research has narrowly focused on [3+2+1] and [2+2+1] cycloadditions for constructing 6- and 5-membered monocyclic rings and on [4.3.0] and [4.4.0] fused bicyclic ring systems. Many authors

have advertised their new reactions as "green" and environmentally friendly mainly because (1) they are run either with no reaction solvent (solvent-free) or in a so-called "green" solvent such as water or an ionic liquid, (2) they are carried out under catalytic conditions where catalysts may or may not be recoverable, or (3) some kind of new technology such as microwave irradiation, ultrasound, continuous flow, or ball milling is used. Despite these claims, an analysis of these reactions according to criteria presented in this work reveals that only 56% of the nearly 2000 reactions examined can be categorized as having an excellent chance of being intrinsically green (Figure S2, Supporting Information). When individual types of ring constructions are examined, the picture is more revealing. Figures S3, S4, and S5 of the Supporting Information show the results for MCRs producing 5-, 6-, and 7-membered moncyclic rings. The proportion of intrinsically green reactions increases with ring size (45% for 5-membered, 64% for 6-membered, and 72% for 7-membered), though there are far fewer examples of 7-membered ring-forming MCRs reported. This observation is a direct consequence of what reactions have been discovered so far for various ring sizes and is likely to change as new reactions are discovered. When we drill deeper into specific ring construction motifs by ring size, we discover interesting patterns. Figures S6−S10 of the Supporting Information show pie charts of probability distributions for various [a+b], [a+b+c], and [a+b+c+d] cycloadditions corresponding to the construction of 3-, 4-, 5-, 6-, and 7-membered monocyclic rings. For 3-membered rings, 50% of [1+1+1] MCR cycloadditions are intrinsically green, whereas 44% of [2+1] MCR cycloadditions are in the lowest probability category. For 4-membered rings, 80% of [2+2] MCR cycloadditions have a *p* value equal to 1, and 30% of [2+1+1] MCR cycloadditions
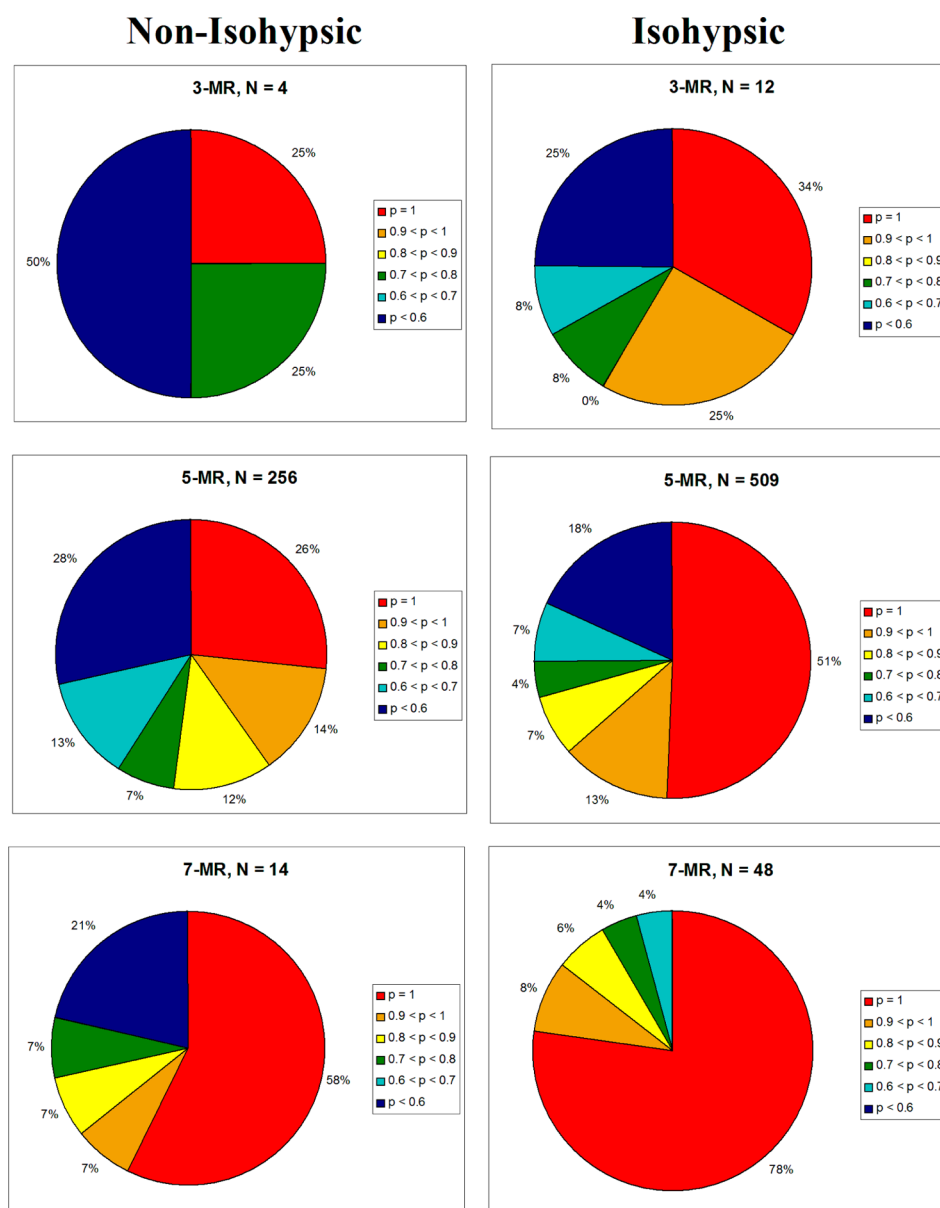
Figure 10. Pie charts showing distribution of probability ranges for nonisohypsic and isohypsic MCRs producing odd numbered monocyclic ring sizes (*ungeraderings*). Note: 3-MR denotes a 3-membered ring.

