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Article

End-to-End Automated Synthesis of C(sp^3)-Enriched Drug-like Molecules *via* Negishi Coupling and Novel, Automated Liquid−Liquid Extraction

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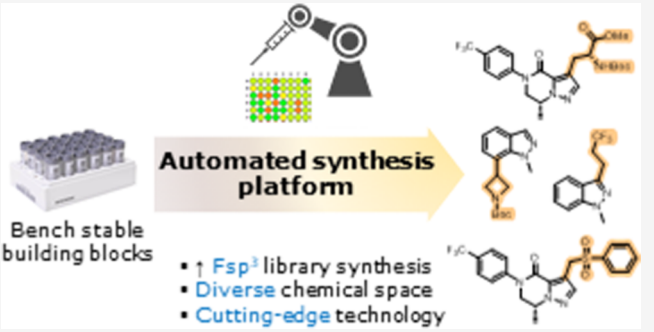
ABSTRACT: Herein, we report an end-to-end process including synthesis, work-up, purification, and post-purification with minimal human intervention using Negishi coupling as a key transformation to increase Fsp^3 in bioactive molecules. The main advantages of this protocol are twofold. First, the automated sequential generation of organozinc reagents from readily available alkyl halides offers a large diversity of alkyl groups to functionalize (hetero)aryl halide scaffolds *via* Pd-catalyzed Negishi coupling in continuous flow. Second, a fully automated liquid−liquid extraction has been developed and successfully applied for unattended operations. The workflow was completed with mass-triggered preparative high-performance liquid chromatography HPLC, providing an efficient production line of compounds with enriched sp^3 character and better drug-like properties. The modular nature allows a smooth adaptation to a wide variety of synthetic methods and protocols and makes it applicable to any medchem laboratory.



INTRODUCTION

Drug discovery teams across the pharmaceutical industry are currently under increasing pressure to deliver bioactive molecules with the appropriate physicochemical properties in a faster and more efficient manner. One approach that has been recently highlighted is the increasing fraction of C(sp^3) atoms or Fsp^3 in final target compounds.[1] This approach has been linked to improvement in drug-like properties such as solubility and crystallinity, increasing the likelihood to reach the market.[2] However, the diverse introduction of C(sp^3) fragments in drug-like molecules is still a challenge for medicinal chemistry as there is not a robust and general tool to explore this chemical space in a broad and high-throughput manner despite the recent progress in this field.[3] As a matter of fact, high-throughput chemistry in pharma has been dominated by a small set of reactions, the so-called "big five": amide coupling, Suzuki coupling, reductive amination, nucleophilic substitution, and sulfonamide formation.[4]

In this regard, recent advances in chemistry automation have demonstrated the impact of automated synthetic platforms on the drug discovery process. The application of these technologies has enabled a faster and broader exploration of the chemical space in a more efficient and reproducible manner.[5] Such automated protocols had already been applied in life-science laboratories for a long time, including high-throughput screening platforms. However, the adoption of these technologies by synthetic chemistry laboratories had fallen behind due to intrinsic chemistry challenges that could be attributed to the heterogenicity of organic synthesis of widely diverse compounds. Historically, Merrifield and Stewart proposed the first automated system for solid-phase peptide synthesis in 1965,[6] which laid the groundwork for the development of mechanized systems designed to perform identical tasks within synthetic organic chemistry. However, it was not until a few decades later that some of the "big five" synthetic methods were automated in the context of combinatorial chemistry.[7] Later, high-throughput experimentation[8] has also benefited from the incorporation of robotic platforms for micro- and nanoscale reaction screening and analysis, showing outstanding applications. Nowadays, parallel synthesis is evolving and embracing these robotic platforms in order to develop synthetic methodologies and user-friendly automation platforms capable of broadening the accessible chemical space.

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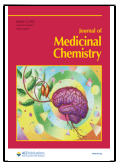

Figure 1. General scheme of the automated workflow.

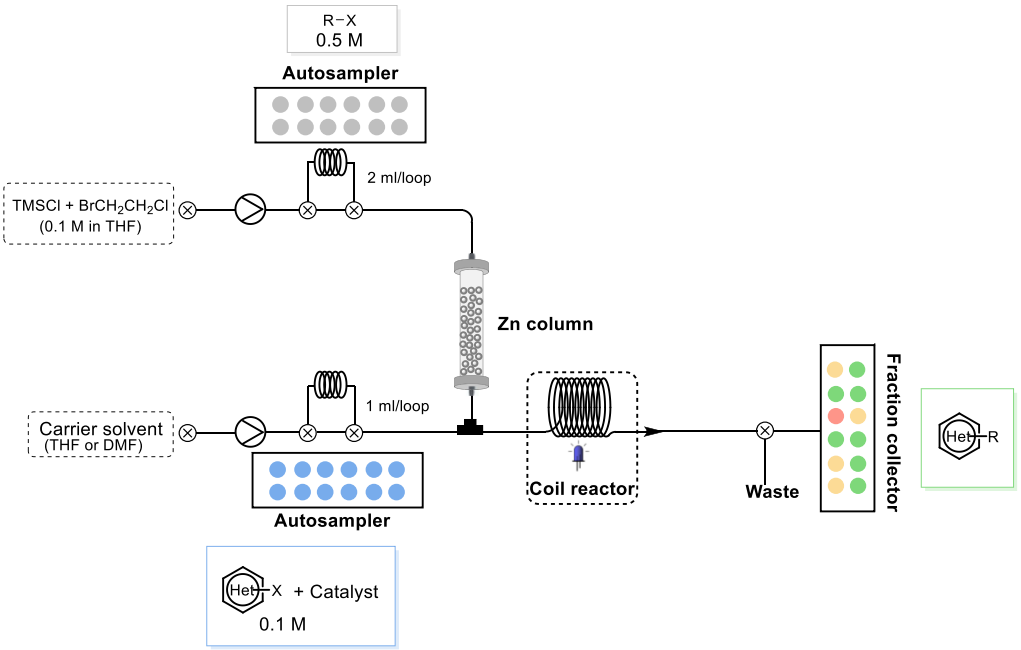

Figure 2. Schematic representation of the automated flow system.

In this context, the development of an automated high-throughput platform that enables the introduction of C(sp^3)-enriched motifs in drug-like molecules is considered an unmet need in medicinal chemistry.[3b,9] Among the synthetically available methodologies for C(sp^2)−C(sp^3) coupling, the palladium-catalyzed Negishi coupling reaction has proven to be a broadly applicable tool to introduce diverse alkyl groups with a high functional group tolerance.[4c] However, the lack of commercially available organozinc reagents and the complexity of the chemistry required for their preparation in a high-throughput manner have limited its applicability for library synthesis.[4e,10] Herein, we report an end-to-end workflow combining several robotic platforms for the automated synthesis of drug-like molecules with C sp^3-enriched fragments. This workflow includes a library synthesis platform in continuous flow from commercially available alkyl halides, an automated liquid−liquid extraction (LLE) with conductivity-based interface detection, analytical liquid chromatography−mass spectrometry (LC−MS), high-throughput purification (HTP) with MS-triggered preparative high-performance LC (HPLC), and post-purification protocols with liquid handlers to deliver compounds for biological assays with minimal human intervention (Figure 1).

RESULTS AND DISCUSSION

Library Synthesis in Continuous Flow. Flow chemistry has demonstrated its value in the simple, reproducible, and robust preparation of highly reactive and unstable intermediates, such as organozinc reagents.[11] The fact that they can be generated *in situ* and reacted immediately in a subsequent Negishi reaction opens the possibility for their use in a high-throughput format. Automated flow approaches for the Negishi reaction have been reported in the literature; however, they are limited in the number of compounds that can be prepared and the diversity of heterocyclic cores and alkyl reagents that can be used, that is, electron-deficient heteroaromatic systems or cyclobutyl analogues.[12]

Intending to further expand the scope of the Negishi reactions, we have recently reported the acceleration of this cross-coupling in the presence of blue light irradiation.[13] This

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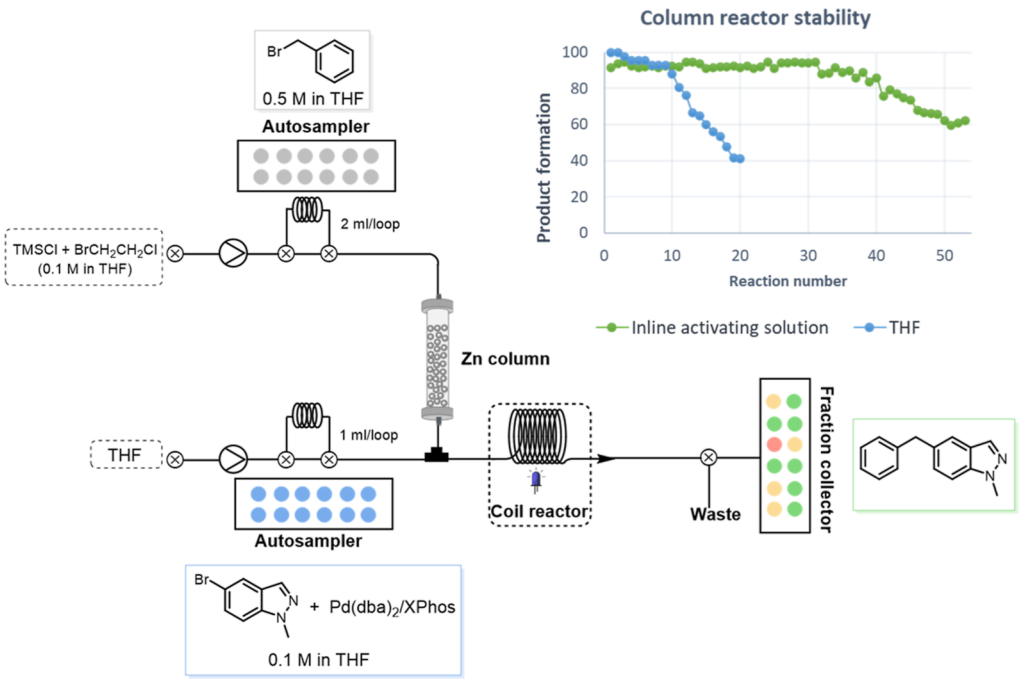
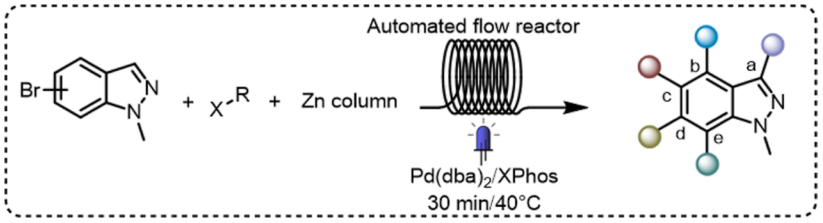


Figure 3. Stability study of the Zn column over sequential runs.

Table 1. Combinatorial Library of Indazoles[a]



A	**(3a)** 42%	**(4a)** 44%	**(5a)** 38%	**(6a)** 46%	**(7a)** 45%	**(8a)** 21%
B	**(3b)** 100%	**(4b)** 71%	**(5b)** 45%	**(6b)** 40%	**(7b)** 100%	**(8b)** 19%
C	**(3c)** 91%	**(4c)** 67%	**(5c)** 55%	**(6c)** 59%	**(7c)** 100%	**(8c)** 18%
D	**(3d)** 100%	**(4d)** 55%	**(5d)** 39%	**(6d)** 30%	**(7d)** 100%	**(8d)** 16%
E	**(3e)** 100%	**(4e)** 64%	**(5e)** 46%	**(6e)** 55%	**(7e)** 100%	**(8e)** 40%

[a]LC−MS conversion based on all identified byproducts.

new methodology has allowed the expansion of the reaction scope to electron-rich systems and organozinc reagents, one of the main reasons for its limited application in parallel medicinal chemistry.[4a] Moreover, the accelerated reaction kinetics makes this approach more suitable for a flow setup. These findings prompted us to further explore this type of reaction as a tool for library synthesis of C(sp^3)-enriched drug-like molecules in an automated manner.

We started our investigation by building up a system where we could generate the organozinc reagents *in situ* and directly use them in flow with the corresponding coupling partner.[2b,c] The flow setup was designed using a column reactor filled with metal zinc, where the organozinc reagent is formed, followed by a T-mixer where the substrate and the catalytic system are mixed before entering the photoreactor where the Negishi reaction takes place under blue light-emitting diode (LED) irradiation. The injection of the two solutions in each reactor at two different times is controlled using the automated loop injector and system software, which calculates the flow rates and the injection time for each step, based on the reactor volume and residence time. The outcome solution is collected using an automated fraction collector (Figure 2).

