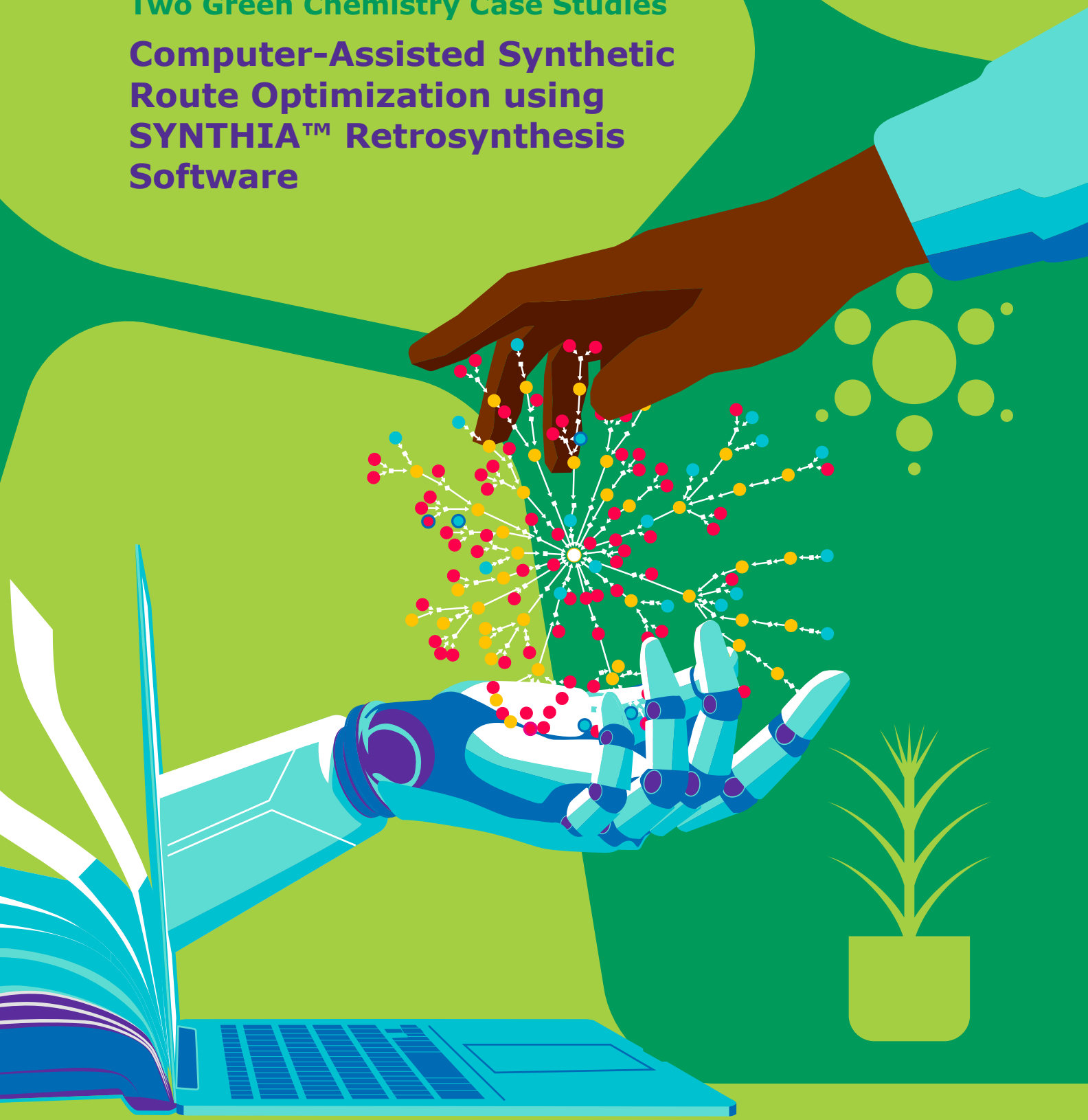
Two Green Chemistry Case Studies

Computer-Assisted Synthetic Route Optimization using SYNTHIA™ Retrosynthesis Software



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Computer-Assisted Synthetic Route Optimization using SYNTHIA™ Retrosynthesis Software