have a *p* value less than 0.6. For 5-membered rings, the best performers are [2+2+1] and [4+1] cycloadditions, and the worst performer is the [3+2] cycloaddition. For 6-membered rings, the far and away winner is the [3+2+1] motif, while the worst is the [2+2+1+1] motif. Finally, for 7-membered rings, the [3+2+2], [3+3+1], [4+2+1], [4+3], and [5+2] cycloadditions all perform well, while the worst performer is the [5+1+1] cycloaddition. Generally, rings comprised of an even number of atoms are easier to construct conceptually than ones with an odd number because there is a nice consecutive alternation of + and − signs corresponding to electrophilic and nucleophilic nodes around the ring. Odd numbered rings will necessarily have a clash of +/+ or −/− signs, which necessitates some kind of redox change to transform a +/+ linkage to a +/− or a −/+ linkage so that a chemical bond can be made. Similarly, a −/− linkage needs to be changed to a −/+ or a +/− link. By analogy with odd and even wave functions in quantum mechanics, we may designate the term *ungeradering* to

describe monocyclic rings having an odd number of atoms and a disruption in alternating signs and the term *geradering* to describe those having an even number of atoms and no disruption in alternating signs. Redox-type MCRs require the use of sacrificial reagents that necessarily results in significant byproduct formation and are characterized as having hypsicity indices that are either positive (hyperhypsic) or negative (hypohypsic).[2,4,77] The term "hypsicity" coined by Hendrickson[78] refers to the oxidation levels of the atoms involved in producing the target bonds in a given reaction. In that formalism, hyperhypsic reactions are associated with reduction-type transformations, and hypohypsic reactions are associated with oxidation-type transformations. Reactions not requiring any redox adjustments in the atoms forming the target bonds are isohypsic and have zero valued hypsicity indices. Figures 9 and 10 show pie charts of the probability distribution ranges for intrinsic greenness for even and odd numbered monocyclic rings that are broken down into nonisohypsic and isohypsic
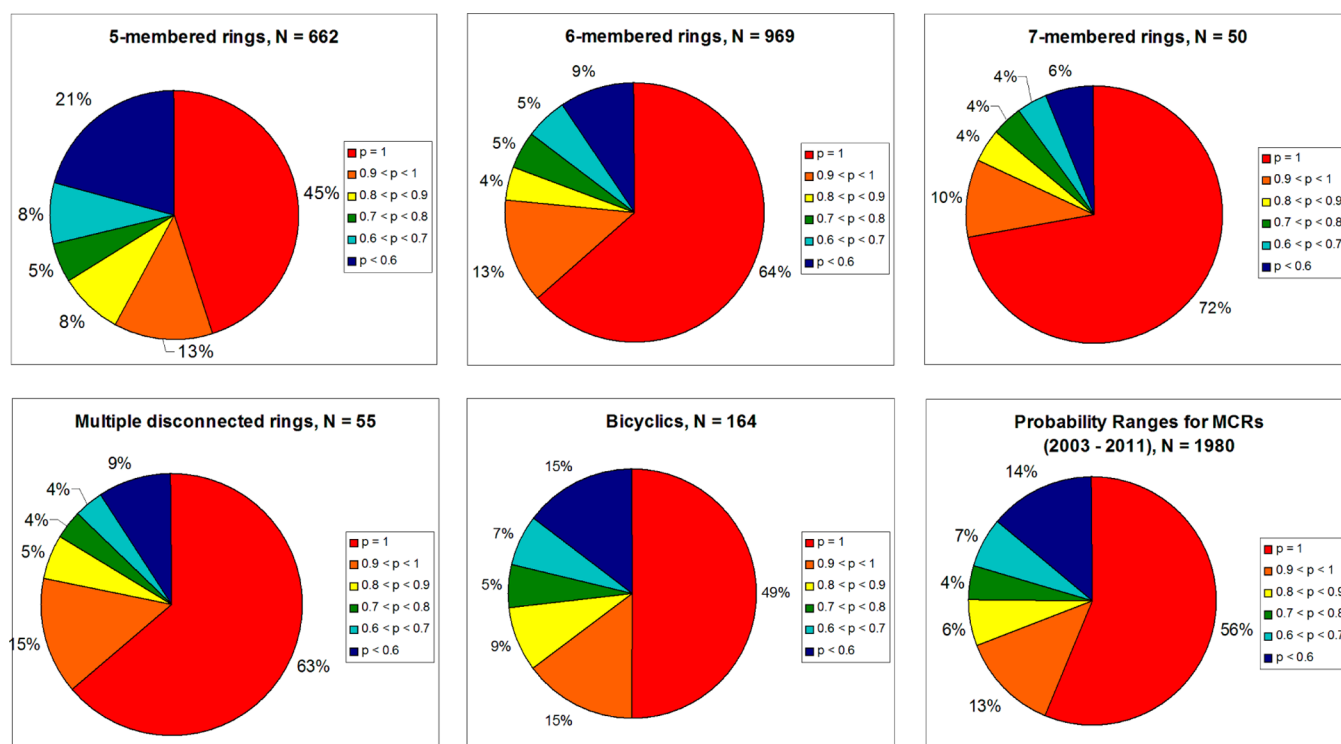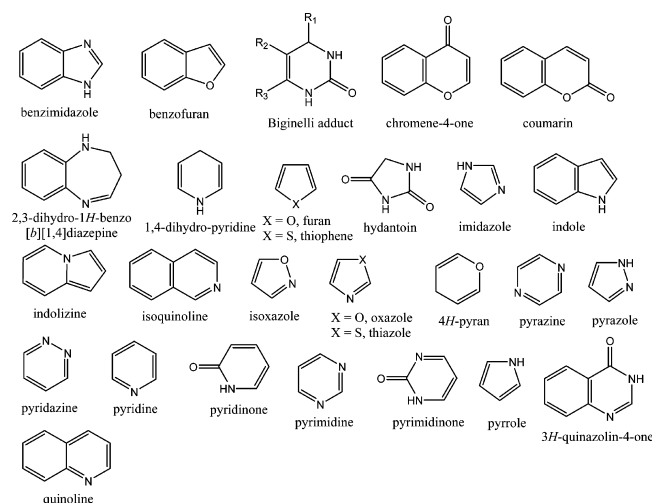
Figure 11. Pie charts showing global distribution of probability ranges for MCRs producing various rings according to ring construction type.

