

Mesentech Inc.

Case Study

**Accelerate de novo
chemical synthesis
using ML-augmented
retrosynthesis tools**



Company profile

Industry

**Biotechnology,
Small Molecule**

Location

**Vancouver, BC,
Canada**

Mesentech is a Canadian, top investor backed biotech startup that has developed novel chemistry that selectively delivers pharmaceuticals to a specific tissue. Its first clinical program utilizes tissue-selective distribution to deliver a prostaglandin analog, a potent hormone that triggers the body's own regenerative process, to musculoskeletal tissue to renew and repair muscle and bone. The advantage of its innovative technology is that exposure to the active pharmaceutical occurs only in the targeted tissues, thereby eliminating toxicity to unrelated organs.

“Utilizing ChemAIRS from Chemical.AI is analogous to incorporating a chemist with decades of experience into your research team. Retrosynthesis module from ChemAIRS examines synthesis from various potential angles and provides pertinent references. These suggested reactions are chemically plausible, though they may not have been previously employed to synthesize similar compounds.

In contrast, Reaxys and SciFinder serve as exceptional librarians, possessing comprehensive knowledge of all published reactions for synthesizing analogous molecules. However, they are not as proficient in proposing novel synthetic approaches. Together, these tools are highly complementary.”

Dr. Gang Chen
Director of Chemistry at Mesentech

Challenges

Synthesis of Novel Structures Require Out-of-Box Inspiration

Novel molecules contain unreported and never-made substructures, causing uncertainties in literature research and method feasibility.

Chemists Wearing Multiple Hats in a Growing Startup

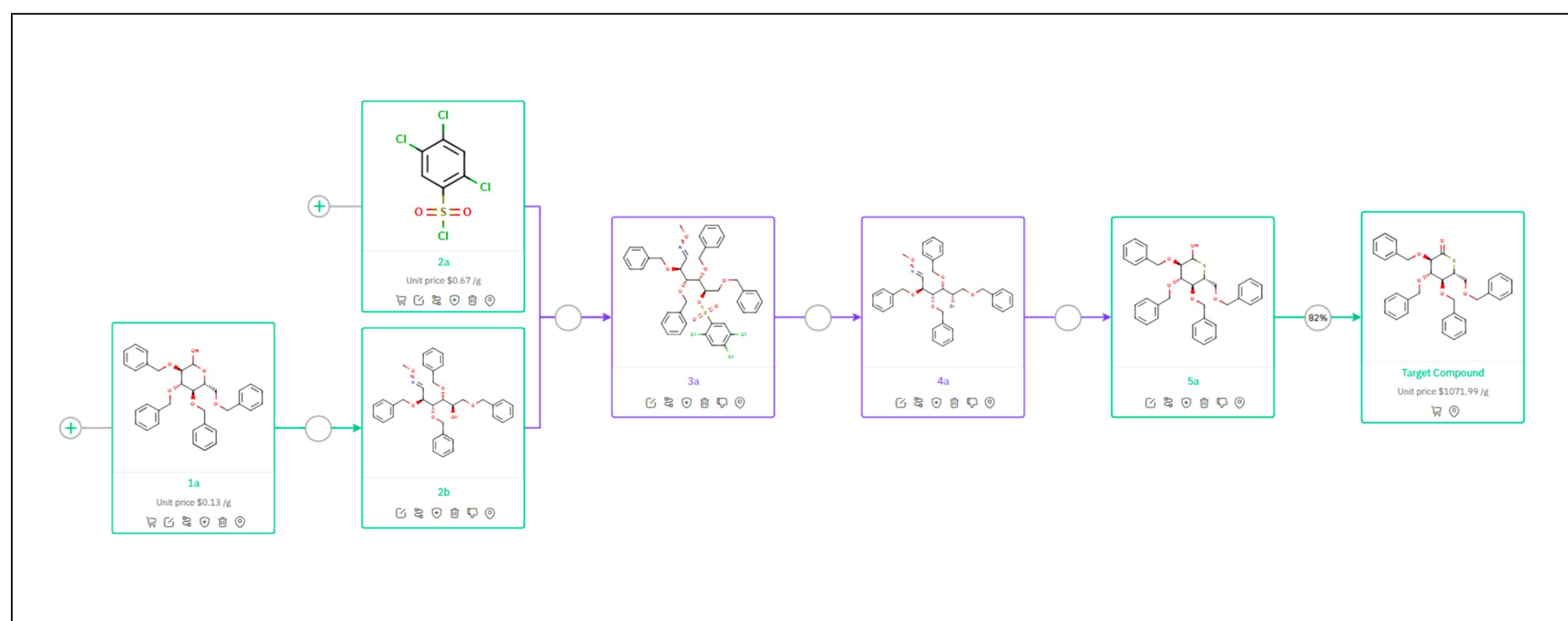
Limited time and bandwidth will prevent researchers to exhaustively search for synthetic strategies.

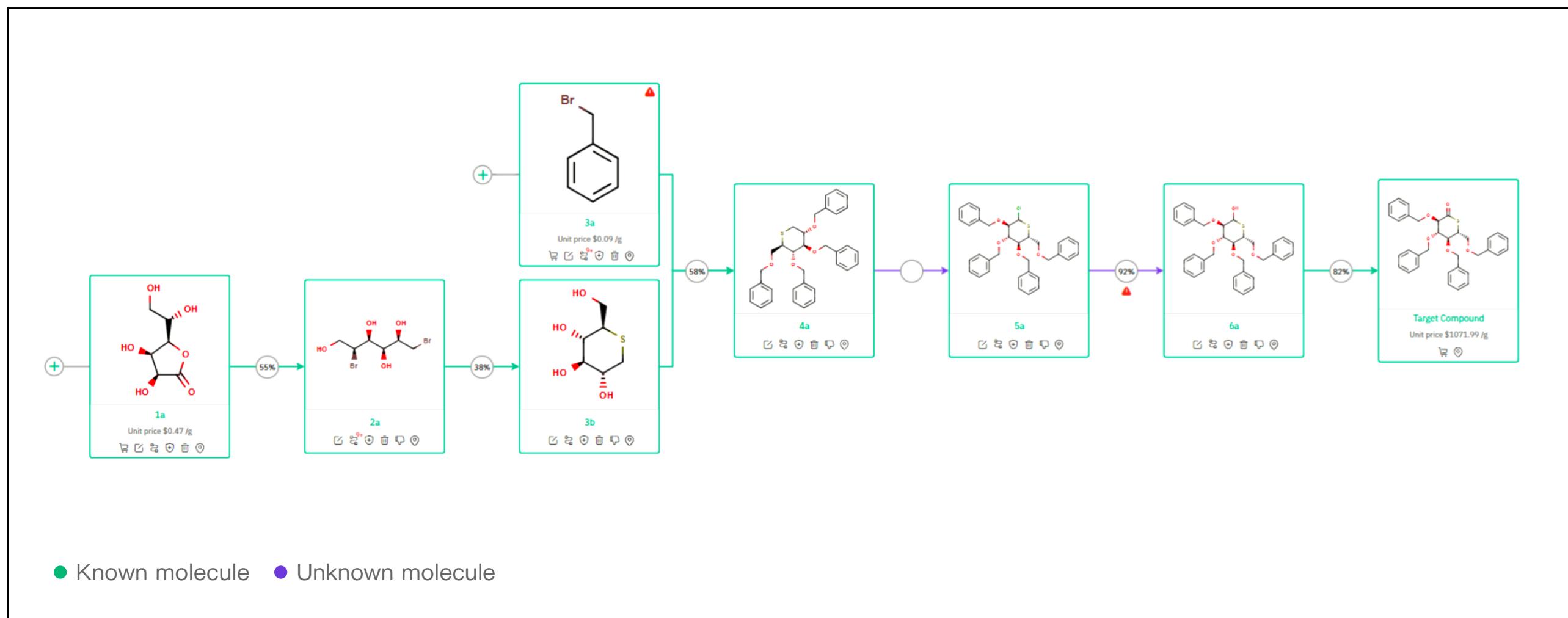
Tricky to Balance the Speed, Costs, and the Pressure to Pursue New Compounds

The costs and availability of starting materials of synthesizing a new compound introduce additional uncertainties on top of method development.

Case in point: Challenges in Replacing Nitrogen with Sulfur in Thio-Sugars

One example Dr. Srinivas Kantham, Senior Scientist at Mesentech, showed was a synthetic pathway for thiosugars. As an expert in this field, Dr. Kantham appreciates that the synthesis of thiosugars poses a significant challenge in medicinal chemistry due to the difficulty of substituting nitrogen with sulfur to form thio-analogues of azasugars. This is vital as thiosugars exhibit promising glycosidase inhibitory activities, relevant to numerous diseases. Below are proposed synthetic schemes from ChemAIRS for the synthesis of thiosugars.





