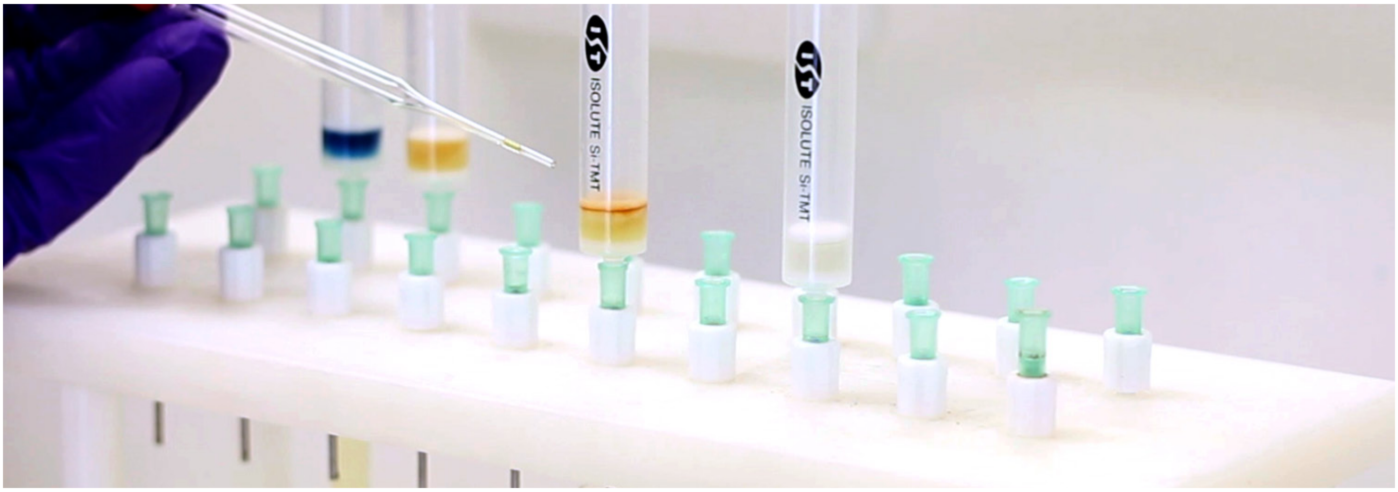
Metal Scavengers

Metal Mitigation, Extractables and Regulatory Perspectives



Introduction

This study was conducted in 3 parts.

- Metal scavengers were investigated for inherent metals content by ICP analysis methods.
- Additionally these scavengers were extracted in a range of common solvents in order to show extractable/leachable levels.
- We demonstrate an example metal scavenging mitigation step, looking at the corresponding API mass yield, purity and also metals data.

Background

Compliance with GMP is a necessary practice for drug authorizations. GMP yields practices which espouse quality and process risk mitigation however the scrutiny that it demands can pose local engineering and chemistry pressures.

In recent years, impurities have become a major issue in pharma. The commercial time required for drug candidates to reach the market has increased the pressure on the process to be successful. Some very elegant and efficient solutions have been adopted over the years. Examples include the use of greener

