opnMe by Boehringer Ingelheim

opn2EXPERTS – High-throughput mechanochemistry to reduce chemical waste

Applying high-throughput experimentation (HTE), how would you propose to screen and optimize chemical reactions under controlled mechanochemical conditions to avoid using dipolar aprotic solvents?

Answers to this question including a proposal for collaboration can only be considered if they arrive no later than April 18, 2023, 11:59 pm PST.

Have a chance to win up to USD 80,000 when your submission has been selected.

Boehringer Ingelheim

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What is the context of the problem that we would like to solve?

Solvents account for more than 50% (ca. 90% considering water) of the total mass used in the synthesis of active pharmaceutical ingredients (APIs). Dipolar aprotic solvents (such as DMSO, DMF, etc) are a unique class of solvents which are often key for the success of several chemical transformations because of their remarkable polarities and solubilities. However, they have many undesirable characteristics including high toxicity, low stability, and low recoverability because of their high boiling point and high-water miscibility.

A reduction of their use is therefore highly desirable from a health, safety, economic, and ecological point of view. Finding safer and greener alternatives to dipolar aprotic solvents would allow us to access large process spaces for common reaction classes under more sustainable conditions.

Applying mechanochemistry to chemical reactions may represent an effective approach to increase sustainability. Mechanochemistry may increase reaction rates by applying mechanical energy. Interestingly, it typically operates under solvent-free conditions thus reducing chemical waste.

Notably, when applied to reactions usually needing dipolar aprotic solvents, such as nucleophilic aromatic substitutions[1], mechanochemistry has the key potential to reduce the use of this problematic solvent class during both initial screenings and optimization phases, using e.g., high-throughput experimentation (HTE) approaches, and later on during scale up (using e.g. extruders).

High-throughput experimentation (HTE) maximizes experimental efficiency by increasing the number of experiments per time unit while minimizing material consumption. HTE has been increasingly used to optimize experimental conditions in a number of fields, but its applications to mechanochemistry is currently missing[2].

We are looking for solutions that can help to reduce the use of dipolar aprotic solvents by being able to screen in parallel several mechanochemical conditions using HTE. In particular, we would like to evaluate the use of different HTE platforms for mechanochemical screening in microtiter plates in standard SLAS (Society for Laboratory Automation and Screening) format.

For this call, we seek proposals for high-throughput mechanochemistry platform(/s), whose readouts have been validated through an established technology such as low-throughput ball mill reactors.

In addition, if the proposal also includes the aspect of testing the applicability of the newly designed platform for the screening and optimization of more complex reaction classes typically using dipolar aprotic solvents (such as cross-couplings), it would be an added advantage.

Depending on the success of the project, we would like to expand on the transferability of the screening and optimization results to scale up platforms[3].

The challenge has been released as part of the Boehringer Ingelheim's Innovation Unit (IU) More Green Grants program, whose intent is to minimize the environmental footprint of future medicines through sustainable science, technology, and innovation. Founded in 1885 and family-owned ever since, Boehringer Ingelheim takes a long-term perspective. Its commitment to contribute towards a healthier and more sustainable future is firmly anchored in our corporate philosophy since its founding. Hence our question:

Applying high-throughput experimentation (HTE), how would you propose to screen and optimize chemical reactions under controlled mechanochemical conditions?

What potential solutions could be in scope?

- Our main objective is to find validated technological solutions that allow us to screen simple reactions (such as nucleophilic aromatic substitution reactions) under temperature controlled mechanochemical conditions in standard microtiter plates.
- An upside would be to test the applicability of the newly designed platform for the screening and optimization of more complex reaction classes typically using dipolar aprotic solvents (such as cross-couplings).
- An additional upside would be if the proposal could also demonstrate scalability of the screening results using large-scale mechanochemical reactors.

What potential solutions would be out of scope?

- Proposals not including the usage of standard microtiter plates
- Proposals not addressing controlled temperature conditions
- Proposals focusing only on process scalability using extruders

What benefits do we offer to you in exchange for having submitted a solution?

If your project is selected, you will have the opportunity to directly collaborate with the IU Sustainability team of the Chemical Development Department located in Biberach, Germany, and you gain exclusive access to BI expertise and know-how.

You can expect appropriate funding for the intended 12-month collaboration period. Your exact funding request should be outlined in your proposal. As a framework, we suggest that your initial funding request is structured by milestones and does not exceed USD 80,000 (including all direct, indirect, overhead costs, as required)

The opportunity for a funded stay at Boehringer Ingelheim for technology exchange / training is potentially available.