Two Case Studies

S. Sinha, M. Obkircher, M. Yaragani, R. Deokar, S. Kumar MD, E. Gardener

Introduction

Various challenges and considerations exist when designing an efficient process for synthesizing a target compound depending upon the scope of the project and industry. SYNTHIA™ retrosynthesis software is a powerful tool for organic chemists that employs expert-coded chemistry rules to predict feasible routes starting from commercially available raw materials. Using SYNTHIA™ to aid in the route design process allows a chemist to quickly select pathways that meet key criteria of the project, including using commercial starting materials within a set price range or avoiding certain hazardous reagents or reaction types. In addition to the expert-coded rules, SYNTHIA™ utilizes the published literature to incorporate previously reported synthetic steps alongside the computer-generated steps. Because the algorithms are designed to optimize potential routes based on price, step count, and atom economy, it often leads to more efficient and cost-effective routes than a chemist might design on their own or than those which have already been reported in literature.

To demonstrate the practical utility of incorporating SYNTHIA™ retrosynthesis software into the route planning process, we present two case studies highlighting the improved syntheses of known compounds that were designed with the help of SYNTHIA™ to reduce step count and increase overall yield. An evaluation regarding the Green Chemistry aspects of proposed routes was also performed using the DOZN™ tool. Experimental details on the two case studies are provided towards the end.

Case 1 – Lithium Chromoionophore

Dyes have been used throughout human history to color textiles. Early dyes consisted of natural products derived from insects, bark, leaves, berries, and fungi. The synthetic dye industry was born in 1856 when an 18-year-old William Henry Perkin serendipitously discovered mauveine during a failed attempt at synthesizing quinine.[1] Since the commercialization of the first aniline dye, originally named 'aniline purple' for its rich purple hue, the dye industry has expanded beyond coloring textiles to include applications in photography and optical information recording media.

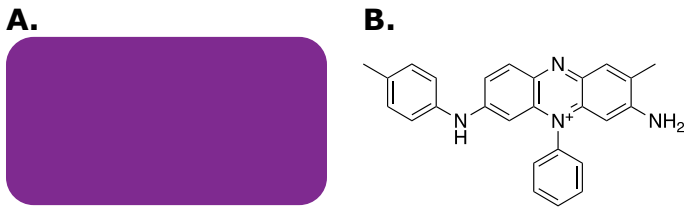


Figure 1. A. The color of the first synthetic dye, mauveine. B. Chemical structure of mauveine A, the major component of mauveine dye[2].

One such purple-blue colored molecule with potential applications in optical information recording media is the indoaniline dye shown in **Figure 2**. This molecule also carries a mono aza-crown ether moiety, making it a chromoionophore which can selectively complex ions to cause a change in absorption and emission properties. Such ion-sensors have potential applications in trace-metal detection in biological systems, as well as for molecular data processing.[3]

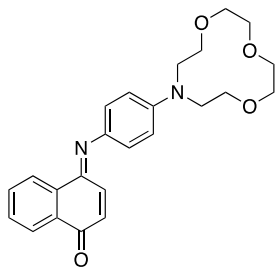
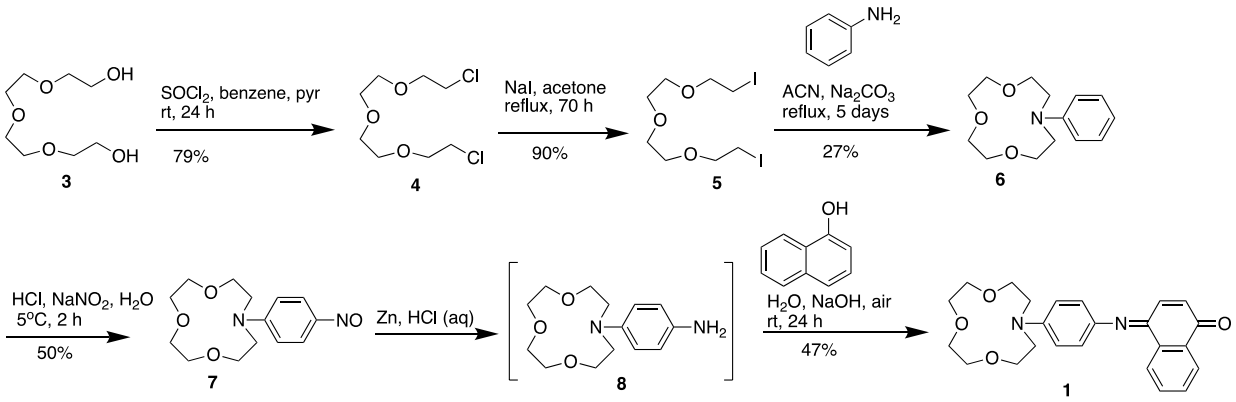


