



Wiley ChemPlanner[™]
Synthesis Solved

Wiley ChemPlanner predicts experimentally verified synthesis routes in medicinal chemistry

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Executive Summary

In this case study, ChemPlanner was applied to help a chemist identify alternative and shorter synthetic routes to target molecules. Options that were not known to the chemist and would likely not have been identified by searching the literature with traditional search tools were found. ChemPlanner thus helped the chemist to increase the efficiency of the synthesis development process by reducing the time and resources spent.

Content

1. Introduction to basic ChemPlanner features
2. Results and discussion
3. Conclusion

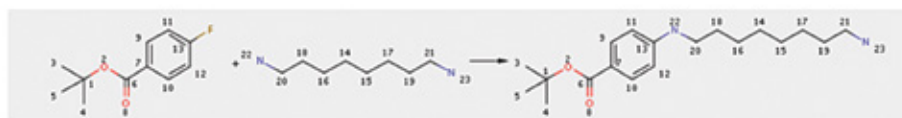
1. Introduction to basic ChemPlanner features

1.1 The reaction database

The synthesis routes that ChemPlanner predicts are based on transformation rules, which are built by algorithmically perceiving actual examples of reactions from the literature. The predicted routes contain actual transformations if they are experimentally available but the most important feature is the prediction capability. ChemPlanner predicts numerous synthetic routes to new targets that are not yet documented elsewhere.

1.2 Reaction perception

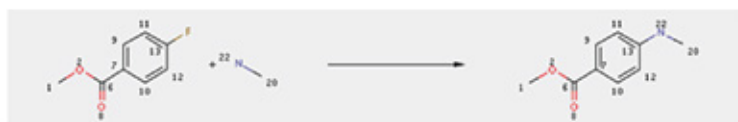
Source reaction:



Reaction file with atom mapping

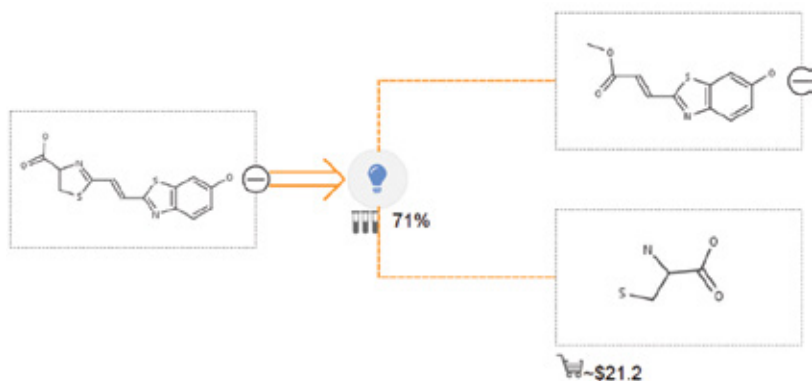
The reactions in the ChemInform database are mapped. These mappings are curated by the experts responsible for data extraction. The relevant transformations (extended cores) are extracted from these reaction records.

Extended core

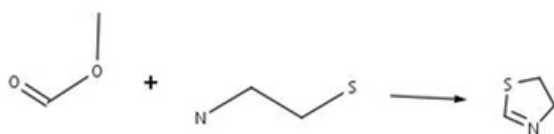


It is important to note that not only the cores (reaction centers) are taken into account, but also the chemical environment because it has influence on the reaction as shown in the example above. The carbonyl in the para position to the reaction center influences the reaction.

The last step in a retrosynthetic route is shown below. The bulb means that it is a predicted step, that is, such a transformation has not yet been reported in the literature but ChemPlanner predicts that it should be possible based on the reaction rules in the database.



The rule that is applied in the given case is shown below.



The rule is alternative number 18 and is based on 49 examples in the database that follow the same rule. There are 65 alternatives to synthesize the target in total.

Predicted transformation Options ▶

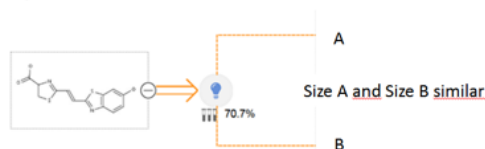
Alternative 18 of 65

70.7% average yield

49 similar examples

ChemPlanner always displays what is predicted the best route to be first. The best route is determined by scoring against a number of factors.