The first set of experiments was designed to determine the number of reactions that could be carried out in the system

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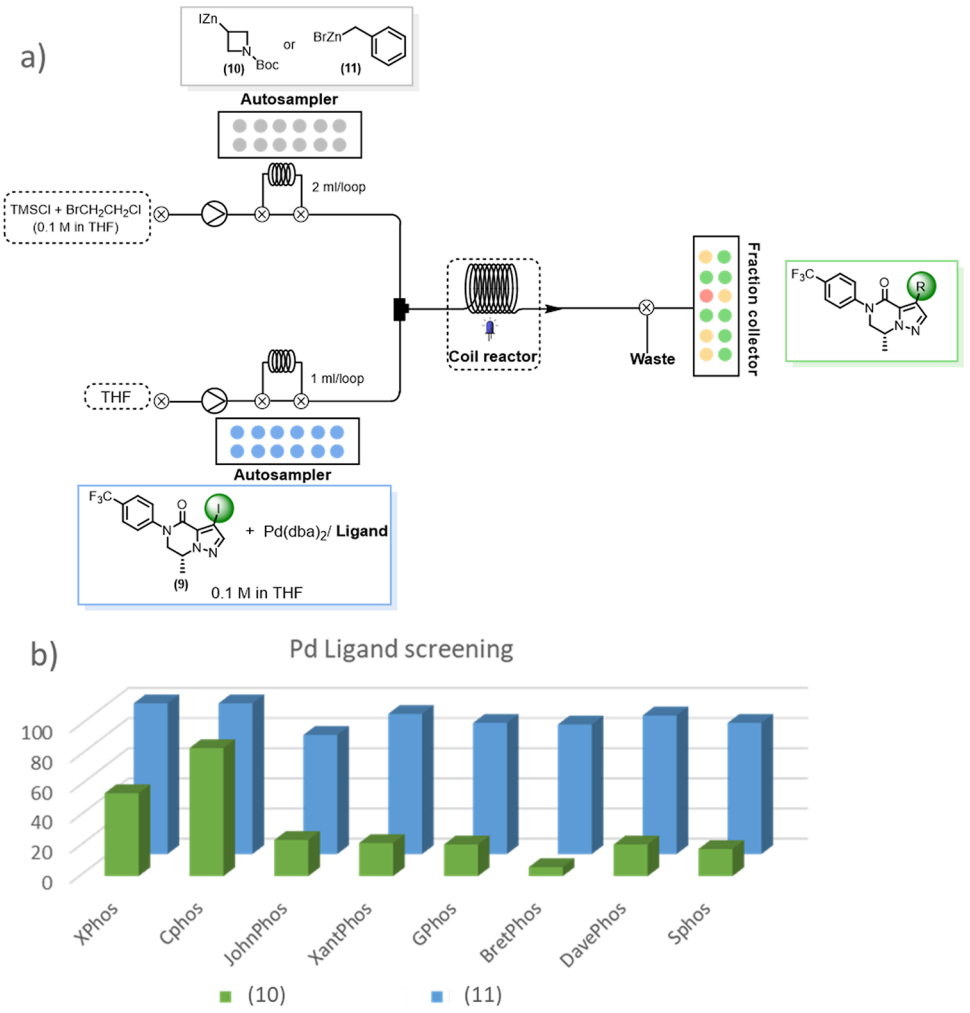

Figure 4. Palladium ligand screening on the mGluR2 NAM core. (a) System setup for Pd ligand screening and (b) product conversion using different Pd ligands combined with organozinc **10** and **11**.

without a decline in its performance. An important factor to consider is that due to the continuous consumption of metal Zn during the organozinc formation, a chromatographic effect will take place, thus increasing the dispersion of the alkyl halide solution inside the column.[14] To overcome this issue, we decided to use double volume of the alkyl halide compared to that of the substrate solution to ensure that the mixture of both solutions occurred in the center of the peak of the organozinc solution where the concentration is not affected by the dispersion. To validate the setup, the cross-coupling between 5-bromo-1-methyl-1*H*-indazole and benzylzinc bromide was used as a benchmark reaction using our previously reported conditions.[13] Reaction conversion was calculated by LC−MS using an internal standard (see the Supporting Information). When tetrahydrofuran (THF) was used as carrier fluid for both lines, a clear drop in conversion to the product was observed after the sixth reaction showed the presence of the benzyl bromide in LC−MS (Figure 3).

This data suggested that for a continuous production of organozinc reagents sequentially, it was necessary to keep the column continuously activated while running the sequential reactions. Therefore, we tested different concentrations of inline activating solution[11] by running sequentially the same reaction. We concluded that a 0.1 M solution of trimethylsilyl-chloride (TMSCl) and $BrCH_2CH_2Cl$ in THF was necessary to keep the column activated and ensure the sequential high-quality production of the organozinc reagents. A higher concentration of inline activating solution generated an increased pressure in the system due to the formation of ethene gas, a known side product formed during the activation of the zinc column.[11,15] Once the best carrier solvent was identified, a set of 54 Negishi reactions were carried out in a sequential automated manner (Figure 3). We observed that the yield remained stable between 90 and 95% during the first 31 experiments; however, a constant decay in assay yield was observed from experiment number 32 onward. We hypothesized that this decay might be due to Zn consumption and the corresponding change in residence time of the organozinc reagent.

As a follow-up experiment, we decided to expand the exploration around *N*-methyl indazole to its 5 vectors of growth with 6 organozinc reagents formed *in situ* in a combinatorial way to provide a matrix of 30 final products (Table 1). Alkyl halides were selected to cover different functionalities with medicinal chemistry interests such as alkyl, fluorinated alkyl, protected amines, amides, ethers, and sulfones. All products were obtained with moderate to excellent conversion depending on the reactivity of the organozinc reagent and the bromo-indazole coupling partners. As expected, functionalization at position 3 of the indazole

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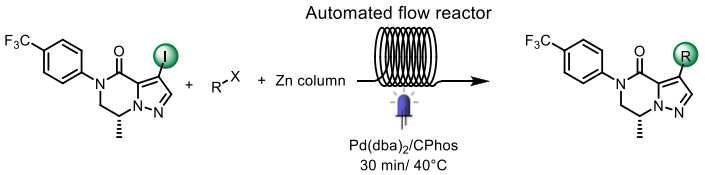
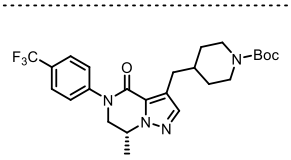
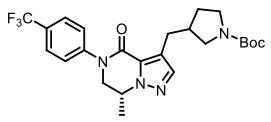
Scheme 1. Diverse C(sp^3) Library on the mGluR2 NAM Scaffold[a]

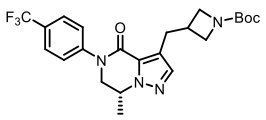




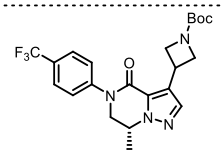
(12) 78% (59%)*



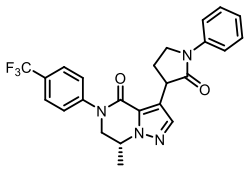
(13) 88% (63%)*



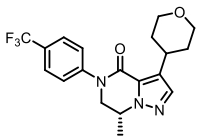
(14) 94% (53%)*



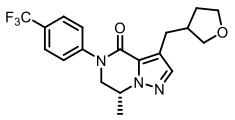
(15) 80% (52%)*



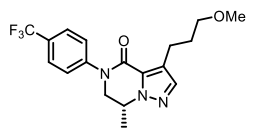
(16) 100% (21%)**



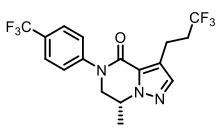
(17) 52% (22%)*



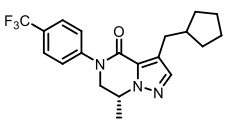
(18) 45% (23%)*



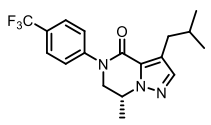
(19) 31% (15%)*



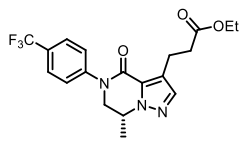
(20) 97% (48%)*



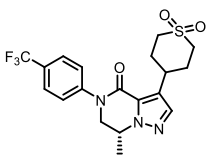
(21) 37% (16%)*



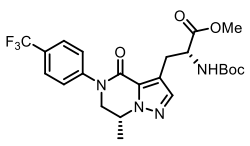
(22) 44% (23%)*



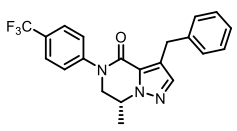
(23) 50% (10%)**



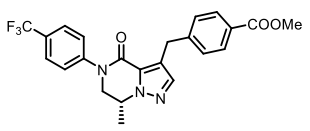
(24) 68% (30%)*



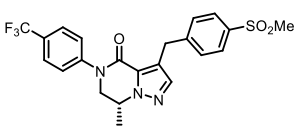
(25) 31% (14%)*



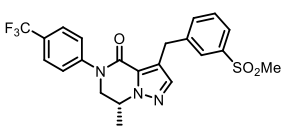
(26) 80% (33%)*



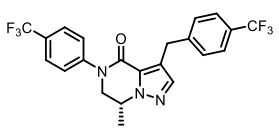
(27) 80% (35%)*



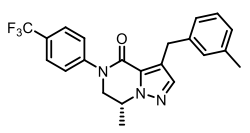
(28) 85% (46%)*



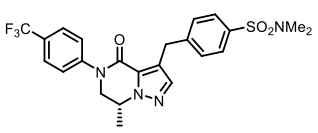
(29) 85% (50%)*



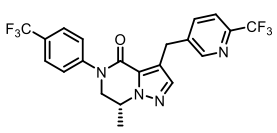
(30) 55% (32%)*



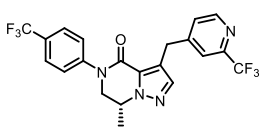
(31) 80% (39%)*



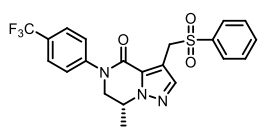
(32) 41% (15%)*



(33) 68% (38%)*



(34) 65% (35%)*



(35) 26% (6%)*

[a]* Isolated yield after reversed-phase (RP)-HPLC on an HTP system and ** isolated yield after second RP-HPLC.

provided the desired products, albeit lower yields (**3a**, **4a**, **5a**, **6a**, **7a**, and **8a**). It is important to highlight that the bromomethyl phenyl sulfone used to prepare compounds **8a**−**e** was not previously reported in Negishi reactions.

After completing the combinatorial library successfully, we then turned our attention to applying this new platform to increase Fsp^3 in a highly functionalized scaffold from a medicinal chemistry project. Intermediate **9** (Figure 4) was selected as it has been used for the preparation of compounds with mGlu2R negative allosteric modulator (NAM) activity *via* different cross-coupling reactions.[16] However, no reaction to introduce C(sp^3) motifs was applied toward the functionalization of the 3-position of the dihydropyrazole core.

Before delving into the library synthesis, we performed a continuous-flow ligand screening with diverse representative building blocks in order to account for differences in their reactivity, as we observed a significant change in the catalytic performance of XPhos upon changing the nature of the organozinc reagent. To minimize the effects of the concentration of the organozinc reagent, the zinc column was removed from the system, and stock solutions of organozinc **10** and **11** were prepared offline and used in the

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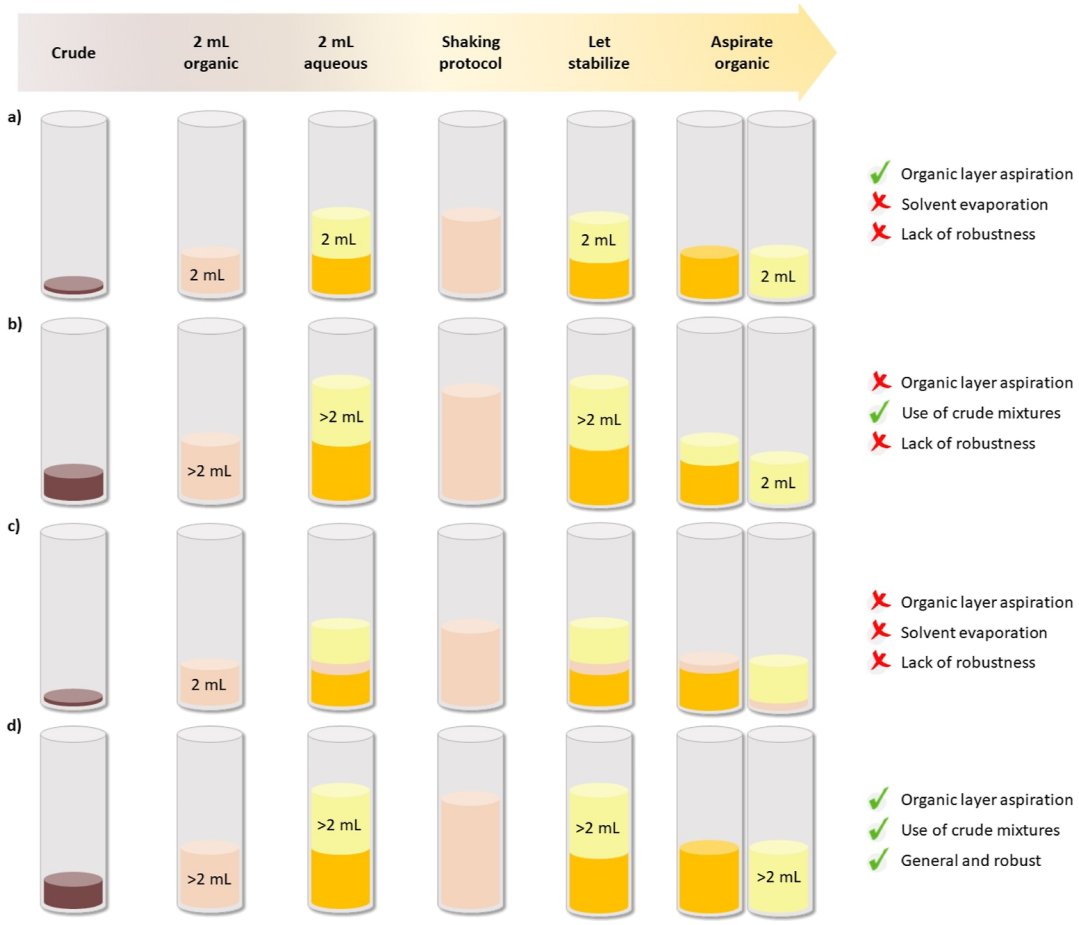

Figure 5. Schematic representation of the volume-based and conductivity-based LLE workflows. (a) Volume-based LLE starting from a dry crude. (b) Volume-based LLE starting from the reaction mixture. (c) Volume-based LLE starting from a dry crude where there is no clear cut. (d) Conductivity-based LLE starting from the reaction mixture.

subsequent experiments (Figure 4). A set of 16 reactions, 8 of them with the organozinc solution **10** and 8 of them with **11**, was designed, and the reactions were run sequentially in the automated system. After this screening, the catalytic system that balanced the highest yields for both substrates turned out to be CPhos (97 and 85%, respectively) (Figure 4). We believe that this difference in reactivity is due to the stronger electron-donating nature of CPhos compared to that of XPhos which can accelerate the oxidative addition, accelerating the catalytic cycle.[17]

With the optimized conditions in our hands, we ran a library of 24 compounds using 24 different alkyl halides as organozinc precursors. Consequently, the library of non-commercially available organozinc reagents was clearly expanded to highly functionalized primary and secondary alkyl halides when using this approach. Boc-protected amines were introduced with very good yields of 78−94% (compounds **12**, **13**, **14**, and **15**, Scheme 1), and the protecting group could be removed in a second step to generate free NH or be further functionalized in the next steps. In addition to amines, secondary amide **16** was introduced with excellent (100%) conversion. Moreover, alkyl halides with H-bond donors proved to be compatible with the organozinc formation, allowing the introduction of an amino acid group into the core giving compound **25** with moderate (33%) conversion based on LC−MS.