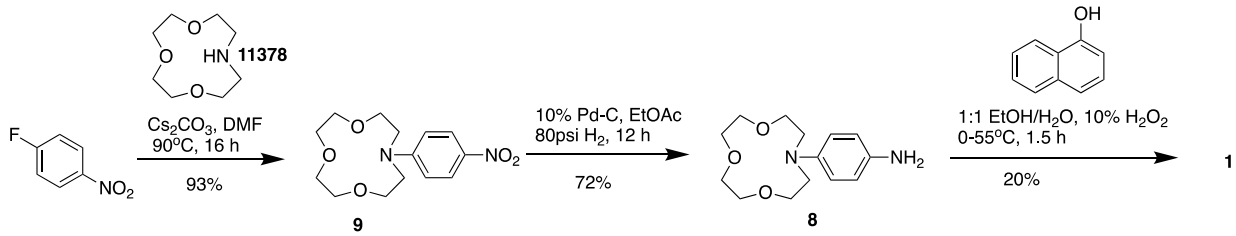
Figure 2: Aza-crown indoaniline dye **(1)**

The synthesis of **1** was originally reported in 2000 by S.-H. Kim *et al*. **(Scheme 1)**. The route starts with a series of functional group conversions from tetraethylene glycol **3**, followed by a low-yielding intramolecular cyclization with aniline to generate the aza-crown ether **6**. This is functionalized with HNO_2 to generate the nitroso intermediate **7**, which is subsequently reduced to amine **8** with Zn/HCl. The final step consists of a condensation with alpha-naphthol in basic solution at room temperature with air oxidation. This 6-step process produced **1** with a 5% overall yield.



Scheme 1: Published synthesis of 1

When tasked with preparing this molecule, the goal was to find a shorter route to improve the overall yield and reduce the synthesis time. SYNTHIA™ identified a commercially available aza-crown ether that could be directly coupled with fluoronitrobenzene in the first step, eliminating the need for the first two functional group transformations and the low yielding cyclization. This reduced the overall cycle time for the steps to core structure **7** from almost nine days to one day, after which nitro intermediate **9** was isolated in 93% yield after purification via silica-gel chromatography. In the second step, SYNTHIA™ recommended reduction of the nitro group, which was performed via catalytic hydrogenation with activated Pd on carbon. After filtration of the reaction mixture through celite and evaporation of the solvent, crude **8** was obtained as a pale-yellow liquid and used immediately without further purification. Although not proposed by SYNTHIA™, the last step was adapted from the original publication. The condensation of **8** with alpha-naphthol in the presence of hydrogen peroxide (H_2O_2) produced **1** in 20% yield as a purple-blue solid after purification via neutral alumina chromatography.



Scheme 2: 3-step synthesis of **1** developed with SYNTHIA™

Using SYNTHIA™ to identify a key first step from commercially available starting materials allowed us to develop a 3-step synthesis to **1** with a 13% overall yield. This represented a 260% overall yield improvement and a 50% step reduction over the original synthesis. Additionally, the labor costs were reduced by 60%, which led to an overall savings of 49% compared to the original route, assuming a labor rate of USD 150/hr.

