

EvolvedComplexity as a Total Synthesis Assessment Metric: Strychnine as a Case Study of Scoring Functions

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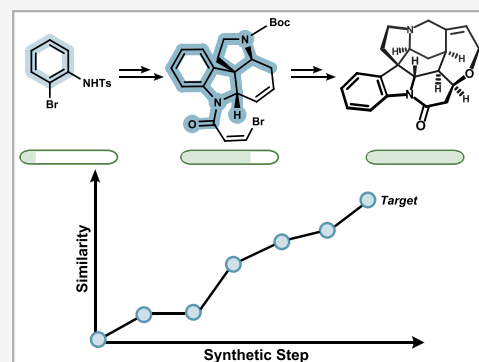


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ABSTRACT: The selection of synthetic routes to a small molecule of interest is enabled by the use of various tools to assess the chemical complexity of a given intermediate. While prior approaches assess the intrinsic molecular complexity or the facility with which an intermediate can be synthesized, in this study, we introduce an alternative approach that tracks the progress toward the target structure in a given synthesis. A simple metric, EvolvedComplexity, was developed that compares the chemical similarity of a pair of molecules on the basis of the Tanimoto distance between chemical fingerprints. This complementary approach to assessing progress in the synthesis may prove to be a useful tool for planning synthetic routes and developing novel chemistries.



INTRODUCTION

Retrosynthetic planning is a cornerstone in the synthesis of complex natural products, where the challenge lies in deconstructing a target molecule into simpler, commercially available building blocks through a series of transformations.^{1,2} This process, traditionally guided by the expertise of synthetic chemists, has increasingly been augmented by computer-aided synthetic planning (CASP) tools, an idea originally pioneered by EJ Corey in the 1960s that has seen a resurgence in recent decades, owing to advances in computation.^{1,3,4} Early CASP systems relied heavily on rule-based approaches using expert knowledge to guide retrosynthesis.^{2,5} Recently, CASP approaches have evolved from these rule-based methods to data-driven, predictive algorithms.^{4,6} This transition was enabled by the automated extraction of reaction rules from vast chemical data sets, transforming how synthetic routes are identified.⁷ These tools offer improved feasibility of a selected chemical route in the synthesis of a complex small molecule.

Automated retrosynthesis tools benefit from an assessment of molecular complexity in order to provide directionality to a retrosynthetic operation.⁸ While human-guided retrosynthesis considers complexity reduction as a combination of the application of the logic of chemical synthesis and intuition, an automated approach requires an automated assessment. Each retrosynthetic step creates several more retrosynthetic possibilities leading to a tree whose search space increases exponentially with each additional step.⁹ Selecting an individual pathway can be guided by molecular complexity where further consideration of given branches can be limited on the basis of molecular complexity (i.e., routes that lead to

increasingly complex intermediates do not need to be considered further). Several methods for the evaluation of molecular complexity, hereafter referred to as scoring functions (SFs), have been developed to quantify complexity, providing chemists with a metric to gauge the structural and synthetic challenges of a molecule.^{9–11}

SFs can generally be divided into one of two categories: complexity-based methods and reaction-based methods.⁹ Complexity-based methods employ rule-based systems to estimate the complexity of the target structures. The first widely applicable index of molecular complexity was introduced by Bertz, who utilized principles of graph theory combined with information theory to analyze and quantify molecular topology (Figure 1A).¹² Graph theory treats molecules as mathematical graphs, where atoms are represented as vertices and bonds as edges.¹³ This abstraction enables rigorous analysis of molecular topology, including connectivity, cyclic structures, and branching patterns, using combinatorial and algebraic methods. Information theory, on the other hand, quantifies the amount of information contained in the system, which involves assessing how diverse or ordered the arrangement of atoms and bonds is within a molecule.^{14,15} This approach evaluates how much information

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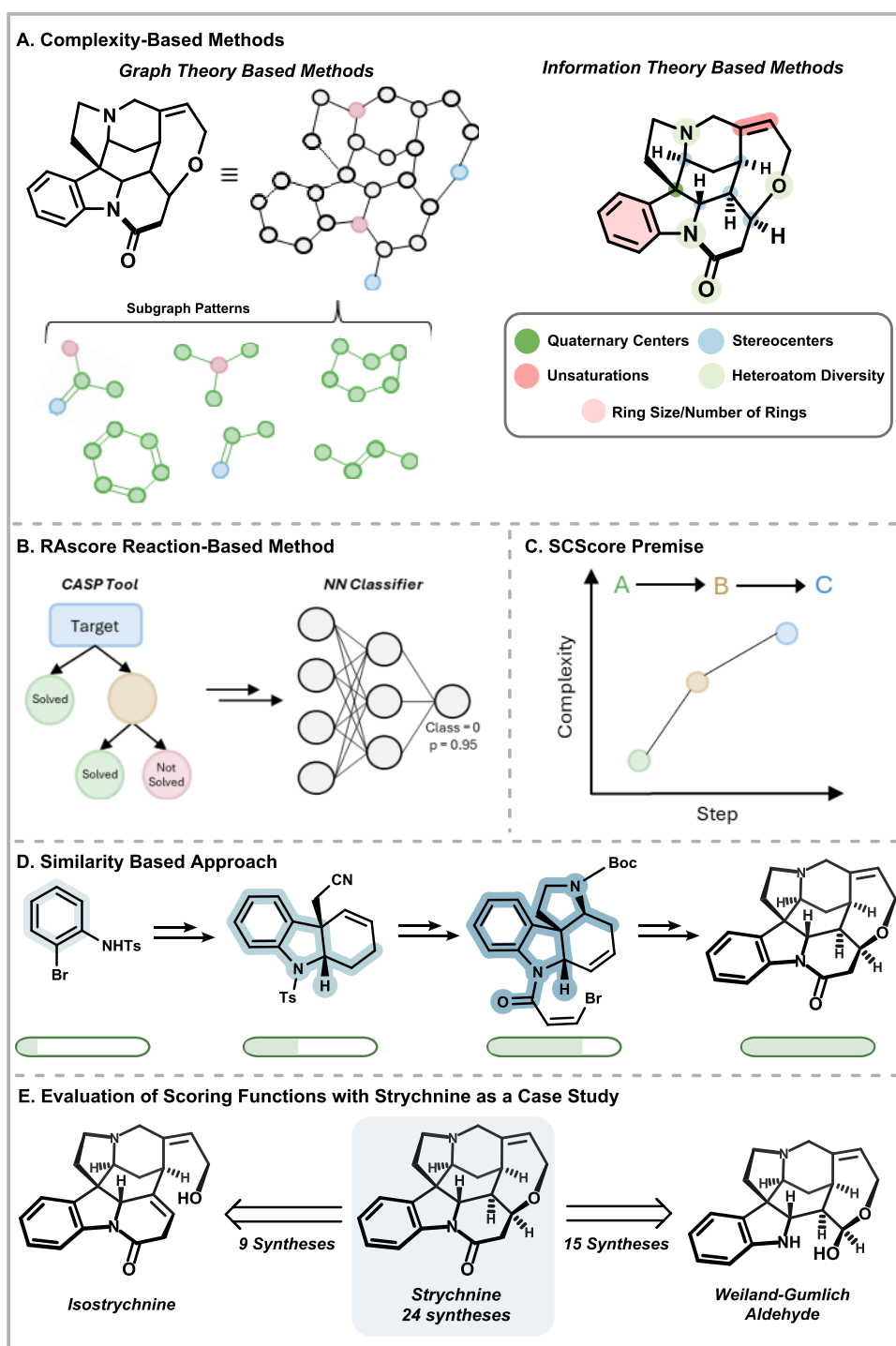