- Price of starting materials matching the reactants and their coverage
- Whether the transformation is based on a generated rule (prediction) or an exact matching reaction from CIRX
- Number of example reactions from which the applied rule was generated (in case of prediction)
- Wastage percentage
- Yield percentage
- Decomposition balance



Decomposition balance means that the larger both reactants in a retrosynthetic step, the better.

2. Case Study

S.A. Stark synthesized a triazole and an amide target according to procedures shown in scheme 1. ChemPlanner was applied to investigate the following questions.

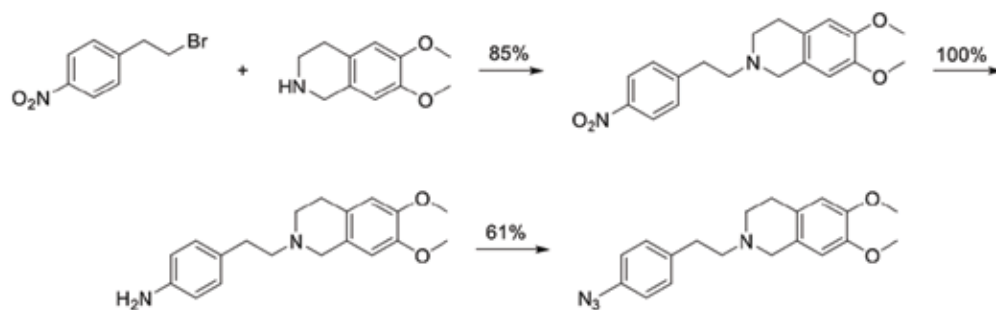
- Does ChemPlanner predict plausible alternative routes?
- Are the chemist's routes reproducible in ChemPlanner?

2.1 Does ChemPlanner predict plausible alternative routes?

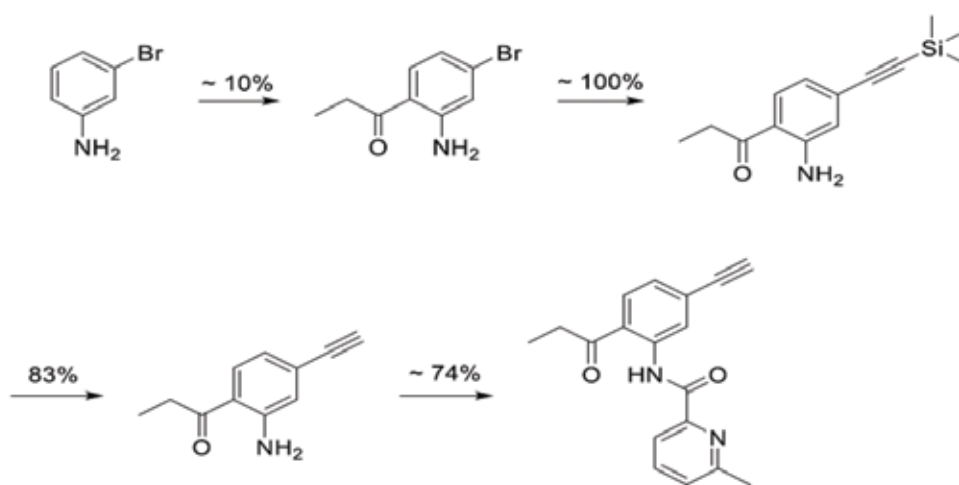
2.1.1 Triazole target

Scheme 1 shows the synthesis routes to the triazole target (1) as developed by the chemist.