Case 2 – 6-Formylpterin

The second project focused on the synthesis of 6-formylpterin (6-FPT), which is a heterocyclic compound of the pterin family. It is formed as a byproduct of photo degradation of folic acid, an essential vitamin that acts as a cofactor in metabolic reactions such as DNA and amino acid synthesis **(Figure 3)**. The photoproduct, 6-FPT **2** is found in a wide variety of biochemical environments including human blood and cells and has been studied in association with cancer and other diseases.[4]

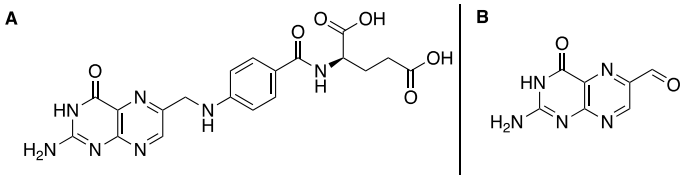
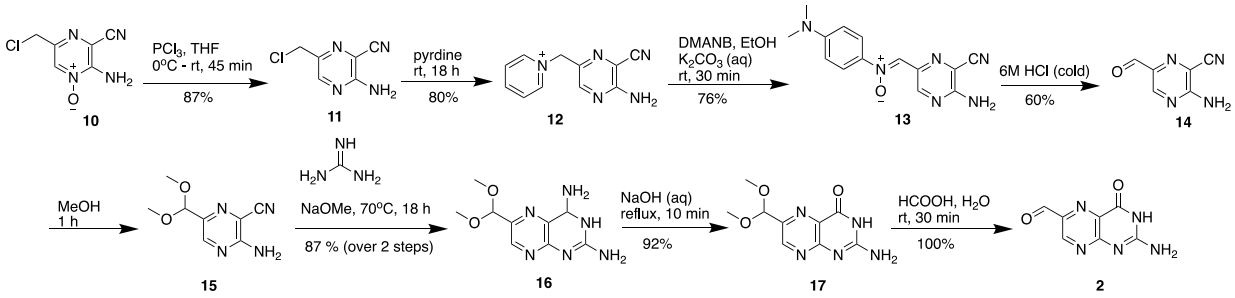


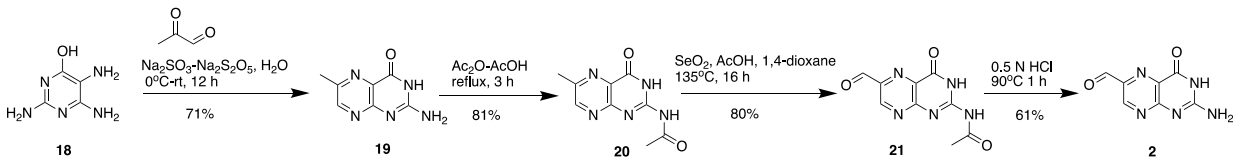
Figure 3: A. Folic acid **B**. 6-Formylpterin **2**

Preparation of 6-formylpterin has been reported in a single step from folic acid;[5] however, this reaction was not reproducible in the lab. An alternative preparation reported in the literature requires a lengthy synthesis from expensive starting materials **(Scheme 3)**.[6]



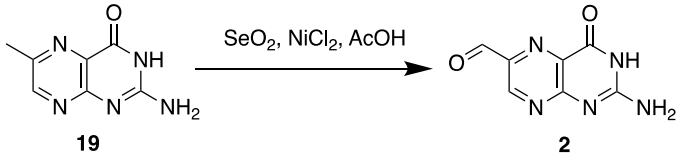
Scheme 3: Synthesis of 6-formylpterin by Freisleben *et al.,* 2002

The reported synthesis starts from pyrazine oxide **10** which is reduced by phosphorus trichloride (PCl_3) in the first step and then coupled with pyridine. Subsequent substitution with N,N- dimethylaminonitrosobenzene (DMANB) produces intermediate **13**, which is hydrolyzed in acid to provide formylpyrazine **14**. Following acetal protection of the formyl group, pyrazine **15** is coupled with guanidine to form the second ring of pterin. Finally, sodium hydroxide is used to convert the C4 amino group to the required carbonyl, and formic acid is used to remove the acetal protecting group to reveal the final 6-formylpterin **2**. In addition to being a lengthy synthesis with 8 steps, this route was not ideal due to the expense of the starting material **10** (USD 640/g), the use of toxic PCl_3 in the first step, and low atom economy resulting from substitutions using pyridine and DMANB. As a result, a shorter and more atom economical approach to this target was sought with the help of SYNTHIA™, and an alternative preparation from an inexpensive starting material, requiring only 4 synthetic steps could be developed **(Scheme 4)**.



