



2013 ACS GCI Pharmaceutical Roundtable Research Grant for Greener Solvent Research

The ACS GCI Pharmaceutical Roundtable (Roundtable) 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 include Amgen, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Codexis, Dr. Reddy's, DSM Pharmaceutical Products, Eli Lilly and Company, GlaxoSmithKline, Johnson & Johnson, Merck & Co., Inc., Novartis, Pfizer Inc, Roche, Sanofi, and ACS GCI.

The ACS GCI Pharmaceutical Roundtable is seeking a 1 year R&D commitment to assist the Roundtable's greener solvents initiative. The R&D will be focused toward developing greener solvent(s) as potential replacements for polar aprotic solvents such as DMF, NMP and DMAc. These solvents are widely used in industry, but pose significant reproductive health hazards. The new solvent(s) should be successfully evaluated in chemistries which are important to the pharmaceutical industry such as, but not limited to, nucleophilic aromatic substitution chemistry. Proposals are invited from public and private institutions of higher education worldwide. One grant is planned to be awarded to a research group and the total award is limited to \$100,000 for a grant period of 12 months. Interested Principal Investigators are required to provide a written proposal describing the investigator's capability to carry out the Roundtable's proposed research. The proposal should include specific details of the solvent of interest and plans for a comparative performance analysis relative to DMF, NMP and DMAc. Deadline for receipt of proposals is **January 15, 2013 at 5 pm EDT**. All submissions must be emailed to gcipr@acs.org. The Principal Investigator with the selected proposal will be notified by **April 15, 2013**. It is expected that the research will commence in the principal investigator's lab by **July 2013** and last approximately 12 months.

Requirements for Submission

Proposals will only be accepted from public and private institutions of higher education. The grant is not limited to institutions in the United States; proposals are accepted from institutions worldwide. All proposals must be submitted by email to gcipr@acs.org 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

Polar aprotic solvents such as DMF, NMP and DMAc are widely used in the pharmaceutical industry and due to their powerful solvating properties, organic reactions occur which often cannot be achieved in less polar solvents. Frequently, these polar aprotic solvents are important for both solubilization of reactants and desired product. A significant drawback though is often the large quantity of aqueous extractions needed to remove these polar aprotic solvents from processes. This can result in high process mass intensity and substantial wastewater contamination. However, the main disadvantage is

that DMF, NMP and DMAc are known reproductive hazards. It is possible that over the next few years, REACH and other legislation could make the use of DMF, DMAc and NMP difficult or impossible to use in developed nations. Consequently, a strategic priority for the Pharmaceutical Roundtable is the development of pharmaceutically acceptable replacement solvent(s) for DMF, NMP and DMAc which would not pose health hazards or issues associated with waste generation and disposal.

The parameters considered important to achieving the Pharmaceutical Roundtable goals are:

- Widespread utility: the new solvent(s) should perform comparable or better in pharmaceutically important reactions where DMF, NMP and DMAc presently operate.
- A justification needs to be provided why the proposed new solvent (s) would provide human health benefits relative to DMF, NMP and DMAc. This could include toxicological modeling data.
- If not commercially available in <\$20 /kg bulk, a green synthesis for the new solvent must be supplied which can deliver the target solvent in >99% purity and can be readily produced on a multi kilogram scale. Ideally, the alternative solvent(s) are obtained from renewable source(s).
- If the proposed solvent(s) are commercially available, details of availability, material specifications and synthesis must be provided.
- Potential replacement solvents which the Pharmaceutical Roundtable recommends for comparative analysis, but not limited to, are *N*-formyl morpholine (CAS # 4394-85-8), propylene carbonate (CAS# 108-32-7), and dimethylisoxorbide (CAS# 5306-85-4). Proposals which expand the minimum stated scope will receive priority.
- Out of scope solvents: DMSO, acetonitrile.
- Simplification of work-up / purification methods: The proposed new solvent(s) and the Pharmaceutical Roundtable solvents of interest (*N*-formyl morpholine, propylene carbonate and dimethylisoxorbide) should be exemplified in reactions on a minimum 10 g scale with a process mass intensity of NMT 20.
- An example target compound synthesis is provided which should be evaluated with the new solvent (s):
Toczko, J. F.; Kim, A.; Powers, J. D. *J. Org. Chem.* **2006**, 71, 2170. Synthesis of compound 10.
See Appendix 1 for further details.