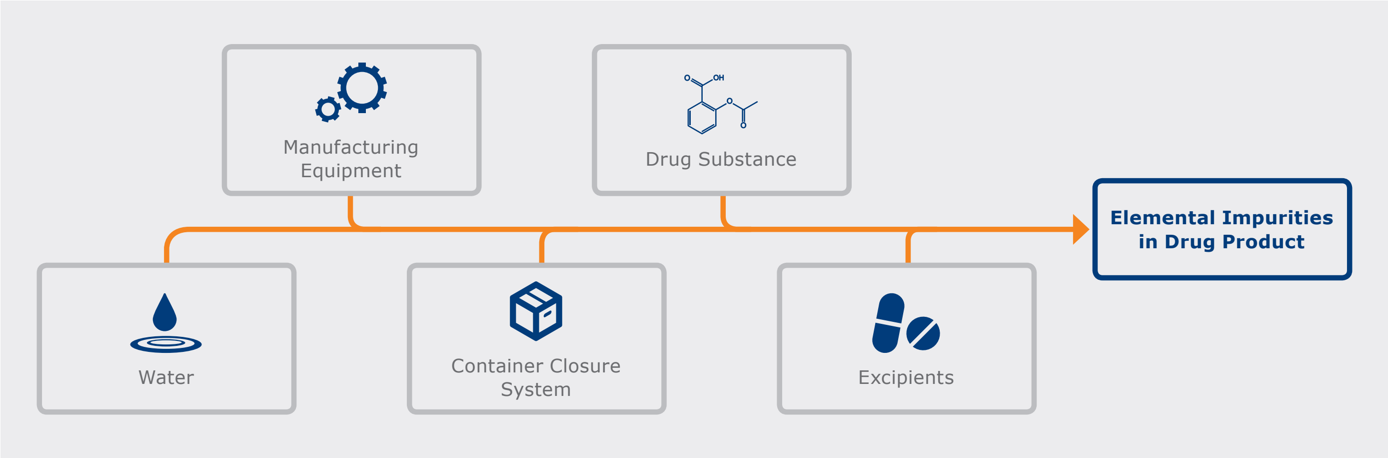


Figure 1. Potential sources of elemental impurities in drug production.

and more efficient catalytic chemistries (such as those involving transition metals) which are now more prevalent in chemistry from lead optimization to early scale-up.

Understanding extractables is familiar to the industry but recently the relatively new concern of metals mitigation has been formally clarified in the form of clear guidance to the industry.

The International Conference on Harmonisation (ICH) has completed the Q3D guidelines for metal elemental impurities in new drugs and new formulations containing known ingredients. It requires a comprehensive analysis of potential and actual risks of metal contamination in a process to comply (Figure 1).

When it comes to process chemistry, a number of methods are employed to mitigate residual metals. However they each have advantages and disadvantages which may not be universally applicable, or provide variable results. In the case of metals removal using carbon for example, the risk of loss of API yield is high so a carbon strategy is unlikely to be cost effective with small molecules containing conjugated pi systems or hetero-atoms. For over 15 years, Biotage has supplied metal scavengers that can be added directly to reactions to undertake metals removal. Metal scavengers are clean heterogeneous additives that are completely removed by simple filtration methods.

Conclusions

Based on recent ICH guidance, the metal scavengers we tested were very effective at removing metals to accepted limits form solution. More importantly the scavengers did not contain impurity (either inherent trace metals or other extract-able components) that could contaminate API in a process environment.

Thus ICP analysis of the five metal scavengers in the Biotage screening kit revealed systematically very low elemental metals composition (<10ppm for the metals tested), which ultimately will assist in risk assessment and mitigation strategy for QA purposes. When applied to a model scavenging reaction, our API analogue was recovered in 100% yield, indicating no non-specific interactions were present. In a process, these characteristics translate into higher mass yields and recovery, leading to better process economics.

When compared to a number of commercially available metal scavengers, it was clear that not all metal scavengers on the market have the same degree of affinity for metal or cleanliness. After elimination of poor candidates, a screening approach is the recommended method for identifying a viable metal scavenging solution.

Example – Scavenging Palladium

Figure 2a. Crude Pd / mother liquors (500 ppm Palladium) is applied to Si-TMT.

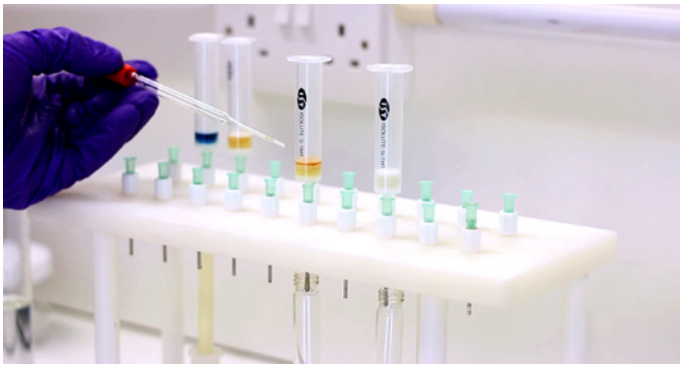


Figure 2b. Product passes through and palladium is efficiently retained in a tight ligand.

