DNDi
Drugs for Neglected Diseases *initiative*

Request for Proposal

Pharmaceutical Development Drug Substance Process Development and GMP API delivery of COVID Moonshot candidate(s)

Dated: September 29, 2021

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1. PURPOSE

COVID Moonshot is a highly accelerated discovery project aiming to identify an orally available treatment for COVID-19, with the current aim of being Phase I ready by 3Q2022. In order to perform all preclinical activities required to enable Phase I studies, DNDi is now sourcing a Contract Development and Manufacturing Organization (CDMO) offering process research and manufacturing capabilities to provide Drug Substance API for use in Phase I clinical trials.

1.1. COVID-19

The COVID-19 pandemic requires little introduction. Despite major efforts and breakthroughs in both vaccine development and deployment as well as therapeutic drug repurposing, at time of writing it remains clear that there is a significant need for SARS-CoV2-specific anti-viral therapeutics to control the pandemic.

A variety of high profile accelerated campaigns seeking novel anti-viral therapeutics are moving quickly through the clinic, most notably those from Pfizer (PF-07321332) which are currently completing Phase I studies. To maximize the chance of successful delivery of an orally available anti-viral treatment to patients, and to ensure global equitable access to all, DNDi have forged a partnership with the open-science Covid Moonshot project to enable rapid acceleration of a SARS-CoV2 main protease (MPro) inhibitor candidate towards the clinic. This work receives significant financial support from the Wellcome Trust, acting on behalf of the ACT-A initiative.

1.2. Lead compound history

The COVID Moonshot project originates with a high throughput crystallography fragment screen against the Main Protease, run at the Diamond Light source in March 2020. A highly effective crowdsourcing initiative was enabled to project to move towards low molecular weight, non-peptidomimetic and non-covalent inhibitors of the main protease, with the best compound demonstrating in vitro anti-SARS-CoV2 efficacy in the low nM range.

This work was achieved almost exclusively through an open science network engaging in-kind contributions from individuals, academics, experience pharmaceutical R&D consultant as well as biotech SMEs and pharmaceutical companies. Work has been performed in many labs worldwide, with the majority of the medicinal synthetic chemistry run at Enamine (Kiev, Ukraine). Pharmacology support comes from various sources including Weizmann Institute of Science, University of Oxford, Memorial Sloan Kettering Cancer Centre and Mount Sinai University Hospital, among others.

The accelerated nature of this project requires many of the classical drug discovery processes and paradigms to be run early on and “at risk”. The funding of this project, from Wellcome Trust, is focused on speed of delivery. As such, the project aims to identify (up to) five optimized lead compounds (OpLeads) and progress these through a well-defined preclinical cascade in parallel. Note that these five compounds will all come from the same

chemical series and therefore share significant structural similarity and possibly overlapping synthetic routes.

These five compounds will be triaged down to two Preclinical Candidate compounds (PreCC) at the exploratory / DFR toxicology stage, and then down to a single clinical candidate (CC) following the DRF toxicology evaluation, for progression through GLP toxicology and pharmaceutical development targeting a "Phase 1 ready" status for this final candidate compound, including submission of a Clinical Trial Application (CTA) dossier with the relevant health authority identified for the eventual Phase I studies. This will include having all material in hand ready for First in Human study.

The accelerated nature of the project therefore requires a pharmaceutical development package running "at risk" in parallel, with process development focused initially on all five optimized leads (OpLeads), building in the flexibility to triage down to the selected candidate molecules as the preclinical data is generated. An overview of this process is seen in Section 4.1, Fig 1.

2. RFP INSTRUCTIONS

2.1. General information

a) DND*i* invites you as a Service Provider to submit one proposal covering all services described in Section 4.

b) This entire RFP and all the related discussions, meetings, information exchanges and subsequent negotiations that may occur are subject to the confidentiality terms and conditions of the Intent to Participate attached as Annex 1.

c) All bidders are required to complete and return the Intent to Participate letter.

d) The issuance of this Request for Proposal in no way commits DND*i* to make an award. DND*i* is under no obligation to justify the reasons of its service provider's choice following the competitive bidding. DND*i* could choose not to justify its business decision to the participants of the RFP.

e) DND*i* reserves the right to:

- Reject any proposal without any obligation or liability to the potential service provider.
- Withdraw this RFP at any time before or after the submission of bids without any advance notice, explanation or reasons.
- Modify the evaluation procedure described in this RFP.
- Accept another proposal than the lowest one.
- Award a contract on the basis of initial proposals received without discussions for best and final offers.
- Award all services to only one supplier or allocate them to different suppliers according to what DND*i* will consider necessary.

f) Late submission proposals are subject to rejection.

g) DND*i* reserves the right to request additional data, information, discussions or presentations to support their proposal. All bidders must be available to discuss details of their proposal during the RFP process.

h) All offers should be submitted in an electronic format.

i) The proposed timelines below indicate the process DND*i* intends to follow. If there are changes to this timeline, DND*i* will notify you in writing.