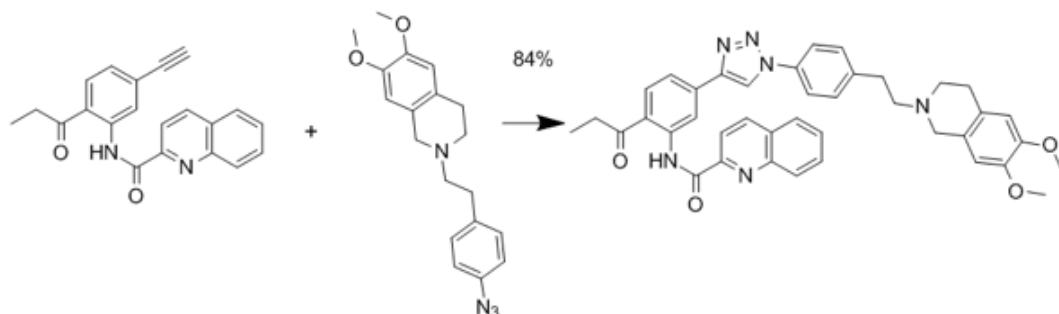
Azido precursor



Alkyne precursor



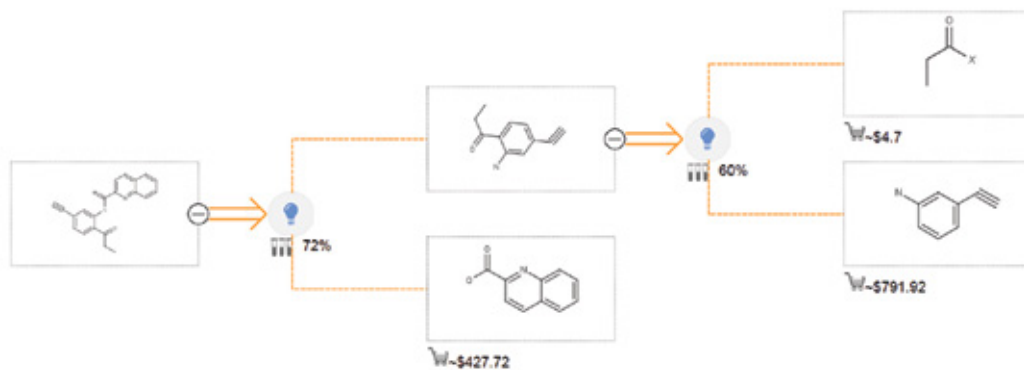
Last retrosynthetic step



Scheme 1 Chemist's synthesis routes to the azido and alkyne precursors, which react to give the triazole target.

Scheme 2 shows the best route found by ChemPlanner

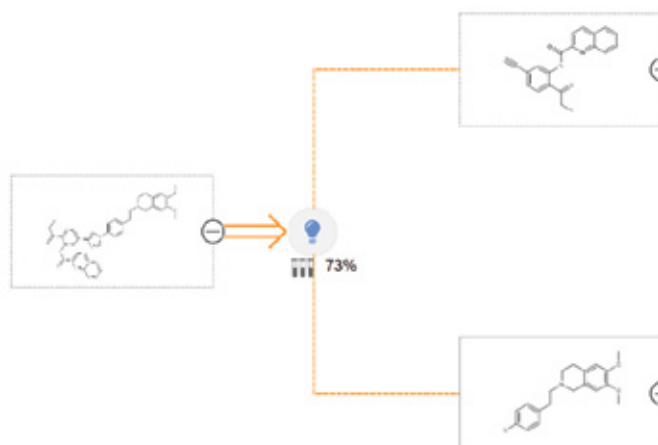
Alkyne precursor



Amine precursor



Last retrosynthetic step

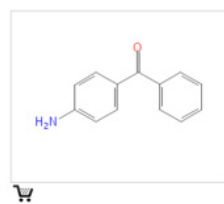


Scheme 2 Four-step route to the triazole target⁽¹⁾ predicted by ChemPlanner.

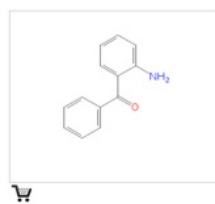
ChemPlanner suggests the same alkyne precursor. The only difference in the synthesis of the alkyne precursor predicted by ChemPlanner and that developed by the chemist is the first step. The chemist applied a Sugasawa reaction, whereas ChemPlanner suggests a Friedel-Crafts acylation.

The Sugasawa reaction gave a low yield of the desired product in the laboratory but was the only method that rendered the desired regioselectivity. Although Friedel-Crafts reactions with amines may not be successful because of complexation of the amine to the aluminium catalyst, there are some examples in the literature where a supported aluminium catalyst can overcome this limitation. Whether the required regioselectivity could be achieved in this case would require further experiments in the lab. Another possibility is to go via a nitro intermediate with subsequent reduction, but again regioselectivity would need to be tested and 1-(3-ethynyl-5-nitrophenyl)propan-1-one would be the possible undesired product.