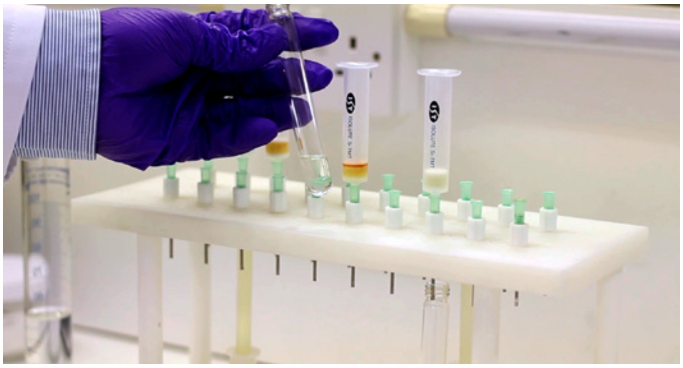


Figure 2c. Metal mitigation complete, the result is a clear product extract.

Figure 2d. Comparison, the clear product extract to the left and the original palladium catalyst to the right.

Biotage

Experimental Section

Results Part 1 – Inherent Metals Content

The metal scavengers were used as supplied, and analyzed by ICP for a range of chemically relevant metals. ICP analysis revealed systematically low elemental metals composition (<10ppm for the metals tested), which ultimately will assist in risk assessment and mitigation steps for QA purposes. Data points from other commercially available scavengers are shown in parenthesis for comparison purposes.

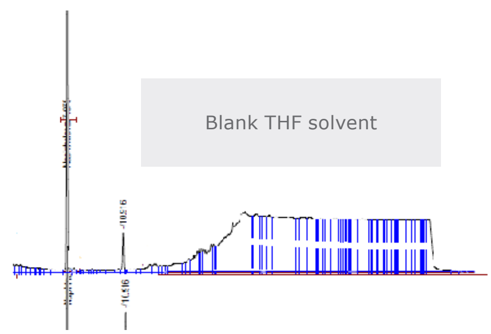
	As	Cd	Co	Cr	Cu	Hg	Li	Mo	Ni	Sb	Sn	V
MP-TMT	0	0.5	0	2	2.2	0	0	2	2	0	9	0
Si-Thiol	0 (13)*	1.1	0	2	1.5	0 (4)*	0	4	0	0	0	1 (13)**
Si-TMT	0	1.3	0	4	2.4	3	0	1	0	0	0	2
SCX-2	0	0.6	0	2	1.2	3	0	2	0	0	0	0
Si-Trisamine	0	0.7	0	2	1.2	0	0	0	0	0	0	1

Table 1. Inherent metals content

* Competitor S
** Competitor P

Results Part 2 – Solvent Extraction

Each metal scavenger was exhaustively extracted in solvent and the extract analyzed by GC. All traces showed a high degree of cleanliness, THF traces indicated a solvent based impurity that was present in the blank (so can be eliminated).