2.2. Timelines

Process steps	Responsible party	Timelines
Launch RFP	DNDi	Sept 29th 2021
Q&A sent to DNDi	Service Provider	Oct 11th 2021
DNDi responses to Q&A	DNDi	Oct 15th 2021
Reception of proposals	DNDi	Oct 22nd 2021
Bid Defence Meetings (if any)	DNDi	4th week of October 2021
Bidder selection	DNDi	Nov 3rd 2021

2.3. RFP processes and contact information

2.3.1. Instructions

All bidders may request further clarifications regarding this RFP by addressing their questions in writing to the dedicated key contacts identified below. These questions should be submitted to DND*i* at the date mentioned in the section 2.2 Timelines of the RFP.

In order to keep a fair bidding process, questions related to this RFP will only be answered in a document shared with all the bidders on the date indicated in section 2.2. Timelines of the RFP.

To submit your questions, please use the form attached as Annex 2.

2.3.2. Confirmation of Intent

Please transmit your intent to participate by using and signing the document attached in Annex 1.

Each bidder is required to provide DND*i* with a written confirmation of intent or decline to participate by the date as indicated in the section 2.2.

Confirmations of intent should be sent by email to Bruno Discini (contacts details below).

Questions types	Contact person	Title	Contact information
Contractual	Bruno Discini	Senior Procurement Manager	Email: bdiscini@dndi.org
Technical	Anthony Simon	Pharmaceutical Development Manager	Email: asimon@dndi.org

2.3.3. Format and content of the proposal

Responses to this RFP must be in English and should contain the following information:

- A cover letter including:
  - Name and address of the service provider.
  - Name, title, phone number and email address of the person authorised to commit contractually the service provider.
  - Name, title, phone number and email address of the person to be contacted in regards of the content of the proposal, if different from above.
  - Signature of this letter done by a duly authorised representative of the company
  - Acceptance of the consultation principles.

- Administrative information
  - Business/Company information: directors and officers, creation date, corporate headquarters, locations, business turnover of the past 3 years (global and in the field of service provided), headcounts (global and in the field of service provided), general services provided, customer's reference, pricing strategy for NGOs.
  - Any other relevant information enabling DND*i* to assess the opportunity of contracting with your company.

- A technical proposal
  - Detailed proposal explaining how your company approach will enable DND*i* team to meet project timelines, deliverables and ensure quality results.
  - Information about the available manufacturing equipment

- A financial proposal
  - Budget to be provided for all activities detailed in section 4, the cost breakdown by Work Packages and by molecule should be respected for DS and DP Services.
  - Payment Terms and payment schedule should be detailed in the quotation.

2.3.4. Conflict of Interest

The Company shall disclose any actual or potential conflicts of interest in the Intent to Participate letter.

3. DNDi OVERVIEW

Neglected tropical diseases continue to cause significant morbidity and mortality in the developing world. Yet, of the 1,556 new drugs approved between 1975 and 2004, only 21 (1.3%) were specifically developed for tropical diseases and tuberculosis, even though these diseases account for 11.4% of the global disease burden.

Founded in 2003 to address the needs of patients with the most neglected diseases, DNDi is a collaborative, patient's needs driven, not for profit drug R&D organization.

Acting in the public interest, DNDi bridges existing R&D gaps in essential drugs for these diseases by initiating and coordinating drug R&D projects in collaboration with the international research community, the public sector, the pharmaceutical industry, and other relevant partners.

DNDi's primary focus has been the development of drugs for the most neglected diseases, such as Human African Trypanosomiasis (HAT, or sleeping sickness), visceral leishmaniasis (kala-azar), and Chagas disease, while considering engagement in R&D projects for other neglected diseases to address unmet needs that others are unable or unwilling to address.