Scheme 4: Executed synthesis of **2** based on key step from SYNTHIA™

Initial SYNTHIA™ results proposed a two-step procedure based on a published report[7] that relied on a selenium dioxide (SeO_2) oxidation of methylpterin **19 (Scheme 5)**. The methylpterin precursor was prepared in a single step from commercially available pyrimidinol **18** and 2-oxopropanal based on an established protocol.[7] While this approach was appealing due to the low step count and high atom economy, the oxidation was unfortunately unsuccessful in the presence of the unprotected amine.



Scheme 5: Key step to **2** proposed by SYNTHIA™

Therefore, an acetyl protecting group was chosen to minimize the impact to atom economy. Accordingly, **19** was treated with acetic anhydride in acetic acid to prepare N-acetyl methylpterin **20**. As predicted, the SeO_2 oxidation of this protected intermediate was successfully achieved after heating at 135°C in acetic acid/dioxane for 16 hours. Acetyl-formylpterin **21** was isolated in an 80% yield following purification via silica-gel chromatography. Finally, the acetyl group was removed using 0.5 N hydrochloric acid to afford 6-formylpterin **2** in a 28% overall yield.

In this case study, the key SeO_2 step proposed by SYNTHIA™ was able to reduce the step count by 50%, improve overall atom economy, and eliminate the use of undesired reagents. This route reduced the cost of materials by 98% and the labor cost by 38%, leading to an estimated 77% overall cost reduction compared to the published route using the same labor assumption as explained in the first case study.

Green Chemistry Evaluation with DOZN™

The **DOZN™ tool** uses the **12 principles of green chemistry** to quantitatively evaluate the relative greenness of a chemical route or process based on three major categories: improving resource use, efficient use of energy, and minimizing human and environmental hazards. DOZN™ provides a numerical score for the overall process, with a lower score representing a greener process.

DOZN™ was used to compare the greenness of the published route and the route developed with SYNTHIA™ for both case studies. In both cases, there was an improvement in the DOZN™ score with the SYNTHIA™ developed route over the published route, as indicated by the lower DOZN™ scores. In the case of the 6-formylpterin synthesis, DOZN™ indicated a substantial improvement in greenness with the SYNTHIA™ route (44 vs. 61), while in the case of the lithium chromoionophore only a small improvement with regards to the 12 principles of green chemistry could be achieved (57 vs. 59).

Conclusion

The use of SYNTHIA™ Retrosynthesis Software, enabled the R&D team to quickly find improved routes to two different target molecules. The final synthetic routes executed in the lab had reduced step counts, improved yields, and improved atom economy when compared with the published routes. In both cases, the final optimized routes employed a combination of reactions proposed by SYNTHIA™ and those derived from the literature, and our own chemistry experience. Our experience with computer assisted synthesis planning emphasizes the power of adding SYNTHIA™ to the chemists' toolbox to generate new ideas and support decision-making in the modern organic chemistry lab.

Table 1. Summary of benefits using SYNTHIA™ proposed route.

	Literature Route	SYNTHIA™ Route
Case 1 - Lithium Chromoionophore		
Manufacturing cost (1g, USD150/hr)	100%	51%
DOZN Score (1g)	59	57
Case 2 - 6-Formylpterin		
Manufacturing cost (1g, USD150/hr)	100%	23%
DOZN Score (1g)	61	44

Experimental Details

Case Study 1 -

Synthesis of Aza-crown indoaniline dye

10-(4-Nitrophenyl)-1,4,7-trioxa-10-azacyclododecane **(9)**: To a stirred solution of 1,4,7-trioxa-10-azacyclododecane (4 g, 22.82 mmol) in DMF (40 mL) at RT, Cs_2CO_3 (8.60 g, 27.38 mmol), and 1-fluoro-4-nitrobenzene (12.88 g, 91.28mmol) were added and stirred at 90°C for 16 hours. The completion of reaction was monitored by TLC. Reaction mixture was quenched with ice cold water and extracted with dichloromethane (DCM; 2x500 mL). The combined organic layer was washed with brine, dried over sodium sulfate, and evaporated under vacuum to yield the crude product as a sticky solid (7.3 g). The crude material was subjected to column chromatography using silica gel (100-200 mesh) and eluted with 2-3% methanol/DCM to afford **9** as yellow solid (6.3 g, 93% yield).