Sulfone moieties are present in many pharmaceutical drugs and continue to be a substructure of hits and leads in medicinal chemistry programs.[18] By generating the corresponding organozinc *in situ*, we were able to couple a secondary cycloalkyl sulfone **24** in good yield (68%) and a sulfonyl benzene **35** in moderate yield (26%). The latter compound is of high interest from the synthetic point of view because it is highly challenging to obtain it in a single step otherwise. Furthermore, lipophilic chains (**20**, **21**, and **22**), polar groups—such as ethers—(cyclic **17** and **18** or linear **19**), and esters (**23**) were obtained in moderate to high yields. A diverse set of substituted benzyl groups bearing aryl (**26**−**32**) and heteroaryl rings (**33** and **34**) were successfully obtained in moderate to good yields. It is important to highlight that the protocol allowed the use of different solvents such as THF, THF·LiCl (0.5 M), and dimethylformamide (DMF) for the preparation of the organozinc compounds.

Once all reactions were completed, the workflow continued with solvent removal *in vacuo* using a Genevac. Then, the plate was directly transferred to a Tecan liquid handler to perform quenching with aqueous ammonium chloride, automated LLE, and aliquoting for LCMS analysis.

Automated Liquid−Liquid Extraction. As important as automating the synthesis, the incorporation of robotic platforms in subsequent steps has proven to be a key factor to accelerate the design−make−test−analyze cycle and avoid shifting the bottleneck to subsequent steps down the workflow. In this regard, we turned our attention to developing an efficient, robust, and fully unattended parallel LLE as the most

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general work-up procedure used in organic synthesis for the cleanup of reaction mixtures.

In order to achieve this goal, we developed a conductivity-based interface detection and subsequent extraction using the Tecan liquid handler. This robotic platform has the capability of detecting liquids based on pressure or conductivity. By a careful tweak of the conductivity detection parameters, we have been able to efficiently detect the interface between the non-conductive organic layer (typically based on ethyl acetate; top layer) and the highly conductive aqueous layer (bottom layer). Following this approach, we overcame the challenges of interface detection, achieving a more efficient recovery of the organic layer, circumventing the need to pre-evaporate the crude mixtures, and also avoiding the aspiration of aqueous-containing emulsions (Figure 5d).

Over the last decades, several LLE platforms have been developed in the context of organic synthesis.[32] For example, Abbott used an interface detection using a refractometer flow cell with a capacity of up to 80 samples per screen,[19] BMS built a visualization plate able to manually analyze up to 24 samples in parallel,[20] GSK developed an automated LLE screening workflow able to analyze 24 samples,[21] and Merck recently developed an automated image analysis using an integrated camera onto a liquid handler.[22] Another remarkable precedent is the use of hydrophobic extraction plates equipped with a liquid handler reported by P&G for the removal of water-soluble amine impurities.[23] Most of these batch approaches are condition screening platforms focused on the optimization of the LLE of an advanced active pharmaceutical ingredient on a small scale to then transfer this knowledge to the scale-up synthesis. Moreover, most of these approaches use visual guidance (manual or integrated cameras) for the detection of the interface, which often requires an additional pick-and-place gripper arm that makes this a sequential process. Recently, Zinsser Analytic has reported the use of its robotic platform Speedy to perform automated LLEs with fixed volumes of the organic layer.[33]

To the best of our knowledge, the development of an automated parallel LLE platform able to aspirate variable quantities of organic extracts including interface detection remains an unresolved challenge.

In the context of continuous flow, several authors have reported the development of LLE devices based on hydrophobic membranes,[24] settling tanks,[25] selective wetting,[26] and counter-current flow hydrophobic/hydrophilic membranes.[27] Nonetheless, the application of these tools often requires fine-tuning for each process (*e.g.*, flow rates, solvent mixtures) in order to ensure a high and clean recovery of the organic extract, limiting a broad application across drug discovery programs and synthetic methodologies. In addition, the use of these devices has been successful for optimized reactions and scale-up, but their use in a library format with complex and diverse solvent mixtures and diverse structures and solubilities may hamper sequential automation. Therefore, the development of a robust and unattended LLE was a clear need to enable such automation.

For these reasons, we focused on developing a general, robust, and user-friendly automated LLE platform for parallel synthesis. Some of the considerations and challenges we took into account were related to the fact that each reaction may have different solvent composition and behave differently with the potential formation of emulsions and differences in the solubility or partition coefficient. Some of these issues can be avoided beforehand with some optimization, while others are intrinsic to the diverse set of reactions and products submitted to this protocol.

For this purpose, we used a Tecan liquid handler (Freedom EVO200, Air LiHa equipped with disposable tips). Initially, we evaluated the use of a simple volume-based LLE. In this case, the liquid handler is programed to retrieve the same volume as that of the organic solvent added. This aspiration occurs from the liquid level with tracking.[34] The first approach we considered consisted of evaporating the reaction mixtures to dryness and using the crude materials dried. After the addition of the corresponding organic solvent and aqueous solution and assuming that a clear cut occurred between the phases, the liquid handler would be able to aspirate the organic layer for all the wells in an automated fashion (Figure 5a). This operation could be programed to be repeated as many times as needed. Ideally, we would like to avoid the evaporation step and submit our crude reaction mixtures directly to the LLE step. In order to follow this approach, a few considerations were made. First, the reaction solvent might unevenly distribute between the phases depending on its nature; second, our desired product would also distribute between the aqueous and organic layers depending on the solvent mixture composition; and third, the total volume of the organic extract to be aspirated would be variable. Based on these considerations, a portion of the organic layer always remained in the original vial without being extracted when following this volume-based LLE approach, thus making this approach suboptimal (Figure 5b). Furthermore, in the event where a clear cut was not observed, this approach also failed as the liquid handler often aspirated a mixture of organic and aqueous layers (Figure 5c). For these reasons, we envisioned that having an automated interface detection and being able to aspirate efficiently the organic layer would be highly beneficial for a parallel synthesis workflow.

In our experience, the problematic formation of emulsions can be greatly minimized by performing a screening with several aqueous solutions and additives using the same automated platform.[29] In order to minimize emulsion formation, we also optimized the shaking protocol by gradually decreasing the shaking speed (3 mm rotation amplitude in an integrated Te-Shake).[28] This gentle swirl emulates the same protocol that is often used in a manual LLE with a separatory funnel, where the contact of the emulsion with the glass surface helps its disruption.[30]

In summary, a general protocol for our automated LLE proceeds as follows (24-well plate, 2D vials): Ethyl acetate and the desired aqueous solution are added to the reaction mixture (generally 2 mL of each), followed by a shaking procedure to ensure good mixing between the two layers while minimizing the formation of emulsions.[28] Then, the Tecan liquid handler detects the interface and aspirates the organic layer without tracking (fixed aspiration height) from a pre-determined height of 2 mm above the interface, in volume portions of 1 mL (limit volume set for this liquid handler). Once the whole organic layer is extracted once, another portion of ethyl acetate (2 mL) is added, and the process is repeated. This protocol has been scripted in a way that the user has the option to input several parameters such as the number of extractions per reaction (typically 3), volume of aqueous and organic solutions (typically 1−2 mL), the number of vials, and temperature (typically 25−50 °C). After the extraction is completed, we have also programed the liquid handler to take an aliquot of the aqueous layer from the maximum depth of the original vial

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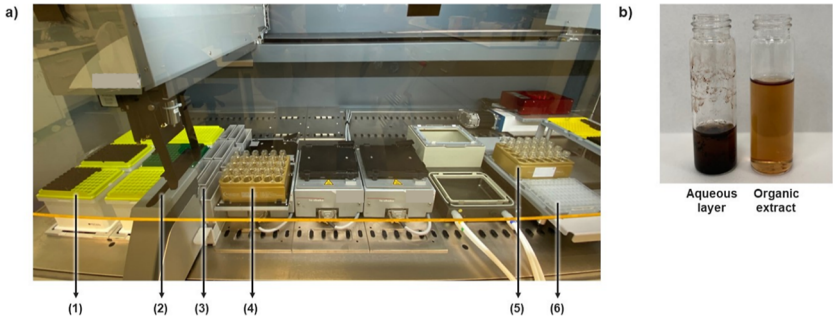

Figure 6. (a) Configuration of the Tecan EVO200 deck with (1) disposable tips, (2) tip waste, (3) solvent troughs, (4) reaction plate on a Te-Shake, (5) collection plate, and (6) analysis plate. (b) Representative example of the outcome of the automated LLE for a Negishi coupling.

and another one from the organic layer from the liquid surface of the collection plate. Both aliquots are diluted by the liquid handler to the standard concentration for LC−MS analysis. The whole workflow takes 60 min on average for 24 samples and 3 extractions per sample, with a maximum consumption of 48 disposable tips (one per sample and eight per solvent used).

Once we validated the automated LLE using a Tecan platform, this protocol was applied to both Negishi libraries, obtaining translucent organic extracts in the collection plate (Figure 6b). Both the aqueous layer and the organic extracts were aliquoted and analyzed by LC−MS, showing complete recovery of the target compounds in the organic layer with a cleaner profile in comparison to that of the crude mixtures.

After the LLE step, samples were submitted to evaporation under reduced pressure in the Genevac and returned to the Tecan liquid handler for reformatting the preparation of the HTP samples. The standard automated protocol consists of redissolution in a mixture of dimethylsulfoxide, methanol, and aqueous ammonium bicarbonate; shaking at 50 °C for 2 min; and filtration over a filter plate containing a palladium scavenger in the Tecan. Target compounds were then submitted to standard MS-triggered RP-HPLC completing the workflow.[31]

Automated LC−MS and HTP. Fractions coming from the extraction were aliquoted and plated for LC−MS analysis. Automated OpenLynx rpt LC−MS reports are generated after the analytical plate is analyzed. In each reaction, the target peaks are identified based on the ionization trace, and their Rt is obtained. Then, RP-HTP purification is performed considering the retention time for each compound, applying focused gradients within the same the standard condition.[31] In the HPLC system, the fractions are collected in barcoded vials which are aliquoted for doing QC analysis (LC−MS and NMR). The selected fractions are picked and concentrated *in vacuo* using the Genevac, and the dried vials are weighted on a weighing station, obtaining the net weight for each compound.

CONCLUSIONS

In summary, we have developed an automated end-to-end workflow including synthesis, work-up, and purification to generate C(sp^3)-enriched drug-like compounds. This workflow is based on the Negishi coupling in continuous flow, subsequent LLE in parallel, and MS-triggered HTP. This protocol allows the preparation and use of unstable organozinc reagents as valuable building blocks for C(sp^3)−C(sp^2) cross-coupling reactions starting from stable and commercially available alkyl halides. 54 final compounds with enriched Fsp^3 were prepared using the automated flow setup in two different libraries: a matrix library functionalizing an indazole scaffold in its 5 vectors of growth with 6 different organozinc reagents and a diverse exploration of a drug-like scaffold with 24 different organozinc reagents. Additionally, an automated parallel LLE featuring an interface detection based on conductivity was developed. The workflow was completed with HTP using MS-triggered preparative HPLC. The novelty of this protocol stands in the fully autonomous generation of the organozinc reagents and the subsequent Negishi couplings. It has emerged as a key tool protocol in our group for the automated high-throughput synthesis of libraries with enriched Fsp^3. We believe that this end-to-end automated platform will be of high impact for medicinal chemistry as it allows access to novel diverse chemical space with increased Fsp^3, opening new avenues for drug discovery.

EXPERIMENTAL SECTION

General Information. Unless otherwise specified, reagents were obtained from commercial sources and used without further purification. The zinc used is Sigma-Aldrich granular, 30−100 mesh, 99%, CAS: 7440-66-6, 565148-1KG. Flow reactions were carried out in flow equipment Vapourtec R2S+/R4 using an Omnifit column 6 × 10 mm and a UV-150 Vapourtec photoreactor with 24 W blue LEDs and a 450 nm lamp. All microfluidic fittings were purchased from IDEX Health and Science. The solutions for the autosampler were prepared in 20 mL high-recovery vials closed with septum isolated caps (reference: CG-4916-33).

The LLE was performed in a Tecan Freedom EVO200 liquid handler equipped with an eight-channel disposable tip Air LiHa (Tecan disposable tips #30057817) and a Te-Shake (Tecan #10760726). All operations used aluminum blocks as the source and destination plates for the extraction (Analytical Sales & Services #24017) or plastic microtiter plates for analysis (Waters #186002643).