Scheme 2. Heterocyclic Ring Structures Made by MCR Strategies

classes. On the basis of the database of reactions examined so far, for 3-membered rings the proportion of nonisohypsic MCRs that fall in the $p < 0.6$ sector (blue) is larger than that for isohypsic MCRs. Also, the proportion of isohypsic MCRs that fall in the $p = 1$ sector (red) is larger than that for nonisohypsic MCRs. The same observations can be made for the 5- and 7-membered rings. When we look at 6-membered rings, again the same observation holds up; however, it breaks down for 4-membered rings probably because there are so few examples documented in the literature so far for this ring size. When taken together, 61% of isohypsic MCRs producing 3- to 7-membered rings have a 100% chance of being intrinsically green, whereas 12% have less than 60% chance (Figure S11, Supporting Information). For all the nonisohypsic MCRs

examined that produce 3- to 7-membered rings, 37% fall in the $p = 1$ category and 22% fall in the $p < 0.6$ category (Figure S12, Supporting Information). The Supporting Information also contains similar juxtaposed pie charts categorized according to the main ring construction types (Figures S13−S27, Supporting Information). Figures S28 and S29 of the Supporting Information show results for MCRs producing fused bicyclics and multiple disconnected rings. About half of the fused bicyclics and 63% of the multiple disconnected rings can be considered intrinsically green. From Figure S30 of the Supporting Information, we find that the proportions of intrinsically green reactions for [3.3.0], [4.3.0], [4.4.0], and [5.3.0] bicyclics are 34%, 38%, 59%, and 64%, respectively. The proportions of low probable green reactions for the same set of bicyclics are 25%, 17%, 8%, and 18%, respectively. These results suggest that [4.4.0] bicyclics have the best chance to be constructed by green synthesis strategies, whereas the [3.3.0] framework has the least chance. About two-thirds of MCRs producing multiple disconnected rings in the same molecule, such as two separate 5-membered rings made by two [3+2] cycloadditions, for example, fall in the $p = 1$ category (Figure S31, Supporting Information). Figure 11 shows summary global pie charts for all reactions in the main ring-forming MCR categories for which there is the largest number of examples.

We also examined the intrinsic greenness of the syntheses of important heterocyclic ring structures found in pharmaceuticals, shown in Scheme 2, using MCR strategies. Table 2 summarizes the number of MCRs analyzed according to heterocyclic ring type and ring construction motif. Figure 12 shows summary pie charts for the distribution of probability ranges for various heterocyclic ring types by MCR strategies. The present literature survey of heterocyclic ring structures commonly found in pharmaceuticals shows that Biginelli adducts, 2,3-dihydro-1H-benzo[b][1,4]diazepines, 1,4-dihydropyridines,