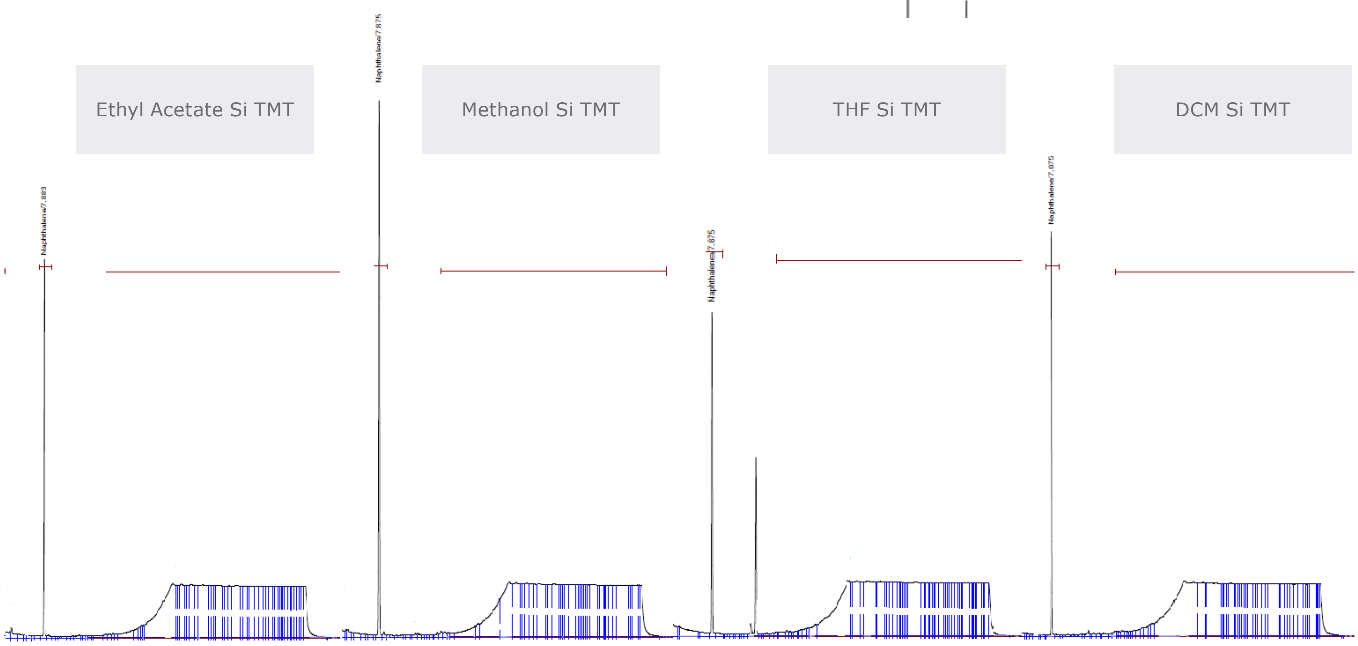


Figure 3. Si-TMT extraction by EtOAc, MeOH, THF and DCM

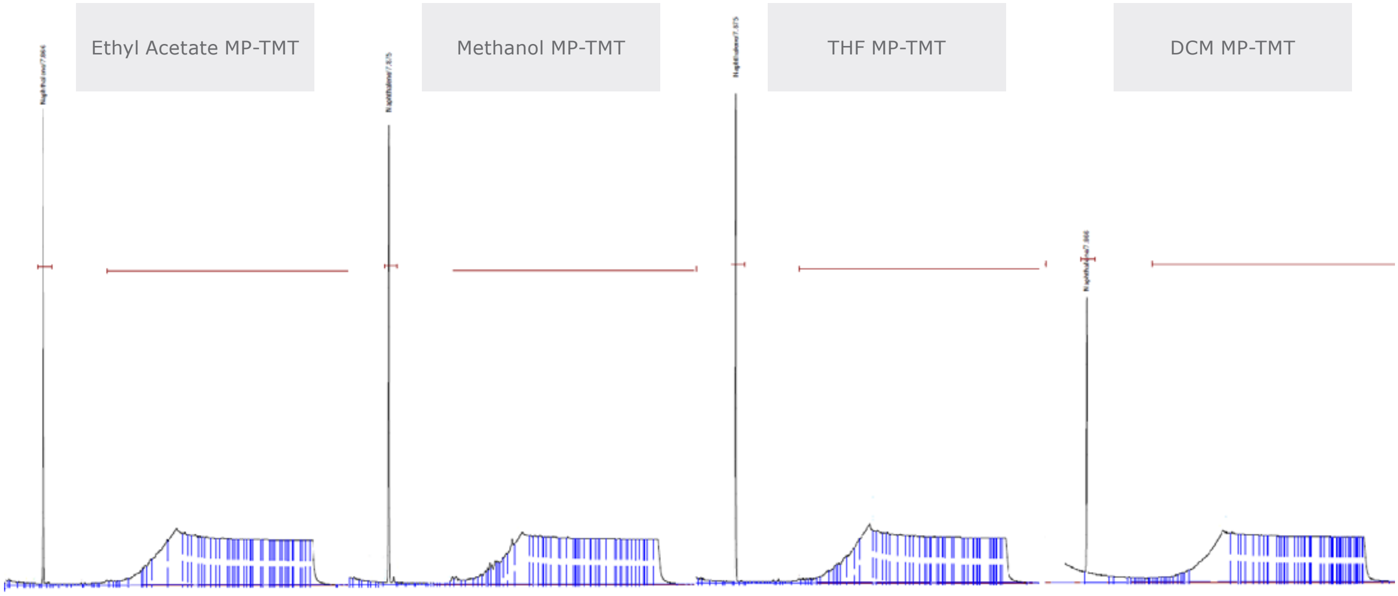


Figure 4. MP-TMT extraction by EtOAc, MeOH, THF and DCM