4-(1,4,7-Trioxa-10-azacyclododecan-10-yl)aniline (**8**): Compound **9** (6.3 g, 21.26 mmol) was dissolved in ethyl acetate (180 mL) and transferred to a 500 mL Parr shaker vessel. To the vessel 30% w/w of 10% Pd/C (2.0 g) was added carefully. The reaction mixture was stirred at room temperature under hydrogen atmosphere at a pressure of 80 psi for 12 hours. The progress of the reaction was monitored by TLC (70% ethyl acetate in hexane). The reaction mixture was filtered through a celite bed, which was then washed with ethyl acetate (2 X 100 mL). The filtrate was collected and evaporated under vacuum to provide crude **8** as a pale-yellow liquid (4.1 g, 72%).

4-((4-(1,4,7-Trioxa-10-azacyclododecan-10-yl)phenyl) imino)naphthalen-1(4H)-one (**1**): To a stirred solution of 8 (4.0 g, 15.02 mmol) and naphthalen-1-ol (2.59 g, 18.02 mmol) in ethanol/water (1:1, 40/40 mL) at 0°C, 10% H_2O_2 (40 mL, 10%), was added carefully and stirred at room temperature. for 30 minutes, then warmed to 55°C and stirred for 1 hour. The progress of reaction was monitored by TLC. Following completion as assessed by TLC, the reaction mixture was quenched with cold water and extracted with DCM (2x500 mL). The combined organic layer was washed with brine, dried over sodium sulfate, and concentrated to provide crude product. The crude material was purified by neutral alumina column chromatography eluted with 2-3% Acetone/DCM to afford pure **1** as purple-blue solid (1.2 g, 20% yield).

Case Study 2 -

Synthesis of 6-Formylpterin

2-Amino-6-methylpteridin-4(3H)-one (**19**): A 3 L three neck round-bottomed flask equipped with a magnetic stir bar and an N_2 inlet adapter was charged with 2,5,6-triaminopyrimidin-4(3H)-one sulfate (19.0 g) in water (2000 ml) followed by sodium sulfite (228 g) at room temperature. The reaction mixture was cooled to 0°C and 2-oxopropanal (14.3 g) was added. Sodium bisulfite (9 g) in water (100 mL) was added at 0°C over a 40-50 min period with vigorous stirring. The reaction mixture was stirred at room temperature for 12 h, after which a yellow precipitate formed. The precipitate was filtered, washed with water (2x), then with ethanol, and dried to provide **19** as a yellow solid (10 g, 71% yield).

N-(6-Methyl-4-oxo-3,4-dihydropteridin-2-yl)acetamide (**20**): A 500 mL three neck round-bottomed flask equipped with a magnetic stir bar and a N_2 inlet adapter was charged with **19** (10 g) in acetic acid (90 mL) and acetic anhydride (90 mL) at room temperature. The reaction mixture was refluxed for 3 h. After which time, the hot reaction mixture was filtered, and the filtrate was allowed to stand for 1 h at room temperature. Brown precipitate formed and was filtered and dried to provide **20** (10 g, 81%).

N-(6-Formyl-4-oxo-3,4-dihydropteridin-2-yl)acetamide (**21**): A sealed tube (100 mL) was equipped with a magnetic stir bar and charged with N-(6-methyl-4-oxo-3,4-dihydropteridin-2-yl) acetamide (2 g), SeO_2 (2 g) in acetic acid (10 mL) and 1,4-dioxane (20 mL) at room temperature. The reaction mixture was stirred at 135°C for 16 h. The reaction was monitored by TLC (5% methanol in dichloromethane). The reaction color changed to black and was then filtered through celite. The filtrate was concentrated to provide a solid, which was directly loaded on a 100-200 mesh silica gel column. The product eluted with 3% methanol in dichloromethane. The same batch size was repeated four times in a sealed tube to yield at total of 2.2 g of **21** (80% yield).

