Generating Multibillion Chemical Space of Readily Accessible Screening Compounds

HIGHLIGHTS
A strategy for ultra-large readily accessible (REAL) compound libraries is described

Pre-validated two- or three-step three-component reaction sequences are used

A 29-billion chemical space with ~80% synthesis success rate has been easily obtained
Generating Multibillion Chemical Space of Readily Accessible Screening Compounds

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SUMMARY
An approach to the generation of ultra-large chemical libraries of readily accessible (“REAL”) compounds is described. The strategy is based on the use of two- or three-step three-component reaction sequences and available starting materials with pre-validated chemical reactivity. After the preliminary parallel experiments, the methods with at least ~80% synthesis success rate (such as acylation – deprotection – acylation of monoprotected diamines or amide formation – click reaction with functionalized azides) can be selected and used to generate the target chemical space. It is shown that by using only on the two aforementioned reaction sequences, a nearly 29-billion compound library is easily obtained. According to the predicted physico-chemical descriptor values, the generated chemical space contains large fractions of both drug-like and “beyond rule-of-five” members, whereas the strictest lead-likeness criteria (the so-called Churcher’s rules) are met by the lesser part, which still exceeds 22 million.

INTRODUCTION
Modern drug discovery relies heavily on efficient mining of the chemical space, which is a descriptor space of all possible compounds (Dobson, 2004). This task is difficult owing to the enormous size of the accessible chemical space, which is estimated to include at least $10^{60}$ “observable” molecules; such a huge number makes its comprehensive enumeration and synthetic exploration impossible (at least currently). Nevertheless, significant advances in computational techniques allowed virtual exploration of reasonably large portions of chemical space efficiently (Hoffmann and Gastreich, 2019; Walters, 2019). Many recent works addressed enumeration of compounds relevant to drug discovery; a prominent example is given by works of Reymond and co-workers who described the generation of all stable molecules with up to a certain number of heavy atoms (GDB) (Reymond, 2015). In combination with virtual screening as a powerful tool for prioritizing compounds before in vitro biological tests, such databases provide a promising tool to discover chemotypes for further optimization into drug candidates.

The major drawback of many virtually enumerated compound libraries is the unpredictable synthetic feasibility of their particular members, which hampers their experimental validation against the biological targets of interest. A possible approach to address this issue is based on the so-called forward synthetic analysis (Schreiber, 2000) and includes an enumeration of virtual libraries by the combination of synthons representing readily available building blocks. This strategy typically requires a reasonably large pool of reagents with established chemical behavior; it is not surprising therefore that it has been mostly used by the big pharma companies internally (e.g., Merck’s MASSIV [Walters, 2019], Boehringer Ingelheim’s Bi-Claim [Lessel et al., 2009], Eli Lilly’s Proximal Collection [Nicolaeu et al., 2016] or Pfizer Global Virtual Library [PGVL] [Hu et al., 2012]).

More than a decade ago, we have launched a similar project on the generation of a virtual compound database based on the experimentally validated synthetic accessibility (the so-called REAL database, where REAL stands for REadily Accessible) (Shivanyuk et al., 2007). The main idea of this project follows the “forward synthetic analysis” concept described above: the available building blocks with validated reactivity are transformed into synthons with denoted reactivity features, which are then subjected to virtual coupling according to the well-established reactions and exclusion rules based on the reactivity features (Figure 1). The database was growing through the years and has reached 1.2 billion compounds with a 3- to 4-week synthesis time and ca. 85% synthesis success rate (i.e., a fraction of experiments that could produce the...
target compound among all the experiments performed) (Enamine REAL compounds, 2020). Recently, its utility in combination with virtual screening was confirmed by discovery of highly potent AmpC \( \beta \)-lactamase (AmpC) inhibitors, \( D_3 \) dopamine receptor ligands (Lyu et al., 2019), and Kelch-like ECH-associated protein 1 (KEAP1) inhibitors (Gorgulla et al., 2020).

Further extension of this concept led to the development of the REAL Space, a searchable chemical space that is not typically stored as an enumerated database but generated upon query through a chemoinformatics software (Klingler et al., 2019). This feature tree-based (Rarey and Stahl, 2001; Boehm et al., 2008) engine allowed processing very large datasets currently reaching 13 billion molecules. In addition to that, it allowed considering more complex reaction sequences as compared with those shown in Figure 1.

In this work, we describe our approach to the generation of ultra-large, multibillion chemical space of the readily accessible compounds, which is based on the one-pot parallel reactions involving at least three building blocks (Figure 2).

**RESULTS AND DISCUSSION**

**Validation of Parallel Reactions**

To demonstrate the principles of the chemical space generation, we have selected five two- or three-step three-component reactions shown in Scheme 1. In most cases, modification of \( N \)-Boc-monoprotected diamines (building blocks 1) was envisaged, i.e., acylation – deprotection – acylation (reaction \( A \)), acylation – deprotection – arylation (\( B \)), acylation – deprotection – alkylation (\( C \)), and arylation – deprotection – acylation (\( D \)) sequences. In addition to that, the acylation – copper-catalyzed azide-alkyne click reaction sequence involving either amino azides (\( 2 \)) or azido acids (\( 3 \)) was studied. Starting from the available set of bifunctional building blocks 1–3 and capping reagents 4–10 (typically with validated reactivity in the corresponding one-step transformations), \( 5 \times 400 \) members of the libraries 11–15 were generated by random selection and virtual coupling of the corresponding synthons and then subjected to parallel synthesis.