The ultra-high-performance LC (UPLC) measurement was performed using an HClass UPLC system from Waters (Milford, MA, USA) equipped with a quaternary solvent delivery pump, an autosampler with flow through a needle injector, a column compartment with two column positions, a diode array detector (DAD), and a sample organizer module for sample introduction into the system. The standard LC method used is flow: 1 m/L; temperature: RT; solvents: A (HCO_3NH_4 2.5 g/L, 32 mM) and B (CH_3CN); and initial conditions: 10% B. The A gradient was run to 100% B in 2.0 min, kept for 0.5 min, and then equilibration to 10% B in 0.5 min. Column: XBridge C18, 2.5 μm, 2.1 × 50 mm. Flow from the column was brought to a QDa mass spectrometer which was configured with an atmospheric-pressure ion source. Data acquisition was performed with MassLynx v4.2 and processed with OpenLynx browser software.

The HPLC purification was performed using an Autopurify system from Waters (Milford, MA, USA) equipped with a 2545 binary solvent delivery pump and two 515 isocratic pumps (one for the

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introduction of the sample into the column and the other one used as a make-up pump), a system fluidics organizer with two column positions, a 2767 sample manager, a 2998 DAD detector, and a QDa mass spectrometer. The standard HPLC method used is flows: 2545-binary pump: 44 m/L, 515-ACD pump: 1 m/L; make-up pump: 0.5 m/L; temperature: RT; solvents: A (HCO_3NH_4 2.5 g/L, 32 mM) and B (CH_3CN). Based on the Rt in LC−MS, a focused HPLC gradient was performed with a variation in the percentage of the B solvent of 40−50%. At 12.0 min, 100% B was reached and kept for 2.0 min. Equilibration to initial conditions was done in 0.5 min. Column: XBridge C18, 10 μm, 30 × 100 mm. Flow from the column was brought to phase doppler anemometry, and the outlet tubbing was brought to the QDa mass spectrometer which was configured with an atmospheric-pressure ion source. Data acquisition was performed with MassLynx v4.2 and processed with OpenLynx browser software.

^{1}H NMR spectra were recorded on Bruker DPX-400 and Bruker AV-500 spectrometers with standard pulse sequences, operating at 400 and 500 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane, which was used as an internal standard.

Purities of all compounds were determined by relative quantitative (q)HNMR applying eq 1[35] and by analytical RP-HPLC or RP-UPLC coupled to a mass spectrometry detector, using the area percentage method on the UV trace scanning from 200 to 450 nm.

$$P\ [\%] = \frac{\mathrm{nInt_t}\cdot \mathrm{MW_t}}{\mathrm{nInt_t}\cdot \mathrm{MW_t} + \sum_1^u (\mathrm{nInt_u}\cdot \mathrm{MW_u})} \times 100 \quad (1)$$

Eq 1: formula for relative qHNMR calculation according to ref 35. P = purity, $\mathrm{nInt_t}$ = normalized integral target compound, $\mathrm{MW_t}$ = molecular weight target compound, $\mathrm{nInt_u}$ = normalized integral impurity u, and $\mathrm{MW_u}$ = molecular weight impurity u.

General Procedure 1: Synthesis of the Combinatorial Library of the Indazole. Two stock solutions were prepared:

Solution A: the corresponding organozinc precursor (10 equiv, 1 mmol) in 2 mL of THF or DMF.

Solution B: the corresponding bromo-indazole (1 equiv, 0.1 mmol, 21.10 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

Both solutions were placed in the autosampler of the automatic R2-R4 Vapourtec reactor. Solution A was loaded onto loop A and pumped at a flow rate of 0.166 mL/min through the Zn column. The organozinc reagent formed was mixed at the outlet of the Zn column through a T-mixer with solution B at 0.166 mL/min, and this mixture with a total flow rate of 0.33 mL/min was irradiated with blue LEDs of 450 nm through a UV-150 photoreactor with a coil of 10 mL (30 min of residence time). The outcoming solution was collected into a fraction collector using the autosampler.

General Procedure 2: Catalyst Screening. Solution A1: 18 mL of a solution of 0.32 M [1-(*tert*-butoxycarbonyl)azetidin-3-yl]zinc-(II)iodide (**10**) was prepared following Nature Protocols 3 previously reported by the group using 2.54 g of *tert*-butyl 3-iodoazetidine-1-carboxylate in 18 mL of THF·LiCl (0.5 M solution).

Solution A2: 18 mL of a solution of 0.4 M benzyl zinc bromide (**11**) was prepared following Nature Protocols 3 previously reported by the group using 1.54 g of benzyl bromide in 18 mL of dry THF.

Solution B: intermediate **9** (1 equiv, 0.2 mmol, 88.28 mg); $Pd(dba)_2$ (0.05 equiv, 0.01 mmol, 6.04 mg); and the corresponding phosphine ligand (0.1 equiv, 0.02 mmol) in 2 mL of THF.

1 mL of solution B was mixed with 2 mL of solution A1 through a T-mixer at 0.166 mL/min each line, and this mixture with a total flow rate of 0.33 mL/min was irradiated with blue LEDs 450 nm through a UV-150 photoreactor with a coil of 10 mL (30 min of residence time). The outcoming solution was collected into a fraction collector using the autosampler.

General Procedure 3: Library Synthesis from Intermediate 9. Two stock solutions were prepared:

Solution A: the corresponding organozinc precursor (10 equiv, 1 mmol) in 2 mL of THF or DMF.

Solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

Both solutions were placed in the autosampler of the automatic R2-R4 Vapourtec reactor. Solution A was loaded onto loop A and pumped at a flow rate of 0.166 mL/min through the Zn column. The organozinc reagent formed was mixed at the outlet of the Zn column through a T-mixer with solution B at 0.166 mL/min, and this mixture with a total flow rate 0.33 mL/min was irradiated with blue LEDs of 450 nm through a UV-150 photoreactor with a coil of 10 mL (30 min of residence time). The outcoming solution was collected into a fraction collector using the autosampler.

Compound Characterization. *3-Benzyl-1-methyl-1H-indazole (**3a**).* It was obtained as colorless oil (1.5 mg, 7% yield) prepared by following general procedure 1: solution A: benzyl bromide (10 equiv, 1 mmol, 171 mg) in 2 mL of THF and solution B: 3-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{15}H_{14}N_2 + H]^+$: 223.1235 calculated, 223.1201 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.5−7.5 (m, 1H), 7.3−7.4 (m, 3H), 7.2−7.3 (m, 3H), 7.2−7.2 (m, 1H), 7.0−7.1 (m, 1H), 4.33 (s, 2H), 4.03 (s, 3H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ 143.8, 141.1, 139.3, 128.7, 128.4, 126.2, 126.1, 120.7, 119.8, 108.9, 35.2, 33.7; 94% qNMR purity; 99% HPLC purity.

*1-Methyl-3-[(tetrahydro-2H-pyran-4-yl)methyl]-1H-indazole (**4a**).* It was obtained as colorless oil (1.3 mg, 5% yield) prepared by following general procedure 1: solution A: 4-(iodomethyl)tetrahydro-2*H*-pyrane (10 equiv, 1 mmol, 226 mg) in 2 mL of a solution of THF·LiCl 0.5 M and solution B: 3-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{14}H_{18}N_2O + H]^+$: 231.1497 calculated, 231.1583 found. ^{1}H NMR (400 MHz, chloroform-*d*): δ ppm 7.95 (s, 1H), 7.58 (dd, J = 7.4, 1.8 Hz, 1H), 6.99−7.13 (m, 2H), 4.28 (s, 3H), 3.89−4.03 (m, 2H), 3.32 (td, J = 11.8, 2.2 Hz, 2H), 2.99 (d, J = 7.2 Hz, 2H), 1.83 (ttt, J = 11.2, 11.2, 7.4, 7.4, 3.8, 3.8 Hz, 1H), 1.57−1.64 (m, 2H), 1.38−1.51 (m, 2H). ^{13}C NMR (126 MHz, chloroform-*d*): δ ppm 138.84, 133.04, 128.61, 125.65, 122.40, 120.50, 119.40, 67.99, 39.63, 39.27, 37.30, 32.97; >99% qNMR purity; 100% HPLC purity.

*1-Methyl-3-(3,3,3-trifluoropropyl)-1H-indazole (**5a**).*[36] It was obtained as colorless oil (2 mg, 10% yield) prepared by following general procedure 1: solution A: 1,1,1-trifluoro-3-iodopropane (10 equiv, 1 mmol, 223 mg) in 2 mL of a solution of THF·LiCl 0.5 M and solution B: 3-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{11}H_{11}F_3N_2 + H]^+$: 229.0953 calculated, 229.1200 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.6−7.7 (m, 1H), 7.3−7.4 (m, 2H), 7.1−7.2 (m, 1H), 4.01 (s, 3H), 3.2−3.3 (m, 2H), 2.6−2.7 (m, 2H). ^{13}C NMR (101 MHz, chloroform-*d*): δ ppm 141.79, 140.88, 139.55−143.57, 128.23, 126.44, 122.29, 120.06, 119.76, 118.09−131.00, 109.03, 109.13, 35.22, 33.14, 29.42−38.14, 19.67, 14.84−21.88. ^{19}F NMR (471 MHz, chloroform-*d*): δ ppm −66.92 (br s, 3F); 95% qNMR purity; 91% HPLC purity.

*tert-Butyl 3-(1-Methyl-1H-indazol-3-yl)azetidine-1-carboxylate (**6a**).* It was obtained as colorless oil (5 mg, 25% yield) prepared by following general procedure 1: solution A: 1-Boc-3-iodoazetidine (10 equiv, 1 mmol, 283 mg) in 2 mL of a solution of THF·LiCl 0.5 M and solution B: 3-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{16}H_{21}N_3O_2 + H]^+$: 288.1712 calculated, 288.2000 found. ^{1}H NMR (400 MHz, chloroform-*d*): δ ppm 7.73 (d, J = 8.1 Hz, 1H), 7.34−7.45 (m, 2H), 7.14 (ddd, J = 8.0, 6.4, 1.4 Hz, 1H), 4.38−4.46 (m, 2H), 4.29−4.37 (m, 2H), 4.08−4.21 (m, 1H), 4.02 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, chloroform-*d*): δ ppm 135.57−159.70, 105.06−129.20, 79.53, 52.26−58.46, 23.43−38.18; 95% qNMR purity; 92% HPLC purity.

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4-(1-Methyl-1H-indazol-3-yl)-1-phenylpyrrolidin-2-one (**7a**). It was obtained as colorless oil (8 mg, 27% yield) prepared by following general procedure 1: solution A: 3-bromo-1-phenyl-pyrrolidin-2-one (10 equiv, 1 mmol, 240 mg) in 2 mL of a solution of THF and solution B: 3-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{18}H_{17}N_3O + H]^+$: 292.1449 calculated, 292.1100 found. ^{1}H NMR (400 MHz, chloroform-*d*): δ ppm 7.81 (dt, J = 8.1, 0.9 Hz, 1H), 7.65−7.74 (m, 2H), 7.31−7.45 (m, 4H), 7.09−7.24 (m, 2H), 4.36 (t, J = 8.7 Hz, 1H), 4.05−4.12 (m, 1H), 3.97−4.05 (m, 4H), 2.72−2.84 (m, 1H), 2.59−2.71 (m, 1H); ^{13}C NMR (101 MHz, chloroform-*d*): δ ppm 172.87, 141.82, 141.32, 139.61, 128.84, 126.44, 124.56, 122.43, 120.95, 120.39, 119.86, 109.02, 47.30, 43.35, 35.42, 24.82; 97% qNMR purity; 99% HPLC purity.

1-Methyl-3-[(phenylsulfonyl)methyl]-1H-indazole (**8a**).[37] It was obtained as colorless oil (1.6 mg, 3% yield) prepared by following general procedure 1: solution A: bromomethyl phenyl sulfone (10 equiv, 1 mmol, 235 mg) in 2 mL of a solution of DMF and solution B: 3-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{15}H_{14}N_2O_2S + H]^+$: 287.0854 calculated, 287.0315 found. ^{1}H NMR (chloroform-*d*, 500 MHz): δ 7.97 (s, 1H), 7.7−7.7 (m, 1H), 7.6−7.7 (m, 3H), 7.4−7.5 (m, 2H), 6.9−7.0 (m, 1H), 6.7−6.8 (m, 1H), 4.78 (s, 2H), 4.32 (s, 3H). ^{13}C NMR (chloroform-*d*, 126 MHz): δ 134.1, 132.8, 131.4, 129.0, 128.7, 122.5, 120.2, 59.3, 39.4; 92% qNMR purity; 100% HPLC purity.

4-Benzyl-1-methyl-1H-indazole (**3b**).[38] It was obtained as colorless oil (2.7 mg, 12% yield) prepared by following general procedure 1: solution A: benzyl bromide (10 equiv, 1 mmol, 171 mg) in 2 mL of THF and solution B: 4-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{15}H_{14}N_2 + H]^+$: 223.1235 calculated, 223.1265 found. ^{1}H NMR (400 MHz, chloroform-*d*): δ ppm 7.89 (d, J = 0.9 Hz, 1H), 7.14−7.35 (m, 7H), 6.92 (dd, J = 6.8, 0.8 Hz, 1H), 4.28 (s, 2H), 4.05 (s, 3H). ^{13}C NMR (101 MHz, chloroform-*d*): δ ppm 140.21, 140.12, 134.57, 131.65, 128.89, 128.52, 126.45, 126.27, 120.52, 107.12, 39.51, 35.64; 93% qNMR purity; 100% HPLC purity.

