2022 ACS GCI Pharmaceutical Roundtable Research Grant for the Selective Reduction of Aromatic Rings in Advanced Scaffolds

The ACS Green Chemistry Institute 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, Biohaven Pharmaceuticals, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, F. Hoffmann-La Roche Ltd., Gilead, GlaxoSmithKline, Ipsen, Johnson & Johnson, Merck & Co., Neurocrine, Novartis, Novo Nordisk, Pfizer, Takeda, UCB Pharma, Vertex, and the ACS Green Chemistry Institute. Associate members are Ampac Fine Chemicals, Asymchem, Bachem, CatSci, Codexis, Hikal, Hovione, InnoSyn, Kaneka, Novasep, Pharmaron, Polypeptide, Porton, Sai Life Sciences, Solara Active Pharma Sciences Ltd., and WuXi AppTec. Corteva Agriscience, EnzyTag, and PHT International Inc. are affiliate members.

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 overcoming practical challenges associated with the selective reduction of aromatic rings in advanced scaffolds. 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. Interested PIs 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 **May 15, 2022 at 5 p.m. EDT**. Proposals must be received by the deadline to be considered. Submissions must be a single PDF file submitted to gcipr@acs.org. GCIPR will notify the selected PI by **September 6, 2022**. It is expected that research will commence in the Principal Investigator's lab no later than **October 3, 2022** 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

It is becoming more apparent based on perspective analyses of drug discovery programs that increasing the three-dimensional character of lead molecules is linked with a higher probability of clinical success. From a logistical standpoint, this is understandable when one considers that such compounds are intended to interact with a protein, which is three-dimensional and as such matching the shape of the inhibitor to fit the target should enhance potency. In addition, increased saturation has been linked with both improved solubility and lipophilicity. Despite this, over the past 20 years, the emergence of robust

cross-coupling methods to forge sp^2-sp^2 linkages lead to high percentages of "flat" molecules in development. However, this can be exploited as saturation of (hetero)aryl rings presents an opportunity to introduce 3-D character efficiently without a significant increase in MW. While the classical approaches to the saturation (either full or partial) of aromatic rings are well established including high pressure hydrogenation and the Birch reduction, these generally are limited in scope and are not appropriate for the reduction of densely-functionalized drug-like molecules as employ forcing conditions and/or harsh reagents leading to either decomposition or a lack of selectivity.

The purpose of this RFP is to encourage the development of operationally simple methodologies that proceed under mild conditions for the selective reduction of (hetero)aromatic rings applicable to pharmaceutically relevant substrates. Such approaches should be broad in scope and be either catalytic or stoichiometric utilizing sustainable reagents/solvents. Enabling technologies to accomplish this goal including electrochemistry, photoredox catalysis, flow chemistry, or biocatalysis are within scope for proposals submitted to accomplish this goal.

Key Considerations:

- Substrates: One key gap in today's synthetic chemistries is the lack of mild, robust reactions for the selective reduction of (hetero)aromatic rings in complex bioactive compounds. Heterocycles and aryl rings are ubiquitous in drug discovery with a reliance on cross-coupling methodologies leading to the facile incorporation of such fragments into candidate molecules. A variety of nitrogen-rich heterocycles (including those containing unprotected N–H and O–H bonds) are expected to be an important emphasis in proposals. In the substrates of interest themselves, methodologies that highlight selective reduction of a specific (hetero)aromatic moiety (particularly those prevalent in medicinal chemistry, for example, benzene, pyridines etc) with good functional group tolerance are of strategic importance. The ability to employ novel methodologies in a parallel-based fashion (library) or optimize/tune through High Throughput Experimentation (HTE) are also worthy of consideration.

- Chemoselectivity: The formation of sp^2-sp^2 linkages through mainly cross-coupling methodologies is well established and lead to molecules of interest being essentially flat while possessing multiple (hetero)aromatic rings. Thus, focusing on aspects of chemoselectivity are of key interest the proposal as in identifying methods to reduce a specific (hetero)aromatic ring exploiting differences in nature (aromatic vs heterocyclic) or electronic properties. In addition, methodologies designed for the precise, partial reduction of aromatic rings are also considered to be within scope as lead to potential reactive sites for further elaboration of the molecule.

- Control of stereoselectivity: Given that not only is the presence of 3D-rich architectures but also the absolute orientation of substituents from the molecule important in lead optimization, a focus on control of diastereoselectivity should be considered. In particular, methodologies that enable a "modular" control of stereochemistry (both diastereoselective and enantioselective) would bring significant value to the industry.