Database examples show that the para position is preferred ($\text{AlCl}_3\text{-SiO}_2$ cat):

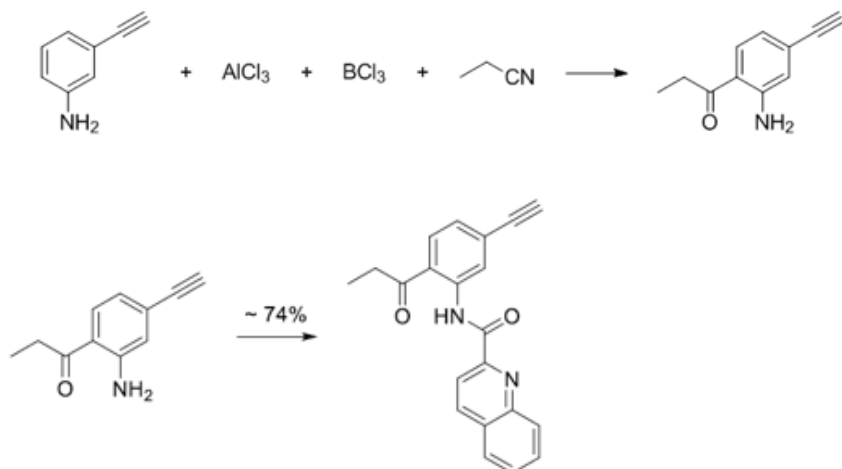


CS: 94%, Yield: 83.7%
C₁₃ H₁₁ N O (mw:197.2325)



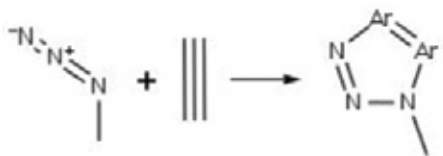
CS: 6%, Yield: 5.3%
C₁₃ H₁₁ N O (mw:197.2325)

ChemPlanner's suggested the route starts from 3-ethynylaniline partly because this compound was found to be commercially available in ChemPlanner's supplier database. The chemist, alerted to the possibility of buying this precursor, later found that the Sugasawa reaction also worked with 3-ethynylaniline as the starting material and consequently the synthesis for the alkyne precursor was drastically shortened in the laboratory, as shown in scheme 3 (cf. scheme 2).



Scheme 3 Chemist's shorter synthesis of the alkyne precursor starting from 3-ethynylaniline after this starting material was shown to be commercially available by ChemPlanner.

A popular option for chemists when considering the retrosynthesis of a 1,2,3-triazole ring is "click" chemistry. Click chemistry is very well-known and might almost be thought of as the "default" option for the synthesis of 1,2,3-triazoles. In this example, however, ChemPlanner provides an alternative to click chemistry. The chemist went through three steps to synthesize the azido precursor. The azido precursor that the chemist used is not suggested as the top-scoring alternative, but is included as one of the suggested alternatives:

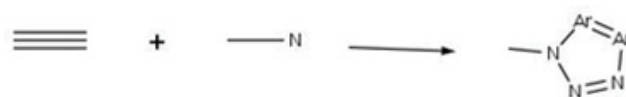


The rule is based on 846 database examples.

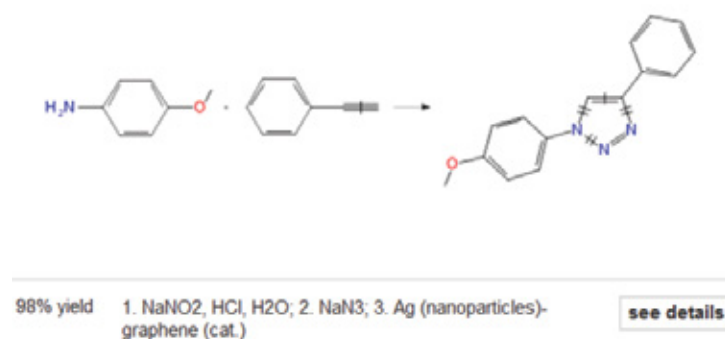
Most frequently used catalysts are:

none	255
CuSO4	104
CuSO4 sodium ascorbate	99
CuI	55
sodium ascorbate CuSO4	22

ChemPlanner suggests the amine precursor shown in scheme 2 instead. The rule behind this transformation is shown below