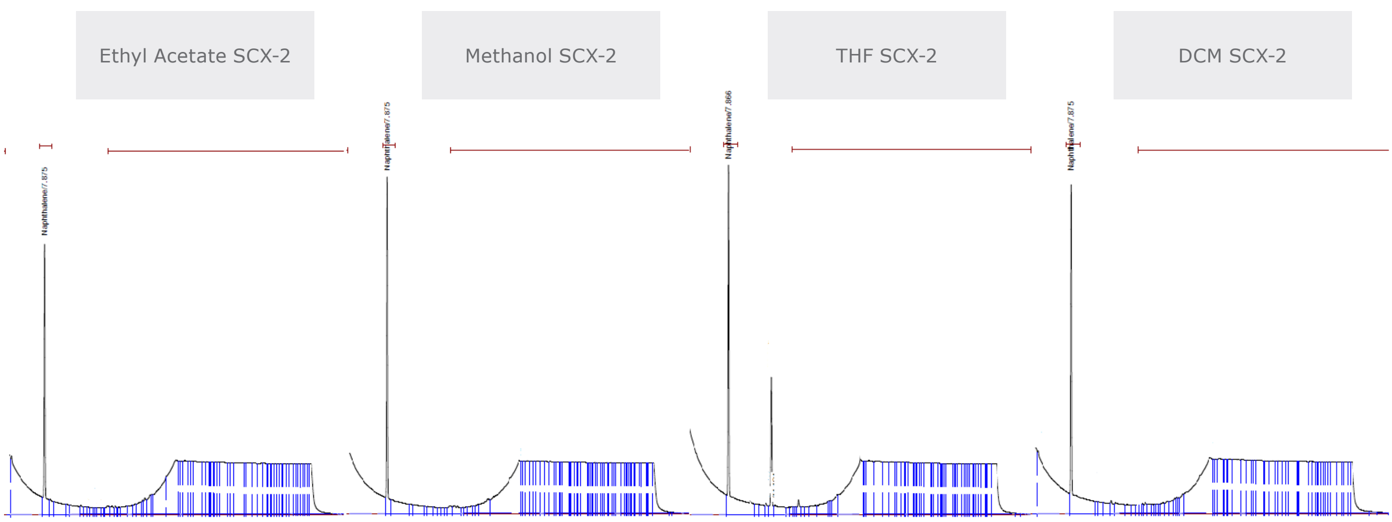


Figure 5. SCX-2 extraction by EtOAc, MeOH, THF and DCM

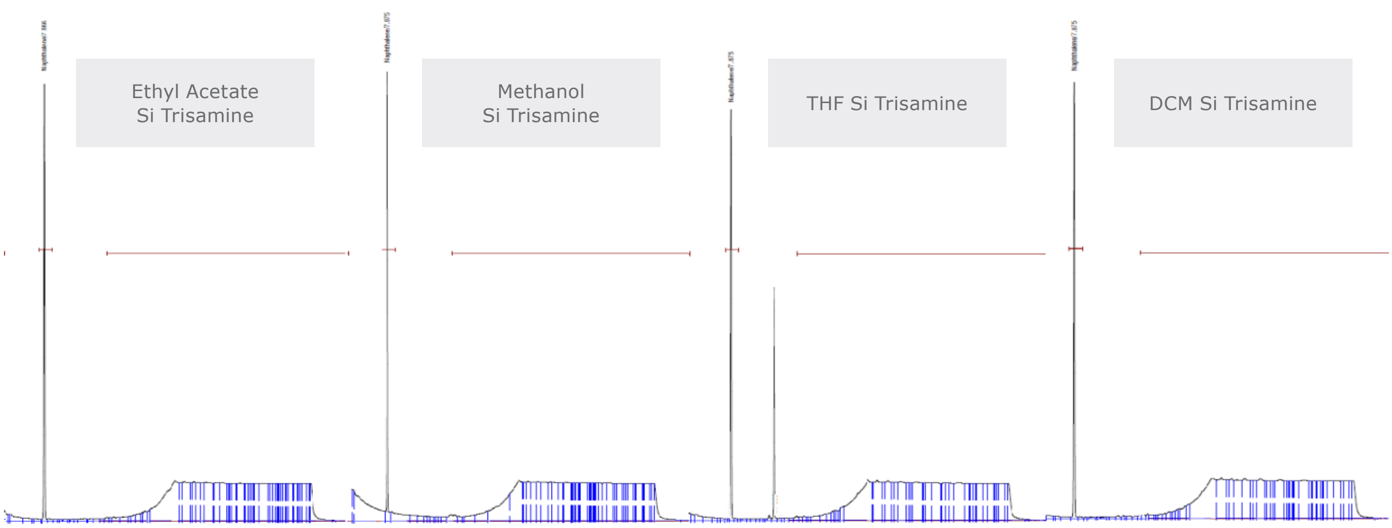


Figure 6. Si-Trisamine extraction by EtOAc, MeOH, THF and DCM

Are all Metal Scavengers the Same?