Outcomes

Rapid Generation of Innovative Ideas as an Extension to In-House Chemistry

Within minutes, Chemical.AI's retrosynthesis platform generated several ideas by providing non-conventional and innovative synthesis routes that might not be immediately apparent to chemists. This technology acts as an extended brain, enhancing the team's creative capabilities and expanding their problem-solving toolkit. As a result, experts such as Dr. Srinivas Kantham can swiftly identify and explore unique pathways, significantly reducing the time from concept to execution.

Cost-Effective Synthesis: Enhancing Accessibility of Therapeutic Compounds

Developing cost-effective synthetic routes using inexpensive starting materials is essential for making therapeutic compounds more accessible. Chemical.AI's retrosynthesis platform can optimize these routes, ensuring efficient use of resources and minimizing risks. This cost-efficiency not only lowers production costs but also enables broader research and application of these compounds, facilitating advancements in therapeutic development.

The Ability to Have Choices of Routes to Suit Real-Time Situations

Chemical.AI's retrosynthesis platform provides multiple viable synthesis routes, allowing Dr. Kantham and team to choose the most suitable path based on current needs and constraints. This flexibility ensures that real-time changes in project requirements, resource availability, or external conditions can be accommodated without significant delays. By offering diverse options, the platform empowers teams to adapt and optimize their strategies dynamically.

AI Revolutionizes Synthetic Route Planning, Enhancing Accessibility and Sustainability in Chemistry

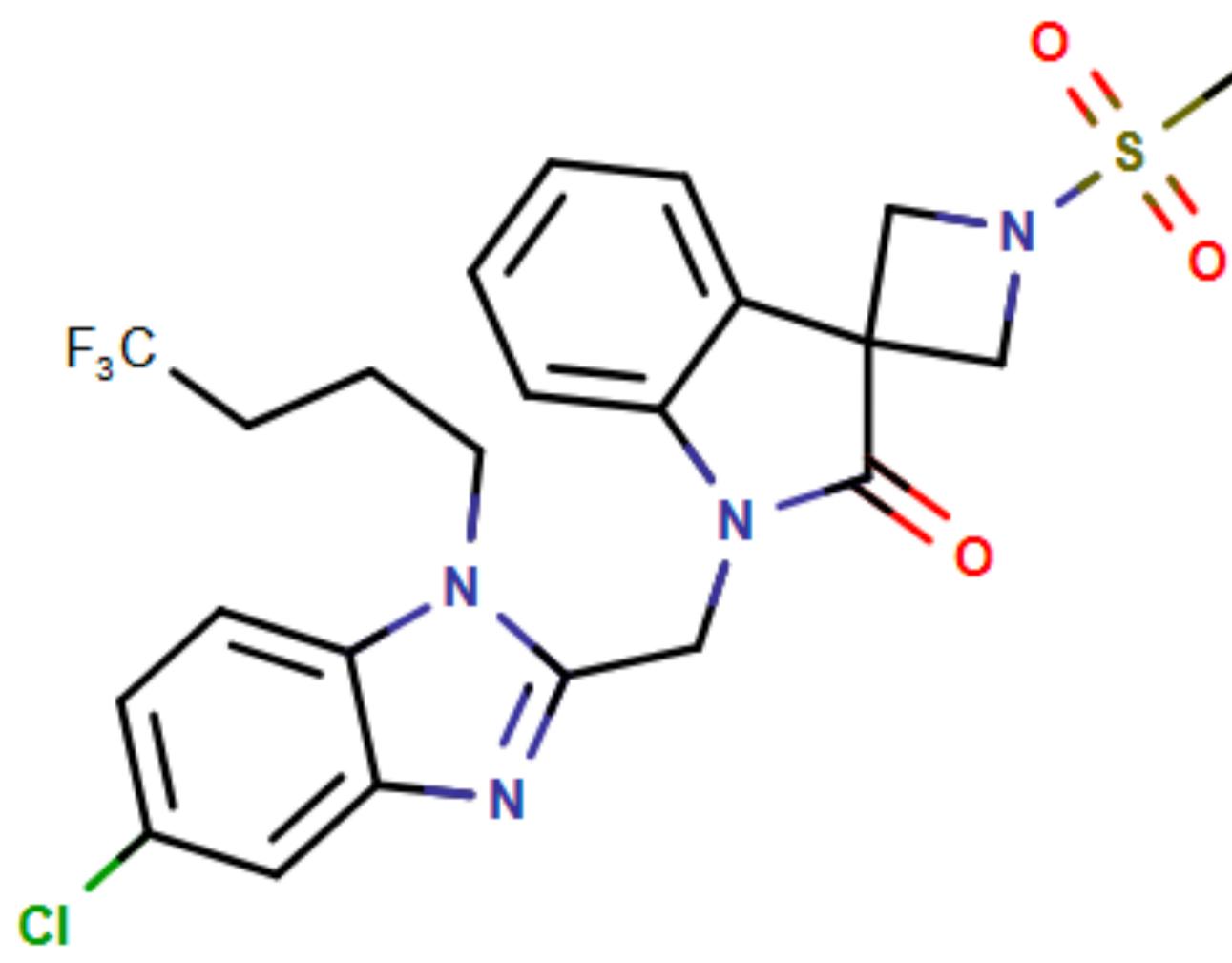
"The advent of AI in chemistry has revolutionized synthetic route planning. Tools like ChemAIRS, developed by Chemical.AI, leverage deep learning algorithms to rapidly design multiple synthetic routes, considering factors such as reaction feasibility and cost-efficiency. This approach accelerates innovation and optimizes the use of inexpensive starting materials, making synthesis more accessible and sustainable."

Dr. Srinivas Kantham

Senior Scientist at Mesentech

Spiro-Azetidine Oxindole for RSV Pre-Exposure Prophylaxis

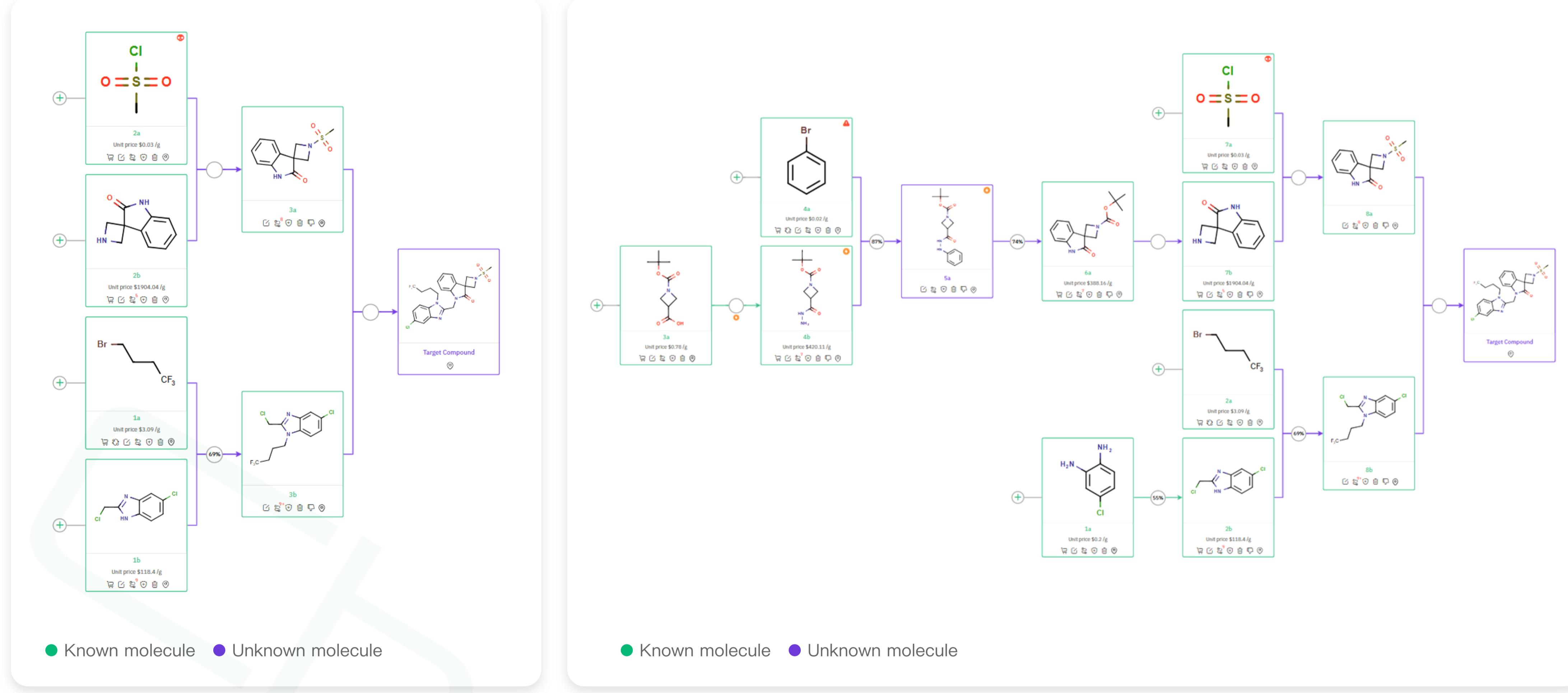
Researchers at Janssen Pharmaceutical have recently discovered spiro-azetidine oxindoles, which act as powerful inhibitors of the RSV fusion protein. RSV, or respiratory syncytial virus, is a significant cause of hospitalizations among pediatric, geriatric, and immunocompromised individuals. Janssen's breakthrough offers promising potential for the preventive treatment of RSV infection in humans. The synthesis of one such RSV fusion inhibitor is detailed below, utilizing the Retrosynthesis function from ChemAIRS.