Figure 1. (A) Complexity-based methods for creating scoring functions include deriving functions from graph-based and information-based methods. (B) Reaction-based workflow used to develop RAScore. (C) Underlying reaction-based premise used to develop SCScore. (D) Similarity metrics for monitoring the reaction progress. (E) General representation of the 24 total syntheses of strychnine proceeding via either the isostrychnine or Wieland–Gumlich aldehyde intermediates.

is required to describe the structure of a molecule, with more complex molecules containing higher information content due to their intricate patterns of bonds and stereochemistry.¹⁵

Later, Whitlock developed a metric for molecular complexity that was designed to emulate a chemist's chemical intuition.¹⁶ It comprises a size metric (S) and complexity metric (H) and is calculated by evaluating the number of atoms, bonds, and specific structural features (e.g., stereocenters or rings) in the

molecule. Building on Whitlock's foundation, Barone and Chanon sought to expand and refine this approach. Choosing to neglect the chiral term, as Bertz does, they also incorporate terms to account for substituents and ring size, two features that had not been accounted for previously in the Whitlock index.¹⁷ The synthetic method complexity metric (SMCM) was developed shortly thereafter to overcome key limitations of earlier SFs, specifically addressing chirality, fused ring

systems, and the presence of functional groups.¹⁸ SMCM incorporates a unique set of multipliers based on the electronegativity of each atom, ring size and type, bond type, and substructures. This nuanced approach successfully minimizes the common bias that links higher molecular weights to greater complexity, a correlation that does not always hold true.

More recently, Böttcher drew from Bertz's systematic approach and Whitlock's intuitive method to create an alternative complexity index. This index measures molecular complexity by examining the information content of each atom's local environment.¹⁵ By employing an entirely additive model, it mitigates the biases found in graph-theoretical methods (Figure 1A) and incorporates crucial aspects, such as symmetry and stereochemistry. This metric has been applied recently to demonstrate a marked increase in molecular complexity in challenging transformations, underscoring the utility of their newly developed methods for achieving these complex reactions more efficiently.¹⁹ In an effort to correlate complexity to biologically relevant properties, Waldmann and co-workers defined spacial score (SPS), an index engineered to closely mimic the fraction of sp^3 -hybridized carbons (F_{sp^3}) and the fraction of stereogenic carbons ($F_{C_{stereo}}$).²⁰ The intentional inclusion of certain molecular properties creates an SF that scales with the relative complexity of the molecule's skeletal structure. Ertl and Schuffenhauer introduced a novel approach to molecular complexity with the synthetic accessibility score (SAscore).²¹ They assign fragment scores to common substructures from the PubChem database, with easier-to-synthesize fragments receiving lower scores and rarer, more complex fragments receiving higher ones. The total fragment score is the sum of these individual scores, further adjusted by a complexity penalty for challenging structural features. SAscore has proven to be a valuable tool, having been successfully applied in the planning, design, and synthesis of numerous inhibitors targeting a variety of drug candidates.²²

An alternative approach to evaluating complexity involves reaction-based SFs. Instead of defining molecular complexity solely based on atomic properties, this approach ranks how readily a molecule can be synthesized given a certain set of chemical transformations (Figure 1C). Coley et al. developed a neural network approach to develop the learned metric synthetic complexity score (SCScore).²³ Another approach to a reaction-based SF is the retrosynthetic accessibility score (RAscore) developed by Thakkar et al.²⁴ This unique approach utilizes a machine learning (ML) classifier trained on the outputs of the CASP tool, AiZynthFinder. Synthetic feasibility is assessed on the basis of the retrosynthetic routes suggested by AiZynthFinder (Figure 1B). After training, RAscore offered synthetic accessibility predictions around 4500 times faster when running on a GPU compared to AiZynthFinder. This increased speed highlights the benefit of using scoring functions to streamline the identification of synthetically tractable routes.

The wide array of approaches and indices for measuring molecular complexity highlights that no single method has proven entirely satisfactory, as each comes with its own limitations. Common criticisms of synthetic accessibility scores include their oversimplification of molecular complexity, failure to account for chirality and stereochemistry, and bias toward larger molecules. Additionally, many approaches are disconnected from the extrapolation of known synthetic methods to new systems and entirely novel chemistries, limiting their

predictive power and alignment with real-world synthetic challenges. Scoring functions have been continually assessed in many different contexts.^{9,10} In this study, we evaluated a wide range of scoring functions within the context of syntheses of the natural product strychnine, which has long served as a benchmark and training ground within the field of total synthesis.