To investigate this, 0.5 g of various metal scavengers obtained commercially were extracted with 2 mL of DCM, ethyl acetate, methanol and THF. Each of the extractions was spiked with internal standard (naphthalene, 20 ppm). The results are shown below.

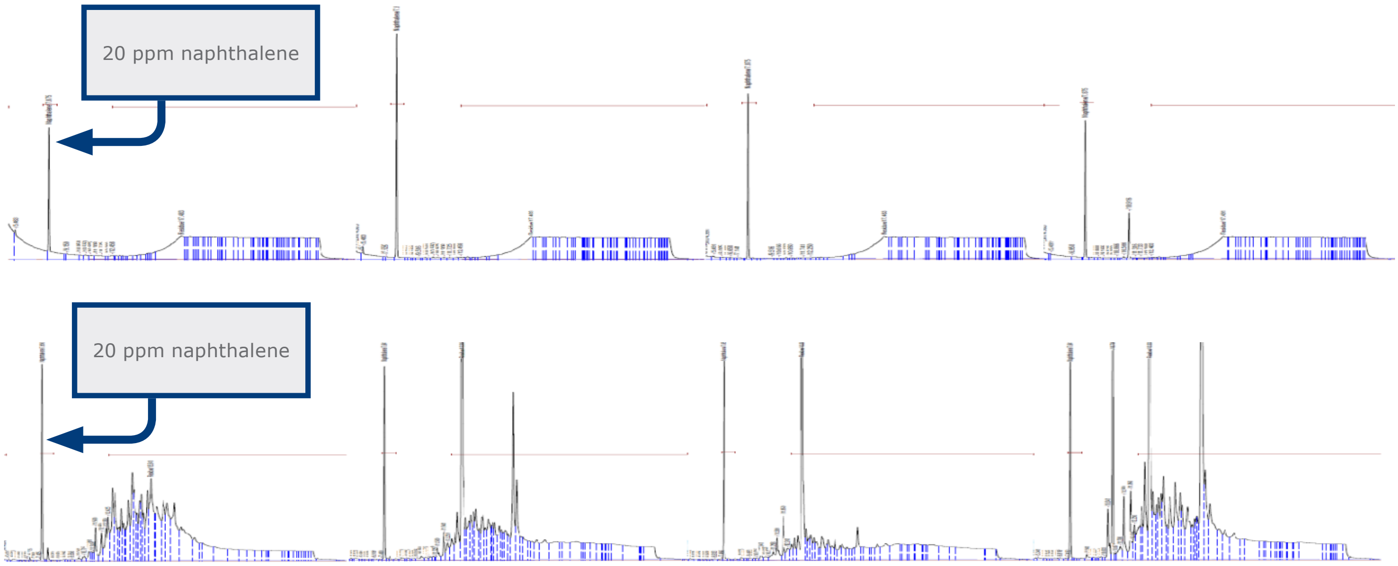


Figure 7. Biotage Si-Thiol vs Competitor 'S' or Competitor 'P'

