ACS Green Chemistry Institute
Pharmaceutical Roundtable

2019 ACS GCI Pharmaceutical Roundtable Research Grant for Greener Medicinal Chemistry

The ACS GCI Pharmaceutical Roundtable (GCIPR) is a partnership between the ACS Green Chemistry Institute® and pharmaceutical-related corporations united by a shared commitment to integrate the principles of green chemistry and engineering into the business of drug discovery and production. Current members are AbbVie, Amgen, AstraZeneca, Bayer, Biogen, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, Gilead, Genentech, GlaxoSmithKline, Ipsen, Johnson & Johnson, Merck & Co., Neurocrine Biosciences, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Takeda, Vertex, and the ACS Green Chemistry Institute. Associate members are Ampac Fine Chemicals, Asymchem, Codexis, Hikal, Pharmaron, and WuXi AppTec. Corteva is an affiliate member.

The ACS GCIPR is seeking a one-year R&D commitment to assist the Roundtable's medicinal chemistry initiative. The focus of the R&D will be toward the development of precious-metal free cross-coupling methodology applicable to substrates such as heterocycles that are widely used in the pharmaceutical industry. Proposals are invited from public and private institutions of higher education worldwide. This project is intended for a student within the selected Principal Investigator's research group. One grant is planned to be awarded, and the total award is limited to $50,000 for a grant period of 12 months. Note that this award will be exclusively for R&D; no portion of this grant will go to institutional overhead. Interested PI's are required to provide a written proposal describing the investigator's capability to carry out the Roundtable's proposed research. The deadline for receipt of proposals is **July 1, 2019 at 5 p.m. EDT.** GCIPR will notify the selected PI by **August 15, 2019.** It is expected that research will commence in the Principal Investigator's lab by October 2019 and last approximately 12 months.

Requirements for Submission

Proposals will be accepted from public and private institutions of higher education. The grant is not limited to institutions in the United States. Proposals must be submitted through the appropriate institutional office for external funding. For international submissions, if there is no comparable office, submit a pdf of a letter signed by an appropriate university official recognizing the terms of the grant.

Detailed Project Description

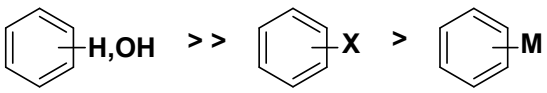
Cross-coupling reactions are foundational tools for the construction of complex pharmaceutical agents. The ability to construct new C–C, C–N, and C–O bonds in a predictable and reliable fashion is critical to our ability to invent novel therapeutics. As such, the 2010 Nobel Prize in Chemistry was awarded "for palladium-catalyzed cross couplings in organic synthesis." While powerful, cross-coupling reactions most commonly require precious transition metals as catalysts. Because of the widespread use of cross-couplings, a focused effort on inventing environmentally friendly variants would be an effective way of significantly decreasing our carbon footprint within the pharmaceutical industry and contributing to long-term global sustainability.

The purpose of this grant is to encourage the development of cross-coupling reactions that do not require precious transition metal catalysts. We delineate below several considerations in proposals submitted to achieving this goal.

- Catalyst: In its most practiced form, cross-coupling reactions require palladium. Greener alternatives should be explored, which may include metal-free couplings or alternately couplings that feature earth-abundant metals (e.g., iron, copper, nickel).

- Type of bond construction: One of the most convenient features of cross-coupling reactions is the broad types of bond constructions that are possible, mostly using ligand-supported palladium catalysts and (hetero)aromatic halides as building blocks. Reactions capable of building C–C, C–N, C–O, and C–X bonds are thus of tremendous value. In recent years, increasingly green cross-couplings have largely been focused on C–C bond construction, with less emphasis on the very industrially relevant C–N and C–O bond constructions. The formation of C–F bonds is also of strategic importance to the medicinal chemist. Hence, proposals which address the breadth of reactivity will be prioritized over ones which will examine a limited set of reaction types.

- Substrates: Heterocycles are ubiquitous in drug discovery. We therefore urge applicants to consider solutions to the cross-coupling problems that may accommodate a plethora of functional groups, including a variety of nitrogen-rich heterocycles featuring unprotected N–H bonds. As another consideration, various (hetero)aromatic halides or (hetero)aromatic metals are available in varying quantities in terms of their commercial availability, with starting materials containing only C–H bonds or other ubiquitous functional groups (e.g., phenols) being attractive starting materials. Noteworthy halide surrogates, such as tosylates, triflates, acetates, and nitriles, should also be considered as potential substrates. Increasingly, accessing reactivity with these types of substrates would be an advantage; however, the use of more sustainable starting materials should not come at the cost of harsh reaction conditions or expensive and non-renewable reagents.



[Cl > Br, OTs >> I]

- Conditions: Since the initial invention of metal-catalyzed cross-coupling reactions, significant effort has been made to improve efficiency (lower catalyst loadings, optimal reactant stoichiometry) with increasingly mild conditions (rt is ideal, but elevated temperature is advantageous over cryogenic conditions). To this end, new sustainable cross-couplings should aim to be mild by nature so as to maximize functional group compatibility. Extremely high temperatures should be avoided and should not be considered a reasonable trade-off for using more 'ideal' starting materials.