Strychnine, an alkaloid derived from the seeds of the *Strychnos nux-vomica* tree, is renowned as a structurally complex and challenging natural product to synthesize.²⁵ Its intricate molecular architecture includes a densely packed polycyclic framework with six fused rings, seven contiguous stereocenters, and a bridged bicyclic amine. The first total synthesis of strychnine was achieved by Woodward et al. in 1954.²⁶ The synthesis involved 29 steps, many of which were pioneering at the time, including the use of strategic cyclization reactions and selective functional group manipulations.²⁷ Since then, strychnine has become a ruler to measure synthetic innovation, with multiple total syntheses having been completed over the decades.²⁸ The synthesis of strychnine remains a hallmark of advanced synthetic chemistry, symbolizing both the intellectual challenge and the art of constructing highly complex natural products. With 24 published synthetic routes to strychnine, the extensive diversity in chemical strategies to complete its synthesis make it an ideal benchmark for evaluating the performance of various SFs.^{26,29–34}

RESULTS AND DISCUSSION

The 10 scoring functions discussed earlier, SAscore, RAscore, SCScore, SPS, nSPS, Böttcher (C_m), Barone and Chanon (BC), Whitlock (S), Bertz (C_T), and SMCM, were applied to evaluate each intermediate across the 24 total syntheses of strychnine (detailed synthetic routes can be found in the Supporting Information). In order to make comparisons across scoring functions, which have a wide range of numerical outputs on different scales, all scores were normalized between 0 and 1. Here, a score of 0 indicates the least complex molecule according to a particular SF, while a score of 1 signifies the most complex molecule.

Several factors, such as atom, redox, and step economy, alongside the overall yield and the cost of commercially available starting materials, play a crucial role in determining the efficiency of a synthetic route. These considerations are integral to retrosynthetic analysis, helping chemists design pathways that balance efficiency with practicality. Nevertheless, one fundamental guideline is that molecular complexity should, on average, increase progressively throughout a multistep synthesis.^{12,23} In retrosynthetic analysis, the goal is to simplify the target molecule into readily available starting materials through sequential transformations that decrease the complexity at each step. This approach helps prioritize retrosynthetic disconnections during automated synthesis planning, ensuring that each step effectively breaks down the structure while moving toward accessible precursors.

Molecular complexity plots (see the Supporting Information) were generated for each intermediate in all of the syntheses. These visualizations provide a clear, 2D representation of how each reaction step builds toward the final target molecule. Beyond illustrating the incremental contributions of each step, these plots also offer a baseline for comparing the different SFs, allowing for a more intuitive assessment of how well each function captures the progression of complexity throughout the synthesis. To evaluate the premise that

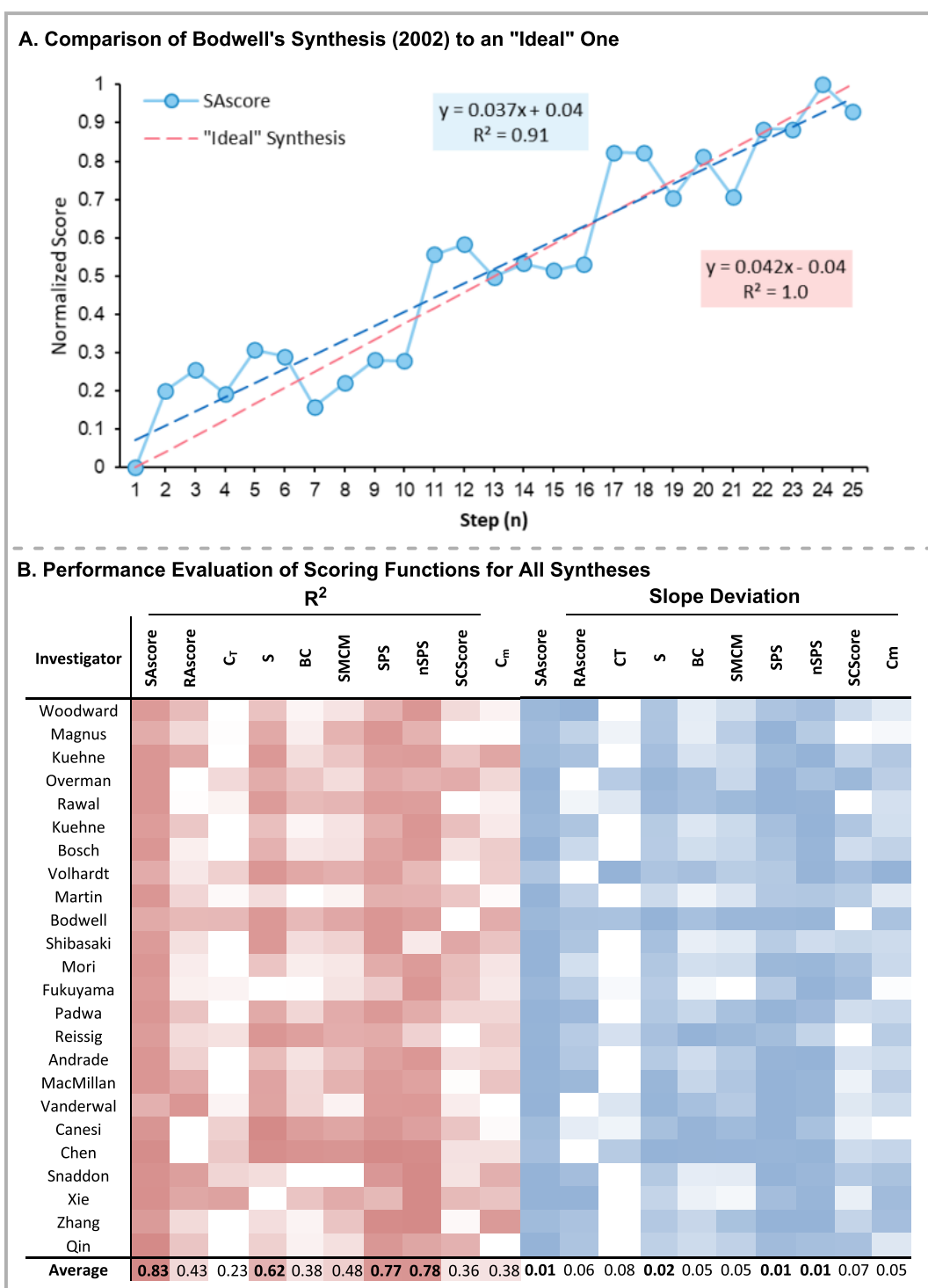


Figure 2. (A) General representation of the assumption that an ideal synthesis should follow a linear trend. The red dashed line represents an ideal synthesis. The blue points and dashed line represent the SAscore progression for the 2002 Bodwell and Li synthesis (selected arbitrarily for demonstration). (B) Heat maps representing R^2 values (red) and deviation from the ideal slope (blue). Higher R^2 and lower deviations are indicative of better scoring function performance (darker red/blue).

molecular complexity should increase progressively over the course of a multistep synthesis, the slope and R^2 values for each scoring function were determined. Given the varying number of steps across different syntheses, an ideal slope was calculated for each based on a theoretical linear progression of complexity from 1 to the total number of steps (n). The absolute deviation between this ideal slope and the actual slope derived from each

SF was then measured, providing a quantitative comparison of how closely each synthesis adhered to a linear increase in complexity (Figure 2A). It should be noted that this assumption simplifies the analysis such that mathematical comparisons can be made, although syntheses generally have at least one step that rapidly increases complexity and, relatedly, overly complex intermediates that are often strategic.