The primary objective of DNDi is to deliver 16 to 18 new treatments by 2023 for leishmaniasis, sleeping sickness, Chagas disease, malaria, paediatric HIV, filarial diseases, mycetoma and hepatitis C, and to establish a strong R&D portfolio that addresses patient needs. Expanding upon R&D networks built on South-South and North-South collaborations, DNDi aims to bring medical innovation to neglected patients by developing field-adapted treatments.

In doing this, DND*i* has two further objectives:

- Use and strengthen existing capacities in disease-endemic countries via project implementation.
- Raise awareness about the need to develop new drugs for neglected diseases and advocate for increased public responsibility.
- Since the start of the COVID-19 pandemic DNDi has engaged a rapid response, coordinating a major clinical trial initiative in Africa (ATICOV) as well as engaging in major repurposing and novel anti-viral discovery approaches.

For more information, please visit DNDi website: http://www.dndi.org/

4. SCOPE OF WORK

4.1. Drug substance

This document is a Request for Proposal for an estimate related to:

A) Parallel process development of the routes towards (up to) five DNDi compounds emerging from the COVID Moonshot project. Structures and med chem routes for these five **Optimized Lead** compounds (**OpLeads A-E**) will be communicated independently as and when they are identified by the project team; project start will be at the communication of the first of the OpLead structures. As a result of this approach the process development work on each will start in a staggered fashion. Goal for this process development would be to route scout for most appropriate route for use in Part C (API production). Although the absolute structure of these five Op Leads is not yet available, a representative compound, along with current med chem route, is provided in Annex 3. *Note: The process development for three of these five OpLeads will eventually be halted after communication from the DNDi project team, and the two remaining compounds promoted to **Preclinical Candidate (PreCC**) status.*

B) Completion of the process development for the two remaining PreCC compounds, through to production of ~2.5 kg demo batch material of each compound using the process route identified for delivery of compounds as Drug Substance.

C) cGMP manufacture of ~5kg of final **Clinical Candidate (CC).**

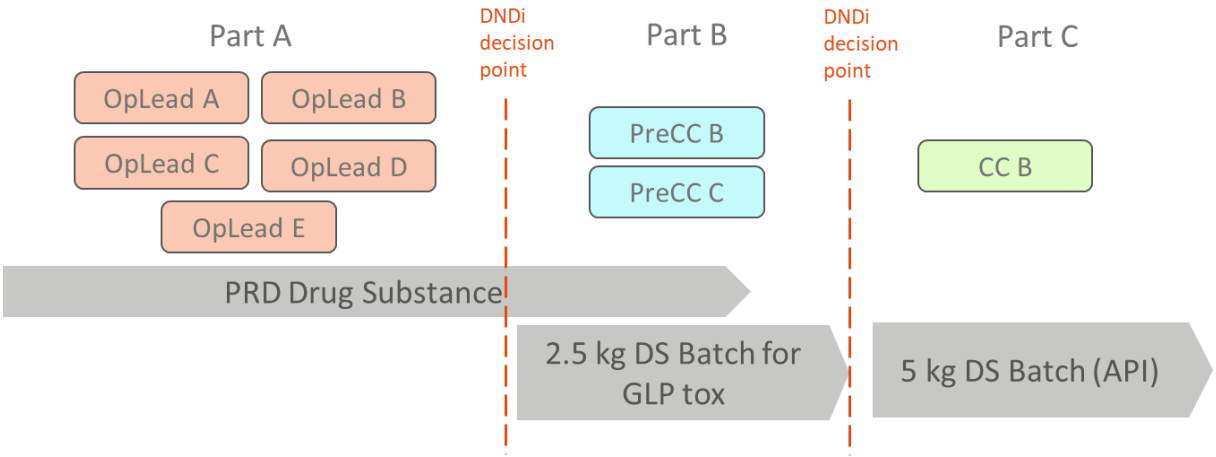


Fig 1; Representative overview of the proposal, starting from 5 optimized leads followed by prioritization down to two preclinical candidates PreCC, followed by prioritization of a single clinical candidate CC. Note the triggers for the DNDi decision points are decoupled from the progress made during PRD process, and are instead informed by preclinical evaluation of the compounds performed in parallel and separate to this proposal, In this representative example compounds B and C are selected for part B, and compound B eventually prioritized for clinical candidate

Within the proposal, the CDMO should provide feedback as to the scalability of the representative route provided (Annex C), and detail in each step any development activities which may be required. If there are specific manipulations which are not feasible for large scale manufacture, these should be discussed in the proposal and alternative methodologies recommended. As a second approach, the CDMO should suggest potential alternative routes considered more viable than the discovery routes. A comparison of the current route and the alternative approaches should be provided and criteria such as expected yield, raw materials prices, number of step, critical steps, chemical hazard, simplicity of the work-up, easy purification, crystallization, potential structural alert, etc should be considered. DNDi also requests the CDMO to develop a robust isolation step on the final stage to get consistent particle size distribution, the desired polymorphic form, impurity level and color. Salt form / desired polymorph form will be determined for each PreCC in a parallel and separate proposal.