2-Amino-4-oxo-3,4-dihydropteridine-6-carbaldehyde (**2**): To a 3 neck 50 mL round-bottomed flask equipped with a magnetic bar and an N_2 inlet adapter was added **21** (2.2 g) in 0.5 N hydrochloric acid (20 mL) at room temperature. The reaction mixture was heated to 90°C for 1 h. The reaction was monitored by ^1H NMR. After 1 h, light brown solid was filtered, dried, and then washed with acetonitrile to enhance purity. This afforded the final product **2** in 61% yield (1.1 g).

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Materials

Description	CAS	Portfolio Brand	Cat.No.
Aza-crown indoaniline Dye synthesis			
1,4,7-Trioxa-10-azacyclododecane	41775-76-2	Sigma-Aldrich	11378
1-Fluoro-4-nitrobenzene	350-46-9	Sigma-Aldrich	F11204
Cesium Carbonate	534-17-8	Sigma-Aldrich	441902
10% Pd on Charcoal	7440-05-3	Sigma-Aldrich	205699
Naphthalen-1-ol	90-15-3	Sigma-Aldrich	N1000
Hydrogen peroxide	7722-84-1	Sigma-Aldrich	216763
6-Formylpterin Synthesis			
2,5,6-Triaminopyrimidin-4-ol sulfate	2050525-14-7	Ambeed	A707612
Sodium sulfite	7757-83-7	Sigma-Aldrich	239321
Sodium bisulfite	7631-90-5	Sigma-Aldrich	243973
2-Oxopropanal	78-98-8	Sigma-Aldrich	M0252
Selenium dioxide	7446-08-4	Sigma-Aldrich	325473

12 principles
of Green Chemistry

Waste Prevention

Atom Economy

Less Hazardous Chemical Synthesis

Designing Safer Chemicals

Safer Solvents and Auxiliaries

Design for Energy Efficiency

Use of Renewable Feedstocks

Reduce Derivatives

Catalysis

Design for Degradation

Real-time Analysis for Pollution Prevention

Inherently Safer Chemistry for Accident Prevention

DOZN™

The DOZN™ tool is a quantitative, industry-first tool that uses the 12 Principles of Green Chemistry for comparing the relative greenness of similar chemicals, synthetic routes, and chemical processes.

These principles distill into three major categories: improving resource use, more efficient use of energy, and minimizing human and environmental hazards.

The results are presented for each principle, for each major category and as an overall aggregated score.

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THE DOZN™ SCALE

Based on the 12 Principles of Green Chemistry*, DOZN helps researchers, scientists, and manufacturers increase performance and efficiency while reducing human and environmental impact.

**Paul T. Anastas and John C. Warner, 1991.*

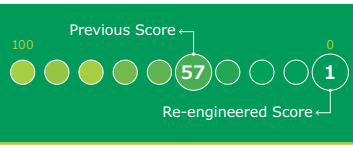
β-AMYLASE

An enzyme commonly found in sweet potatoes—hydrolyzes starch into sugar

	12 Principles of Green Chemistry	Percentage of Improvement	Results
Resource Used	Atom Economy	93%	Increased yield. Used less raw materials.
	Waste Prevention	97%	Eliminated use of organic solvents. Reduced waste.
	Reduce Derivatives	N/A	
	Renewable Feedstocks Use	96%	More efficient sweet potato use. Reduced auxiliary chemicals.
	Real-Time Pollution Prevention	N/A	
	Catalyst	N/A	
	Energy Efficiency Design	100%	Eliminated need for elevated temperature and pressure.
Human & Environmental Hazards Reduction	Less Hazardous Chemical Synthesis	95%	Water-based solutions replaced organic solvents. Removed toxic filtering agents.
	Safer Chemical Design	N/A	
	Safer Solvents and Auxiliaries	100%	Eliminated all organic solvents.
	Design for Degradation	No Change	No increased impact with new procedure.
	Inherently Safer Chemical for Accident Prevention	96%	Eliminated flammability and reactivity dangers.

TOTAL PERCENT IMPROVEMENT 98%

AGGREGATE SCORE
0 is Most Desirable



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