Proposed Routes by ChemAIRS

Our retrosynthetic platform ChemAIRS is able **to propose multiple synthetic strategies within minutes**. However, we also provided a longer, but more economical synthetic route **to avoid expensive intermediates**.

The most concise route for the synthesis of this compound proposed by ChemAIRS (Scheme 1) closely resembles the method reported by Janssen. The procedure initiates with the preparation of two crucial intermediates: spiro-azetidine oxindole sulfonamide 3a and benzimidazole derivative 3b. These two intermediates (3a and 3b) are then coupled via a straightforward displacement reaction to produce the final API.



Scheme 1

Scheme 2

Suggested synthetic pathway for Cost-Effective Solutions

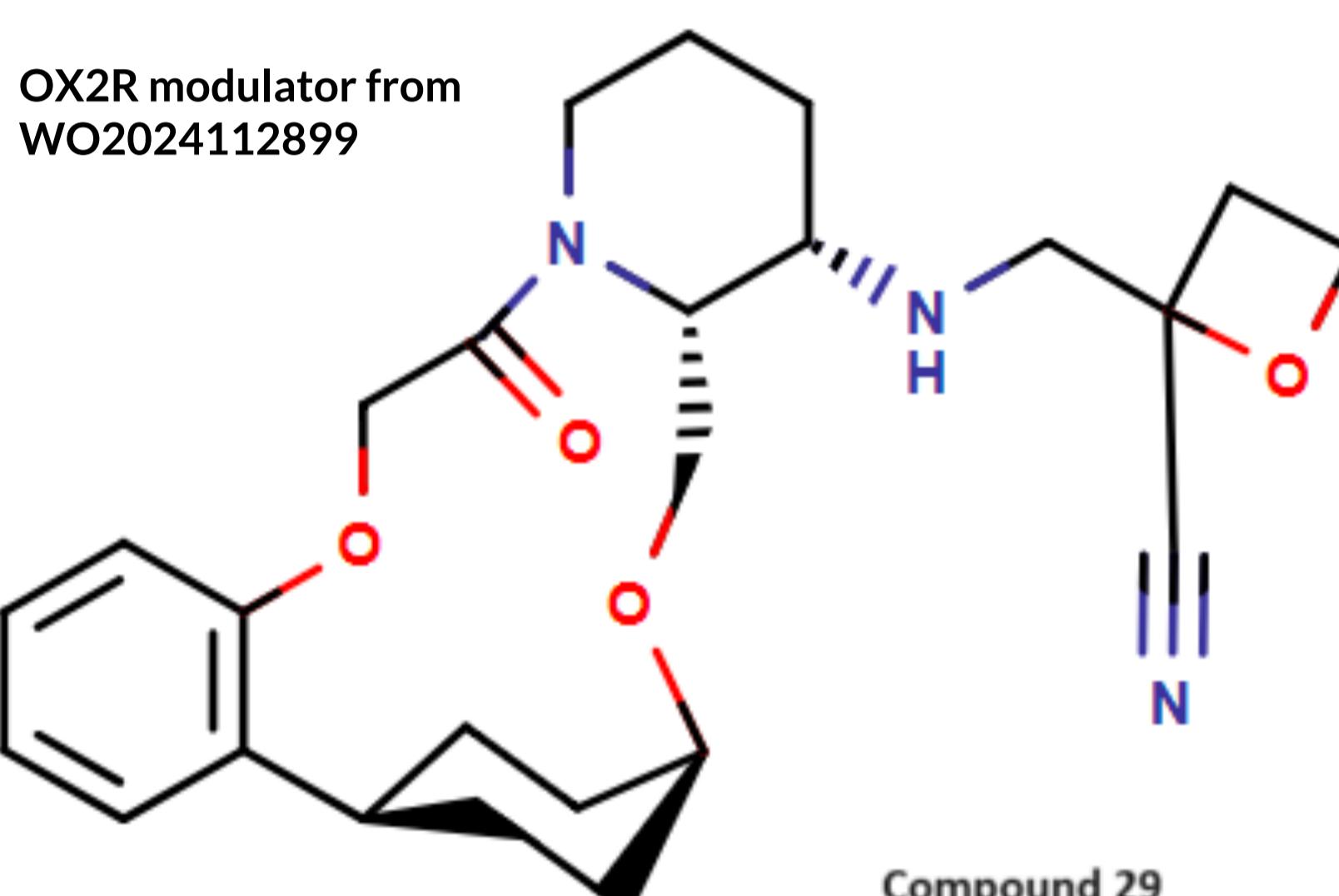
Given the cost and availability issues of one of the starting materials (2b and 1b in Scheme 1), we explored an alternative synthetic route. We tasked the system with proposing a different synthesis method for 8a and 2b, as illustrated in Scheme 2. Compound 7b is synthesized through a four-step sequence, starting from the commercially affordable reagent 3a. A base-induced rearrangement of 5a yields 6a (<https://pubs.acs.org/doi/abs/10.1021/jm00388a014>), which undergoes Boc-deprotection followed by an S-N coupling reaction to produce the desired sulfonamide 8a.

Overall, ChemAIRS demonstrates its proficiency in generating a variety of viable synthetic pathways, providing users with the flexibility to customize the synthetic route according to their specific requirements.

Use ChemAIRS to Investigate Synthesis Strategies of OX2R Modulator, a Vertex Pharmaceuticals' Approach to Narcolepsy Treatment

Macrocyclic Amine Modulators Targeting OX2R: A Promising Narcolepsy Treatment

Orexins, a class of neuropeptides, influence sleep/wake cycles through interaction with G-protein-coupled receptors OX1R and OX2R. Research suggests that OX2R agonists may be promising therapeutic agents for narcolepsy. Vertex Pharmaceuticals has designed macrocyclic amine modulators with high affinity and specificity for OX2R, demonstrating enhanced CNS penetration and favorable pharmacokinetic profiles.

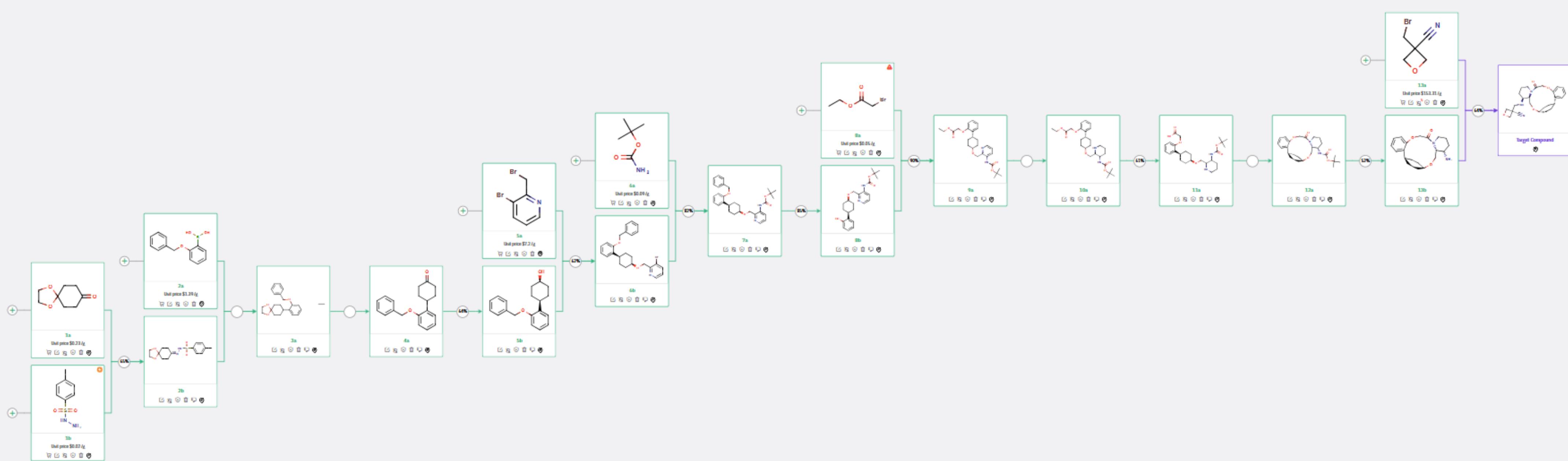


Reference: https://patentscope.wipo.int/search/de/detail.jsf?docId=WO2024112899&_cid=P10-LWUD65-81974-1