1-Methyl-4-[(tetrahydro-2H-pyran-4-yl)methyl]-1H-indazole (**4b**). It was obtained as colorless oil (2.4 mg, 10% yield) prepared by following general procedure 1: solution A: 4-(iodomethyl)tetrahydro-2*H*-pyrane (10 equiv, 1 mmol, 226 mg) in 2 mL of a solution of THF·LiCl 0.5 M and solution B: 4-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{14}H_{18}N_2O + H]^+$: 231.1497 calculated, 231.1491 found. ^{1}H NMR (400 MHz, chloroform-*d*): δ ppm 7.99 (d, J = 0.9 Hz, 1H), 7.27−7.35 (m, 1H), 7.22−7.26 (m, 1H), 6.87−6.93 (m, 1H), 4.07 (s, 3H), 3.87−3.99 (m, 2H), 3.32 (td, J = 11.8, 2.3 Hz, 2H), 2.86 (d, J = 7.2 Hz, 2H), 1.94 (dtq, J = 15.1, 7.5, 7.5, 3.7, 3.7, 3.7 Hz, 1H), 1.59 (s, 1H), 1.52−1.59 (m, 2H), 1.34−1.47 (m, 2H). ^{13}C NMR (126 MHz, chloroform-*d*): δ ppm 140.02; 133.83, 131.49, 126.24, 124.33, 120.67, 106.80, 68.02, 40.91, 36.70, 35.65; 96% qNMR purity; 100% HPLC purity.

1-Methyl-4-(3,3,3-trifluoropropyl)-1H-indazole (**5b**). It was obtained as colorless oil (10 mg, 45% yield) prepared by following general procedure 1: solution A: 1,1,1-trifluoro-3-iodopropane (10 equiv, 1 mmol, 223 mg) in 2 mL of a solution of THF·LiCl 0.5 M and solution B: 4-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{11}H_{11}F_3N_2 + H]^+$: 229.0953 calculated, 229.0952 found. ^{1}H NMR (400 MHz, chloroform-*d*): δ ppm 8.01 (d, J = 0.9 Hz, 1H), 7.29−7.37 (m, 2H), 6.97 (dd, J = 6.8, 0.8 Hz, 1H), 4.10 (s, 3H), 3.15−3.25 (m, 2H), 2.46−2.63 (m, 2H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ 140.1, 132.3, 130.6, 126.5, 119.2, 119.6, 107.7, 34.9, 25.7. ^{19}F NMR (471 MHz, chloroform-*d*): δ ppm −66.71 (br s, 3F); 91% qNMR purity; 90% HPLC purity.

tert-Butyl 3-(1-Methyl-1H-indazol-4-yl)azetidine-1-carboxylate (**6b**). It was obtained as colorless oil (12 mg, 43% yield) prepared by following general procedure 1: solution A: 1-Boc-3-iodoazetidine (10 equiv, 1 mmol, 283 mg) in 2 mL of a solution of THF·LiCl 0.5 M and solution B: 4-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{16}H_{21}N_3O_2 + H]^+$: 288.1712 calculated, 288.1725 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ 8.02 (d, 1H, J = 0.7 Hz), 7.3−7.4 (m, 2H), 7.04 (d, 1H, J = 6.7 Hz), 4.4−4.5 (m, 2H), 4.2−4.2 (m, 2H), 4.08 (s, 3H), 3.6−3.6 (m, 1H), 1.48 (s, 9H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ 156.3, 140.1, 135.2, 130.7, 126.2, 122.2, 118.0, 107.8, 79.5, 55.3, 51.4, 35.6, 32.0, 30.9, 28.3; 95% qNMR purity; 97% HPLC purity.

3-(1-Methyl-1H-indazol-4-yl)-1-phenylpyrrolidin-2-one (**7b**). It was obtained as colorless oil (21 mg, 70% yield) prepared by following general procedure 1: solution A: 3-bromo-1-phenyl-pyrrolidin-2-one (10 equiv, 1 mmol, 240 mg) in 2 mL of a solution of THF and solution B: 4-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{18}H_{17}N_3O + H]^+$: 292.1449 calculated, 292.1423 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.99 (d, 1H, J = 0.7 Hz), 7.7−7.7 (m, 2H), 7.3−7.4 (m, 4H), 7.2−7.2 (m, 1H), 7.0−7.1 (m, 1H), 4.28 (t, 1H, J = 9.0 Hz), 4.07 (s, 3H), 4.0−4.0 (m, 2H), 2.7−2.8 (m, 1H), 2.4−2.5 (m, 1H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ 173.4, 140.3, 139.4, 132.7, 131.1, 128.9, 126.4, 124.7, 123.1, 119.9, 119.4, 108.2, 48.0, 46.9, 35.6, 27.1; 92% qNMR purity; 93% HPLC purity.

1-Methyl-4-[(phenylsulfonyl)methyl]-1H-indazole (**8b**). It was obtained as colorless oil (2 mg, 6% yield) prepared by following general procedure 1: solution A: bromomethyl phenyl sulfone (10 equiv, 1 mmol, 235 mg) in 2 mL of a solution of DMF and solution B: 4-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{15}H_{14}N_2O_2S + H]^+$: 287.0854 calculated, 287.0534 found. ^{1}H NMR (500 MHz, chloroform-*d*): δ ppm 7.71 (d, J = 0.9 Hz, 1H), 7.60−7.65 (m, 2H), 7.56 (tt, J = 7.5, 1.2 Hz, 1H), 7.35−7.43 (m, 3H), 7.27−7.30 (m, 1H), 6.87 (d, J = 7.0 Hz, 1H), 4.64 (s, 2H), 4.04 (s, 3H). ^{13}C NMR (126 MHz, chloroform-*d*): δ ppm 139.84, 137.93, 133.87, 131.19, 128.95, 128.59, 126.07, 124.32, 123.84, 121.19, 109.68, 60.98, 35.71; 97% qNMR purity; 100% HPLC purity.

5-Benzyl-1-methyl-1H-indazole (**3c**).[39] It was obtained as colorless oil (10.7 mg, 48% yield) prepared by following general procedure 1: solution A: benzyl bromide (10 equiv, 1 mmol, 171 mg) in 2 mL of THF and solution B: 5-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{15}H_{14}N_2 + H]^+$: 223.1235 calculated, 223.1245 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.76 (d, 1H, J = 0.9 Hz), 7.4−7.4 (m, 1H), 7.1−7.2 (m, 7H), 3.94 (s, 2H), 3.86 (s, 3H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ ppm 141.3, 138.6, 133.2, 132.2, 128.7, 128.3, 127.9, 126.8, 125.9, 120.2, 108.8, 41.6, 35.3; 95% qNMR purity; 100% HPLC purity.

1-Methyl-5-[(tetrahydro-2H-pyran-4-yl)methyl]-1H-indazole (**4c**). It was obtained as colorless oil (1.2 mg, 5% yield) prepared by following general procedure 1: solution A: 4-(iodomethyl)tetrahydro-2*H*-pyrane (10 equiv, 1 mmol, 226 mg) in 2 mL of a solution of THF·LiCl 0.5 M and solution B: 5-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{14}H_{18}N_2O + H]^+$: 231.1497 calculated, 231.1501 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.90 (d, J = 0.9 Hz, 1H), 7.46 (d, J = 0.7 Hz, 1H), 7.32 (d, J = 8.6 Hz, 1H), 7.20 (dd, J = 8.7, 1.5 Hz, 1H), 4.06 (s, 3H), 3.89−4.00 (m, 2H), 3.33 (td, J = 11.8, 2.3 Hz, 2H), 2.65 (d, J = 7.2 Hz, 2H), 1.78 (ttd, J = 11.3, 7.4, 3.6 Hz, 1H), 1.52−1.57 (m, 2H), 1.29−1.43 (m, 2H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 132.2, 128.1, 120.5, 108.6, 68.0, 43.3, 37.5, 35.5, 33.0; 93% qNMR purity; 90% HPLC purity.

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*1-Methyl-5-[(tetrahydro-2H-pyran-4-yl)methyl]-1H-indazole (**5c**).*[13a] It was obtained as colorless oil (5 mg, 21% yield) prepared by following general procedure 1: solution A: 1,1,1-trifluoro-3-iodopropane (10 equiv, 1 mmol, 223 mg) in 2 mL of a solution of THF·LiCl 0.5 M and solution B: 5-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{11}H_{11}F_3N_2 + H]^+$: 229.0952 calculated, 229.1012 found. ^{1}H NMR (chloroform-*d*, 500 MHz): δ 7.93 (d, 1H, J = 0.9 Hz), 7.5−7.6 (m, 1H), 7.36 (d, 1H, J = 8.5 Hz), 7.2−7.3 (m, 1H), 4.08 (s, 3H), 3.0−3.0 (m, 2H), 2.4−2.5 (m, 2H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ 139.0, 132.3, 131.1, 128.0, 127.1, 125.3, 124.3, 119.8, 109.2, 35.6, 28. ^{19}F NMR (chloroform-*d*, 471 MHz): δ −66.53 (s, 3F) ppm; >99% qNMR purity; 91% HPLC purity.

*tert-Butyl 3-(1-Methyl-1H-indazol-5-yl)azetidine-1-carboxylate (**6c**).* It was obtained as colorless oil (2.5 mg, 9% yield) prepared by following general procedure 1: solution A: 1-Boc-3-iodoazetidine (10 equiv, 1 mmol, 283 mg) in 2 mL of a solution of THF·LiCl 0.5 M and solution B: 5-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{16}H_{21}N_3O_2 + H]^+$: 288.1712 calculated, 288.1613 found. ^{1}H NMR (400 MHz, chloroform-*d*, 27 °C): δ ppm 7.94 (s, 1H), 7.62 (s, 1H), 7.39 (d, J = 1.2 Hz, 2H), 4.38 (t, J = 8.7 Hz, 2H), 4.08 (s, 3H), 4.01 (dd, J = 8.4, 6.1 Hz, 2H), 3.79−3.91 (m, 1H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 156.4, 139.1, 134.4, 132.4, 125.4, 124.1, 118.7, 109.4, 79.5, 56.8, 35.6, 33.5, 28.4; 99% qNMR purity; 97% HPLC purity.

*3-(1-Methyl-1H-indazol-5-yl)-1-phenylpyrrolidin-2-one (**7c**).* It was obtained as colorless oil (1.7 mg, 6% yield) prepared by following general procedure 1: solution A: 3-bromo-1-phenyl-pyrrolidin-2-one (10 equiv, 1 mmol, 240 mg) in 2 mL of a solution of THF and solution B: 5-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{18}H_{17}N_3O + H]^+$: 292.1449 calculated, 292.1371 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.94 (d, 1H, J = 0.9 Hz), 7.7−7.7 (m, 3H), 7.3−7.4 (m, 4H), 7.1−7.2 (m, 1H), 4.07 (s, 3H), 3.9−4.0 (m, 3H), 2.6−2.8 (m, 1H), 2.3−2.4 (m, 1H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ ppm 132.8, 132.6, 129.1, 128.8, 127.0, 126.7, 124.8, 124.5, 120.2, 119.9, 119.7, 109.6, 109.3, 49.6, 46.7, 27.9; 98% qNMR purity; 99% HPLC purity.

*1-Methyl-5-[(phenylsulfonyl)methyl]-1H-indazole (**8c**).* It was obtained as colorless oil (2.4 mg, 8% yield) prepared by following general procedure 1: solution A: bromomethyl phenyl sulfone (10 equiv, 1 mmol, 235 mg) in 2 mL of a solution of DMF and solution B: 5-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{15}H_{14}N_2O_2S + H]^+$: 287.0854 calculated, 287.0904 found. ^{1}H NMR (400 MHz, chloroform-*d*): δ ppm 7.89 (d, J = 0.7 Hz, 1H), 7.54−7.67 (m, 3H), 7.37−7.46 (m, 3H), 7.30 (d, J = 8.8 Hz, 1H), 7.16 (dd, J = 8.8, 1.6 Hz, 1H), 4.41 (s, 2H), 4.06 (s, 3H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ ppm 139.7, 137.9, 133.7, 132.9, 128.9, 128.7, 128.6, 123.8, 120.1, 109.1, 62.8, 35.6; 95% qNMR purity; 93% HPLC purity.

*6-Benzyl-1-methyl-1H-indazole (**3d**).*[40] It was obtained as colorless oil (2 mg, 9% yield) prepared by following general procedure 1: solution A: benzyl bromide (10 equiv, 1 mmol, 171 mg) in 2 mL of THF and solution B: 6-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{15}H_{14}N_2 + H]^+$: 223.1235 calculated, 223.1169 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.91 (d, 1H, J = 0.9 Hz), 7.62 (d, 1H, J = 8.3 Hz), 7.3−7.3 (m, 2H), 7.2−7.2 (m, 3H), 7.17 (s, 1H), 7.0−7.0 (m, 1H), 4.13 (s, 2H), 4.02 (s, 3H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ ppm 140.9, 139.7, 132.5, 128.9, 128.5, 126.2, 122.5, 120.9, 108.5, 42.4, 35.4; >99% qNMR purity; 99% HPLC purity.

*1-Methyl-6-[(tetrahydro-2H-pyran-4-yl)methyl]-1H-indazole (**4d**).* It was obtained as colorless oil (2.5 mg, 10% yield) prepared by following general procedure 1: solution A: 4-(iodomethyl)tetrahydro-2*H*-pyrane (10 equiv, 1 mmol, 226 mg) in 2 mL of a solution of THF·LiCl 0.5 M and solution B: 6-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{14}H_{18}N_2O + H]^+$: 231.1497 calculated, 231.1500 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.91 (d, 1H, J = 0.7 Hz), 7.61 (d, 1H, J = 8.1 Hz), 7.13 (s, 1H), 6.9−7.0 (m, 1H), 4.04 (s, 3H), 3.9−4.0 (m, 2H), 3.3−3.4 (m, 2H), 2.68 (d, 2H, J = 7.2 Hz), 1.8−1.9 (m, 1H), 1.5−1.6 (m, 2H), 1.3−1.4 (m, 2H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ ppm 140.2, 138.6, 132.4, 122.3, 120.5, 108.5, 67.9, 43.9, 37.2, 35.3, 32.9; 90% qNMR purity; 100% HPLC purity.