Our collaboration agreement will provide full transparency about each partner's rights & obligations (including intellectual property rights). If selected, all results and all IP generated by you during the project will be jointly owned by your institute and Boehringer Ingelheim. A final comprehensive report is due one month after the end of the grant period. As part of the agreement, you will be encouraged to publish your results in a peer-reviewed technical journal within 6 months after conclusion of the work. Each publication prepared in connection with the IU More Green Grant shall make acknowledgement in the following manner: "This manuscript was developed with the support of Boehringer Ingelheim's IU More Green Grant program, whose intent is to minimize the environmental footprint of future medicines through sustainable science, technology and innovation."In order to contribute to the advancement of science for the benefit of the public and to allow the scientific community and industry to use any results following joint publication, we propose that both parties should agree to abstain from pursuing exclusive intellectual property protection with respect to any results.

Boehringer Ingelheim is a leading research-driven biopharmaceutical company that creates value through innovation in areas of high unmet medical need, and is working on breakthrough therapies that transform lives, today and for generations to come. Founded in 1885 and family-owned ever since, Boehringer Ingelheim takes a long-term perspective. Its commitment to contribute towards a healthier and more sustainable future is firmly anchored in our corporate philosophy since its founding and translated through the Sustainable Development for Generations (SD4G) framework. More than 52,000 employees serve over 130 markets in the three business areas, Human Pharma, Animal Health, and Biopharmaceutical Contract Manufacturing."

To maintain the highest degree of an open innovation environment, we plan to announce the winner(s) publicly and feature them on opnMe.com and our social media channels. We would guide you through this process, and we kindly ask for your upfront consent, in case our scientific jury selects your proposal.

What are the key success criteria on which we base our selection for the best answer?

We are seeking research collaboration proposals that contain:

- A well-structured proposal outlining the technical feasibility of the proposed technology for screening and optimization of chemical reactions under temperature-controlled conditions including first validation data.
- Solutions making use of microtiter plates in standard SLAS (Society for Laboratory Automation and Screening) format.
- Proven track record in the required field of expertise.

- Ability to implement the outlined solution as part of a scientific collaboration project with Boehringer Ingelheim including access to a laboratory.
- Experience in upscaling of mechanochemical processes, e.g. via extruders, would be desirable but not essential.
- Your exact funding request should be outlined in your proposal based on a well-thought-through project. The project should be structured in milestones and planned with key decision points (clear Go/No-Go criteria). The funding request should not exceed USD 80,000.
- We will only consider project proposals which can be completed within 12 months or less. Within this period, you should be able to generate confirmation about your hypothesis based on predefined experimental milestones, as well as publishable results.

What information should be included in your answer submission?

Please use our answer submission template to provide a 2–3 page non-confidential proposal (available for download on the following site).

If confidential data exists that would strengthen the proposal, please indicate that information is available to share under a Confidential Disclosure Agreement (CDA). If we find the non-confidential concept proposal sufficiently interesting, we will execute a CDA for confidential discussions.

Anticipated Project Phases or Project Plan

Phase 1	Please complete your submission by **April 18, 2023, 11:59 pm PST at** the very latest
Phase 2	Our review of all proposals will be completed by end of May 2023 and scientists will be informed after that.
Phase 3	Potential collaboration starting date in Q3/2023.

Submitting a collaboration proposal

- Check the outline of the opn2EXPERTS "High-throughput mechanochemistry to reduce chemical waste" on opnMe.
- Alternatively, you may click the "Get Submission Template" banner to access the material transfer template.
- Follow the instructions to upload your submission document (requires login or registration).

- The upload allows you to attach additional application files if desired.
- You will be able to access your final submitted collaboration proposal in your personal dashboard and follow its review status.
- Please also visit the FAQ section on opnMe.com to learn more about our opn2EXPERTS program.

References

1. Andersen J. M., Starbuck H. F. Rate and Yield Enhancements in Nucleophilic Aromatic Substitution Reactions via Mechanochemistry *J. Org. Chem.* **2021**, 86, 86(20):13983-13989. DOI: 10.1021/acs.joc.0c02996, PubMed.
2. Mennen S. M., Alhambra C., Allen C. L., Barberis M., Berritt S., Brandt T. A., Campbell A. D., Castañón J., Cherney A. H., Christensen M., Damon D. B., de Diego J. E., García-Cerrada S., García-Losada P., Haro R., Janey J., Leitch D. C., Li L., Liu F., Lobben P. C., MacMillan D. W. C., Magano J., McInturff E., Monfette S., Post R. J., Schultz D., Sitter B. J., Stevens J. M., Strambeanu I. I., Twilton J., Wang K., Zajac M. A. The Evolution of High-Throughput Experimentation in Pharmaceutical Development and Perspectives on the Future *Org. Process Res. Dev.* **2019**, *23*, 1213–1242. DOI: 10.1021/acs.oprd.9b00140.
3. Bolt R. R. A., Raby-Buck S. E., Ingram K., Leitch J. A., Browne D. L. Temperature-Controlled Mechanochemistry for the Nickel-Catalyzed Suzuki-Miyaura-Type Coupling of Aryl Sulfamates via Ball Milling and Twin-Screw Extrusion *Angew. Chem. Int. Ed. Engl.* **2022**, 61(44):e202210508. DOI: 10.1002/anie.202210508, PubMed.