



Breaking Boundaries in Complex Synthesis: TLC Successfully Produces N-Nitroso Ticagrelor, CAS# 2476859-55-7

Pushing scientific limits has always been part of TLC's DNA — and our recent successful synthesis of N-Nitroso Ticagrelor (TLC# T-81180) exemplifies that commitment.

The Context: Why It Matters

Ticagrelor, a widely used antiplatelet medication, plays a vital role in preventing cardiovascular events. As global regulatory agencies increase focus on nitrosamine impurities, the need for well-characterized nitrosated reference standards continues to grow — especially for complex molecules such as Ticagrelor. However, the synthesis of N-Nitroso Ticagrelor had long been regarded as unfeasible. Reports suggested that under nitrosation conditions, the molecule would favor intramolecular cyclization, yielding 4,5-Dihydroisoxazole Ticagrelor instead.

The Challenge

When a client approached TLC with this project, it came with uncertainty. Some in the industry had concluded that direct nitrosation of Ticagrelor could not yield the intended structure. Rather than accepting this limitation, TLC's scientific team explored the chemistry in depth, combining mechanistic understanding with precise control of reaction conditions. Through careful experimentation and analytical confirmation, the team achieved what had been considered by some as unattainable.

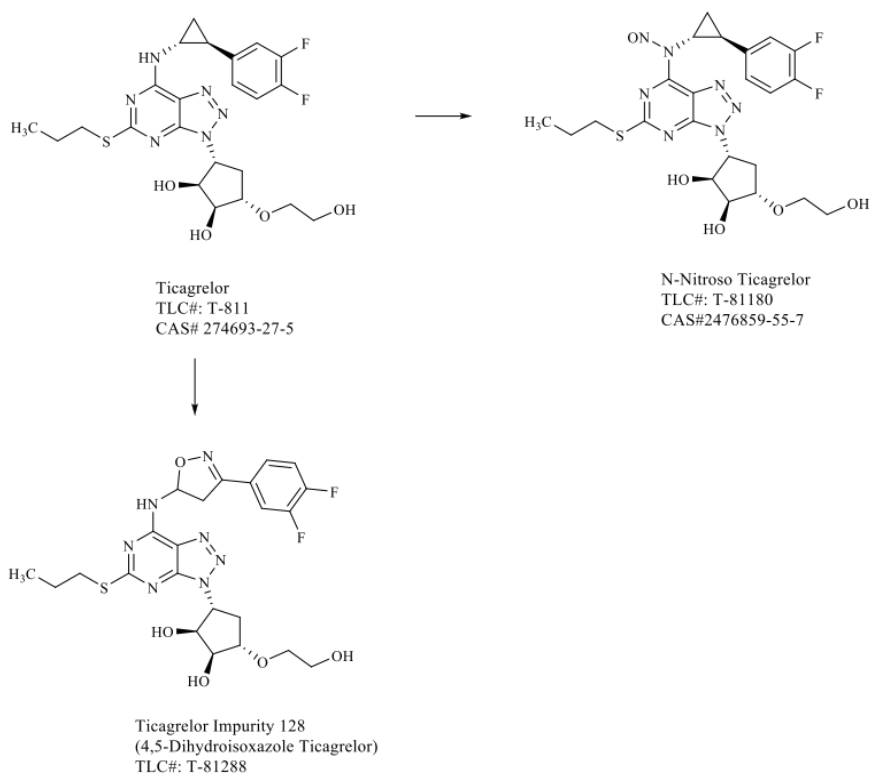
The Results

TLC successfully synthesized and fully characterized N-Nitroso Ticagrelor (TLC# T-81180). To validate the outcome, the team also synthesized the competing structure — 4,5-Dihydroisoxazole Ticagrelor (TLC# T-81288) — and performed direct analytical comparison. Comprehensive HPLC, LC-MS, and NMR studies demonstrated:

- Distinct NMR profiles between the two compounds, confirming structural differences; and co-injection of both products proved the separation and differentials with retention time in HPLC analysis.
- HPLC-MS evidence of transient formation of both products under certain conditions.
- Stability behavior consistent with a true nitrosamine: T-81180 showed partial reversion to the parent API (Ticagrelor), while the isoxazole analog remained stable.



Figure 1 — Competing Reaction Pathways



Direct nitrosation of Ticagrelor leads to N-Nitroso Ticagrelor (T-81180), while competing cyclization yields 4,5-Dihydroisoxazole Ticagrelor (T-81288). TLC's process successfully controlled conditions to favor formation of the nitrosated product.

A Reflection of TLC's Approach

This project highlights TLC's commitment to scientific rigor, adaptability, and persistence. The team's success underscores a defining trait of TLC's culture — the determination to find solutions to complex challenges through disciplined experimentation and collaboration.

A Proven Partner for the Hardest Projects

TLC continues to support clients globally in the synthesis and characterization of complex impurities, metabolites, and nitrosamines — particularly where conventional approaches have not succeeded. Our success with N-Nitroso Ticagrelor (TLC# T-81180) stands as a clear example of TLC's capability and the scientific depth that drives our work every day. When the chemistry becomes more challenging, TLC delivers results built on precision and integrity.

■ Contact Us

Interested in learning how TLC can assist with your next complex synthesis project?
Contact our team → research@tlcstandards.com