*1-Methyl-6-(3,3,3-trifluoropropyl)-1H-indazole (**5d**).*[41] It was obtained as colorless oil (2.4 mg, 5% yield) prepared by following general procedure 1: solution A: 1,1,1-trifluoro-3-iodopropane (10 equiv, 1 mmol, 223 mg) in 2 mL of a solution of THF·LiCl 0.5 M and solution B: 6-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{11}H_{11}F_3N_2 + H]^+$: 229.0952 calculated, 229.1012 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.9−8.0 (m, 1H), 7.66 (d, 1H, J = 8.3 Hz), 7.20 (s, 1H), 7.0−7.0 (m, 1H), 4.06 (s, 3H), 3.0−3.1 (m, 2H), 2.4−2.5 (m, 2H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ 140.2, 137.5, 132.6, 128.0, 125.2, 122.9, 121.3, 108.0, 35.4, 28.7. ^{19}F NMR (471 MHz, chloroform-*d*): δ ppm −66.71 (br s, 3F); 92% qNMR purity; 100% HPLC purity.

*tert-Butyl 3-(1-Methyl-1H-indazol-6-yl)azetidine-1-carboxylate (**6d**).* it was obtained as colorless oil (2 mg, 3% yield) prepared by following general procedure 1: solution A: 1-Boc-3-iodoazetidine (10 equiv, 1 mmol, 283 mg) in 2 mL of a solution of THF·LiCl 0.5 M and solution B: 6-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{16}H_{21}N_3O_2 + H]^+$: 288.1712 calculated, 288.1700 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.96 (d, 1H, J = 0.7 Hz), 7.72 (d, 1H, J = 8.3 Hz), 7.30 (s, 1H), 7.1−7.2 (m, 1H), 4.41 (t, 2H, J = 8.7 Hz), 4.0−4.1 (m, 5H), 3.8−3.9 (m, 1H), 1.5−1.5 (m, 9H). ^{13}C NMR (chloroform-*d*, 126 MHz): δ ppm 140.8, 132.6, 121.5, 119.8, 106.6, 79.7, 35.6, 34.0, 28.4; 99% qNMR purity; 100% HPLC purity.

*3-(1-Methyl-1H-indazol-6-yl)-1-phenylpyrrolidin-2-one (**7d**).* It was obtained as colorless oil (4 mg, 7% yield) prepared by following general procedure 1: solution A: 3-bromo-1-phenyl-pyrrolidin-2-one (10 equiv, 1 mmol, 240 mg) in 2 mL of a solution of THF and solution B: 6-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{18}H_{17}N_3O + H]^+$: 292.1449 calculated, 292.1447 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.94 (d, 1H, J = 0.9 Hz), 7.7−7.7 (m, 3H), 7.4−7.4 (m, 3H), 7.2−7.2 (m, 1H), 7.1−7.1 (m, 1H), 4.06 (s, 3H), 3.9−4.0 (m, 3H), 2.7−2.8 (m, 1H), 2.3−2.5 (m, 1H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ ppm 173.8, 140.2, 139.4, 137.7, 132.6, 128.9, 124.7, 121.5, 120.8, 119.9, 108.3, 50.1, 46.8, 35.5, 28.0, 20.1; 95% qNMR purity; 84% HPLC purity.

*1-Methyl-6-[(phenylsulfonyl)methyl]-1H-indazole (**8d**).*[42] It was obtained as colorless oil (5 mg, 9% yield) prepared by following general procedure 1: solution A: bromomethyl phenyl sulfone (10 equiv, 1 mmol, 235 mg) in 2 mL of a solution of DMF and solution B: 6-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{15}H_{14}N_2O_2S + H]^+$: 287.0854 calculated, 287.0902 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.95 (d, 1H, J = 0.9 Hz), 7.6−7.7 (m, 2H), 7.6−7.6 (m, 2H), 7.4−7.5 (m, 2H), 7.20 (s, 1H), 6.8−6.8 (m, 1H), 4.46 (s, 2H), 4.01 (s, 3H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ ppm 133.8, 132.7, 128.9, 128.7, 123.1, 121.2, 111.5, 110.0, 63.3; >99% qNMR purity; 100% HPLC purity.

*7-Benzyl-1-methyl-1H-indazole (**3e**).*[43] It was obtained as colorless oil (3.4 mg, 8% yield) prepared by following general procedure 1: solution A: benzyl bromide (10 equiv, 1 mmol, 171 mg) in 2 mL of

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THF and solution B: 7-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{15}H_{14}N_2 + H]^+$: 223.1235 calculated, 223.1200 found. ^{1}H NMR (400 MHz, chloroform-*d*): δ ppm 7.95 (s, 1H), 7.64 (dd, J = 7.1, 2.0 Hz, 1H), 7.26−7.31 (m, 2H), 7.18−7.25 (m, 1H), 7.03−7.13 (m, 4H), 4.49 (s, 2H), 4.08 (s, 3H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ ppm 132.8, 129.0, 128.7, 128.3, 126.4, 120.8, 119.9, 39.0, 38.2; >99% qNMR purity; 100% HPLC purity.

*1-Methyl-7-[(tetrahydro-2H-pyran-4-yl)methyl]-1H-indazole (**4e**).* It was obtained as colorless oil (1.7 mg, 8% yield) prepared by following general procedure 1: solution A: 4-(iodomethyl)tetrahydro-2*H*-pyrane (10 equiv, 1 mmol, 226 mg) in 2 mL of a solution of THF·LiCl 0.5 M and solution B: 7-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{14}H_{18}N_2O + H]^+$: 231.1497 calculated, 231.1519 found. ^{1}H NMR (400 MHz, chloroform-*d*): δ ppm 7.92 (d, J = 0.7 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.13 (s, 1H), 6.96 (dd, J = 8.3, 1.2 Hz, 1H), 4.05 (s, 3H), 3.90−4.02 (m, 2H), 3.34 (td, J = 11.8, 2.1 Hz, 2H), 2.70 (d, J = 7.2 Hz, 2H), 1.84 (dtq, J = 15.0, 7.5, 7.5, 3.7, 3.7, 3.7 Hz, 1H), 1.59 (br d, J = 1.8 Hz, 2H), 1.28−1.48 (m, 2H). ^{13}C NMR (126 MHz, chloroform-*d*): δ ppm 138.81, 132.54, 125.29, 122.48, 120.69, 108.68, 68.06, 44.10, 37.38, 35.48, 33.09; >99% qNMR purity; 100% HPLC purity.

*1-Methyl-7-(3,3,3-trifluoropropyl)-1H-indazole (**5e**).*[44] It was obtained as colorless oil (1.3 mg, 3% yield) prepared by following general procedure 1: solution A: 1,1,1-trifluoro-3-iodopropane (10 equiv, 1 mmol, 223 mg) in 2 mL of a solution of THF·LiCl 0.5 M and solution B: 7-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{11}H_{11}F_3N_2 + H]^+$: 229.0952 calculated, 229.1105 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.96 (s, 1H), 7.6−7.6 (m, 1H), 7.0−7.2 (m, 2H), 4.30 (s, 3H), 3.3−3.4 (m, 2H), 2.4−2.6 (m, 2H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ 138.4, 133.1, 127.8, 127.2, 125.7, 125.1, 121.3, 120.9, 120.1, 39.1, 24.5. ^{19}F NMR (chloroform-*d*, 376 MHz): δ −66.62 (s, 3F); 93% qNMR purity; 90% HPLC purity.

*tert-Butyl 3-(1-Methyl-1H-indazol-7-yl)azetidine-1-carboxylate (**6e**).* It was obtained as colorless oil (1.5 mg, 5% yield) prepared by following general procedure 1: solution A: 1-Boc-3-iodoazetidine (10 equiv, 1 mmol, 283 mg) in 2 mL of a solution of THF·LiCl 0.5 M and solution B: 7-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{16}H_{21}N_3O_2 + H]^+$: 288.1712 calculated, 288.1700 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.94 (s, 1H), 7.62 (d, 1H, J = 7.6 Hz), 7.42 (d, 1H, J = 7.4 Hz), 7.1−7.2 (m, 1H), 4.3−4.4 (m, 2H), 4.21 (s, 3H), 4.2−4.2 (m, 2H), 4.0−4.1 (m, 1H), 1.47 (s, 9H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ ppm 156.2, 138.2, 132.9, 123.5, 120.8, 120.0, 79.7, 79.4, 55.2, 51.8, 39.1, 30.9, 29.1, 28.3; 95% qNMR purity; 100% HPLC purity.

*3-(1-Methyl-1H-indazol-7-yl)-1-phenylpyrrolidin-2-one (**7e**).* It was obtained as colorless oil (5 mg, 9% yield) prepared by following general procedure 1: solution A: 3-bromo-1-phenyl-pyrrolidin-2-one (10 equiv, 1 mmol, 240 mg) in 2 mL of a solution of THF and solution B: 6-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{18}H_{17}N_3O + H]^+$: 292.1449 calculated, 292.1441 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.97 (s, 1H), 7.7−7.8 (m, 2H), 7.6−7.7 (m, 1H), 7.4−7.4 (m, 2H), 7.2−7.2 (m, 2H), 7.1−7.1 (m, 1H), 4.6−4.7 (m, 1H), 4.36 (s, 3H), 4.0−4.1 (m, 2H), 2.7−2.8 (m, 1H), 2.3−2.5 (m, 1H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ ppm 173.6, 139.2, 132.9, 129.0, 125.9, 124.9, 122.2, 120.9, 120.4, 120.0, 46.7, 45.2, 39.5, 28.0; 96% qNMR purity; 99% HPLC purity.

*1-Methyl-7-[(phenylsulfonyl)methyl]-1H-indazole (**8e**).* It was obtained as colorless oil (3 mg, 5% yield) prepared by following general procedure 1: solution A: bromomethyl phenyl sulfone (10 equiv, 1 mmol, 235 mg) in 2 mL of a solution of DMF and solution B: 6-bromo-1-methyl-1*H*-indazole (1 equiv, 0.1 mmol, 21.10 mg), $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg), and XPhos (0.1 equiv, 0.01 mmol, 4.7 mg) in 1 mL of THF.

HRMS $[C_{15}H_{14}N_2O_2S + H]^+$: 287.0854 calculated, 287.0800 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.97 (s, 1H), 7.7−7.8 (m, 1H), 7.6−7.7 (m, 3H), 7.4−7.5 (m, 2H), 6.9−7.0 (m, 1H), 6.79 (d, 1H, J = 6.9 Hz), 4.78 (s, 2H), 4.31 (s, 3H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ ppm 134.1, 132.8, 131.4, 129.0, 128.7, 122.5, 120.2, 110.0, 59.3, 39.4, 29.7; 97% qNMR purity; 100% HPLC purity.

*tert-Butyl (S)-4-((7-Methyl-4-oxo-5-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)methyl)piperidine-1-carboxylate (**12**).* It was obtained as a sticky oil (30.4 mg, 59% yield) prepared by following general procedure 3: solution A: *tert*-butyl-4-(iodomethyl)piperidine-1-carboxylate (10 equiv, 1 mmol, 325 mg) in 2 mL of THF·LiCl 0.5 M solution and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{25}H_{31}F_3N_4O_3 + H]^+$: 493.2426 calculated, 393.2400 found (-Boc). ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.70 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.41 (s, 1H), 4.63−4.74 (m, 1H), 4.20 (dd, J = 12.5, 4.2 Hz, 1H), 4.01−4.15 (m, 2H), 3.96 (dd, J = 12.6, 7.5 Hz, 1H), 2.74 (br s, 2H), 2.63−2.70 (m, 2H), 2.61 (s, 1H), 1.69−1.80 (m, 2H), 1.64−1.68 (m, 3H), 1.44 (s, 9H), 1.15 (qd, J = 12.3, 4.6 Hz, 2H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 158.0, 154.8, 144.3, 140.6, 129.0, 128.4, 126.3, 125.3, 125.1, 79.2, 54.6, 52.4, 43.9, 41.0, 38.6, 36.9, 31.9, 30.8, 28.4, 21.9, 17.0, 13.4. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.53 (s, 3F); 97% qNMR purity; 98% HPLC purity.

*tert-Butyl 3-(((S)-7-Methyl-4-oxo-5-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)methyl)pyrrolidine-1-carboxylate (**13**).* It was obtained as colorless oil (31.4 mg, 63% yield) prepared by following general procedure 3: solution A: 1-Boc-3-(iodomethyl)-pyrrolidine (10 equiv, 1 mmol, 311 mg) in 2 mL of THF·LiCl 0.5 M solution and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{24}H_{29}F_3N_4O_3 + H]^+$: 479.2270 calculated, 479.2300 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.70 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.44 (s, 1H), 4.60−4.78 (m, 1H), 4.20 (dd, J = 12.5, 4.2 Hz, 1H), 3.96 (br dd, J = 12.3, 7.6 Hz, 1H), 3.37−3.53 (m, 2H), 3.15−3.30 (m, 1H), 2.77−3.07 (m, 3H), 2.51 (dt, J = 15.1, 7.5 Hz, 1H), 1.96 (br s, 1H), 1.52−1.62 (m, 1H), 1.46 (d, J = 1.4 Hz, 3H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 157.9, 154.6, 139.9, 126.2, 125.0, 78.9, 54.6, 52.4, 51.1, 45.4, 40.9, 39.5, 38.7, 31.6, 30.7, 28.5, 27.4, 16.9, 7.7. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.52 (s, 3F); 93% qNMR purity; 89% HPLC purity.