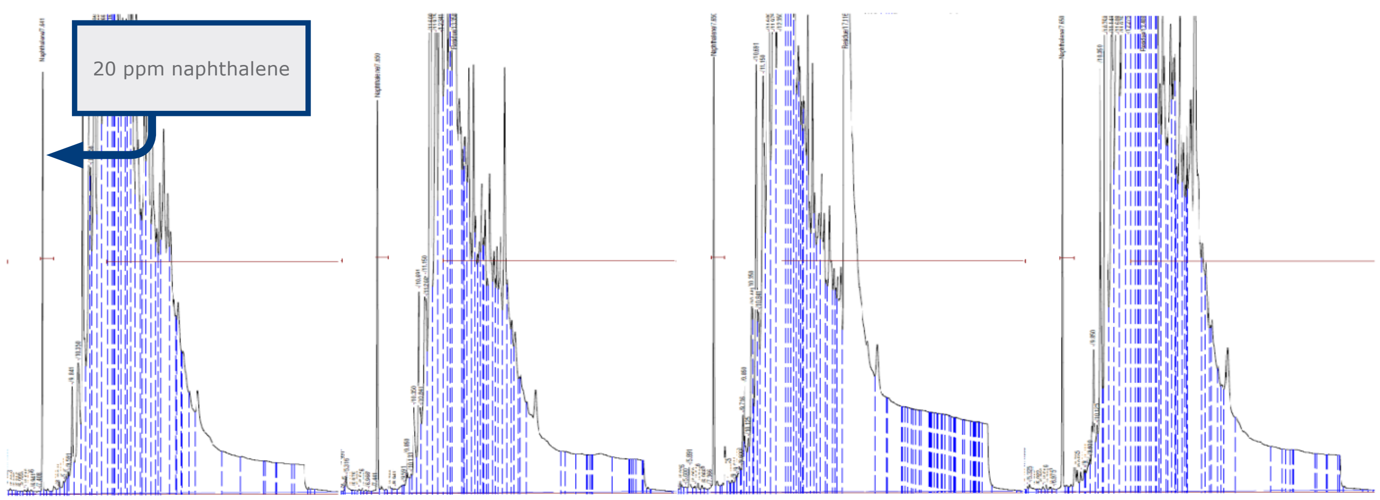


Figure 8. Competitor ‘P’ Si-Thiol

Results Part 3 – API Scavenging

Method

Ethyl acetate (29 mL), 2-methyl-5-phenylbenzoxazole (3 g, 14 mmol), dichlorobis (TPP) Pd II (500 ppm) as 1 mL THF) was stirred at room temperature for 16 hours with metal scavenger (300 mg, 0.1 mmol, 0.007–0.027 equiv. with respect to API analogue). The contents of the vials were filtered and dried. Isolated product was analyzed directly by GC and ICP methods without further purification.

Metal Scavengers Screened

Si-TMT, MP-TMT, Si-Thiol, SCX-2 and Si-Trisamine (example conditions: 10 weight % scavenger with respect to API stirred in a 10% wt./vol. solution).

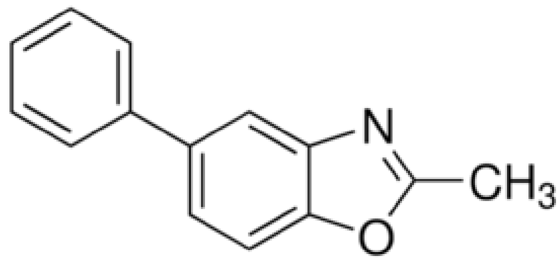


Figure 9. 2-methyl-5-phenylbenzoxazole ($C_{14}H_{11}NO$)MW 209.14

Metal Scavenger Treatment	Initial Pd	Final Pd
Si-TMT	500	BDL
MP-TMT	500	BDL
Si-Thiol	500	BDL
SCX-2	500	150*
Si-Trisamine	500	BDL

* Not a recommended scavenger for the API/Pd combination; results (as expected) were fair

Metal Scavenger Treatment	API (theory) wt%*				API (found) wt%*				Structure Confirmed?
	C	H	N	S	C	H	N	S	
Si-TMT	80.4	5.3	6.7	0	81.4	5.4	6.7	0	✓
MP-TMT	80.4	5.3	6.7	0	81.4	5.4	6.7	0	✓
Si-Thiol	80.4	5.3	6.7	0	81.0	5.4	6.6	0	✓
SCX-2	80.4	5.3	6.7	0	81.0	5.3	6.6	0	✓
Si-Trisamine	80.4	5.3	6.7	0	81.1	5.3	6.7	0	✓

*Remaining oxygen not measured

Mass Yield / Gravimetric Analysis

Metal Scavenger Treatment	Initial mass	Recovered mass /g*	% Recovery*
Si-TMT	3.0	3.08	100
MP-TMT	3.0	3.09	100
Si-Thiol	3.0	3.09	100
SCX-2	3.0	3.04	100
Si-Trisamine	3.0	3.04	100

*samples found to be slightly wet but following high vacuum, quantitative recovery was achieved

Table 2. Metal scavenger screening results.