Table 2. Summary Data for Heterocyclic Ring Structures Made by Mcr Strategies

heterocyclic ring type	number of MCRs	ring construction motif (number of examples)
benzimidazoles	6	[3+1+1] (1), [4+1] (5)
benzofurans	6	[3+1+1] (2), [4+1] (4)
Biginelli adducts	29	[2+2+1+1] (2), [3+2+1] (27)
chromene-4-ones	5	[3+2+1] (3), [5+1] (2)
coumarins	6	[2+1+2+1] (1), [3+2+1] (1), [4+1+1] (1), [4+2] (3)
2,3-dihydro-1H-benzo [b][1,4]-diazepines	7	[4+2+1] (6), [4+3] (1)
1,4-dihydropyridines	123	[2+1+2+1] (56), [2+2+2] (1) [3+2+1] (65), [3+3] (1)
furans	34	[2+1+1+1] (3), [2+2+1] (17), [3+1+1] (10), [3+2] (2), [5+0] (2)
hydantoins	8	[2+1+1+1] (1), [2+2+1] (6), [3+2] (1)
imidazoles	45	[1+1+1+1] (1), [2+1+1+1] (32), [2+2+1] (5), [3+1+1] (6)
indoles	17	[2+2+1] (5), [3+1+1] (3), [3+2] (3), [4+1] (3), [5+0] (3)
indolizines	3	[2+2+1] (1), [3+2] (2)
isoquinolines	2	[3+2+1] (1), [4+2] (1)
isoxazoles	6	[2+2+1] (1), [3+1+1] (2), [3+2] (2), [4+1] (1)
oxazoles/thiazoles	23	[2+1+1] (1), [2+2+1] (2), [3+2] (8), [4+1] (8), [5+0] (4)
4H-pyrans	151	[2+1+2+1] (3), [3+2+1] (133), [3+3] (1), [4+2] (12), [4.3.0] (2)
pyrazines	7	[4+1+1] (3), [4+2] (4)
pyrazoles	15	[2+2+1] (8), [3+1+1] (1), [3+2] (6)
pyridazines	2	[2+2+2] (2)
pyridines	117	[2+1+2+1] (24), [2+2+2] (6), [3+2+1] (75), [3+3] (3), [4+2] (5), [5+1] (1), [4.3.0] (1), [4.4.0] (2)
pyridinones	21	[2+1+2+1] (3), [2+2+2] (2), [3+2+1] (14), [4+1+1] (1), [4.3.0] (1)
pyrimidines	29	[2+1+1+1+1] (1), [2+2+1+1] (1), [2+2+2] (5), [3+1+1+1] (2), [3+2+1] (14), [4+1+1] (1), [5+1] (2), [4.4.0] (3)
pyrimidinones	2	[3+2+1] (2)
pyrroles	56	[2+1+1+1] (2), [2+2+1] (43), [3+1+1] (5), [3+2] (4), [4+1] (1), [4.3.0] (1)
3H-quinazolin-4-ones	32	[3+2+1] (1), [4+1+1] (27), [5+1] (2), [4+2] (1), [4.4.0] (1)
quinolines	28	[3+2+1] (26), [5+1] (2)
thiophenes	19	[2+2+1] (16), [3+1+1] (2), [4+1] (1)
total	799	

furans, 4H-pyrans, pyridinones, and thiophenes can be made by strategies with a high probability of intrinsic greenness. The following heterocyclic ring structures have been found to require further improvements in synthesis design strategy by this criterion: chromene-4-ones, coumarins, indoles, isoxazoles, and pyrazoles.

Finally, we present two examples on how the probability of intrinsic greenness according to eqs 16−19 can be applied to the total synthesis of generalized scaffold structures that involve multicomponent reactions. This would be very useful in the development of compound libraries where several synthesis strategies could be analyzed and compared so that a synthesis route could be found that is both robust in producing many structural analogues as well as being intrinsically green with respect to the minimization of byproducts. The first example shown in Scheme 3 is for analogues of praziquantel, a pharmaceutical used to treat schistosomiasis.[68] The molecular

Scheme 3. Synthesis of Praziquantel Analogues According to the Dömling Strategy[a]
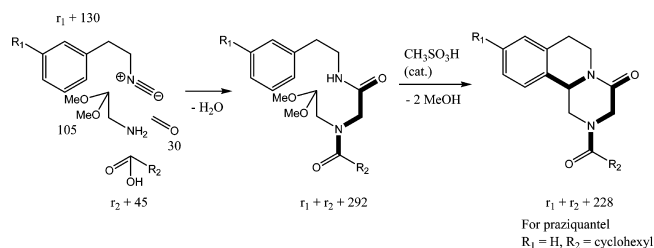
[a]Molecular weights are shown beside structures and target bonds are shown in bold.

Table 3. Summary of Parameters for Synthesis Plan to Praziquantel Scaffold Assuming ε(min) = 0.8 and α = 0.618 for Each Step

step	reaction	byproducts	AE(min)[a]	p[a]
1	4-CR	H_2O	0.947	1
2	[(5+1) + (6+0)] cycloaddition	2 MeOH	0.801	1
overall			0.759	1

[a]Calculated based on R groups having a minimum molecular weight of 15 g/mol corresponding to methyl groups.

weight of each structure is shown and target bonds are highlighted in bold for each reaction step. In this strategy developed by Dömling, the first step involves a 4-component condensation that produces an acyclic intermediate that is then cyclized in a second step to produce a [4.4.0] fused bicyclic target product. In this case, the MCR step does not produce a ring but produces an intermediate that is predisposed to produce two rings in a single subsequent step. Table 3 summarizes the AE(min) values and probabilities of intrinsic greenness for each step assuming thresholds of ε(min) = 0.80 (80% yield) and α = 0.618 for kernel RME for each step. Because both steps produce low molecular weight byproducts and do not require sacrificial reagents, both steps have each a 100% chance of achieving the target kernel RMEs. The overall probability of intrinsic greenness is found by multiplying the individual probabilities since each reaction is considered to be independent. This plan is clearly satisfying the attributes of greenness with respect to synthesis design.