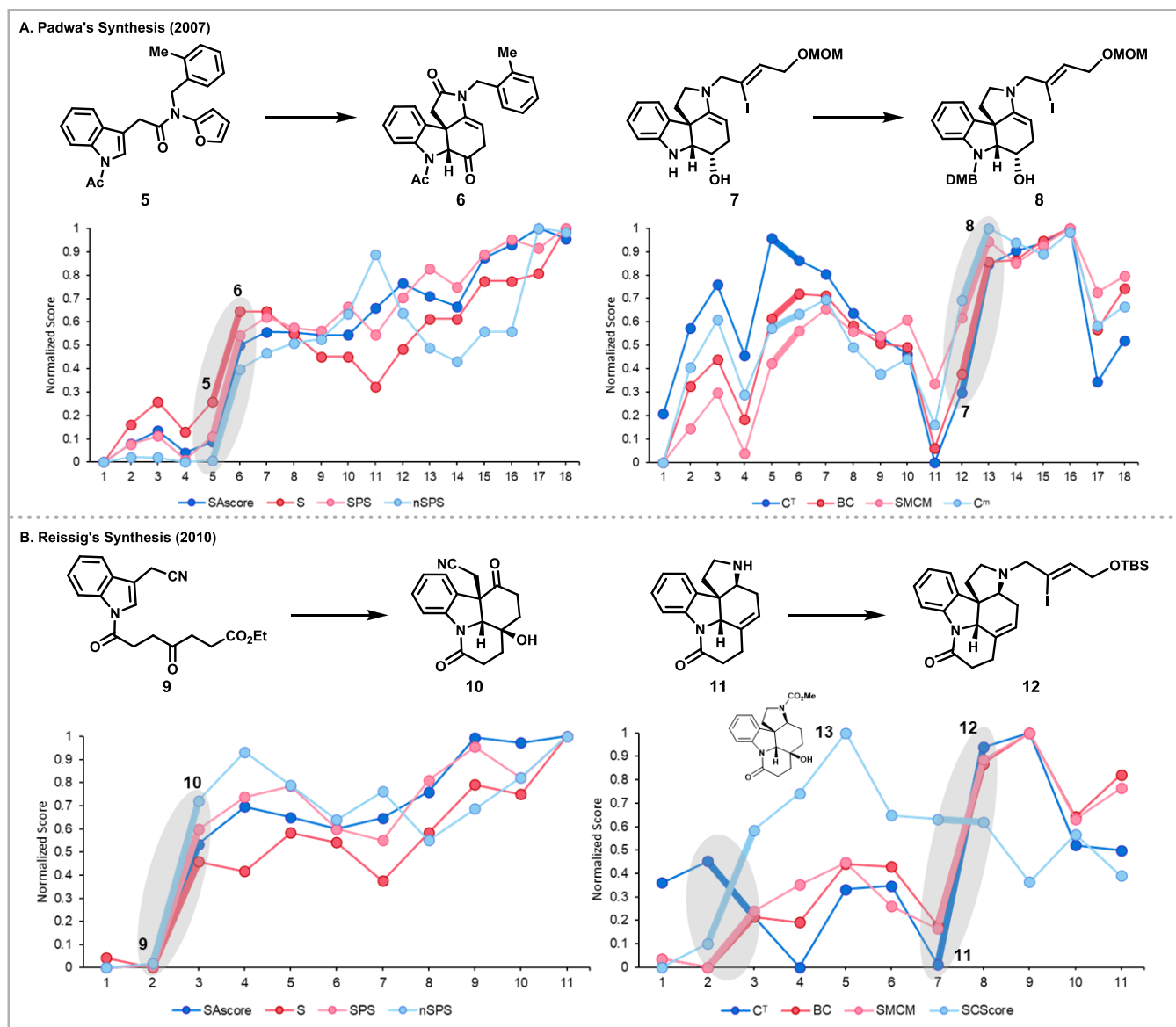


Figure 3. Examples of early stage complexity introduction. (A) Example of SAScore, Whitlock's index (S), SPS, and nSPS performance (left) compared to Bert's index (C_T), Barone and Chanon (BC), SMCM, and Böttcher's index (C_m). (B) Similar comparison of scoring functions for Reissig's 2010 synthesis.

Heat maps were generated to visualize the R^2 and slope metrics for each SF (Figure 2B). For every synthesis, each SF is associated with an R^2 value, where an R^2 of 1 represents a synthesis that follows a perfectly linear progression in complexity. Among the SFs, SAScore demonstrated the highest average R^2 of 0.83. SPS and nSPS followed, with average R^2 values of 0.77 and 0.78, respectively. Whitlock's index also showed notable linearity, with an average R^2 of 0.62. A parallel trend emerged from deviations from the ideal slope. SAScore again exhibited the most consistent linearity, with an average deviation of just 0.007, while SPS, nSPS, and Whitlock showed slightly larger deviations but still indicative of overall linear behavior.

While this type of analysis can provide valuable insight, it is inherently insufficient for comparing SFs due to the complexity of chemical syntheses. In practice, synthetic routes require the use of protecting groups, functional group interconversions, and nonstrategic redox manipulations, which lead to deviations

from the linear progression of molecular complexity.³⁵ While the slope and R^2 offered a useful starting point for highlighting scoring functions that aligned reasonably well with the assumed linear increase in complexity, visual inspection remained critical. Since some syntheses deviate from this assumption to some degree, a case-by-case visual assessment was necessary to more accurately judge how well each SF captured the true complexity profile of a given route.