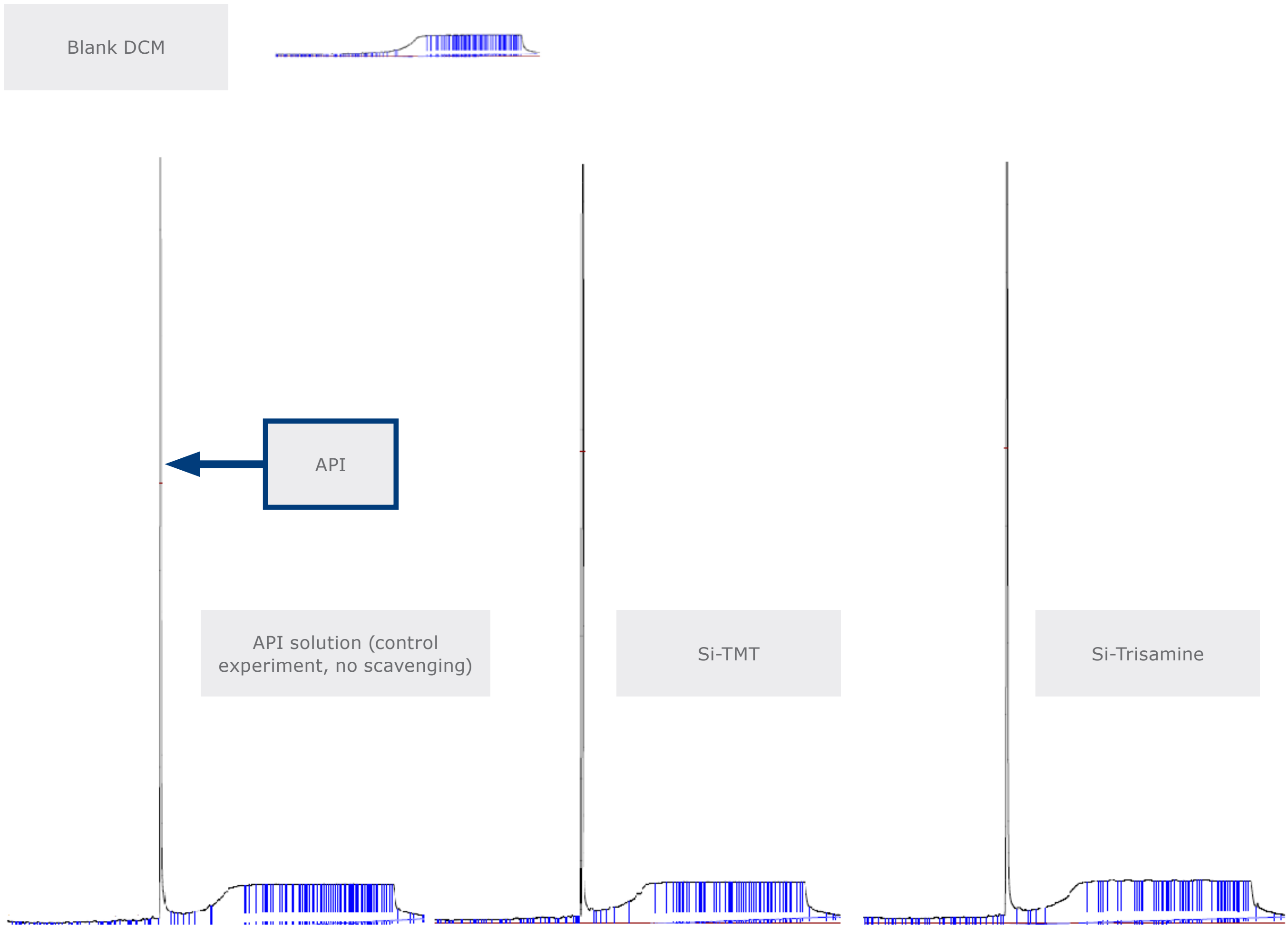


Figure 10. Representative GC Purity Assessment

All of the successful metal scavengers tested in this paper are available in an easy to use convenient scavenger kit (part number K-MS-2) which comes with full instructions for use and example case studies. For more information contact your local Biotage representative.

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