The results of these validation experiments are shown in Table 1. Thus, methods \( A \) and \( D \) worked well and gave the target products with 77% and 81% synthesis success rate, as well as 44% and 38% average yield. Two-step reaction sequence \( E \) was even more efficient (80% synthesis success rate, 51% average yield). On the contrary, methods \( B \) and \( C \) (acylation – deprotection – arylation/alkylation) showed lower success rate (60% and 53%, respectively); the corresponding library members 12 and 13 were obtained with 43% and 31% average yield, respectively. Analysis of the crude reaction mixture showed that competitive aryla-

Taking into account the results described above, as well as the acceptable synthesis success rate for the REAL Database and the REAL Space (around 80%), only methods \( A \), \( D \), and \( E \) can be used to generate...
the ultra-large chemical space in further steps of this work. Methods B and C require further optimization before their incorporation into the toolbox of the studied strategy is possible; they might still be applicable for the library synthesis but with lower confidence.

In addition to that, success rates were analyzed for each of the reagents 1–3 to identify those demonstrating poor efficiency. Owing to the limited size of the dataset, only the building blocks for which at least 10 experiments were performed were taken into account. Figure 3 shows examples of the reagents showing both excellent and low reactivity in the reaction sequence studied. An obvious reason for the poor efficiency observed for compounds 1\{256\} and 3\{5\} is related to steric hindrance. Therefore, building blocks 1\{256\} and 3\{5\} were excluded from the further generation of the REAL chemical space.

**Generation of the Chemical Space**

First of all, building blocks 1–5 and 8–10 necessary for reaction sequences A and E were transformed into the synthons ready for the virtual coupling (see Figure 4 and Scheme 2). Of building blocks 4, 5, and 8–10, only those having validated reactivity in the corresponding one-step parallel syntheses were taken into consideration. In addition to that, cut-offs by molecular weight were applied for 4 and 5. For the bifunctional building blocks 1–3, visual inspection was also applied in addition to the results obtained from the preliminary tests described above. Apart from the SMILES representation (Weininger, 1988), reaction ID, and the role in the reaction sequence, reactivity features for the exclusion rules were recorded for each synthon, denoting steric hindrance around the corresponding functional groups. Again, for building blocks 4 and 5, these reactivity features were taken from the available statistical data for the one-step parallel reactions, whereas for monoprotected diamines 1, they were assigned manually for each of the functional groups after the visual inspection. It should be pointed out that the methodology does not involve quantitative reactivity measures; instead, binary ("yes/no") qualitative reactivity features are introduced for each synthon. For reaction sequence E, the reactivity features related to the steric factor were not taken into account. Although method D is fully suitable for the REAL Space generation, it was not included in the study at this point; the corresponding synthons are currently under development.
As a result, a total of 15,153 and 46,474 synthons were generated for the reaction sequences A and E, respectively (Table 2). Further processing of these synthons followed the workflow shown in Figure 5. The workflow included virtual coupling, application of the exclusion filters (addressing the reactivity features), and duplicate removal (performed with the InChI key representations [Heller et al., 2015] to increase the performance). The synthons with negative overall reactivity feature were excluded from the process prior the coupling. As for the steric factor, combinations of synthons with both negative features were excluded at the corresponding step. Table 3 summarizes the generation of the multibillion parts of the chemical space according to the methods A and E, as well as numbers of the readily accessible compounds that could be achieved.

As it is obvious from Table 3, the number of the “core” (bifunctional) building blocks, as well as sufficient and comparable accessibility of both “capping” reagents types are the key parameters affecting the size of the generated chemical space. Even with reasonably decreased sets of the “capping reagents,” multibillion numbers are easily achieved (as in the case of method A). For method E, both limited availabilities of the azide-containing bifunctional building blocks 2 and 3 and very different accessibility of the reagents 8/9 and 10 are responsible for the fact that the size of the resulting chemical space could only exceed a billion of structures. Nevertheless, even with all these limitations, we could generate a chemical space containing nearly 29 billion of readily accessible compounds using only two reaction sequences. As it was

Table 1. Validation Experiments for the Parallel Synthesis of Libraries 11–15
See Also Tables S1 and S2, Figures S1 and S2.