Various strategies are typically employed when designing a synthesis, including introducing complexity either at the outset or toward the end of the sequence or even generating excess complexity beyond that of the target molecule.¹⁰ Our initial analysis focused on how each SF responded to the early introduction of complexity within the synthetic pathway, assessing how well it captured the increase in molecular complexity during the initial stages (Figure 3).

In 2007, Padwa and co-workers reported a concise, innovative synthesis of strychnine, highlighting the critical

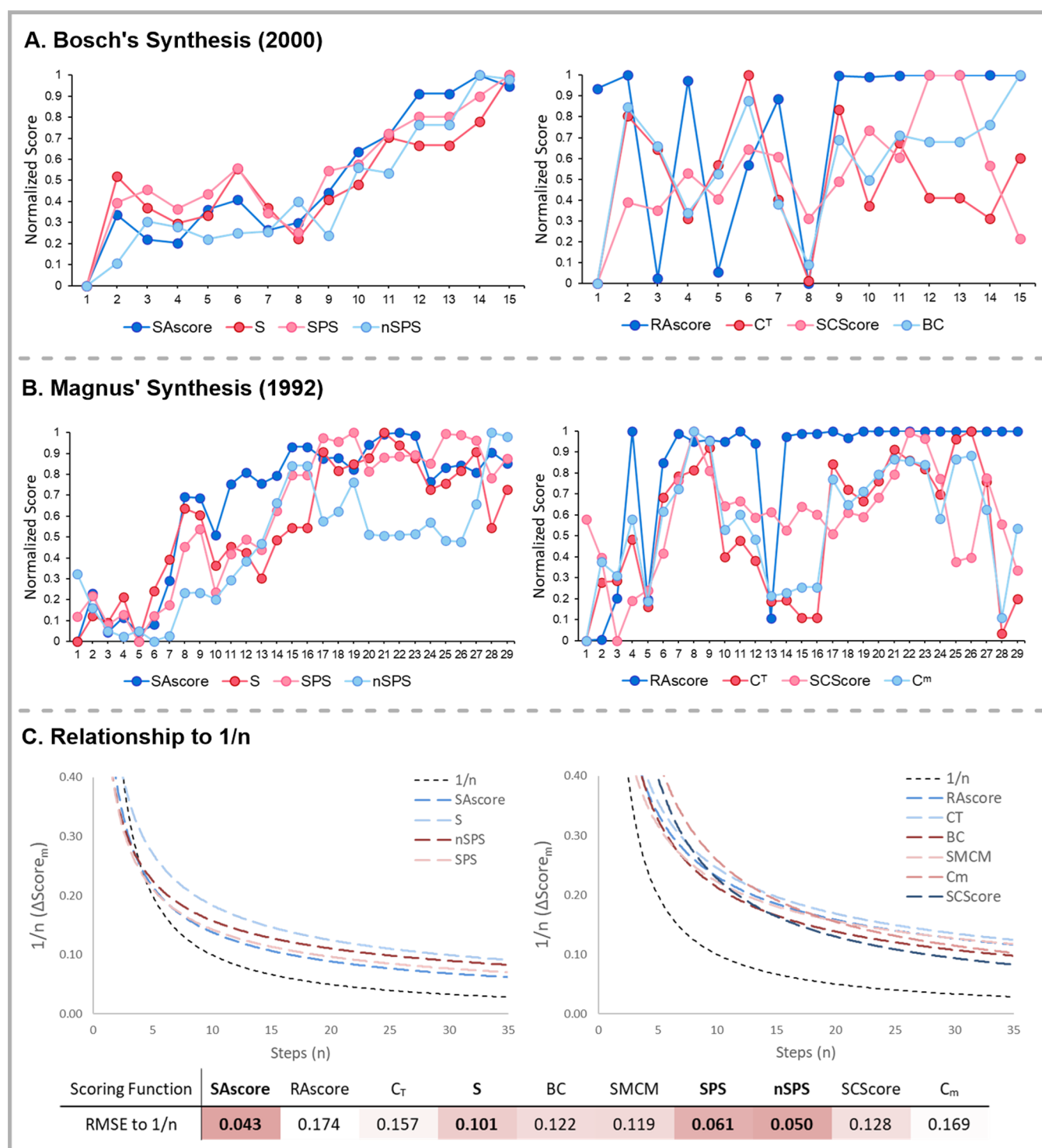


Figure 4. (A) Example of SAscore, Whitlock's index (S), SPS, and nSPS performance (left) compared to Bertz's index (C_T), Barone and Chanon (BC), RAscore, and SCScore (right) for a linear progression of a longer synthesis by Bosch and co-workers.³⁰ (B) Similar comparison for the 1992 synthesis by Magnus et al.³⁰ (C) Comparison of SAscore, Whitlock's index (S), SPS, and nSPS performance (left) to the remaining scoring functions' (right) relation to the ideal $1/n$ curve. The table displays the RMSE of each scoring function to the $1/n$ curve.

role of an intramolecular $[4 + 2]$ cycloaddition/rearrangement cascade of an indolyl-substituted amidofuran **5** to afford the aza-tetracycle **6** (Figure 3A).³³ Since this key reaction occurred early in the sequence, we examined how the SFs responded to the rapid increase in molecular complexity introduced at this stage. SAscore, SPS, nSPS, and the Whitlock index all capture this increase in molecular complexity from **5** to **6**. When

complexity is introduced early in a synthesis, it often creates reactive functionalities that require careful mitigation throughout the remaining steps. SAscore, SPS, nSPS, and the Whitlock index effectively capture the fluctuations in complexity after the initial sharp increase while still reflecting an overall linear upward trend. For the same synthetic step, the BC, SMCM, and Böttcher indices all show only a modest increase in