During the PRD phase, quality/purity of the proposed starting materials should be determined/evaluated to prevent negative impact on the downstream chemistry.

This proposal is not limited to GMP manufacture but should also cover process safety assessment, API Methods development and validation (for assay & purity, residual solvent and cleaning), forced degradation studies, preparation and qualification of reference standards for RSM (Regulatory Starting Material), intermediates and final API and analytical markers and stability testing under ICH conditions.

4.2. API Synthesis: Key data

- Current lead compounds have 5-6 step synthesis; these have not been performed at scale. It is expected that the final compounds selected for PRD evaluation and eventual GMP synthesis will have at least one chiral centre. Representative enantiopure synthesis of key intermediates negating the need for chiral chromatography is currently being investigated and results communicated once available.
- Heavy metal removal may be required.
- Several intermediates purified by silica gel column chromatography.
- Several protection/deprotection steps.

4.3. List of activities to be performed

Work Package 1 (Process research and development) – 5 Compounds	
1.1	Route scouting
1.2	Process development of the selected route
1.3	Crystallisation development
1.4	Process safety assessment

1.5	Development of chiral HPLC methods, including synthesis of racemate and enantiomeric standards (assuming presence of 1 chiral center in each compound)
1.6	Genotox Risk Assessment (GRA) of manufacturing process: Risk assess potential genotoxins in API and develop methods to monitor all class 1 and 2 impurities at appropriate control points (requirement for Phase 1 trials)
Work Package 2 (Demonstration batch) – 2 Compounds	
2.1	Purchase of raw materials/reagents to support demonstration batch manufacture (non-GMP)
2.2	Production of 2.5 Kg Demonstration Batch (non-GMP) with CoA and manufacturing report
Work Package 3 (Analytical methods development and validation) – 2 Compounds	
3.1	API Methods development and qualification (for assay&purity, residual solvent and cleaning) to comply with the Phase I regulatory Requirements (EU) Analytical methods development and validation for final API, including method development focused on enantiomeric purity
3.2	Forced degradation studies for API HPLC method and report (temperature (solid state), acid, base, oxidation, light)
3.3	Preparation and qualification of reference standards for RSM (Regulatory Starting Material), intermediates and final API with CoA
3.4	Elucidation of structure and characterisation of the final API reference standard: elemental (CHN) analysis, counter-ion identity and stoichiometry confirmation, ^{1}H-NMR, ^{13}C-NMR, UV-Vis, IR, LC-MS, XRPD, DSC/TGA
3.5	Preparation and qualification of analytical markers (impurity samples for RSM, intermediates and final API) with CoA, including racemic form and matching (undesired) enantiomer of the API.
Work Package 4 (Stable Isotopically Labelled (SIL) synthesis) 2 compounds	
4.1	Stable Isotopically Labelled (Deuterated) synthesis (3-5g) to support bioanalytical method development, including a Certificate of Analysis
Work Package 5 (GMP API manufacture) – 1 Compound	
5.1	Purchase of raw materials/reagents to support cGMP API manufacture
5.2	Production of ~5 kg cGMP API
5.3	QC release testing including GMP Certificate of Analysis, BSE/TSE compliance statement, release and campaign report
Work Package 6 (Stability studies) 1 Compound	

6.1	Stability program (long term storage 25°C/60%RH, intermediate storage 30°C/75%RH, and accelerated storage 40°C/75%RH) up to 5 years (last two years being optional)

4.4. Overall timelines

Understanding that timelines may vary due to synthetic complexity as well as delays resulting from activities outside the scope of this proposal, we are aiming for the following timelines:

Month 0: First OpLead structure disclosed to CDMO.

Months 1-2 Remaining four OpLead structures disclosed.

Month 4 Triage from 5 x OpLeads to 2 x PreCC (DNDi to communicate).