- Catalysis or stoichiometric: Existing methods to perform (hetero)aromatic reductions are often limited in scope and are typically not applicable to pharmaceutical agents. In one instance, catalytic strategies do not typically perform well in complex settings as typically utilize not only precious metal catalysis but also involve high temperatures and pressures. On the other hand, stoichiometric approaches such as the Birch partial reduction while powerful are limited in scope and somewhat unsustainable typically using sodium in liquid ammonia. In this RFP, applicants are encouraged to consider either approach. That is, can we develop milder catalytic strategies with broad applicability through novel catalyst design based on non-precious metals? Or alternately, can general stoichiometric approaches be rendered more green using sustainable metals and/or reagents?

- Technologies: To overcome the intrinsic challenges of selective (hetero)aromatic reductions, the strategic inclusion of new technologies may be an important avenue to examine. Given that most pharmaceutical agents are complex, containing chiral centers and multiple functionalities, high temperatures/pressures and harsh additives are typically incompatible. We therefore encourage applicants to consider electrochemistry, photoredox catalysis, flow chemistry, or biocatalysis as enabling.

- Solvents, additives, catalysts, conditions: Traditional approaches to aromatic reductions are typically carried out under forcing conditions and generally involve catalysts and additives that do not necessarily align with the twelve principles of green chemistry. (https://www.acs.org/content/acs/en/greenchemistry/principles/12-principles-of-green-chemistry.html). For instance, many aromatic reductions utilize precious metal catalysis and involve stoichiometric quantities of strong acids as an additive while high pressures and temperatures are also often employed. Use of green solvents and reagents should be explored in attempt to remove reliance on unsustainable compounds such as precious metals. For more information, please see the Roundtable's "Solvent Selection" and "Reagent Guide" tools (www.acsgcipr.org/tools-for-innovation-in-chemistry/).

- Scale-up: Ability to perform in a standard medicinal chemistry laboratory, broad reactivity scope and selectivity are the key objectives of this RFP, but demonstrations of possible scale-up to multi-gram scales would be an important future direction to consider. In medicinal chemistry, enabling pre-clinical evaluation is an important area of focus, and establishing line-of-sight to larger scales (kilograms) often informs on considerations down the road of development (for example, life cycle and cost-of-goods analyses).

Project Goal

To develop new and broadly applicable methods to achieve the selective reduction of (hetero)aromatic rings in advanced scaffolds employing sustainable catalysts and reagents.

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. Objectives: Briefly state the project objectives
2. Project Approach: Include specific aims and investigations planned
3. Proposed milestone deliveries with brief description of the manner in which the researcher intends to achieve them
4. Brief description of the PI's research facilities and summary of the student's (undergraduate, graduate student and /or postdoc) capabilities to perform the proposed work
5. References (does not count toward your page limit)

Note: 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.

C) Detailed Estimated Budget: The total amount requested would include all direct costs, student assistantships, etc. The total award is limited to $50,000 for a grant period of up to 12 months. This does not count toward your page limit.

1. Institutional overhead costs (indirect costs) should not be more than 10% of the total budget.
2. Post-doctoral associate salary and benefits are supported.
3. Student stipend and benefits are supported. Proposals for support of advanced graduate students are highly favored.
4. PI salary supplements will not be supported.
5. Laboratory supplies and instrument use charges are supported.

6. No funds may be allocated for travel, equipment purchase or repair, or administrative support.

D) Curriculum Vitae of Project Team Members: Please submit a curriculum vitae of each project team member (up to two pages per team member). This does not count toward your page limit.

Report Requirements

- Progress reports or updates are due monthly or bi-monthly from initiation of research and will be discussed in arranged web-conferences. Reports will be shared with the member companies of the Roundtable.
- 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. This report must be submitted as a PDF document electronically to gcipr@acs.org. In addition, the content of the report should 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 (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 throughout the global chemistry enterprise. The ACS GCI Pharmaceutical Roundtable, composed of pharmaceutical and related industries, was established in 2005 to encourage innovation while catalyzing the integration of green chemistry and green engineering in the pharmaceutical industry. The activities of the Roundtable reflect its member's shared belief that the pursuit of green chemistry and engineering is imperative for business and environmental sustainability.

- Acceptance of a Roundtable Grant will be conditional 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