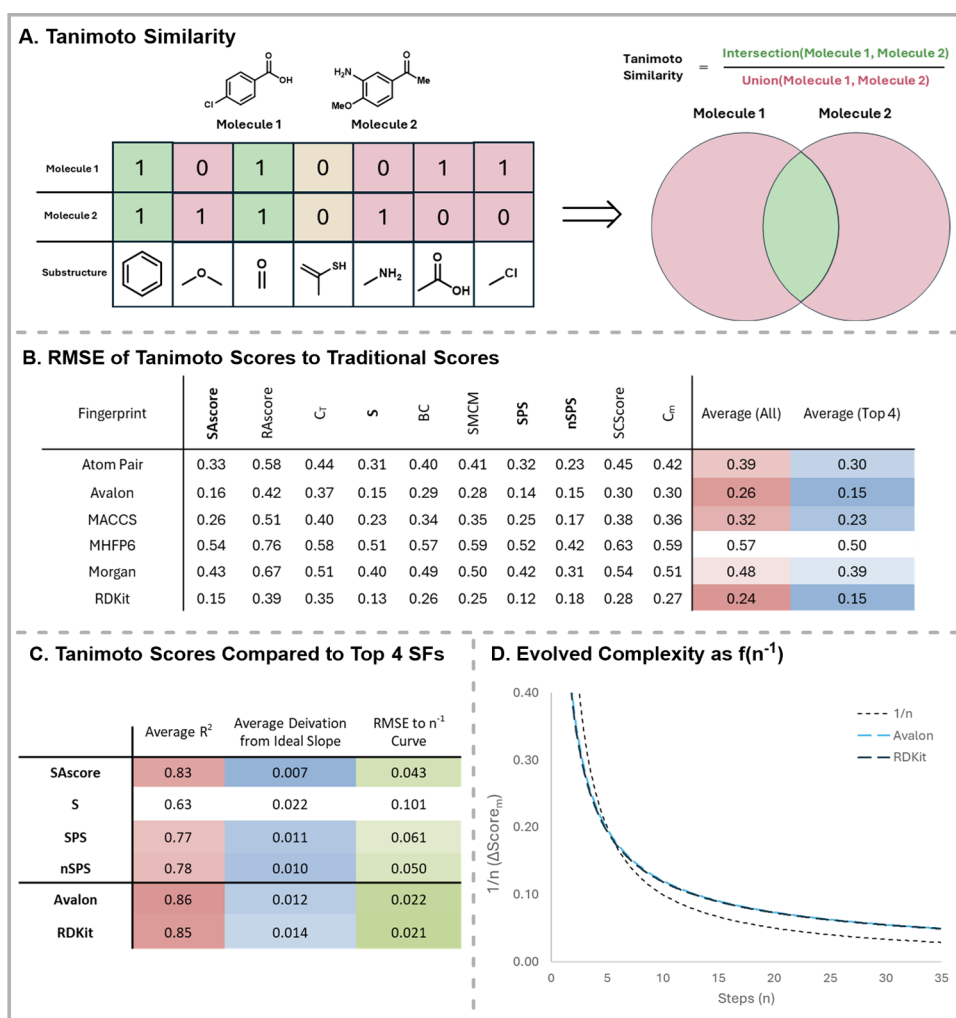


Figure 5. (A) Broad overview of calculating Tanimoto similarity scores from molecular fingerprints. The Tanimoto similarity is calculated by identifying common substructures found in each of the molecules. (B) Average RMSE across all 24 strychnine syntheses was between the various Tanimoto similarity scores based on different fingerprints and the SFs. The right shows the average RMSE for each fingerprinting method. Heat maps (red for all SFs and blue for top 4 SFs) show which fingerprints exhibited the lowest average RMSE (darker colors). (C) Average R², deviation from the ideal slope, and RMSE to 1/n for the top 4 SFs and two best fingerprinting methods. (D) Representative 1/n curve for the top two fingerprinting methods.

complexity, while the Bertz index instead indicates a decrease in complexity. Interestingly, these four SFs showcase an increase in complexity from 7 to 8. Upon inspection, this step is simply the DMB protection of the indole nitrogen.

Beemelmans and Reissig's 2010 synthesis of strychnine is another great example of the introduction of complexity at an early stage.³⁴ The authors denote a SmI₂-induced cascade reaction as the key step (Figure 3B) to afford the desired tetracycle **10**. Similar to the Padwa and co-workers synthesis, SAcore, SPS, nSPS, and the Whitlock index all capture this increase in complexity while maintaining an overall linear progression in complexity for the remainder of the synthesis. While SCScore captures the sharp rise in complexity during this key step, it suggests that intermediate **13** is far more complex than the final target. The Bertz index, on the other hand, shows a decrease in complexity from intermediate **9** to intermediate **10**, while the SMCM and BC reveal only modest increases. Notably, these three indices agree that the alkylation of intermediate **11** introduces the greatest degree of complexity. This reaction, inspired by Rawal and Iwasa's 1994 synthesis and subsequently used in 10 later syntheses,³¹ is consistently

overemphasized by these SFs, exaggerating its complexity change compared to other innovative disconnections.

When developing Whitlock's index, it was proposed that longer syntheses should exhibit more linearity and experience smaller average changes in molecular complexity (ΔScore_m) compared to shorter syntheses.¹⁶ To evaluate this hypothesis, we analyzed two syntheses devoid of early complexity spikes, focusing on how the scoring functions responded to a gradual buildup of molecular complexity. The 2000 synthesis by Bosch and co-workers³² and the 1992 synthesis by Magnus et al.²⁹ provide excellent examples (Figure 4). In both cases, SAcore, SPS, nSPS, and Whitlock's index showed a consistent linear increase in complexity. Conversely, RAcore, Bertz (C_T), SCScore, Böttcher (C_m), and Barone–Chanon (BC) exhibited more significant deviations across the synthetic route. This case-by-case visual analysis demonstrated that the performance of SAcore, SPS, nSPS, and Whitlock's index aligned well with our numerical evaluation, supporting the validity of the quantitative assessment.