The second example is that of analogues of frondosin B, a marine natural product found in the sponge *Dysidea frondosa*, which is an interleukin-8 receptor antagonist.[69] The plan shown in Scheme 4 based on Flynn's strategy consists of 5 steps where this time the MCR produces a benzofuran ring via palladium catalyzed three-component coupling. The furan ring is produced via a [3+2] cyclization. Table 4 summarizes the results of the key parameters. The low probability of 54.8% for the MCR step is due to a low AE(min), which in turn arises as a consequence of significant reaction byproducts. The other low performing step is the double alkylation taking place in step 4 that results in a 55.0% chance of intrinsic greenness. When the probabilities are multiplied out, the result is an overall probability of 28.6% for intrinsic greenness using this synthesis strategy. Though this appears disappointingly low, this strategy is currently the best available one to date that is able to deliver the target skeletal framework[4] as shown by the rankings of all plans for frondosin B summarized in Table 5. Not surprisingly, the highest ranking plan with respect to overall probability of

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dx.doi.org/10.1021/sc3001614 | ACS Sustainable Chem. Eng. 2013, 1, 496–512

intrinsic greenness is also the one with the least number of steps and the highest AE(min). It also produces the least mass

of kernel waste (byproducts and unreacted reagents) when actual experimental yields and atom economies for each step
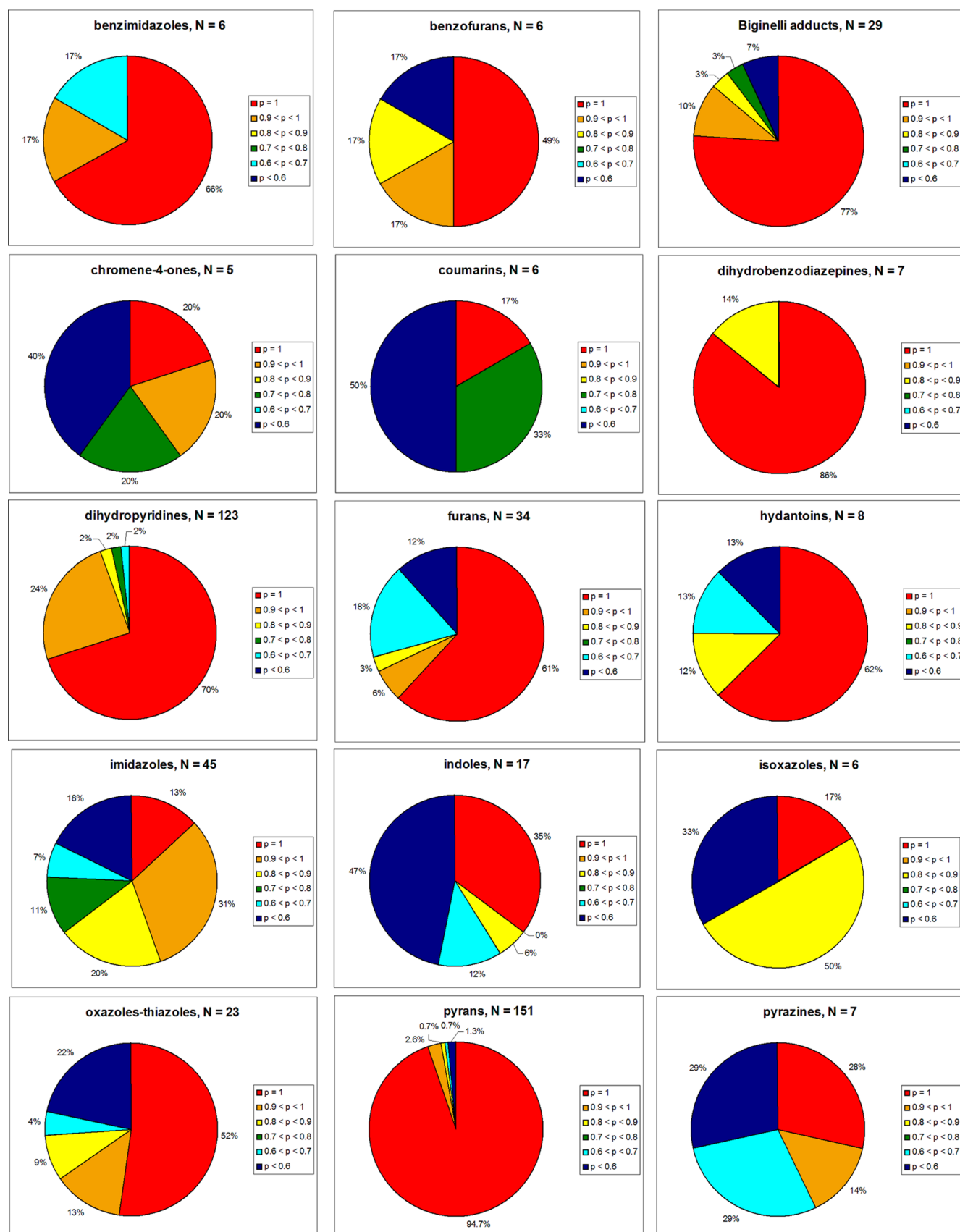