Month 7 Delivery of 2 x PreCC at 2.5 Kg scale; Triage down to 1 x CC.

Month 12 Delivery of CC at 5 kg cGMP.

5. CRITERIA FOR SELECTING SERVICE PROVIDERS

The decision to award any contract as a result of this RFP process will be based on Service Providers' responses and any subsequent negotiations or discussions. The decision-making process will consider the ability of each service provider to fulfil DNDi's requirements as outlined within this RFP and the total cost of the offer.

Proposals will be assessed against the main following criteria but not limited to:

- **Technical criteria**
  - Ability to apply appropriate process development and analytical activities suitable to support FIH requirements (fit for purpose).
  - The CDMO will have the capability and experience/expertise to perform all the activities in a licensed facility at the scale outlined in paragraph 1.2.
  - The CDMO is able to work to the short timelines required for this accelerated COVID-19 response project with a high degree of flexibility.
  - DND*i* is looking for a CDMO that has renowned credentials in running successful development projects for small organizations.
  - Track records with regulatory bodies and regulatory inspections outcome.
- **Capacity to deliver**
  - DND*i* would like to work in partnership with the CDMO and expects the CDMO to provide strong intellectual input and ownership on the project.
  - Project management expertise, responsiveness from various business units, clear and open communication channels as well as on-time and on-budget delivery are expected. A single point of contact for project management with senior experience will need to be appointed.
  - Past positive experience with similar activities/scale.
- **Financial criteria**
  - Realistic costing of the proposal with NGO rates whenever possible.

6. PROPOSAL REQUIREMENTS, DELIVERABLES & TIMELINES

6.1. Proposal requirements

Following the issuance of the RFP, all interested bidders are invited to submit a proposal that describes:

- General information of the company as described in section 2.3.3.
- Complete scope of work description, with a full list of activities (CMC, Regulatory, Quality) to be performed for each work package of the project.
- Budget with full details of your offer including fixed costs and Pass-Through Costs, clearly broken down by Work Package per compound for DS and DP Services. Include estimations as to how these costs may vary once presented with the actual compound structures (e.g. impact of fewer steps, more steps).
- Projected timeline, including any discrepancy or issue with the propose timelines in 4.4.
- Project team involved.
- List of tasks and responsibilities.
- Realistic project Gantt Chart detailing the project schedule from start to finish, including multiple options if appropriate.
- Any other relevant information.

6.2. Terms and Timelines

- All services will be performed under a Quality Agreement.
- Beginning of Services (WP1) planned between mid-end Nov 2021.
- Timelines for each activity subset should be clearly defined.
- Completion of the service (including one month ICH stability data on the capsule clinical batches) in Jan 2023 at the latest.

6.3. Additional information

After receiving their Intent to Participate letter, DND*i* will provide the bidders with the documentation listed below:

- Quality questionnaires
- Pharmaceutical Development Services Agreement template

Technical documentation on representative compounds can be provided on request via the Q&A process.

Full technical details on the eventual confirmed OpLeads, including analytical details and medicinal chemistry synthesis route, will be provided prior to the initiation of Work Package 1.

7. ANNEXES

Annex 1: Intent to Participate letter

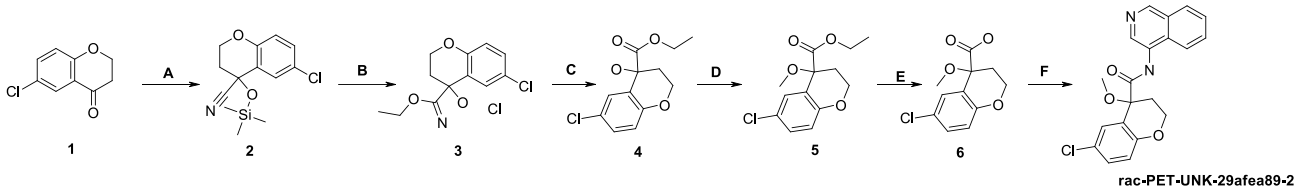
Annex 2: Q & A Form

Annex 3 (below): Current route to a representative compound

Annex 3 – Current route to a representative compound from the series (form only)

Notes:

- *This is not a compound structure which will eventually be proposed for synthesis, it is used as representative example from the chemical series for the purposes of benchmarking quotes*
- *The final compound will require resolution of active enantiomer if present*