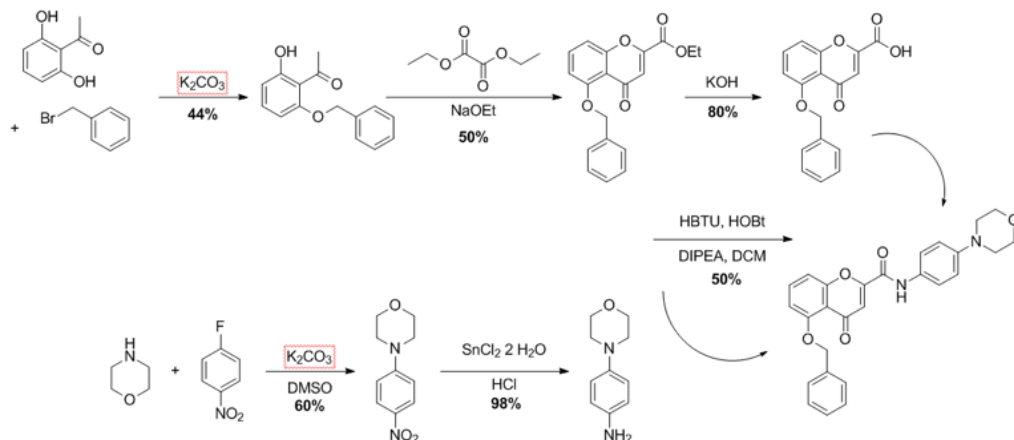
The rule is based on 50 database examples, e.g.:



ChemPlanner predicts that the triazole ring could be synthesized from the amine and alkyne precursors via the azide intermediate in a one-pot reaction catalyzed by silver nanoparticles, during which the azide is not isolated. This option involves fewer steps to the target, which is a contributing factor in the ranking of possible routes, but silver nanoparticles could be a more expensive option than a copper-catalyzed click reaction. A click chemistry route may also offer more opportunities in terms of library construction. Therefore, exploration of options that may fit specific development needs is possible.

2.1.2 Amide target

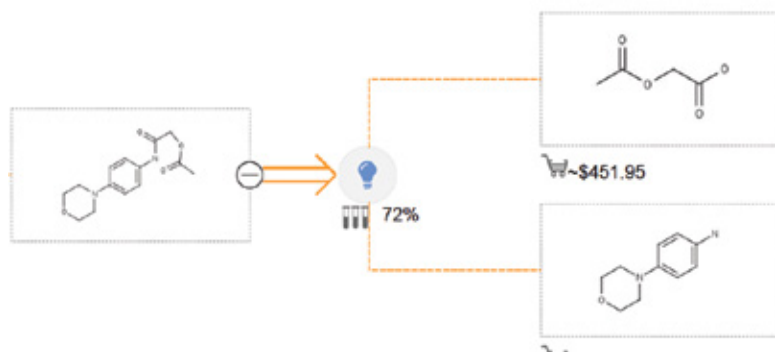
Scheme 4 shows the synthesis route developed by the chemist.



Scheme 4 Chemist's synthesis of the amide target. The acid precursor is synthesized in three steps and the amine precursor in two steps.

Scheme 5 shows the best route found by ChemPlanner.