Building on Whitlock's assumption, the ΔScore_m is expected to scale proportionally with 1/n, where n is the number of

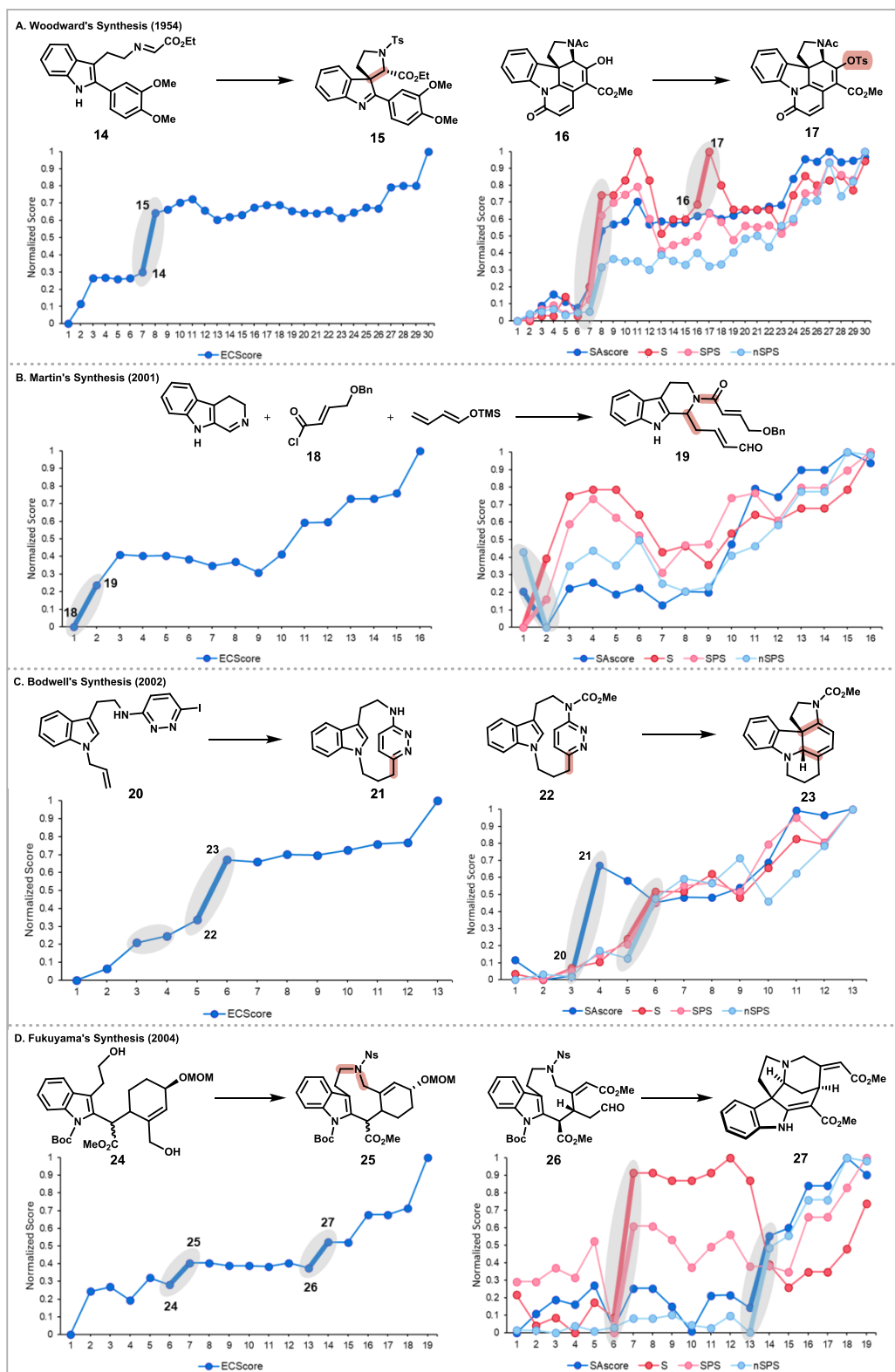


Figure 6. (A) Comparison of the RDKit fingerprinting method for Tanimoto similarity scores compared to SAScore, Whitlock's index (S), SPS, and nSPS. Highlighted here is the early stage construction reaction and protecting group manipulation.²⁶ (B) Similar analysis for the early stage construction reaction in Martin's 2001 synthesis.³⁰ (C) Analysis of the SF response to the macrocycle formation in Bodwell and Li's 2002 synthesis.³⁰ (D) Similar analysis as to the macrocycle formation and transannular cyclization for Fukuyama and co-workers' 2004 synthesis.³⁰

steps in the synthesis—meaning that longer syntheses should yield smaller ΔScore_m values and shorter ones larger. For each of the 24 syntheses, the theoretical $1/n$ value was calculated and plotted based on the number of steps for that synthesis,

and a regression line was fit through these points (black dashed line, Figure 4C). The ΔScore_m for each synthesis was then computed across all scoring functions, with separate regression lines fit for each SF (see the Supporting Information for

additional details). Figure 4C (left) displays the regression curves for the top four performing SFs, while the remaining six are shown in Figure 4C (right). To quantify agreement with the theoretical trend, the root-mean-square error (RMSE) was calculated between each SF's regression curve and the $1/n$ reference line (Figure 4C). SAScore achieved the lowest RMSE (0.043), with SPS, nSPS, and Whitlock's index closely following, outperforming the remaining six scoring functions in this analysis. While this analysis may not be definitive and could have some limitations, we showed that some SFs do not appear to be applicable to this context, and the most applicable SFs appear to have some disagreement.

In an effort to develop a scoring function that performed well across these varied methods for SF assessment, we considered an alternative approach that does not evaluate the inherent molecular complexity or synthetic complexity. Instead, we were interested in developing an SF that assesses how much progress toward the target structure is achieved in any given chemical step (Figure 1D). To do so, we applied the Tanimoto similarity metric to measure the amount of complexity that evolves over the course of a synthesis, defined here as EvolvedComplexity (EC).

The Tanimoto similarity is a key metric in cheminformatics for evaluating the structural similarity of chemical compounds.³⁶ Derived from the Jaccard index, which measures the similarity and diversity of sets, the Tanimoto coefficient specifically assesses molecular fingerprints—binary vectors representing molecular structures (Figure 5A).^{37,38} It calculates the ratio of shared features to total features between two vectors, yielding a similarity score from 0 (completely dissimilar) to 1 (identical). This score provides a valuable tool for chemists to compare compounds and explore their structural relationships in various contexts, including virtual screening and structure–activity relationship studies.³⁸ Cernak and co-workers introduced a graph edit distance as a method to identify key steps from automated outputs.³⁹ Relatedly, Genheden and Shields reported a method to compute a similarity score between any two routes toward the same target, enabling the filtering of redundant pathways generated by retrosynthetic algorithms.⁴⁰ We aimed to investigate the potential of employing Tanimoto similarity as a metric for tracking the progression of the synthetic pathways over time. By quantifying the structural similarities between intermediates and the target molecule, we sought to gain insights into how these structural relationships mirrored the overall evolution of complexity throughout the synthesis. By treating the four selected scoring functions as benchmarks for evaluating molecular complexity in complex natural products, we used them as a reference to assess how well Tanimoto similarity scores perform as an alternative type of complexity metric. We began our analysis by calculating the Tanimoto similarity between each intermediate and the final target, strychnine. We evaluated several fingerprinting methods that include MACCS keys, MHFP6, RDKit, Avalon, Morgan, and atom pair fingerprints. To ensure consistency, similarities for each synthesis were normalized on a scale from 0 to 1. As a preliminary assessment, we calculated the RMSE between the normalized Tanimoto similarities and the traditional SFs to evaluate whether their behavior was consistent with that of the previously identified top four scoring functions. Figure 5B compares the performance of the Tanimoto fingerprinting methods against all SFs. MHFP6, atom pair, and Morgan fingerprints had the highest average RMSEs, both across all SFs