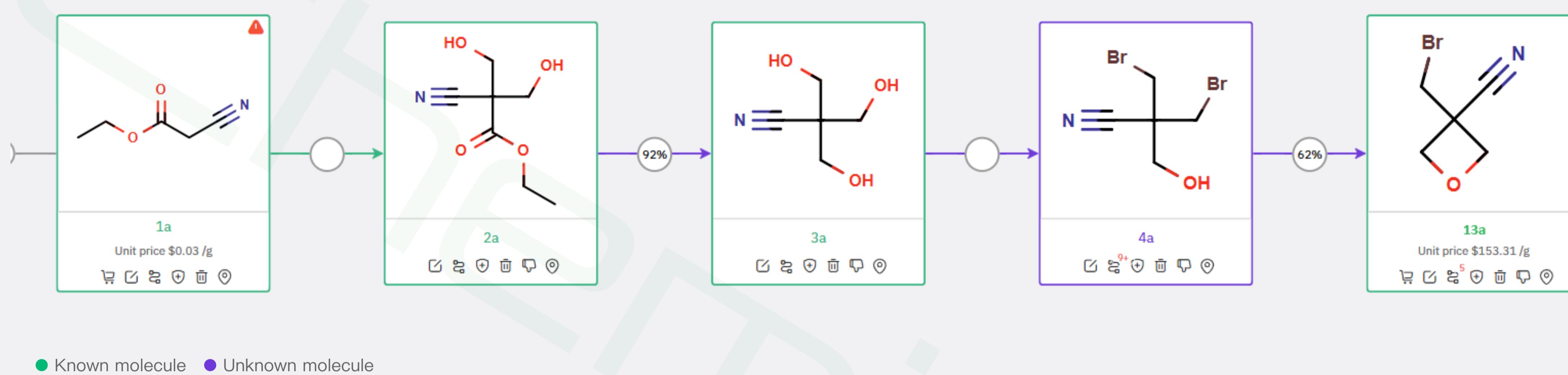
Replication of the Reported Synthesis Route of OX2R Modulator

ChemAIRS examined the synthesis of an OX2R modulator, specifically focusing on compound 29 from Vertex's patent. The synthesis involved two key intermediates, 13a and 13b, with 13a being commercially sourced (Scheme 1). The pathway to 13b closely follows the method described by Vertex Pharmaceuticals, where the precursor cyclohexanol 5b was stereoselectively obtained via ketone 4a reduction. A crucial chirality-inducing step included the reduction of Boc-amino pyridine (9a) to Boc-amino piperidine (10a), producing a racemic mixture subsequently resolved via chiral chromatography.

In the final synthetic step, ChemAIRS recommended a direct one-step synthesis to the final compound using the commercially available 3-(bromomethyl)oxetane-3-carbonitrile (13a), in contrast to a previous three-step process starting from 3-(hydroxymethyl)oxetane-3-carbonitrile. Additionally, to offer a more economical path to obtain 13a, ChemAIRS proposed a cost-effective synthetic route for 13a as depicted in Scheme 2.



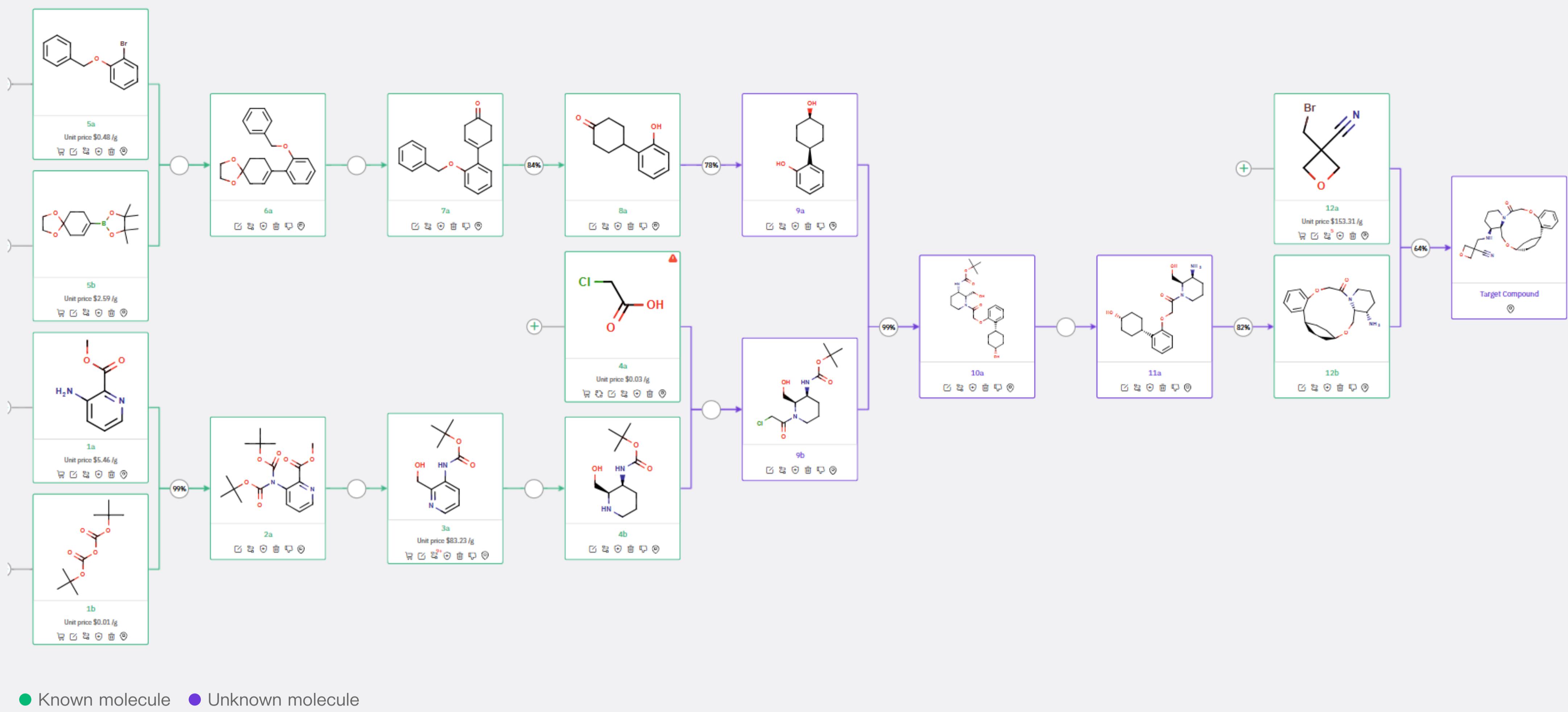
Scheme 1: ChemAIRS predicted a synthetic pathway for an OX2R modulator, which closely aligns with Vertex's patented report



Scheme 2: Proposed synthetic strategy for 13a from ChemAIRS

Proposing Alternative Synthetic Strategies for OX2R Modulator

ChemAIRS not only identified a synthetic route similar to previously reported methods but also proposed alternative strategies for synthesizing the final API, as illustrated in Schemes 3 and 4. Scheme 3 outlines the synthesis of two chiral molecules, 9a and 9b, from commercially available precursors, which are then condensed to form 10a and further processed to yield the key intermediate 12b. Scheme 4 describes the synthesis of chiral 4-phenylcyclohexanol 2a in a single step, followed by its reaction with bromo-pyridine 2b and subsequent reduction of an additional aromatic ring, leading to the formation of chiral piperidinyl carbamate 5a. ChemAIRS also suggested various strategies for synthesizing a macrocyclic molecule, such as the condensation of 11a to produce 12b (Scheme 3) or the intramolecular etherification of 7a to yield 8a (Scheme 4).