Figure 12. continued

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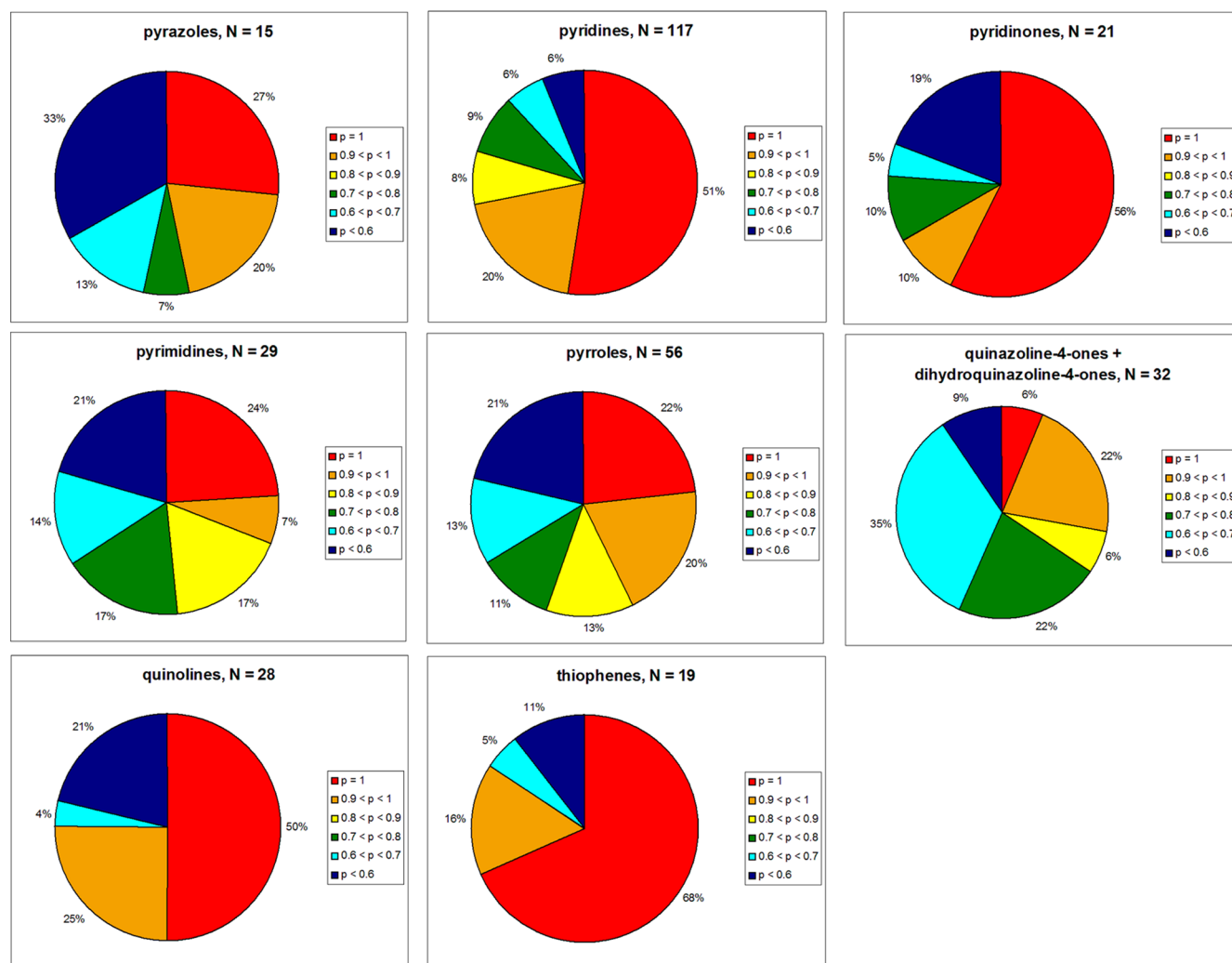dx.doi.org/10.1021/sc3001614 | ACS Sustainable Chem. Eng. 2013, 1, 496–512

Figure 12. Pie charts showing distribution of probability ranges for intrinsic greenness for various heterocyclic ring types produced by MCR strategies.

Table 4. Summary of Parameters for Synthesis Plan to Frondosin B Scaffold Assuming $\varepsilon(\min) = 0.8$ and $\alpha = 0.618$ for Each Step

step	reaction	byproducts	AE(min)[a]	p[a]
1	aromatic bromination	HBr	0.698	0.949
2	3-CR	2 CH$_4$	0.433	0.548
		2 MgBr$_2$		
3	ring closing metathesis	CH$_2$=CH$_2$	0.908	1
4	double alkylation	TiCl$_4$	0.436	0.550
		2 NH$_3$		
		H$_2$O		
5	catalytic hydrogenation	none	1	1
overall			0.249	0.286

[a]Calculated based on R groups having a minimum molecular weight of 15 g/mol corresponding to methyl groups.

Table 5. Summary of Overall Performance Metrics for Various Synthesis Plans to Frondosin B

p[a]	AE(min)	number of steps[b]	kernel mass of waste (kg)[c]	synthesis plan
0.286	0.249	5	4.2	Flynn[69]
0.199	0.210	8	5.0	Danishefsky[79,80]
0.129	0.210	6	5.6	MacMillan[81]
0.0796	0.136	13	17.2	Davies[82]
0.0366	0.113	12	28.0	Ovaska[84]
0.0023	0.063	19	27.0	Trauner[83]

[a]Calculated as described in the text. [b]In longest linear sequence. [c]Basis is 1 mol of frondosin B.