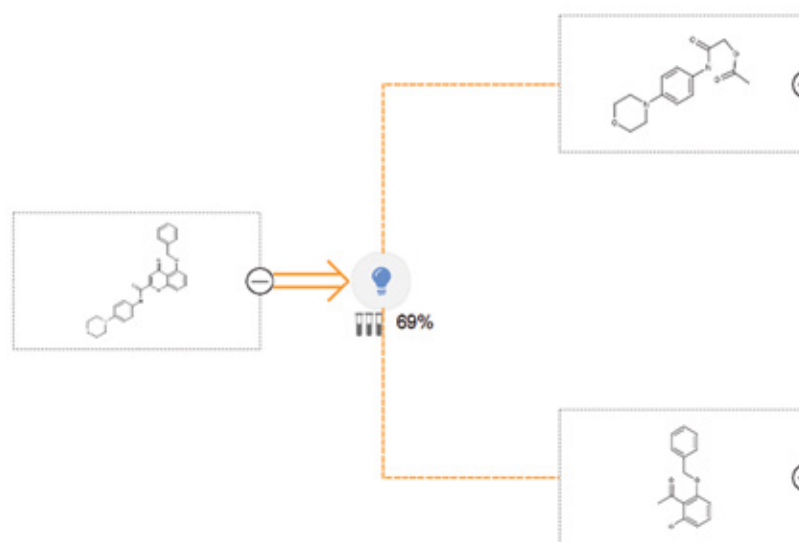
Precursor 1



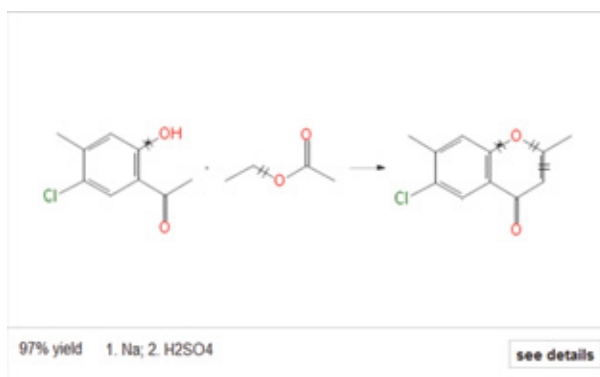
Precursor 2



Last retrosynthetic step



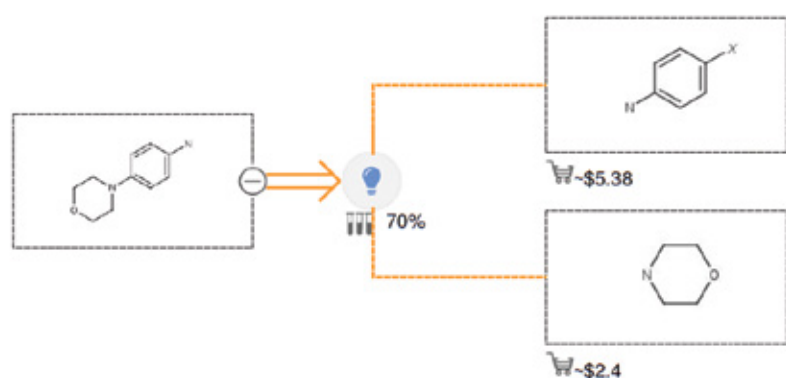
Experimental data example for the last retrosynthetic step



Scheme 5 Three-step route to the amide target predicted by ChemPlanner.

ChemPlanner suggests a different route, which requires different precursors in the last retrosynthetic step. The last retrosynthetic step is based on chromone formation. As shown in the example, high yields are achievable in this type of reaction.

The amine precursor synthesized by the chemist is commercially available, albeit at a relatively high price. ChemPlanner suggests 20 alternative synthesis routes among which was the synthesis used by the chemist (two steps); a cheap one-step route is shown in scheme 6.

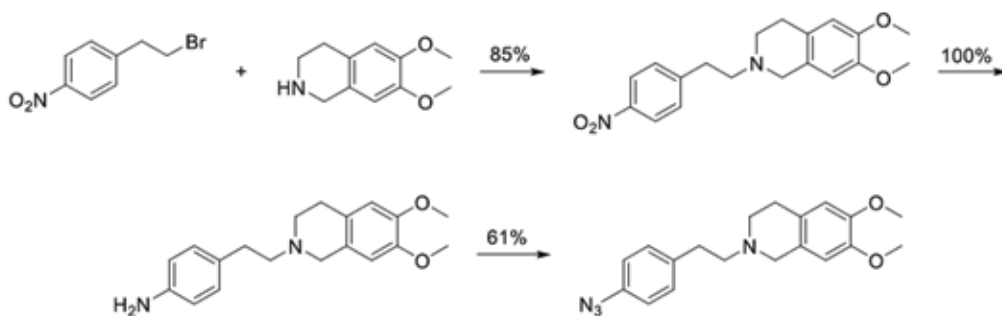


Scheme 6 Alternative route for the synthesis of the amine precursor predicted by ChemPlanner. High yields (up to quantitative) are achievable either under neat reaction conditions or with Pd as a catalyst. The price is significantly lower than that in the catalogue (US\$479/ mol).