*tert-Butyl (S)-3-((7-Methyl-4-oxo-5-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)methyl)azetidine-1-carboxylate (**14**).* It was obtained as colorless oil (25.7 mg, 53% yield) prepared by following general procedure 3: solution A: 1-Boc-3-(iodomethyl)azetidine (10 equiv, 1 mmol, 297 mg) in 2 mL of THF·LiCl 0.5 M solution and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{23}H_{27}F_3N_4O_3 + H]^+$: 465.2113 calculated, 465.2100 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.70 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.42 (s, 1H), 4.63−4.75 (m, 1H), 4.20 (dd, J = 12.7, 4.2 Hz, 1H), 3.90−4.02 (m, 3H), 3.62 (dd, J = 8.8, 5.3 Hz, 2H), 3.08 (br d, J = 7.6 Hz, 2H), 2.80−2.94 (m, 1H), 1.68 (d, J = 6.5 Hz, 3H), 1.40−1.45 (m, 9H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 157.8, 156.4, 144.1, 139.6, 129.0, 128.7, 128.4, 126.2, 125.0, 124.3, 79.2, 54.6, 53.8, 52.4, 41.0, 31.7, 28.8, 28.7, 28.4, 16.9. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.52 (s, 3F); 97% qNMR purity; 100% HPLC purity.

*tert-Butyl (S)-3-{7-Methyl-4-oxo-5-[4-(trifluoromethyl)phenyl]-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl}azetidine-1-carboxylate (**15**).*[16b] It was obtained as colorless oil (24.4 mg, 52% yield) prepared by following general procedure 3: solution A: 1-Boc-3-iodoazetidine (10 equiv, 1 mmol, 283 mg) in 2 mL of THF·LiCl 0.5

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M solution and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{22}H_{25}F_3N_4O_3 + H]^+$: 451.1957 calculated, 451.3700 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.84 (s, 1H), 7.72 (d, 2H, J = 8.6 Hz), 7.50 (d, 2H, J = 8.3 Hz), 4.6−4.6 (m, 1H), 4.19 (br d, 2H, J = 2.3 Hz), 3.84 (br d, 2H, J = 5.3 Hz), 2.54 (br d, 1H, J = 4.4 Hz), 1.9−2.0 (m, 2H), 1.7−1.7 (m, 3H), 1.4−1.4 (m, 9H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ 157.0, 156.7, 156.6, 143.8, 138.6, 130.1, 127.3, 126.4, 125.2, 80.1, 61.6, 59.2, 54.3, 52.8, 28.4, 24.2, 18.0. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.59 (s, 3F); >90% qNMR purity; 83% HPLC purity.

(7S)-7-Methyl-3-(2-oxo-1-phenylpyrrolidin-3-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (**16**). It was obtained as colorless oil (10 mg, 21% yield) prepared by following general procedure 3: solution A: 3-bromo-1-phenylpyrrolidine-2-one (10 equiv, 1 mmol, 240 mg) in 2 mL of THF and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{24}H_{21}F_3N_4O_2 + H]^+$: 455.1694 calculated, 455.3370 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.65−7.72 (m, 2H), 7.63−7.67 (m, 1H), 7.63 (s, 1H), 7.51−7.53 (m, 1H), 7.50 (d, J = 8.3 Hz, 2H), 7.34−7.41 (m, 2H), 7.12−7.21 (m, 1H), 4.66−4.78 (m, 1H), 4.45−4.55 (m, 1H), 4.11−4.32 (m, 1H), 3.95−4.07 (m, 1H), 3.83−3.94 (m, 2H), 2.66−2.78 (m, 1H), 2.61−2.65 (m, 1H), 2.13−2.30 (m, 1H), 1.70−1.75 (m, 1H), 1.71 (dd, J = 6.7, 1.8 Hz, 2H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 173.3, 157.6, 144.2, 139.6, 139.4, 126.3, 125.1, 124.6, 120.0, 54.7, 52.5, 46.7, 41.0, 40.5, 27.6, 17.2, 16.8. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.52 (s, 3F); 95% qNMR purity; 94% HPLC purity.

(S)-7-Methyl-3-(tetrahydro-2H-pyran-4-yl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (**17**). It was obtained as colorless oil (8.7 mg, 22% yield) prepared by following general procedure 3: solution A: 4-iodo-tetrahydro-2*H*-pyrane (10 equiv, 1 mmol, 212 mg) in 2 mL of THF·LiCl 0.5 M solution and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{19}H_{20}F_3N_3O_2 + H]^+$: 380.1585 calculated, 380.3040 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.70 (d, J = 8.6 Hz, 2H), 7.45−7.55 (m, 3H), 4.69 (quind, J = 6.8, 4.2 Hz, 1H), 4.20 (dd, J = 12.5, 4.2 Hz, 1H), 3.99−4.04 (m, 2H), 3.95 (dd, J = 12.6, 7.5 Hz, 1H), 3.52 (tt, J = 11.8, 2.4 Hz, 2H), 3.43 (tt, J = 12.0, 3.8 Hz, 1H), 1.89 (dddt, J = 11.2, 7.2, 3.7, 1.9 Hz, 2H), 1.71−1.80 (m, 2H), 1.69 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 158.0, 144.2, 137.5, 131.8, 126.2, 125.1, 68.2, 54.5, 52.4, 41.0, 33.2, 31.1, 17.0. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.54 (s, 3F); >99% qNMR purity; 98% HPLC purity.

(7S)-7-Methyl-3-[(tetrahydrofuran-3-yl)methyl]-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (**18**). It was obtained as colorless oil (9.2 mg, 23% yield) prepared by following general procedure 3: solution A: 3-(iodomethyl)oxolane (10 equiv, 1 mmol, 212 mg) in 2 mL of THF·LiCl 0.5 M solution and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{19}H_{20}F_3N_3O_2 + H]^+$: 380.1585 calculated, 380.3073 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.70 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.46 (s, 1H), 4.62−4.78 (m, 1H), 4.20 (ddd, J = 12.5, 4.2, 1.8 Hz, 1H), 3.95 (ddd, J = 12.6, 7.5, 2.1 Hz, 1H), 3.81−3.91 (m, 2H), 3.75 (q, J = 7.4 Hz, 1H), 3.46 (dd, J = 8.4, 6.6 Hz, 1H), 2.81−2.96 (m, 2H), 2.56−2.66 (m, 1H), 2.02 (dtdd, J = 12.5, 7.6, 5.3, 2.4 Hz, 1H), 1.69 (dd, J = 6.6, 1.3 Hz, 3H), 1.62−1.66 (m, 1H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 158.0, 144.2, 140.0, 126.2, 126.0, 125.1, 73.0, 67.9, 54.6, 52.4, 39.7, 32.2, 27.6, 17.0. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.53 (s, 3F); >99% qNMR purity; 99% HPLC purity.

(S)-3-(3-Methoxypropyl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (**19**). It was obtained as colorless oil (5.7 mg, 15% yield) prepared by following general procedure 3: solution A: 1-iodo-3-methoxypropane (10 equiv, 1 mmol, 200 mg) in 2 mL of THF and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{18}H_{20}F_3N_3O_2 + H]^+$: 368.1585 calculated, 368.2800 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.67−7.71 (m, 2H), 7.48−7.52 (m, 2H), 7.47 (s, 1H), 4.63−4.73 (m, 1H), 4.19 (dd, J = 12.6, 4.0 Hz, 1H), 3.91−3.97 (m, 1H), 3.41 (t, J = 6.5 Hz, 2H), 3.33 (s, 3H), 2.84−2.90 (m, 2H), 1.86−1.95 (m, 2H), 1.68 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 158.0, 144.4, 139.9, 127.2, 126.2, 125.0, 72.2, 58.6, 54.6, 52.4, 30.1, 20.9, 17.0. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.51 (s, 3F); 93% qNMR purity; 100% HPLC purity.

(S)-7-Methyl-5-[4-(trifluoromethyl)phenyl]-3-(3,3,3-trifluoropropyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (**20**).[16b] It was obtained as colorless oil (19.6 mg, 48% yield) prepared by following general procedure 3: solution A: 1,1,1-trifluoro-3-iodopropane (10 equiv, 1 mmol, 223 mg) in 2 mL of THF·LiCl 0.5 M solution and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{17}H_{15}F_6N_3O + H]^+$: 392.1197 calculated, 392.1200 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.71 (d, J = 8.6 Hz, 2H), 7.44−7.53 (m, 3H), 4.70 (quind, J = 6.8, 4.2 Hz, 1H), 4.20 (dd, J = 12.7, 4.2 Hz, 1H), 3.96 (dd, J = 12.6, 7.5 Hz, 1H), 2.98−3.09 (m, 2H), 2.39−2.54 (m, 2H), 1.69 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 157.7, 144.1, 139.8, 126.3, 125.1, 54.7, 52.5, 34.5, 34.3, 34.0, 33.7, 17.4, 16.9. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.56 (s, 3F), −66.49 (s, 3F); 93% qNMR purity; 100% HPLC purity.

(S)-3-(Cyclopentylmethyl)-7-methyl-5-[4-(trifluoromethyl)-phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (**21**). It was obtained as colorless oil (6.3 mg, 16% yield) prepared by following general procedure 3: solution A: (iodomethyl)cyclopentane (10 equiv, 1 mmol, 210 mg) in 2 mL of THF and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{20}H_{22}F_3N_3O + H]^+$: 378.1793 calculated, 378.3630 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.69 (d, J = 8.6 Hz, 2H), 7.48−7.53 (m, 2H), 7.45 (s, 1H), 4.60−4.74 (m, 1H), 4.19 (dd, J = 12.5, 4.2 Hz, 1H), 3.94 (dd, J = 12.5, 7.6 Hz, 1H), 2.81 (d, J = 7.4 Hz, 2H), 2.09−2.26 (m, 1H), 1.70−1.80 (m, 2H), 1.66−1.70 (m, 3H), 1.58 (br s, 2H), 1.55 (br s, 2H), 1.17−1.27 (m, 2H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 158.1, 144.4, 140.1, 137.8, 127.6, 126.2, 125.1, 54.6, 52.3, 40.6, 32.5, 30.1, 25.1, 17.0. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.50 (s, 3F); 98% qNMR purity; 97% HPLC purity.

(S)-3-Isobutyl-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (**22**).[16b] It was obtained as colorless oil (8.5 mg, 23% yield) prepared by following general procedure 3: solution A: 1-iodo-2-methylpropane (10 equiv, 1 mmol, 184 mg) in 2 mL of THF and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{18}H_{20}F_3N_3O + H]^+$: 352.1636 calculated, 352.2800 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.69 (d, J = 8.6 Hz, 2H), 7.48−7.53 (m, 2H), 7.43 (s, 1H), 4.63−4.72 (m, 1H), 4.16−4.22 (m, 1H), 3.94 (dd, J = 12.5, 7.4 Hz, 1H), 2.68 (d, J = 7.2 Hz, 2H), 1.92 (quind, J = 13.5, 6.8 Hz, 1H), 1.66−1.70 (m, 3H), 0.92 (dd, J = 6.7, 0.7 Hz, 6H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 158.1, 144.4, 140.5, 126.2, 125.1, 54.6, 52.4, 33.1, 29.2, 22.4, 17.0. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.51 (s, 3F); 93% qNMR purity; 90% HPLC purity.

Ethyl (S)-3-{7-Methyl-4-oxo-5-[4-(trifluoromethyl)phenyl]-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl}propanoate (**23**). It was obtained as colorless oil (2.6 mg, 6% yield) prepared by following general procedure 3: solution A: ethyl 3-iodopropanoate (10 equiv, 1 mmol, 228 mg) in 2 mL of THF and solution B: intermediate **9** (1

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equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{19}H_{20}F_3N_3O_3 + H]^+$: 396.1535 calculated, 396.3020 found. ^{1}H NMR (400 MHz, chloroform-*d*): δ ppm 8.03 (s, 1H), 7.76 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.3 Hz, 2H), 5.64−5.73 (m, 1H), 4.75 (dd, J = 13.1, 4.0 Hz, 1H), 4.36 (q, J = 7.2 Hz, 1H), 4.17−4.24 (m, 2H), 3.09−3.27 (m, 2H), 2.79−2.89 (m, 2H), 1.72 (d, J = 6.5 Hz, 3H), 0.90 (s, 3H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ 172.9, 157.8, 144.2, 140.0, 126.2, 125.0, 109.3, 60.3, 54.7, 52.4, 34.6, 19.8, 17.0, 14.2. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.63 (s, 3F); >90% qNMR purity; 100% HPLC purity.

(S)-3-(1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one ***(24)***. It was obtained as colorless oil (13.4 mg, 30% yield) prepared by following general procedure 3: solution A: 4-iodotetrahydro-2*H*-thiopyran 1,1-dioxide (10 equiv, 1 mmol, 260 mg) in 2 mL of THF and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{19}H_{20}F_3N_3O_3S + H]^+$: 428.1255 calculated, 428.3400 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.70−7.75 (m, 2H), 7.52−7.54 (m, 1H), 7.46−7.52 (m, 2H), 4.66−4.78 (m, 1H), 4.17−4.26 (m, 1H), 3.98 (dd, J = 12.6, 7.7 Hz, 1H), 3.46−3.56 (m, 1H), 3.05−3.19 (m, 4H), 2.25−2.42 (m, 4H), 1.71 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 157.9, 143.9, 139.9, 137.2, 126.4, 125.1, 54.6, 52.5, 51.4, 31.7, 30.6, 16.9. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.59 (s, 3F); 98% qNMR purity; 94% HPLC purity.