- Solvent: Traditionally employed solvents include dioxane, NMP, DMF, or toluene most commonly. Greener alternatives should, at the very least, be explored. For more information on green solvents, please see the Roundtable's solvent selection tool: https://www.acsgcipr.org/tools-for-innovation-in-chemistry/solvent-tool

- Additives/oxidants/reductants: Many modern couplings, particularly those featuring C–H activation, employ stoichiometric silver or copper salts as terminal oxidants. We reiterate the fact that more sustainable starting materials should not be considered at the expense of these types of reagents. We also specifically mention that the use of O_2 atmosphere, while green in principle, may lead to potentially dangerous reaction situations. Additionally, we discourage the use of high-energy functionality or high-hazard reagents (e.g., GHS Category 1 flammables, pyrophorics, and oxidizers).

- Technologies: Another optional area for considering novel cross-coupling methods is the inclusion of new techniques which may act as surrogates for high temperature or harsh reaction conditions. For instance, the recent interest around the field in photoredox catalysis has allowed the use of light as an energy source. Coupled with advances in flow chemistry, new reactions of these types may offer many advantages to existing methods. Likewise, the use of electricity as a source of energy (i.e., electrochemistry) has potential to impact the field broadly.

Project Goal

Development of cross-coupling conditions circumventing the need for precious metals that are broadly applicable to a wide variety of substrates that are commonly encountered in medicinal chemistry.

Project Timeline

It is anticipated that one year of research support will be sufficient to provide progress toward intended goals.

Proposal Format (Maximum 3 pages as described below + CVs)

All of the information below must be submitted as a single PDF file. All components described in sections A, B, and C must be included in the same PDF file to assure the proposal is reviewed in its entirety.

A) Title Page (1 page, 12 pt font, 1-inch margins)
1. Project Title:
2. Principal Investigator:
3. Title / Position(s):
4. Telephone Number(s):
5. Fax Number(s):
6. Postal Mailing Address:
7. Email Address:
8. Research Group website:

B) Proposed Plan of Work *(2 pages, 12 pt font, 1-inch margins)*
1. Summarize the student's (undergraduate, graduate student and /or postdoc) capabilities to perform the Roundtable's proposed work.
2. Brief description of the PI's research facilities.
3. Proposed milestone deliveries (primary project and side project) with brief description of the manner in which the researcher intends to achieve them.

4. The PI should list any existing background intellectual property and/or collaborations they are aware of that might limit the freedom to operate any of the results arising from any research funded by ACS GCIPR. The priority of the Roundtable is to encourage research utilizing reaction conditions that are commercially available with the freedom to use.
5. References (does not count toward your page limit).

C) Curriculum Vitae of Project Team Members: Please submit a curriculum vitae of each project team member (two pages per team member). Note that this does not count toward your page limit.

Report Requirements

- Progress reports are due at one-month intervals from initiation of research and discussed in arranged monthly teleconferences.
- Reports are to include research milestones/significant outcomes, summary of progress to date noting any deviations from the proposal, and research plans for upcoming months.
- A final comprehensive report is due one month after the end of the grant period.
- Reports must be submitted as a PDF document electronically to gcipr@acs.org. Reports will be shared with the member companies of the Roundtable. In addition, the content of the report will be targeted for publication in a peer-reviewed technical journal. The paper will be co-authored by the principal investigator and student (s) performing the work with the guidance of member companies of the ACS GCIPR.

Intellectual Property, Publication Acknowledgement, and Terms of the Grant

- The primary purpose of this grant is the public dissemination of research through publication.
- Every patent, United States or foreign, that results from research funded (in part or in its entirety) by the ACS GCIPR Research Grant shall be immediately dedicated to the public, royalty free.
- Publication of results is expected within 6 months of work completion.
- Each publication prepared in connection with the ACS GCIPR Research Grant shall make acknowledgement in the following manner: "This manuscript was developed with the support of the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (https://www.acsgcipr.org). The ACS GCI is a not-for-profit organization whose mission is to catalyze and enable the implementation of green and sustainable chemistry and engineering throughout the global chemistry enterprise and across the Society. The ACS GCI Pharmaceutical Roundtable is composed of pharmaceutical and biotechnology companies and was established to encourage innovation while catalyzing the integration of green chemistry and green engineering in the pharmaceutical industry. The activities of the Roundtable reflect its members' shared belief that the pursuit of green chemistry and engineering is imperative for business and environmental sustainability."
- Acceptance of a Roundtable Grant will be conditioned upon agreement by the grantee institution that in the event the Principal Investigator is unable for any reason to conduct the research proposed, the funds, if previously paid by the Roundtable, shall, upon demand, be returned in full to the Roundtable, and further, that in the event the PI is unable for any reason to continue with the research after it has commenced, this grant shall be terminated forthwith and the unexpended and unencumbered balance of any funds theretofore advanced shall be returned to the Roundtable.

- The grantee institution, by acceptance of this grant, provides assurance that support normally provided by the institution for research of the faculty member will not be diminished.
- Applicants may have only one research grant with the ACS GCIPR at a time. In order to close a grant, the ACS GCIPR must receive and approve the required reports.

For additional information:
Website: www.acsgcipr.org
Email: gcipr@acs.org