and the top four performing SFs, suggesting a less optimal representation of molecular complexity in these cases. In contrast, Avalon and RDKit fingerprints consistently exhibited the lowest RMSEs in both categories, indicating that they are particularly well-suited for capturing the progression of molecular complexity during a synthesis. This strong alignment with the best-performing SFs suggests that these fingerprints possess advantageous properties for tracking structural changes throughout a synthetic sequence.

Next, we assessed the average R^2 , deviation from the ideal slope, and RMSE relative to the ideal $1/n$ curve. Once again, Avalon and RDKit fingerprints showed the best overall performance. For the average R^2 , Avalon and RDKit fingerprints had the highest values of 0.86 and 0.85, respectively. Interestingly, the SAScore exhibited a lower average deviation from the ideal slope, by nearly half, across all syntheses (Figure 5C). However, the fingerprinting methods achieved a lower RMSE to the $1/n$ curve (Figure 5D). Given these nuanced differences, we explored individual chemistries from various syntheses to further analyze their behaviors. Since RDKit and Avalon fingerprints demonstrated comparable performance, we present only the RDKit results for clarity.

Beginning with Woodward et al.'s 1954 synthesis (Figure 6A),²⁶ all SFs capture the important construction step from **14** to **15**. Interestingly, Whitlock's index indicates a significant increase in complexity compared to all other SFs from **16** to **17**, which is simply a protecting group installation. Here, we define a significant increase in complexity as one that exceeds 2 times the value of $1/n$. While the SPS score also increases, albeit only slightly, all other SFs agree that little to no change in complexity occurs in this stage of the synthesis. For the first step of Martin and co-workers' 2001 synthesis,³⁰ an important construction step via a vinylogous Mannich reaction of **18** is employed to afford **19** (Figure 6B). The Tanimoto scores, SPS, and Whitlock's index all reflect an expected increase in molecular complexity; however, SAScore and nSPS mark a decrease in complexity for this bond-forming step.

In Bodwell and Li's 2002 synthesis,³⁰ a marked distinguishing feature in SAScore behavior can be observed. The sequential hydroboration/intramolecular B-alkyl Suzuki–Miyaura cross-coupling reaction from **20** to cyclophane **21** triggered a significant spike in complexity according to SAScore, while other SFs showed little to no increase (Figure 6C). This pronounced shift can be attributed to SAScore's built-in complexity penalty, which imposes a substantial penalty on the presence of macrocycles (rings of size ≥ 8). A similar pattern in the treatment of the macrocycle formation is evident in Fukuyama and coworkers' 2004 synthesis (Figure 6D).³⁰ When diol **24** underwent the Mitsunobu reaction yielding the nine-membered Ns-amide **25**, both SAScore and the Tanimoto scores reflected the anticipated rise in molecular complexity. However, SPS and Whitlock's index indicated a dramatic surge in complexity at this step. During the key transannular cyclization to form the pentacyclic core of strychnine, **27**, SAScore, nSPS, and the Tanimoto scores captured the presumed increase in complexity, whereas Whitlock's index, surprisingly, reported a sharp drop for this pivotal C–C bond formation step.

While by no means exhaustive, the new approach to scoring functions focusing on similarity disclosed herein (EC) generally agrees with changes in molecular and synthetic complexity throughout the course of complex natural product syntheses. By capturing these structural transformations, EC

provides an insightful reflection of the dynamic nature of a synthetic strategy, aligning well with a nuanced progression of molecular changes. It is important to note, however, that EC relies on the definition of directionality, assigning a value of 1 to the synthetic target, to interpret similarity changes over the course of a synthesis. This approach does not directly measure complexity increase or decrease but rather tracks similarity-based movement, which surprisingly corresponds well with the behavior of traditional complexity-based scoring functions.

CONCLUSIONS

In this study, we evaluated the utility of several molecular complexity SFs alongside a novel similarity-based metric, EvolvedComplexity, derived from Tanimoto similarity scores. Our analysis revealed that the four selected SFs, SAScore, SPS, nSPS, and Whitlock's index, excelled in capturing the intricate changes in molecular complexity during the synthesis of complex natural products, such as strychnine. However, no one metric uniformly captures changes in molecular and synthetic complexity across a trajectory of a multistep synthesis.

By incorporating Tanimoto similarity into this framework, we aimed to explore how well a similarity-based approach could complement traditional SFs. Our findings suggest that EvolvedComplexity captures key structural changes in a manner consistent with established SFs, particularly in reactions involving significant structural reorganization such as transannular cyclizations. While not a substitute for complexity scoring, which can easily compare different classes of small molecules, ECscore offers a promising complementary tool for evaluating synthetic pathways and cheminformatics studies.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article, in its online [Supporting Information](#), and openly available in a python implementation of ECScores at <https://github.com/johnpaulwebster/ECScores> and www.ec-scores.com.

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.5c01393>.

Computational procedures for the calculation of all scoring functions, details of all 24 synthesis of strychnine, plots for all scoring functions for each of the 24 syntheses of strychnine (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

A version of this manuscript can be found on the preprint server ChemRxiv.⁴¹

The authors declare no competing financial interest.

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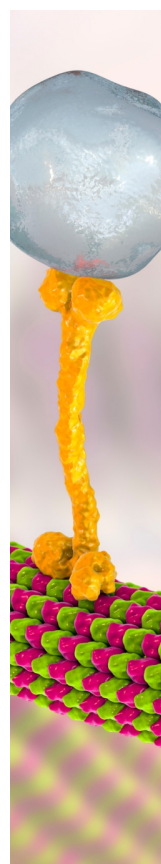
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