are taken into account. What we observe with the Flynn plan is a successful synergy of optimization among all metrics. All of these observations are consistent with and reinforce the importance of incorporating highly efficient design elements in a synthesis plan from the outset as a key strategy to achieve overall relative intrinsic greenness for a desired target molecule. Closer examination of the results in Table 5 shows a

counterintuitive result. The MacMillan convergent plan is two steps shorter than the Danishefsky linear plan, yet the latter produces less kernel waste though they both have the same overall minimum atom economy. This oddity is explained by the fact that the lowest yield (35%) for the MacMillan plan occurred in step 2 out of a sequence of 6 steps. The reaction was an acid catalyzed [5+0] cyclization of a hemiacetal precursor giving 5-methoxybenzofuran. This unfortunate occurrence early in the plan puts a significant penalty on overall mass efficiency performance because the scale of mass
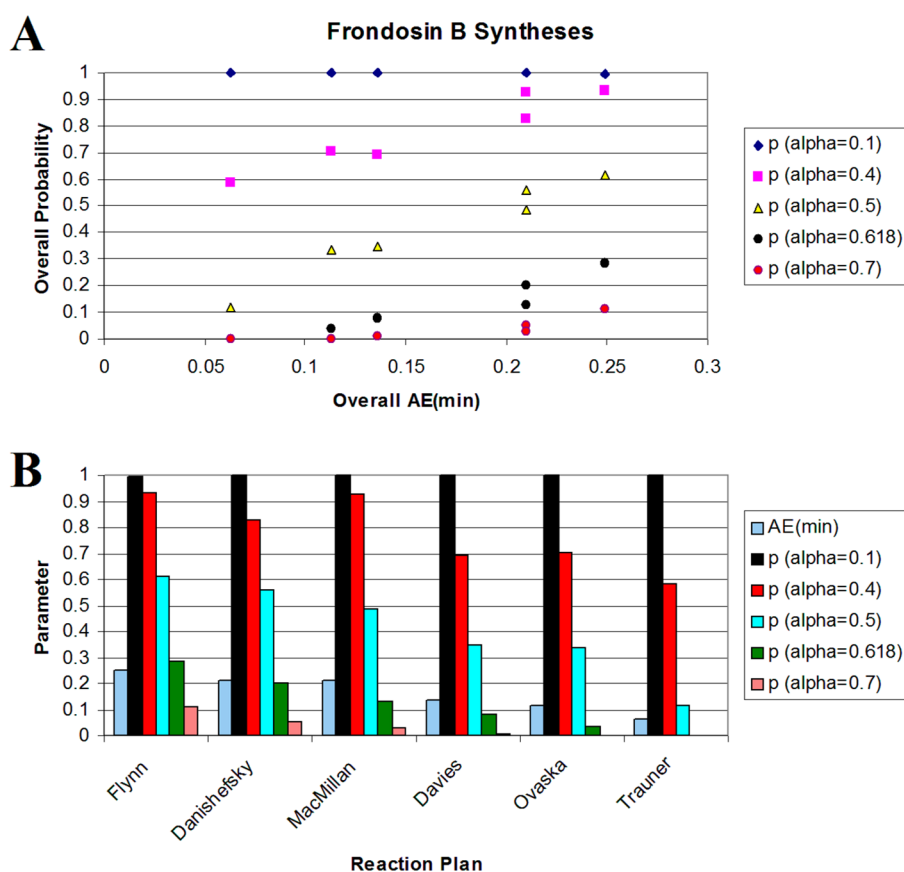
Figure 13. (A) Plot of overall probability versus overall AE(min). (B) Histogram of plan performances ranked in descending order of AE(min) for frondosin B syntheses.

loss of the desired intermediate at that stage is high. By contrast, the Danishefsky plan has no reaction below 67% yield over its 8 steps to the desired ring frame. These kinds of anomalous results are a direct consequence of nonsynchronous optimization where only a subset of variables is optimized. The emphasis is on global optimization of all variables in order to achieve overall intrinsic greenness as is demonstrated by the Flynn plan.

If the six plans are reworked using variable threshold α values other than 0.618, we find that the relative order of ranking of overall probabilities for intrinsic greenness remain invariant as shown by the plot in Figure 13. We observe that the probability increases as the threshold α value decreases and vice versa, consistent with the earlier observation concerning eq 5. Also, the probability appears to have a weak linear dependence on AE(min) with diminishing slope as the threshold α value is lowered and increasing slope as the threshold is raised. At the lowest threshold of $\alpha = 0$, all probabilities converge to 1, but the plans are separated by their relative overall AE(min) values. In fact, it may be argued that for the purpose of ranking plans according to overall intrinsic greenness it is sufficient to determine overall AE(min) values without having to work out probabilities. The determination of intrinsic greenness probability values is useful when classifying individual reaction performances. It is an additional powerful green metric in a repertoire of metrics that can be determined subject to defined constraints and has utility in identifying intrinsically green reactions in a synthesis plan.