Thyl (R)-2-[(tert-Butoxycarbonyl)amino]-3-((S)-7-methyl-4-oxo-5-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]-pyrazin-3-yl)propanoate ***(25)***. It was obtained as colorless oil (24.3 mg, 14% yield) prepared by following general procedure 3: solution A: methyl (*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-iodopropanoate (10 equiv, 1 mmol, 329 mg) in 2 mL of DMF and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{23}H_{27}F_3N_4O_5 + H]^+$: 497.2012 calculated, 497.31 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ 7.70 (d, 2H, J = 8.3 Hz), 7.51 (br d, 2H, J = 8.3 Hz), 7.48 (s, 1H), 5.69 (br d, 1H, J = 7.6 Hz), 4.6−4.7 (m, 1H), 4.5−4.6 (m, 1H), 4.1−4.2 (m, 1H), 3.9−4.0 (m, 1H), 3.72 (s, 3H), 3.1−3.3 (m, 2H), 1.69 (d, 3H, J = 6.5 Hz), 1.39 (s, 9H). ^{13}C NMR (chloroform-*d*, 101 MHz): δ 172.5, 158.2, 144.1, 140.6, 139.9, 129.9, 126.3, 125.2, 121.3, 120.7, 109.3, 79.5, 54.8, 54.5, 52.4, 52.3, 28.3, 26.7, 16.8. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.53 (s, 3F); 94% qNMR purity; 94% HPLC purity.

(S)-3-Benzyl-7-methyl-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one ***(26)***. It was obtained as colorless oil (13.4 mg, 33% yield) prepared by following general procedure 3: solution A: (bromomethyl)benzene (10 equiv, 1 mmol, 171 mg) in 2 mL of THF and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{21}H_{18}F_3N_3O + H]^+$: 386.1480 calculated, 386.2700 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.70 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.37 (s, 1H), 7.26−7.32 (m, 4H), 7.16−7.22 (m, 1H), 4.62−4.71 (m, 1H), 4.16−4.22 (m, 3H), 3.94 (dd, J = 12.5, 7.4 Hz, 1H), 1.67 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 158.0, 144.3, 140.4, 140.1, 128.8, 128.4, 126.5, 126.2, 126.1, 125.1, 54.6, 52.4, 41.0, 30.2, 17.0. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.50 (s, 3F); >99% qNMR purity; 100% HPLC purity.

Methyl (S)-4-((7-Methyl-4-oxo-5-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)methyl)benzoate ***(27)***. It was obtained as colorless oil (16.2 mg, 35% yield) prepared by following general procedure 3: solution A: methyl 4-(bromomethyl)-benzoate (10 equiv, 1 mmol, 229 mg) in 2 mL of THF and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{23}H_{20}F_3N_3O_3 + H]^+$: 444.1535 calculated, 444.3000 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.92−7.97 (m, 2H), 7.70 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.39 (s, 1H), 7.36 (d, J = 8.3 Hz, 2H), 4.64−4.74 (m, 1H), 4.24 (s, 2H), 4.20 (dd, J = 12.5, 4.2 Hz, 1H), 3.92−3.98 (m, 1H), 3.89 (s, 3H), 1.68 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 167.0, 157.9, 145.8, 144.2, 140.1, 129.8, 128.8, 128.1, 126.3, 125.1, 54.7, 52.5, 52.0, 41.0, 30.2, 17.0. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.52 (s, 3F); 99% qNMR purity; 97% HPLC purity.

(S)-7-Methyl-3-[4-(methylsulfonyl)benzyl]-5-[4-(trifluoromethyl)-phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one ***(28)***. It was obtained as colorless oil (22.5 mg, 46% yield) prepared by following general procedure 3: solution A: 1-(bromomethyl)-4-(methylsulfonyl)benzene (10 equiv, 1 mmol, 249 mg) in 2 mL of THF and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{22}H_{20}F_3N_3O_3S + H]^+$: 464.1256 calculated, 464.2600 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.81−7.85 (m, 2H), 7.70 (d, J = 8.3 Hz, 2H), 7.47−7.52 (m, 4H), 7.43 (s, 1H), 4.64−4.76 (m, 1H), 4.25−4.29 (m, 2H), 4.18−4.24 (m, 1H), 3.97 (dd, J = 12.7, 7.6 Hz, 1H), 3.02 (s, 3H), 1.69 (d, J = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 157.8, 147.0, 144.1, 140.0, 138.3, 129.6, 127.5, 126.3, 125.1, 124.4, 54.7, 52.5, 44.5, 41.0, 30.1, 16.9. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.53 (s, 3F); 98% qNMR purity; 99% HPLC purity.

(S)-7-Methyl-3-[3-(methylsulfonyl)benzyl]-5-[4-(trifluoromethyl)-phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one ***(29)***. It was obtained as colorless oil (24.4 mg, 50% yield) prepared by following general procedure 3: solution A: 1-(bromomethyl)-3-(methylsulfonyl)benzene (10 equiv, 1 mmol, 249 mg) in 2 mL of THF and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{22}H_{20}F_3N_3O_3S + H]^+$: 464.1256 calculated, 464.2800 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.83−7.86 (m, 1H), 7.77 (dt, J = 7.7, 1.3 Hz, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.61 (d, J = 7.9 Hz, 1H), 7.50 (d, J = 9.0 Hz, 2H), 7.44−7.48 (m, 1H), 7.40 (s, 1H), 4.71 (quind, J = 6.8, 4.2 Hz, 1H), 4.28 (d, J = 2.3 Hz, 2H), 4.21 (dd, J = 12.5, 4.2 Hz, 1H), 3.97 (dd, J = 12.7, 7.6 Hz, 1H), 3.02 (s, 3H), 1.69 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 157.9, 144.1, 142.3, 140.6, 140.0, 134.2, 129.4, 127.3, 126.3, 125.1, 124.6, 54.7, 52.5, 44.4, 29.9, 16.9. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.51 (s, 3F); >99% qNMR purity; 98% HPLC purity.

(S)-7-Methyl-3-[4-(trifluoromethyl)benzyl]-5-[4-(trifluoromethyl)-phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one ***(30)***. It was obtained as colorless oil (15.4 mg, 32% yield) prepared by following general procedure 3: solution A: 1-(bromomethyl)-4-(trifluoromethyl)benzene (10 equiv, 1 mmol, 239 mg) in 2 mL of THF and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{22}H_{17}F_6N_3O + H]^+$: 454.1354 calculated, 454.2900 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.70 (d, J = 8.6 Hz, 2H), 7.51 (t, J = 8.9 Hz, 4H), 7.37−7.43 (m, 3H), 4.64−4.74 (m, 1H), 4.23−4.26 (m, 2H), 4.17−4.23 (m, 1H), 3.92−3.98 (m, 1H), 1.68 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 157.9, 144.5, 144.2, 140.0, 129.1, 126.3, 125.4, 125.1, 54.7, 52.5, 41.0, 30.0, 17.0. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.36 (s, 3F), −62.53 (s, 3F); >99% qNMR purity; 99% HPLC purity.

(S)-7-Methyl-3-(3-methylbenzyl)-5-[4-(trifluoromethyl)phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one ***(31)***. It was obtained as colorless oil (16.4 mg, 39% yield) prepared by following general procedure 3: solution A: 1-(bromomethyl)-3-methylbenzene (10 equiv, 1 mmol, 185 mg) in 2 mL of THF and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

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HRMS $[C_{22}H_{20}F_3N_3O + H]^+$: 400.1637 calculated, 400.3420 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.67−7.72 (m, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.38 (s, 1H), 7.14−7.20 (m, 1H), 7.08−7.13 (m, 2H), 6.99−7.03 (m, 1H), 4.67 (quind, J = 6.7, 4.4 Hz, 1H), 4.19 (dd, J = 12.7, 4.2 Hz, 1H), 4.15 (s, 2H), 3.90−3.97 (m, 1H), 2.31 (s, 3H), 1.64−1.69 (m, 3H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 158.0, 144.3, 140.3, 140.2, 138.0, 129.6, 128.3, 126.9, 126.6, 126.2, 125.9, 125.1, 54.6, 52.4, 41.0, 30.1, 21.4, 17.0. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.49 (s, 3F); >99% qNMR purity; 100% HPLC purity.

*(S)-N,N-Dimethyl-4-((7-methyl-4-oxo-5-(4-(trifluoromethyl)-phenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)methyl)-benzenesulfonamide (**32**).* It was obtained as colorless oil (7.9 mg, 15% yield) prepared by following general procedure 3: solution A: 4-(bromomethyl)-*N*,*N*-dimethylbenzenesulfonamide (10 equiv, 1 mmol, 278 mg) in 2 mL of THF and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{23}H_{23}F_3N_4O_3S + H]^+$: 493.1521 calculated, 493.2800 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.65−7.74 (m, 4H), 7.44−7.54 (m, 4H), 7.41−7.42 (m, 1H), 4.67−4.77 (m, 1H), 4.26−4.28 (m, 2H), 4.19−4.25 (m, 1H), 3.98 (dd, J = 12.5, 7.6 Hz, 1H), 2.70 (s, 6H), 1.68−1.72 (m, 3H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 157.9, 146.3, 145.7, 144.1, 140.1, 133.4, 129.3, 128.0, 126.3, 125.1, 124.7, 54.7, 52.5, 41.0, 37.9, 30.0, 17.0. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.54 (s, 3F); 98% qNMR purity; 93% HPLC purity.

*(S)-7-Methyl-5-[4-(trifluoromethyl)phenyl]-3-{[2-(trifluoromethyl)pyridin-4-yl]methyl}-6,7-dihydropyrazolo[1,5-a]-pyrazin-4(5H)-one (**33**).* It was obtained as colorless oil (16.8 mg, 35% yield) prepared by following general procedure 3: solution A: 4-(bromomethyl)-2-(trifluoromethyl)pyridine (10 equiv, 1 mmol, 240 mg) in 2 mL of DMF and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{21}H_{16}F_6N_4O + H]^+$: 455.1306 calculated, 455.2940 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 8.59 (d, J = 5.1 Hz, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 0.7 Hz, 1H), 7.47−7.52 (m, 3H), 7.40−7.44 (m, 1H), 4.68−4.77 (m, 1H), 4.25−4.28 (m, 2H), 4.18−4.25 (m, 1H), 3.98 (dd, J = 12.7, 7.6 Hz, 1H), 1.71 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 157.7, 151.4, 150.0, 143.9, 140.0, 126.7, 126.3, 125.1, 122.8, 120.7, 54.7, 52.6, 41.0, 35.5, 29.6, 16.9. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.57 (s, 3F), −67.93 (s, 3F); 93% qNMR purity; 96% HPLC purity.

*(S)-7-Methyl-5-[4-(trifluoromethyl)phenyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]methyl}-6,7-dihydropyrazolo[1,5-a]-pyrazin-4(5H)-one (**34**).* It was obtained as colorless oil (18 mg, 38% yield) prepared by following general procedure 3: solution A: 5-(bromomethyl)-2-(trifluoromethyl)pyridine (10 equiv, 1 mmol, 240 mg) in 2 mL of DMF and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{21}H_{16}F_6N_4O + H]^+$: 455.1306 calculated, 455.3040 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 8.65 (d, J = 1.6 Hz, 1H), 7.81 (dd, J = 8.0, 1.5 Hz, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.54−7.59 (m, 1H), 7.49 (d, J = 8.3 Hz, 2H), 7.45−7.46 (m, 1H), 4.65−4.75 (m, 1H), 4.26 (s, 2H), 4.18−4.23 (m, 1H), 3.93−4.00 (m, 1H), 1.69 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 157.7, 150.2, 144.0, 139.9, 139.3, 137.5, 129.0, 126.3, 125.1, 123.8, 120.2, 54.7, 52.6, 41.0, 27.4, 16.9. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.56 (s, 3F), −67.73 (s, 3F); 93% qNMR purity; 98% HPLC purity.

*(S)-7-Methyl-3-[(phenylsulfonyl)methyl]-5-[4-(trifluoromethyl)-phenyl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (**35**).* It was obtained as colorless oil (2.7 mg, 6% yield) prepared by following general procedure 3: solution A: [(bromomethyl)sulfonyl]benzene (10 equiv, 1 mmol, 235 mg) in 2 mL of DMF and solution B: intermediate **9** (1 equiv, 0.1 mmol, 44.17 mg); $Pd(dba)_2$ (0.05 equiv, 0.005 mmol, 3.02 mg); and CPhos (0.1 equiv, 0.01 mmol, 4.3 mg) in 1 mL of THF.

HRMS $[C_{21}H_{18}F_3N_3O_3S + H]^+$: 450.1099 calculated, 450.2860 found. ^{1}H NMR (chloroform-*d*, 400 MHz): δ ppm 7.75−7.79 (m, 2H), 7.74 (s, 1H), 7.68 (d, J = 8.3 Hz, 2H), 7.56−7.62 (m, 1H), 7.43−7.49 (m, 2H), 7.30−7.35 (m, 2H), 4.69−4.80 (m, 2H), 4.60−4.68 (m, 1H), 4.09 (dd, J = 12.7, 4.2 Hz, 1H), 3.79 (dd, J = 12.6, 7.1 Hz, 1H), 1.64 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*, 27 °C): δ ppm 156.7, 141.4, 138.3, 133.4, 128.9, 128.6, 126.3, 124.9, 112.8, 54.6, 52.6, 51.5, 17.0. ^{19}F NMR (376 MHz, chloroform-*d*, 27 °C): δ ppm −62.59 (s, 3F); 98% qNMR purity; 97% HPLC purity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jmedchem.2c01646.

System setup scheme, internal volume, system setup, calibration curve, and product conversion (PDF)

■ AUTHOR INFORMATION

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Author Contributions

The manuscript was written with the contributions of all authors. All authors have approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

API, active pharmaceutical ingredient; DMSO, dimethylsulfoxide; DMTA, design−make−test−analyze; F(sp^3), fraction sp^3; HPLC, high-pressure liquid chromatography; HTE, high-throughput experimentation; LED, light-emitting diode; LiHa, liquid handler; LLE, liquid−liquid extraction; LC−MS, liquid chromatography−mass spectrometry; PMC, parallel medicinal chemistry; THF, tetrahydrofuran; TMSCl, trimethylsilylchloride

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