Novel Inhibitors to Modulate Post-Translational Modifications

Virginia Weber[†], Claudia Morren-Sewing^Φ, Max Derks^Φ, Freek Janssen^Φ

[†]Department of Chemistry, Washington & Jefferson College

60 S Lincoln St, Washington, PA 15301

^ΦRadboud University

Comeniuslaan 4 6525 HP Nijmegen, The Netherlands

Introduction

Post-translational modifications (PTMs) of proteins increases the diversity of the human proteome.⁴ Diversity is increased due to PTMs being chemical modifications that help regulate activity, localization, and interaction with other proteins.¹ These modifications either activate or inactivate catalytic activity.

Typical PTMs include phosphorylation, methylation, acetylation, ubiquitination, nitrosylation, glycosylation, and lipidation.³

For example, phosphorylation alters the structural conformation of a protein by introducing a covalently bound phosphate group to serine.⁴ However, a kinase inhibitor prevents phosphorylation from occurring.

The goal for COILED is to modulate post-translational modifications in the proteome with novel inhibitors. New compounds are then tested for effectiveness by a biological assay.

Inhibitor Core Synthesis Overview

Scheme 1: Synthetic route of inhibitor made up of core, linker, and substituents

Step	Reaction	Conditions
1	Buchwald-Hartwig Coupling	K ₂ CO ₃ (3 eq.), Pd ₂ (dba) ₃ (.01 eq.), RuPhos (.05 eq.), tert-butanol (solvent) – 110°C, 1.5 hr
2	Aryl Modification	Functional group modification
3,4	Derivatization	Derivative compounds synthesized
5	Suzuki Coupling	Boronic acid (1 eq.), K ₂ CO ₃ (1 eq.), Tetrakis (.05 eq.), DME (solvent), water (solvent) – 110°C, 1.5 hr

Key Mechanism: Suzuki Coupling²

Conclusions

- Synthesized three advanced intermediates
- Performed 16 successful Suzuki Couplings which resulted in 13 novel compounds
- Biological assay to be determined

References

1. Angel, T. E., Aryal, U. K., Hengel, S. M., Baker, E. S., Kelly, R. T., Robinson, E. W., & Smith, R. D. (2012). Mass Spectrometry-Based Proteomics: Existing Capabilities and Future Directions. *Chem. Soc. Rev.*, 43(31). doi:10.1002/chin.201231280
2. Hajipour, A. R., Karami, K., & Pirisedigh, A. (2011). Application of dimeric orthopalladated complex in Suzuki-Miyaura cross coupling reaction under microwave irradiation and conventional heating. *Inorganica Chimica Acta*, 370(1), 531-535. doi:10.1016/j.ica.2011.01.050
3. Rockland Antibodies and Assays. "Post-Translational Modification (PTM) Antibodies." Retrieved from <https://rockland-inc.com/post-translational-modification-antibodies.aspx>
4. Samanta, L., Swain, N., Ayaz, A., Venugopal, V., & Agarwal, A. (2016). Post-Translational Modifications in sperm Proteome: The Chemistry of Proteome diversifications in the Pathophysiology of male factor infertility. *Biochimica Et Biophysica Acta (BBA) - General Subjects*, 1860(7), 1450-1465. doi:10.1016/j.bbagen.2016.04.001

Results

		R ³ Substituents					
	A		Yield: 89.0%	Yield: 75.0%	Yield: 11.5%	Yield: 53.0%	Yield: 19.7%
	B		Yield: 53.0%	Yield: 90.4%	Yield: 63.3%	Yield: 16.4%	Yield: 41.6%
	C	Yield: 56.3%	Yield: 47.8%	FAILED	Yield: 79.5%		

Table 1: Results of various Suzuki Couplings with several core compounds

*Suzuki reactions were performed on a 30-50mg scale

*All final compounds had purity ≥ 90% by HPLC

Acknowledgments

Special thanks to Prof. Dr. Floris Rutjes of Radboud University and Jac Wijkmans of COILED for the opportunity to do research in the COILED laboratory. Also, thank you to all COILED members, specifically Dr. Freek Janssen, Claudia Morren-Sewing, and Max Derks for daily supervision and research guidance. This research was partially funded by the Washington & Jefferson College Magellan Kelso Award.

Radboud University