Scheme 4. Synthesis of Frondosin B Analogues According to the Flynn Strategy[a]
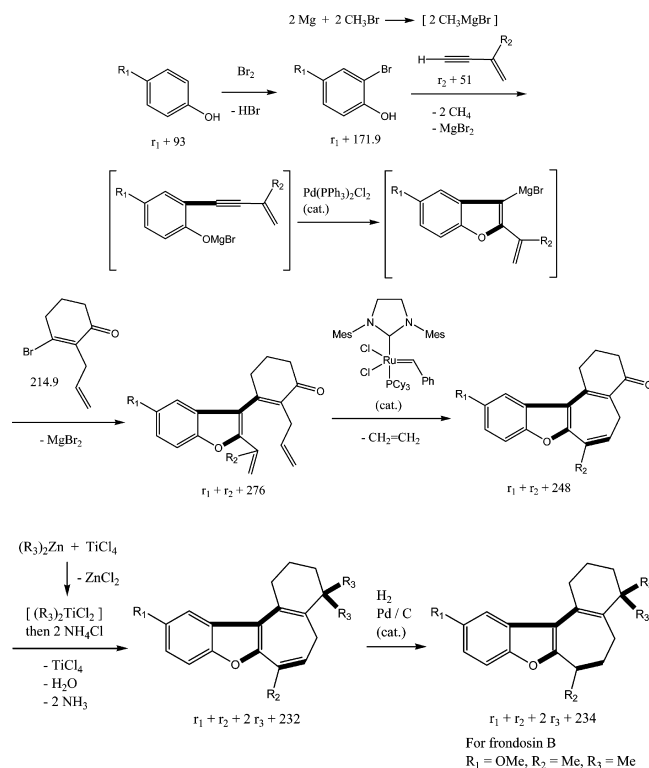
[a]Molecular weights are shown underneath structures and target bonds are shown in bold.

CONCLUSIONS

The parametrization of the probability of intrinsic greenness based on setting lower limit thresholds for kernel RME and reaction yield and using minimum atom economies for generalized chemical transformations based on balanced chemical equations has been demonstrated. The choice of thresholds $\alpha = 0.618$ and $\varepsilon(\text{min}) = 0.8$ have been justified. Practicing synthetic organic chemists may readily determine the intrinsic greenness pertaining to synthesis design strategy for proposed individual reactions or synthesis plans to a desired target molecule by first writing out all the relevant balanced chemical reactions showing waste byproducts in general form using generalized R groups for variable substituents and identifying the core scaffold structures. Then, using the two thresholds, the appropriate domains and equations in Table 1 are used to calculate the required probabilities of intrinsic greenness. The accompanying spreadsheet in the Supporting Information is designed to facilitate this computation because all formulas in Table 1 are embedded, and all the user needs to do is to input the molecular weights of the core scaffold structures appearing in the reactants and products, molecular weights of all waste byproducts, and minimum molecular weights for the R-groups. The spreadsheet will automatically identify the appropriate domain ranges for AE(min) and $\varepsilon(\text{min})$ and calculate the minimum atom economy and target probability. For convenience, a plot like that shown in Figure 1 is also given for each reaction. A detailed study of 2000+ ring-forming MCRs was undertaken and probability distribution pie charts for individual ring construction motifs and their performances according to intrinsic greenness have been analyzed. Overall, a little over half of them may be considered intrinsically green. The proportion of isohypsic reactions that have $p = 1$ is larger than for nonisohypsic MCRs, whereas the proportion of nonisohypsic reactions that have $p < 0.6$ is larger than for isohypsic MCRs. For odd numbered monocyclic rings (*ungeraderings*), the proportion of MCRs that have $p < 0.6$ is larger than for even numbered monocyclic rings (*geraderings*). The converse is true for MCRs having $p = 1$. A survey of MCR syntheses of heterocyclic ring structures commonly found in pharmaceuticals shows that Biginelli adducts, dihydrobenzodiazepines, dihydropyridines, furans, pyrans, pyridinones, and thiophenes can be made by strategies with a high probability of intrinsic greenness. The following heterocyclic ring structures have been found to require further improvements in synthesis design strategy by this criterion: chromene-4-ones, coumarins, indoles, isoxazoles, and pyrazoles. The application of probabilities to synthesis plans for making ring containing scaffold structures appropriate for the synthesis of compound libraries has been demonstrated using praziquantel and frondosin B as examples. By analogy with overall yield as a metric to gauge the material efficiency of a linear synthesis plan, an overall probability of intrinsic greenness can be used to probe the synthetic strategy efficiency of a given route to a given target structure. Research in MCRs has been vigorous in the past decade, particularly because of the drive to invent atom economical reactions for the synthesis of complex structures. Presently, there is a saturation of examples for [3+2+1] and [2+2+1] cycloadditions that can now be considered well worked out. Novel approaches are needed for other ring motifs, particularly for 3-, 4-, and 7-membered monocyclic rings. Particular attention needs to be paid to odd membered rings (*ungeraderings*). Similarly, MCRs for generating [4.3.0] and [4.4.0] fused bicyclics are plentiful. What is needed is to shift MCR research in the direction of other bicyclic ring systems found in many natural products that have therapeutic potential. Though there are in excess of 2000 known MCRs documented in the literature, there is still a huge untapped landscape of possible structures that could be made using this powerful technique.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Part 1: Derivations of eqs 6−12; Figure S1 (plot of eq 5); Tables S1 and S2; complete reference list and schemes for named MCRs; Figure S2 (plots of p{RME > 0.618, Y > 0.8} versus AE(min) and pie charts for MCRs discovered between 2003 and 2011); Figures S3 to S10 (statistics for 3- to 7-membered monocyclic rings); Figures S11−S27 (statistics for 3- to 7-membered monocyclic rings broken down by isohypsic and nonisohypsic categories); Figures S28−S31 (statistics for fused bicyclic and multiple disconnected rings). Part 2A: Database of MCRs published in 2010. Part 2B: Addendum to database for MCRs published in 2010. Part 3: Database of MCRs published in 2011. Microsoft Excel spreadsheet for determining minimum atom economies and threshold probabilities including Biginelli reaction example. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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