Scheme 3: Alternative Synthetic Routes for the OX2R Modulator, initiated with the preparation of two chiral intermediates



Scheme 4: Alternative Synthetic Routes for OX2R Modulator, featuring the formation of the macrocyclic molecule through intramolecular etherification

In summary, ChemAIRS excels in providing synthetic pathways consistent with established methodologies and proposing innovative, practical alternatives. This versatility enables chemists to explore new synthetic avenues, facilitating accelerated innovation in the lab and positioning ChemAIRS as a valuable resource for advancing chemical research and development.

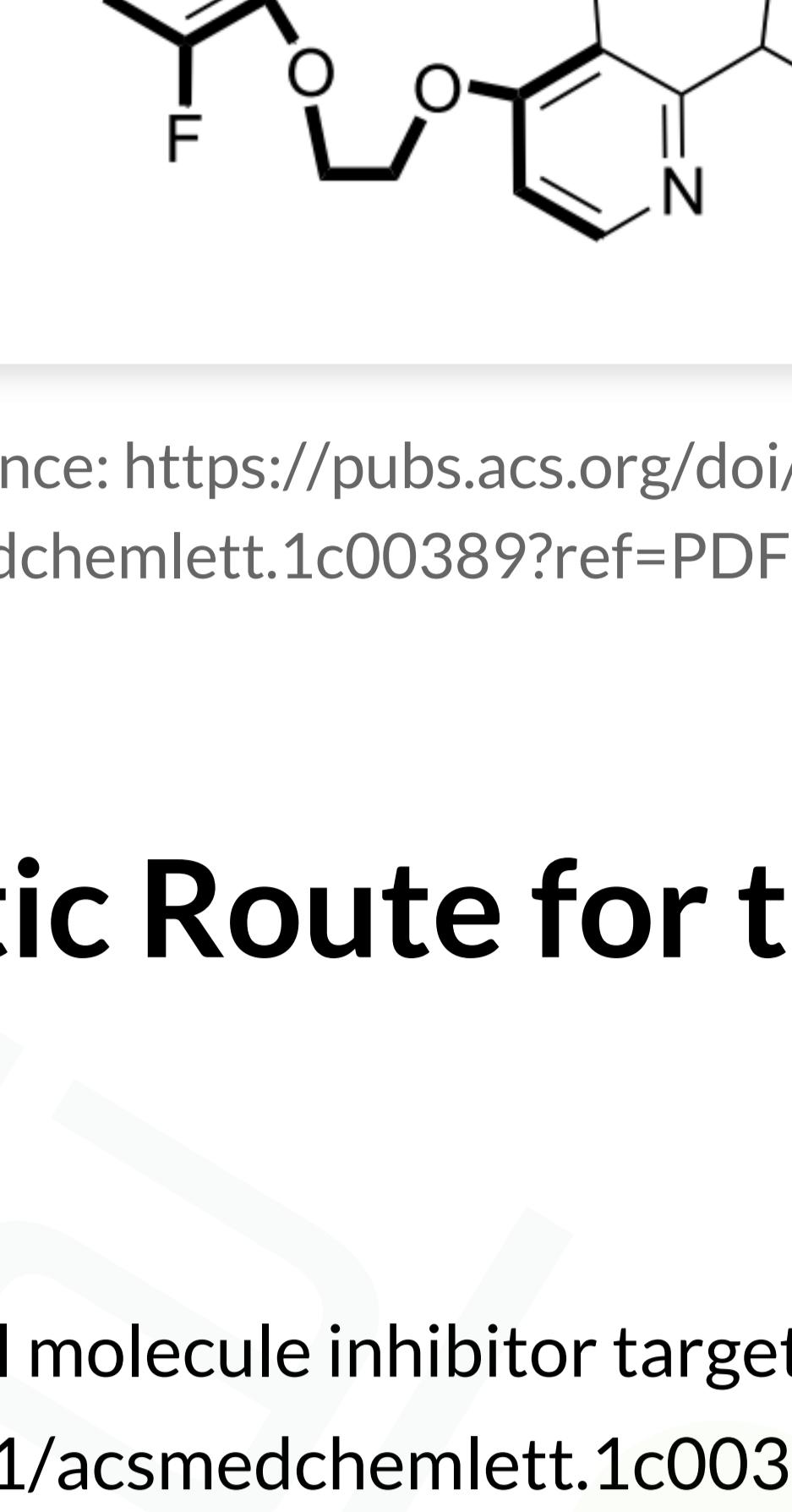
List of references:

1. Sun, L.; Wang, C.; Zhang, J.; Liu, Y. *Bioorg. Chem.* 2018, 80, 396-407.
2. Sato, K.; Yamaguchi, S.; Nakajima, H. *Synthesis* 1997, 1997(11), 1281-1284.
3. Johnson, D. L.; Miller, A. M.; Wong, C. *Org. Process Res. Dev.* 2023, 27(7), 1390-1399.
4. WO2013/130976.
5. Chen, Y.; Lee, J.; Park, H. *J. Org. Chem.* 2009, 74(14), 5075-5078.

Rapidly Identifying Alternative Synthetic Routes for Merck & Co.'s KRAS G12C Inhibitor

Merck's Discovery of Selective G12C Inhibitors for KRAS-Mutant Cancers

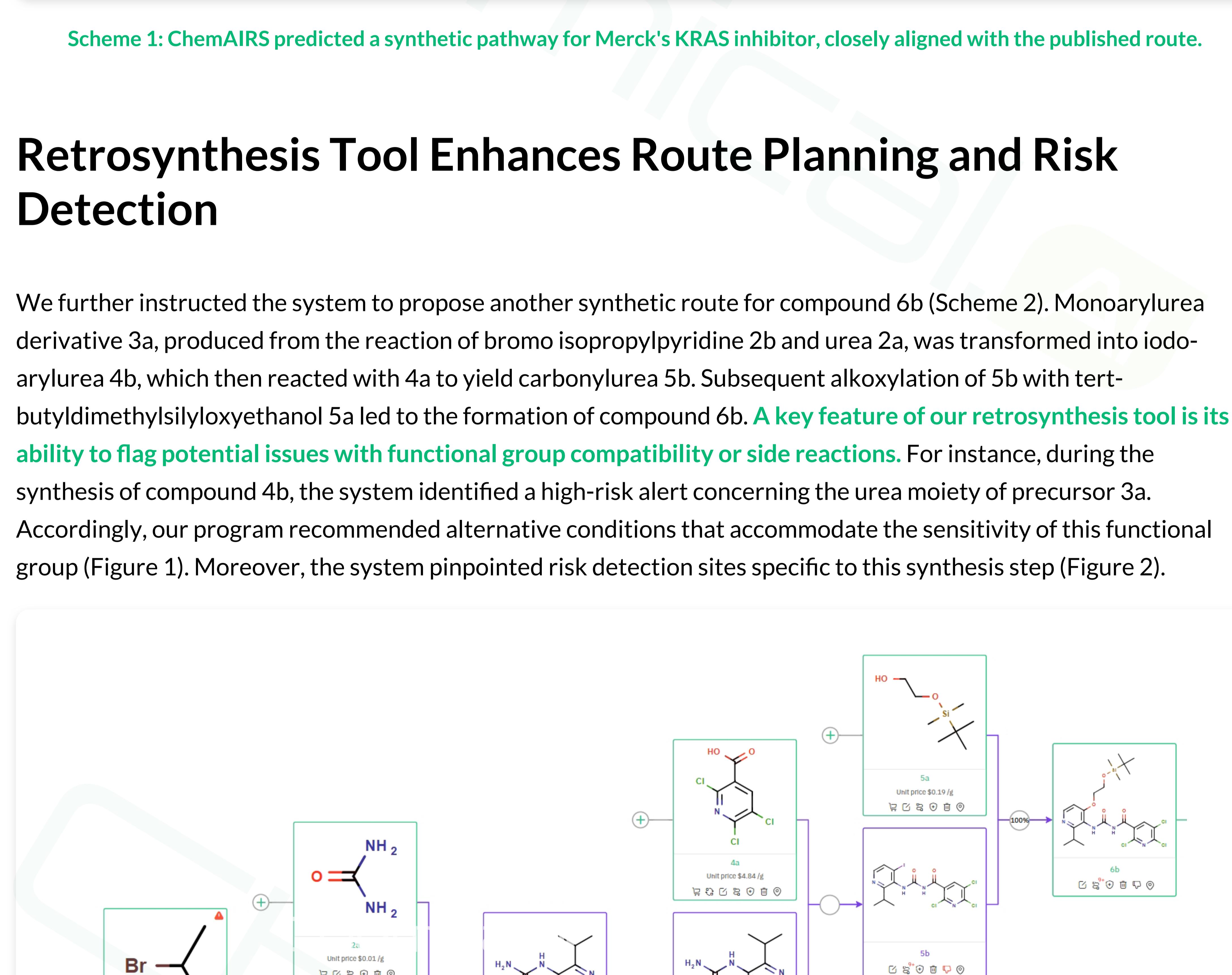
Cancer is the second leading cause of death globally and a major health challenge. The KRAS (Kirsten rat sarcoma) oncogene is frequently mutated in various cancers, causing resistance to standard treatments and poor outcomes. These mutations hyperactivate cell proliferation, thus driving tumor growth. Merck researchers have discovered heteroaryl compounds that selectively inhibit the G12C mutant KRAS protein, offering a promising therapeutic approach.