2.2 Are the chemist's routes reproducible in ChemPlanner?

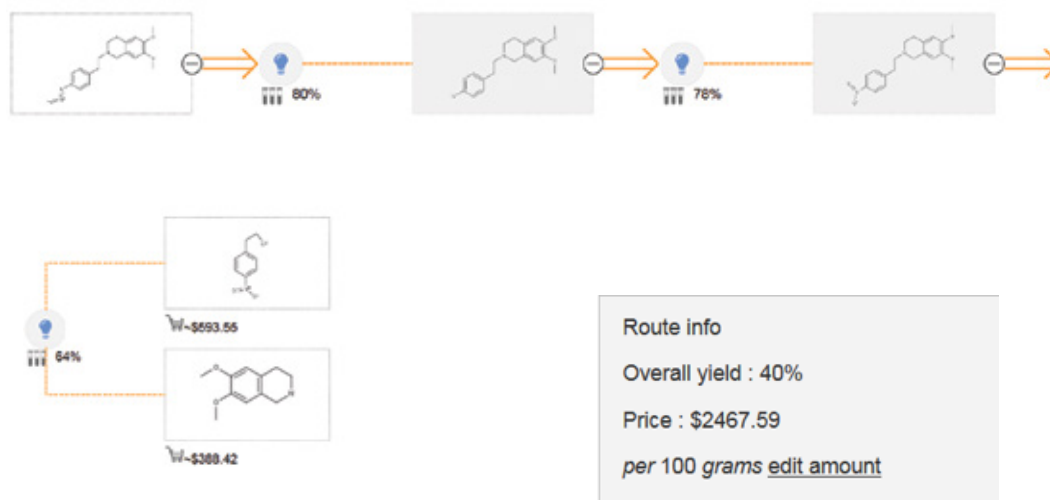
To verify this, the route to the azido precursor shown in scheme 1 was investigated. Scheme 6 shows the synthesis route developed by the chemist.

Azido precursor



Scheme 6 Chemist's synthesis route to the azido precursor.

As shown in scheme 7, all steps of the chemist's route can be reproduced in ChemPlanner.



Scheme 7 The route to the azido precursor developed by the chemist can be exactly reproduced in ChemPlanner beginning with the same starting material. In a subsequent release an interactive search will be included. With this feature the complete route will be reproducible manually.

The predicted overall yield is 40%, whereas the chemist obtained 52%. The yields in the predicted retrosynthetic steps are the average yields of the underlying experimental reaction records. A comparison with the chemist's experimental yields is critical because the rules are the same, but the reaction conditions are not.

3. Conclusion

Based on these results the questions asked at the beginning can be answered as follows:

Does ChemPlanner predict plausible alternative routes?

ChemPlanner found alternative routes with fewer retrosynthetic steps and lower costs. In one case the chemist was alerted that a synthesized compound is commercially available, which helped to shorten the synthesis route in the lab.

Are the chemist's routes reproducible in ChemPlanner?

Almost all routes chosen by the chemist have been found by ChemPlanner. Due to a specific scoring in ChemPlanner the chemist's routes have not been the "best" routes in ChemPlanner. For instance, the number of retrosynthetic steps is a criterion; if ChemPlanner finds a route that involves fewer steps, the scoring is higher.

As this case study demonstrates, ChemPlanner assists expert chemists in exploring the chemical space around their molecules more efficiently. With traditional literature searching tools, synthesis design is a cost and labour-intensive process, the outcome of which often depends on the way that individual chemists approach synthesis problems. In contrast, ChemPlanner offers chemists the opportunity to discover different perspectives that can save time and money, and also fit the development needs of their particular project.

Bibliography

- [1] M. Bause, (*Synthesis of Melanoma Inhibitory Activity Protein Inhibitors, ABCG2 Transporter Modulators, and Neurotensin Mimetics*), PhD thesis, Universität Regensburg (Germany), 2015

Biographies

Simone Alexandra Stark obtained her bachelor's and master's degree in chemistry from the University of Regensburg in 2011 and 2013, respectively. She is currently a PhD student under the supervision of Prof. Dr. Burkhard König in the field of medicinal chemistry. Her research is centered on the design, synthesis and pharmacological evaluation of modulators of ATP-binding cassette (ABC) transporters in a joint project with the group of Prof. Dr. Armin Buschauer (Department of Pharmaceutical/Medicinal Chemistry II, University of Regensburg).

Richard Threlfall studied chemistry at the University of Liverpool and obtained his PhD. in synthetic organic chemistry there in 2008. After a postdoctoral position at the University of Colorado Boulder working on the synthesis of modified nucleic acids for application in RNAi, he took a position as Associate Editor at *Angewandte Chemie*. In 2012 Richard was appointed Editor for the launch of *Asian Journal of Organic Chemistry* until moving to his current role as Product Manager with Wiley Science Solutions in 2016.

Reinhard Neudert obtained his PhD in chemistry at the Technical University of Berlin. He worked more than 10 years in the Central Research Department at BASF, at last as group leader spectroscopy and more than 20 years at Wiley with focus on chemistry software and databases. He is currently engaged in user acceptance testing and demonstrations of the synthesis planning software ChemPlanner.



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