Stage **A**: 6-Chloro-3,4-dihydro-2H-1-benzopyran-4-one (30.0 g, 164.3 mmol) was dissolved in DCM 500 mL, diiodozinc (524.48 mg, 1.64 mmol) was added stirred 5 min and then trimethylsilanecarbonitrile (17.93 g, 180.73 mmol, 22.61 ml, 1.1 equiv) was added and stirred overnight at rt. The mixture flashed through the silica, washed with DCM and concentrated in vacuo to give 6-chloro-4-[(trimethylsilyl)oxy]-3,4-dihydro-2H-1-benzopyran-4-carbonitrile (45.0 g, 95.0% purity, 151.7 mmol, 92.3% yield)

Stage **B**: Acetyl chloride (55.71 g, 709.68 mmol, 10.0 equiv) added dropwise to freshly absolute diethyl ether 200 mL and 200 mL of freshly absolute ethanol on ice bath and stirred 30 min, then 6-chloro-4-[(trimethylsilyl)oxy]-3,4-dihydro-2H-1-benzopyran-4-carbonitrile (20.0 g, 70.97 mmol) was added in one portion and stirrred overnight. The mixture was concentrated in vacuo to give ethyl 6-chloro-4-hydroxy-3,4-dihydro-2H-1-benzopyran-4-carboximidate hydrochloride (28.0 g, 35.0% purity, 33.54 mmol, 47.3% yield) and was used in next step without additional purifications.

Stage **C**: Ethyl 6-chloro-4-hydroxy-3,4-dihydro-2H-1-benzopyran-4-carboximidate hydrochloride (15.0 g, 51.34 mmol) added to 500 mL of water and stirred at 50 °C overnight. After stirring overnight the reaction mixture was extracted by DCM, washed with saturated brine, dry with anhydrous Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography (SiO_2, CHCl3/MTBE) to give ethyl 6-chloro-4-hydroxy-3,4-dihydro-2H-1-benzopyran-4-carboxylate (5.5 g, 21.43 mmol, 41.7% yield)

Stage **D**: Ethyl 6-chloro-4-hydroxy-3,4-dihydro-2H-1-benzopyran-4-carboxylate (695.97 mg, 2.71 mmol) and iodomethane (769.71 mg, 5.42 mmol) were suspended in dry DMF (20 mL),

then cesium carbonate (1.33 g, 4.07 mmol) was added at 20 °C. The reaction mixture was stirred at 35 °C overnight. The resulting solution was concentrated under reduced pressure. The residue was taken up in 50 mL of ethyl acetate, washed with saturated aqueous $NaHCO_3$ solution (3×50 mL), brine (3×50 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The product ethyl 6-chloro-4-methoxy-3,4-dihydro-2H-1-benzopyran-4-carboxylate (700.0 mg, 95.0% purity, 2.46 mmol, 66.5% yield) was obtained as a yellow oil.

Stage **E**: Ethyl 6-chloro-4-methoxy-3,4-dihydro-2H-1-benzopyran-4-carboxylate (0.7 g, 2.59 mmol) was treated with water and sodium hydroxide (0.31g, 7.77 mol). The resulting mixture was stirred at RT for 24 h, then cooled to 5 °C and added acetic acid. The formed precipitate was filtered off and dried to afford the 6-chloro-4-methoxy-3,4-dihydro-2H-1-benzopyran-4-carboxylic acid (0.45g, 1.85 mmol, 71% yield).

Stage **F**: Isoquinolin-4-amine (443.29 mg, 3.07 mmol), ethylbis(propan-2-yl)amine (1.19 g, 9.22 mmol) and [(dimethylamino)(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy)methylidene]dimethylazanium; hexafluoro-lambda5-phosphanuide (1.4 g, 3.69 mmol) were added to a solution of 6-chloro-4-methoxy-3,4-dihydro-2H-1-benzopyran-4-carboxylic acid (746.0 mg, 3.07 mmol) in DMF (5 mL), and the reaction mass was stirred at r.t. overnight. The resulting mixture was poured into ice water (10 mL). The product was extracted with ethyl acetate (3 × 30 mL). The combined organic extract was washed with brine (2 × 50 mL), dried over Na_2SO_4, concentrated under reduced pressure and then purified by HPLC to afford 6-chloro-N-(isoquinolin-4-yl)-4-methoxy-3,4-dihydro-2H-1-benzopyran-4-carboxamide (789.0 mg, 2.14 mmol, 69.6% yield).