Reference: <https://pubs.acs.org/doi/10.1021/acsmedchemlett.1c00389?ref=PDF>

ChemAIRS Predicted the Reported Synthetic Route for the Macroyclic Compound

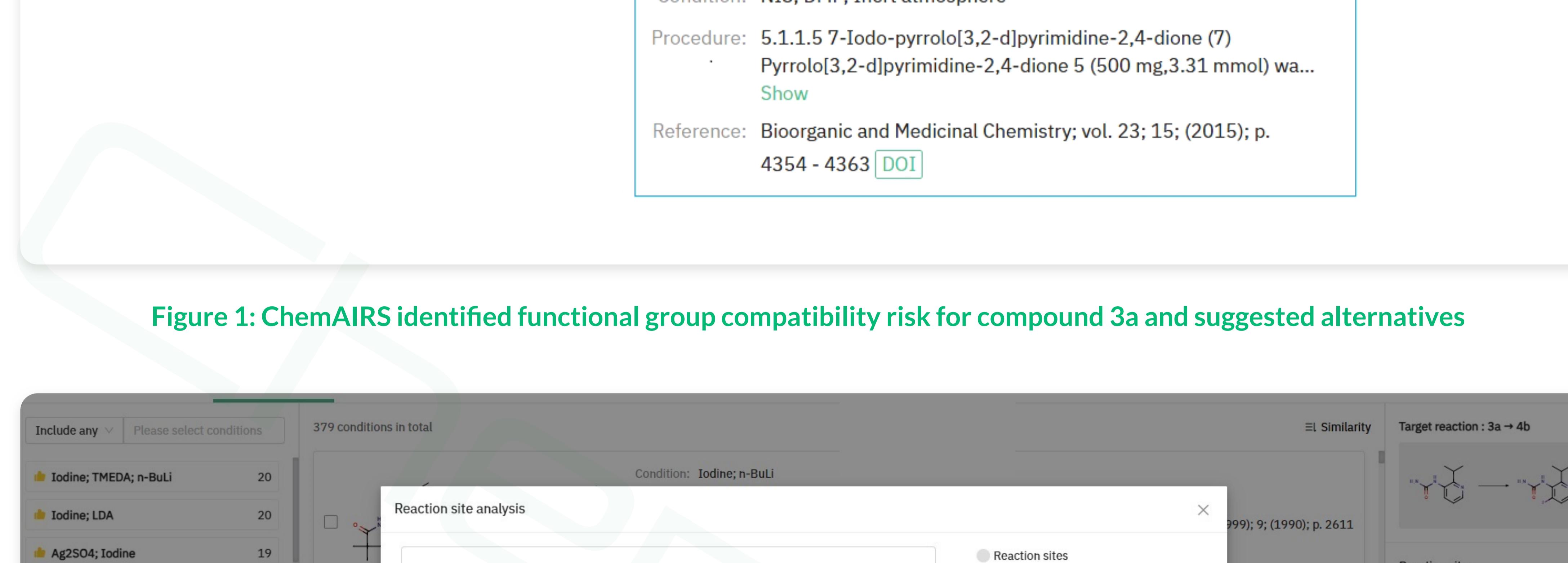
In this report, we tasked our ChemAIRS with proposing a synthetic route for a small molecule inhibitor targeting the KRAS G12C mutant (example 50 in the reference: <https://pubs.acs.org/doi/10.1021/acsmedchemlett.1c00389?ref=PDF>). **In under 3 minutes, ChemAIRS generated multiple synthetic pathways to the target macrocyclic molecule. One of these pathways (Scheme 1) closely aligned with the synthesis recently reported by Merck.** Additionally, our retrosynthesis platform proposed an alternative synthetic route for compound 11a, starting from boronic acid 10 and proceeding via a 2-step process, as opposed to the 3-step synthesis from potassium (3,6-difluoro-2-hydroxyphenyl) trifluoroborate found in the literature. In the final step, the system suggested an alternative reaction condition using acrylic anhydride and methylmorpholine instead of the reported acryloyl chloride/DIPEA combination.



Scheme 1: ChemAIRS predicted a synthetic pathway for Merck's KRAS inhibitor, closely aligned with the published route.

Retrosynthesis Tool Enhances Route Planning and Risk Detection

We further instructed the system to propose another synthetic route for compound 6b (Scheme 2). Monoarylurea derivative 3a, produced from the reaction of bromo isopropylpyridine 2b and urea 2a, was transformed into iodo-arylurea 4b, which then reacted with 4a to yield carbonylurea 5b. Subsequent alkylation of 5b with tert-butyldimethylsilyloxyethanol 5a led to the formation of compound 6b. **A key feature of our retrosynthesis tool is its ability to flag potential issues with functional group compatibility or side reactions.** For instance, during the synthesis of compound 4b, the system identified a high-risk alert concerning the urea moiety of precursor 3a. Accordingly, our program recommended alternative conditions that accommodate the sensitivity of this functional group (Figure 1). Moreover, the system pinpointed risk detection sites specific to this synthesis step (Figure 2).



Scheme 2: ChemAIRS suggested an alternative synthetic route for 6b, a key intermediate for route optimization.

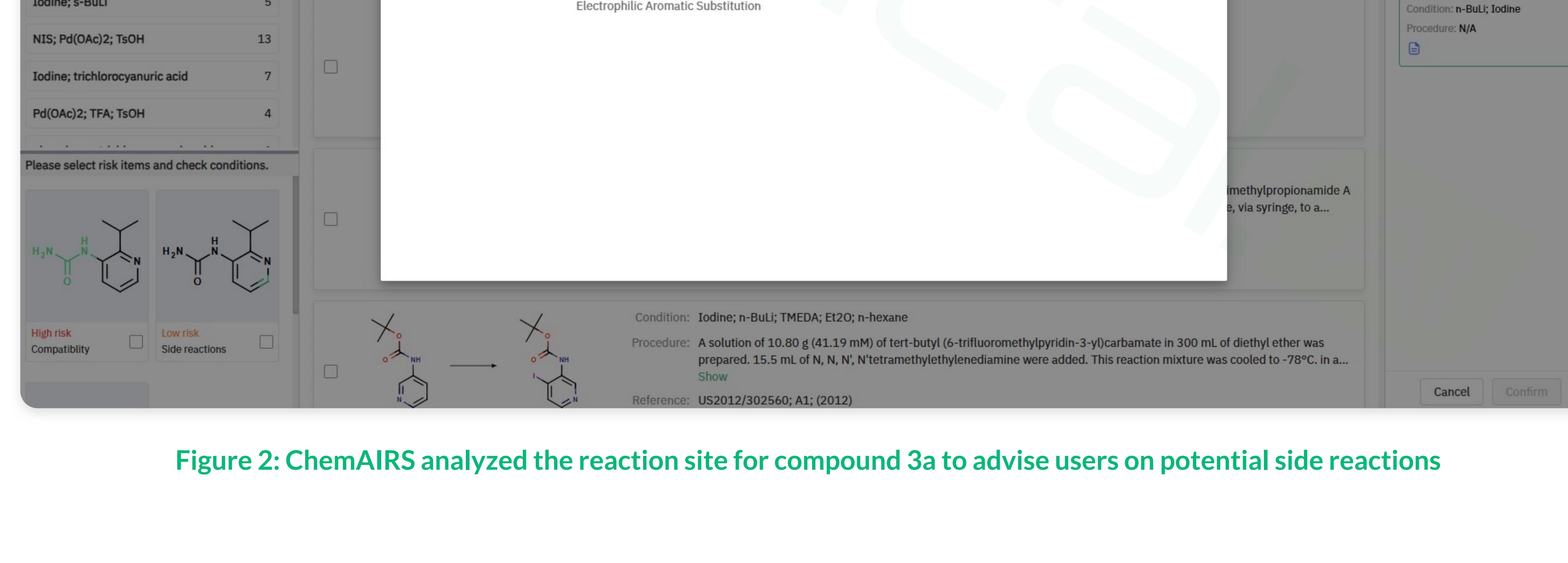
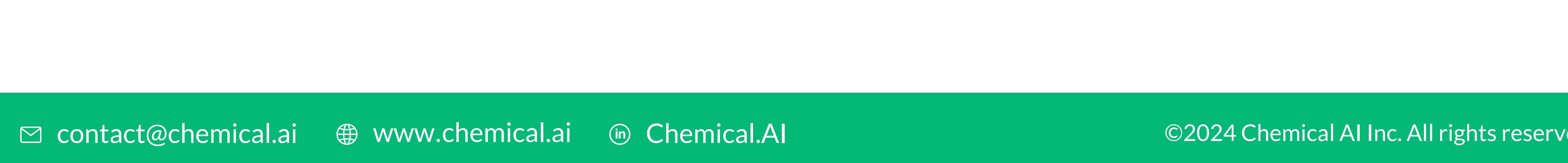