Reactions of Interest :

- Highest priority: Nucleophilic Aromatic Substitution (SNAr)
- Other Priorities: Ligandless Heck and Sonogashira reactions; Copper catalyzed CN coupling and POCl₃ reactions

Project Timeline

It is expected that one year of research support will be sufficient to provide progress toward intended goals and establish feasibility.

Proposal Format (Maximum 10 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. E-Mail Address:
8. Research Group website:

B) Proposed Plan of Work (*9 page limit, 12 pt font, 1-inch margins*)

1. Describe DMF, DMAc and NMP replacement solvent(s) including justification for the selection. Proposals which expand the proposed solvents and reaction class are encouraged.
2. Summarize the student's (undergraduate, graduate student and /or postdoc) capabilities to perform the Roundtable's proposed work.
3. Brief description of the PI's research facilities.
4. Proposed milestone deliveries (primary project and side project) with brief description of the manner in which the researcher intends to achieve them.
5. 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 GCI. The priority of the Roundtable is to encourage research utilizing reaction conditions that are commercially available with the freedom to use.
6. References (Does not count toward your page limit.)

C) Curriculum Vitae of Project Team Members: Please submit a two page curriculum vitae of all project team members. (Does not count toward your page limit.)

Report Requirements

- As a collaborative research project, the Roundtable will work closely with the principal investigator and student(s) to provide industrial direction, when appropriate, in a manner that respects the independence of the researcher/student.
 - Progress updates are due at 1 month intervals from initiation of research and discussed in arranged teleconferences.

- Updates 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 including research outcomes and final budget is due one month after the end of the grant period.
 - The report must be submitted as an Adobe PDF document electronically to gcipr@acs.org. The report will be shared with the member companies of the Roundtable.
 - The content of the report will be targeted for publication in a peer review technical journal within six months of the conclusion of the research. As a collaborative research project, the paper will be written by the principal investigator and student(s) performing the work, with members of the Pharmaceutical Roundtable as co-authors.

Intellectual Property, Publication Acknowledgement, and Terms of the Grant

- The primary purpose of this grant is to publish research to make information publicly available.
- Every patent, United States or foreign, that results from research funded (in part or in its entirety) by the ACS GCI Pharmaceutical Roundtable 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 GCI Pharmaceutical Roundtable Grant shall make acknowledgement to the ACS GCI Pharmaceutical Roundtable Research Grant, in the following manner. “Acknowledgement is made to the ACS GCI Pharmaceutical Roundtable Grant for support (or partial support) of this research.”
- 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 GCI Pharmaceutical Roundtable at a time. In order to close a grant, the required reports must be received and approved by the ACS GCI Pharmaceutical Roundtable.

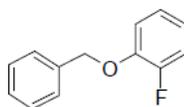
For additional information:

Website: www.acs.org/gcipharroundtable

Email: gcipr@acs.org

Appendix 1

Toczko, J. F.; Kim, A.; Powers, J. D. *J. Org. Chem.* **2006**, *71*, 2170.



2-Fluorophenyl phenylmethyl ether (10). To a solution of KOtBu (2.46 g, 21.9 mmol) and toluene (5 mL), benzyl alcohol (2.8 mL, 27 mmol) was slowly added, followed by DMPU (2 mL). The solution was heated at 80 °C for 30 min. 1,2-Difluorobenzene (**8**, 0.86 mL, 8.8 mmol) was then added and the solution heated for an additional 3 hrs at 80 °C. The reaction mixture was cooled to rt, and washed with water, 10% brine (x 2), dried and concentrated. The resulting oil was purified by flash chromatography (3% EtOAc in hexanes) to produce 1.36 g (77%) of **10** as white crystals mp, 35 °C.⁴

¹H NMR δ 5.14 (s, 2H), 6.86-7.12 (m, 4H), 7.29-7.46 (m, 5H). ¹³C NMR δ 70.1, 115.5, 116.0 (d, *J* = 19 Hz), 121.2 (d, *J* = 7 Hz), 124.7 (d, *J* = 10 Hz), 127.8, 128.0, 128.5, 136.6, 146.2 (d, *J* = 10.7 Hz), 151.9 (d, *J* = 243 Hz). IR 1015, 1106, 1202, 1254, 1280, 1502, 1589, 1613, 2867, 2915, 2924, 3032, 3036, 3078, 3088 cm⁻¹. Analysis calculated for C₁₃H₁₁OF: C, 77.21; H, 5.48. Found: C, 77.18; H, 5.47.