Figure 1: ChemAIRS identified functional group compatibility risk for compound 3a and suggested alternatives

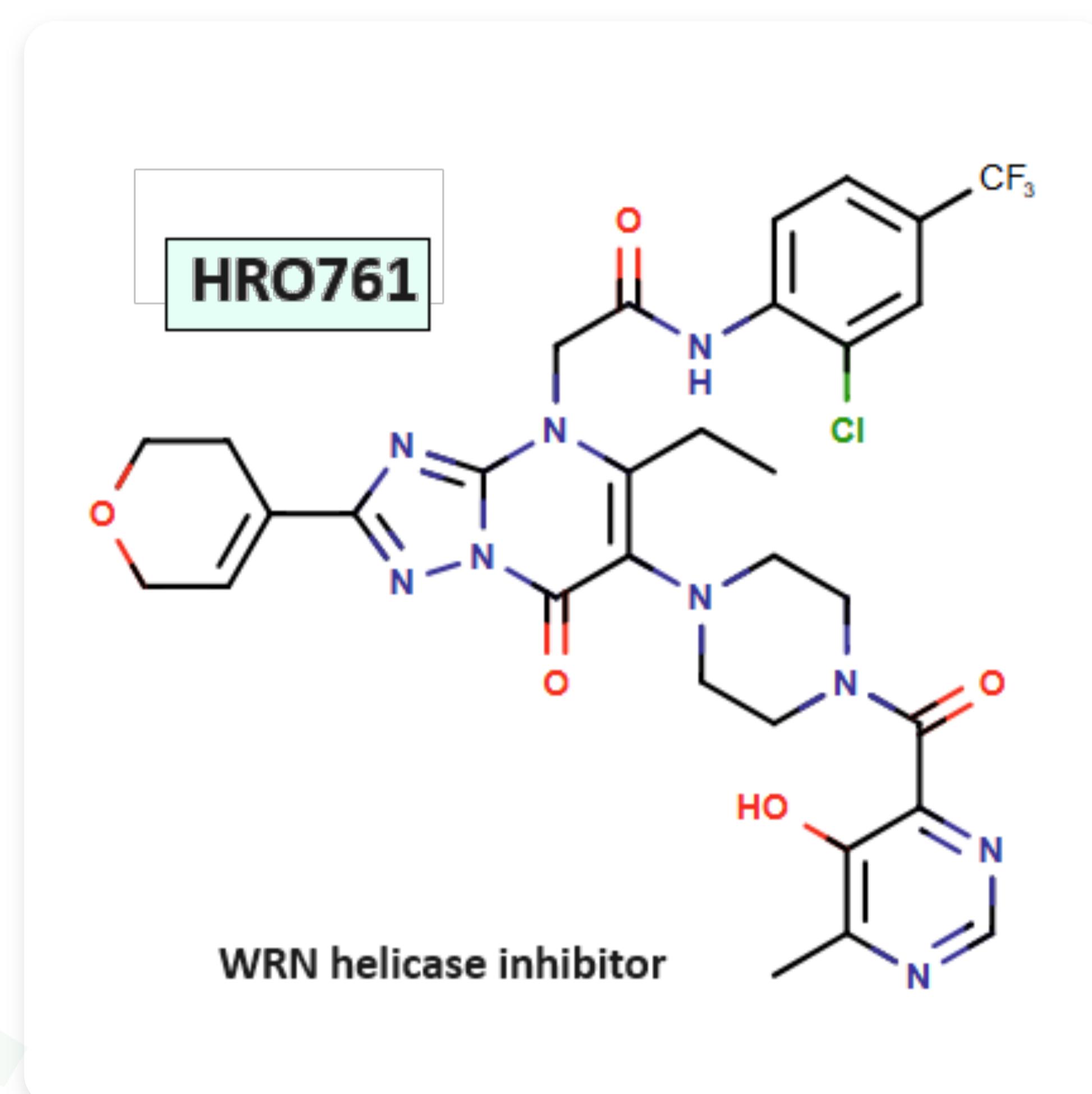


In conclusion, ChemAIRS efficiently proposed synthetic routes for KRAS G12C inhibitors, aligning with known methods and suggesting more efficient alternatives. Additionally, the retrosynthesis tool's ability to detect and address potential risks further ensures the reliability and safety of the proposed synthetic pathways.

Utilizing ChemAIRS to Investigate Synthetic Strategies of WRN Inhibitor HRO761: A Potential Therapeutic from Novartis for MSI Cancers

Targeting WRN in MSI Cancers: A Novel Clinical Approach from Novartis

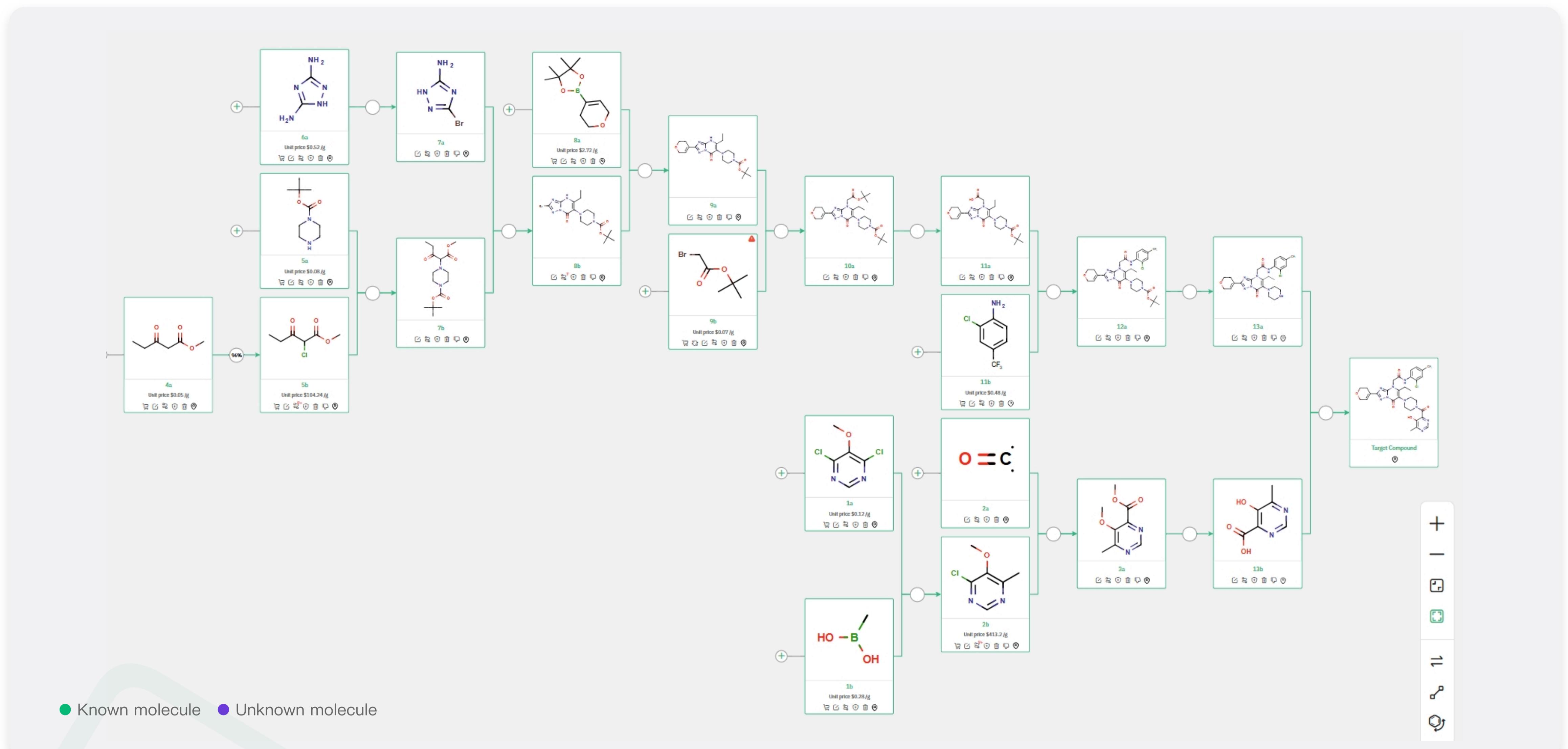
Genetic screens have identified the Werner syndrome RecQ helicase (WRN) as a synthetic lethal target in microsatellite instability (MSI) cancer cells. Despite advances in treatment with immune checkpoint inhibitors, there is an unmet need for the treatment of MSI cancers. Novartis researchers have developed a potent and selective WRN inhibitor, HRO761, which is now undergoing its first human clinical trial to assess its pharmacokinetics, safety, tolerability, and preliminary anti-tumor efficacy in MSI colorectal cancer and other MSI solid tumors.



Ferretti, S., Hamon, J., de Kanter, R. et al. Discovery of WRN inhibitor HRO761 with synthetic lethality in MSI cancers. *Nature* 629, 443–449 (2024). <https://doi.org/10.1038/s41586-024-07350-y>

ChemAIRS Predicted the Reported Synthetic Route for the WRN inhibitor HRO761

ChemAIRS proposed a feasible 13-step synthetic route (Scheme 1) wherein the final target compound was synthesized through an amide coupling reaction between intermediates 13a and 13b, **closely mirroring the methodology reported by Novartis**. Moreover, **ChemAIRS identified a potential risk in the final step, specifically a possible side reaction as depicted in Figure 1**. Notably diverging from the existing patent, ChemAIRS suggested a 3-step synthesis for the key intermediate 13b. This procedure commenced with a Suzuki coupling reaction to form the chloropyrimidine derivative 2b, which was subsequently transformed into the corresponding methyl ester 3a via palladium-catalyzed carbonylation.



Scheme 1: ChemAIRS predicted a synthetic pathway for Novartis's WRN inhibitor HRO761, closely aligned with the published route

Condition Search Literature Condition Experience Condition X

Include any Please select conditions

Literature Condition

652 conditions in total

Condition: HOAt; DIPEA; MeCN; H₂O; Inert atmosphere
Procedure: Under nitrogen was mixed 5-hydroxy-6-methylpyrimidine-4-carboxylic acid (Intermediate DB) (2.61 g, 17.0 mmol) in ACN...

El Similarity

Target reaction : 14a + 14b → Target Compound

Reaction sites Risk reaction sites detected

Selected conditions

Condition: H₂O; MeCN; DIPEA; HO...
Procedure: Under nitrogen was mixed 5-hydroxy-6-...

Please select risk items and check conditions.

High risk Side reactions

Low risk Compatibility

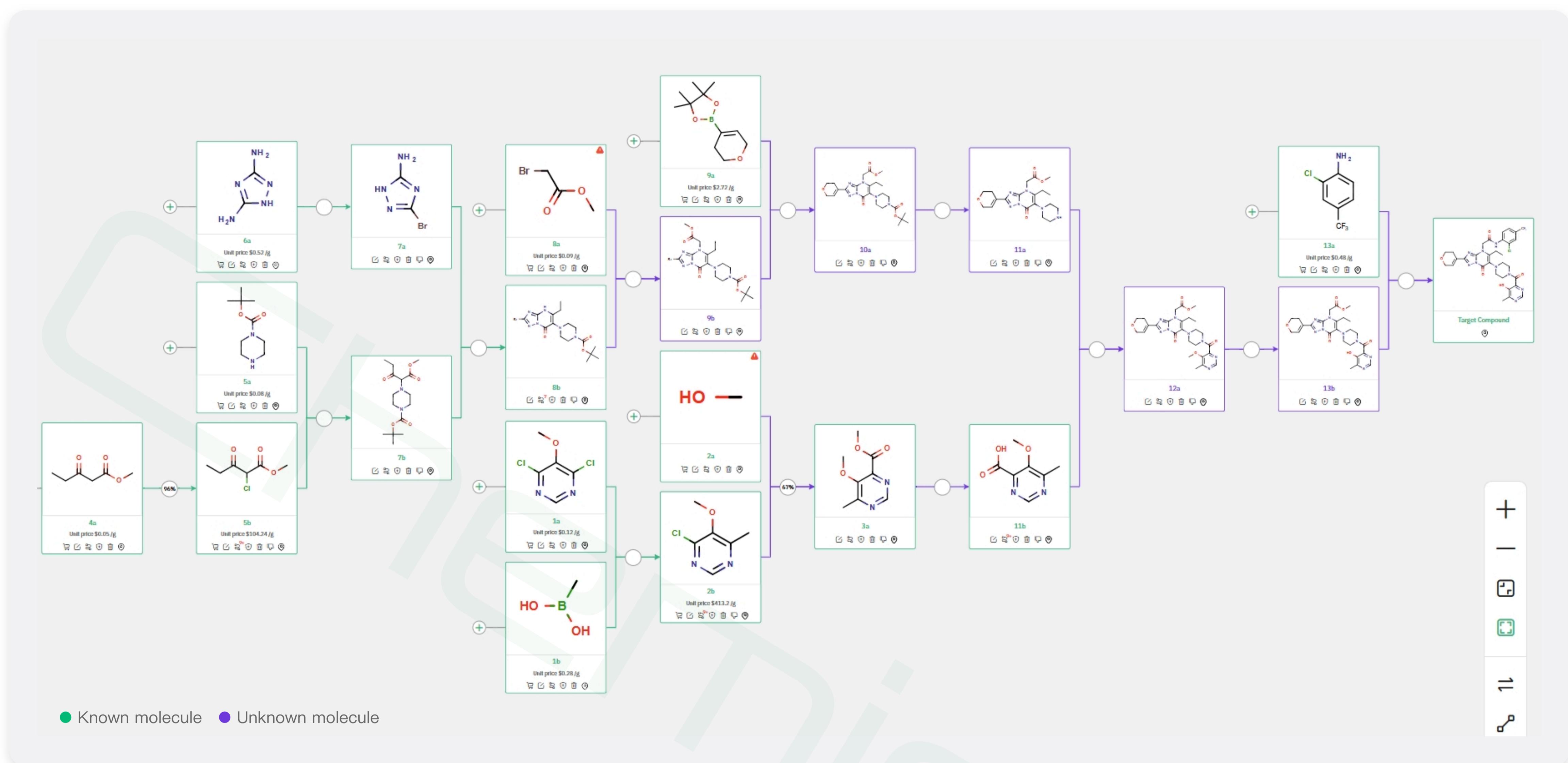
Condition: DIPEA; HATU; DMF
Procedure: To a stirred solution of N-(2-chloro-4-

Cancel Confirm

Figure 1: ChemAIRS identified side reaction risk for the last-step synthesis of target molecule

Revised Synthetic Strategy to Minimize Reaction Risks

Acknowledging a risk associated with the final step of Scheme 1, which involved an amide coupling reaction between intermediate 13a and pyrimidine-carboxylic acid 13b, we tasked ChemAIRS to propose an alternative approach as illustrated in Scheme 2. In this revised scheme, the pyrimidine moiety was introduced earlier in synthesis via an amide coupling reaction between 11a and 11b, followed by a demethylation step to yield 13b. In the final step, trifluoromethylaniline 13a reacted with the intermediate 13b, a strategy intended to minimize the risk of the side reaction mentioned in Figure 1.



Scheme 2: ChemAIRS suggested an alternative synthetic pathway for WRN inhibitor HRO761 to mitigate final step risks

In conclusion, the ChemAIRS Retrosynthesis tool demonstrated its robust capability in identifying potential risks and proposing innovative solutions. Its capability to deviate from existing patents and suggest a synthesis for key intermediates underscores its value in accelerating synthetic organic chemistry projects and ensuring successful outcomes.