| # | Method | Conditions | Library | Success Rate, % | Average Yield, % |
|---|---|---|---|---|---|
| 1 | A. | 1. HATU, i-Pr₂NEt, DMSO, rt, 16 h 2. CF₃COOH, i-Pr₃SiH, H₂O, rt, 6 h 3. HATU, i-Pr₂NEt, DMSO, rt, 16 h | 11 | 77 | 34 44 |
| 2 | B. | 1-2. Same as for A 3. i-Pr₂NEt, NMP, 100°C, 16 h | 12 | 60 | 26 43 |
| 3 | C. | 1-2. Same as for A 3. i-Pr₂NEt, DMF, 80°C, 16 h | 13 | 53 | 16 31 |
| 4 | D. | 1. i-Pr₂NEt, NMP, 100°C, 16 h 2-3. Same as for A | 14 | 81 | 30 38 |
| 5 | E. | 1. HATU, i-Pr₂NEt, DMF, rt, 16 h 2. i-Pr₂NEt, Cu(OAc)₂, 80°C, 16 h | 15 | 80 | 41 51 |

Figure 3. Examples of Reagents 1–3 Showing Excellent and Poor Efficiency in the Methods Studied (Relative Configurations are Shown)
mentioned in the Introduction, this chemical space can be accessed either directly as a pre-enumerated database or through a feature-tree based search engine that performs generation of the corresponding structures upon a query. The current versions of the REAL Database and REAL Space include 0.27 and 9.9 billion members obtained according to methods A or E (since additional cut-offs on the physico-chemical and structural properties, as well as reagent availability, were applied).

**Predicted Physico-Chemical Descriptors**

Over the last decades, it was stressed out that physico-chemical properties of the compounds are important to drug discovery since they have a critical impact on the attrition rate of drug candidates (Grygorenko et al., 2020). It is therefore important to understand the capabilities of the generated chemical space in terms of providing the so-called drug-like or lead-like compounds (Nadin et al., 2012). To address this point, we have calculated physico-chemical descriptors of common interest to medicinal chemistry, i.e., molecular weight (MW), the logarithm of octanol-water partition coefficient (sLogP) (Wildman and Crippen, 1999), hydrogen bond acceptor/donor counts (HAcc/HDon), topologic polar surface area (TPSA), rotatable bond count (RotB), and $sp^3$-hybrid carbon atom fraction ($F_{sp^3}$).

As it follows from Figure 6 and Tables 4 and 5, the part of the chemical space generated by method A complies well with the classical drug-likeness criteria (i.e., Lipinski and Veber rules), whereas method E tends to provide heavier, more lipophilic compounds with higher hydrogen bond acceptor count, polar surface area, and rotatable bond count, an obvious consequence of the less stringent pre-selection of starting building blocks 8–10. Of course, the percentage of the fitting chemical space members goes down rapidly when more stringent lead-likeness criteria are applied. Nevertheless, a considerable number of the compounds remains even after application of the most rigorous Churcher’s rules (21.2, 0.95, and 22.1 Mln members by method A, E, and in total, respectively). Moreover, the significant fraction of the readily accessible “beyond-of-Ro5” members can be sometimes considered even advantageous taking into account the recently increased interest to such compounds in medicinal chemistry (DeGoey et al., 2018).

Comparison of the obtained results with the physico-chemical properties of 2,470 approved drugs deposited in DrugBank database (Wishart et al., 2018) showed that compounds produced by our approach tend to be heavier and slightly more lipophilic and have somewhat lower hydrogen bond donor count, which is
an obvious consequence of the chemical methodology used (Table 4 and Figure 5). They are also more sp³ enriched. All these features are in line with recent trends in drug discovery (good or bad) related to increased molecular complexity of new drug molecules (Grygorenko et al., 2020). On the contrary, the average values of total polar surface area, rotatable bond and hydrogen bond acceptor counts for the library members are more or less in line with those of the known drugs.

A short study was also performed to assess the relationship between the distribution of the synthons and the space covered by the generated databases. In particular, random selections were made from the sets of the synthons used for method A containing from 5% to 95% (with 5% step) of the initial structures, and the corresponding library members were selected from the final database. As it might be expected, the database size followed a cube function of the synthon subset size (Figure 6).

In addition to that, other synthon subsets were prepared by applying molecular weight cut-offs of 100–275 (with 25 MW step) to the initial synthon set used for method A, and the corresponding databases were generated. Owing to the properties of the initial synthon set, the size of the resulting databases increased dramatically for the cut-off range 100–200 (the so-called rule-of-two for building blocks [Goldberg et al., 2015]) and reached a maximum value after MW = 275 (a general cut-off used in the design of the initial set) (Figure 7A). Expectedly, distribution of physico-chemical properties (i.e., MW and sLogP) within the resulting virtual libraries correlated with increase in the corresponding values for the synthons (Figure 7B).

One might argue that the technology described in the current work is mostly based on very simple chemical transformations; therefore, its capability of producing novel, complex, and diverse molecules might be questionable. Nevertheless, a recent analysis by AstraZeneca scientists shows that this is not the case: even using only the amide formation reaction, very good results can be obtained in the early drug discovery provided that sufficient access to the corresponding building blocks is possible (Tomberg and Bostro¨m, 2020).

The physico-chemical features of the chemical space generated in this work are similar to those of DNA-encoded libraries (Kunig et al., 2018). In both cases, this is related to the fact that final library members are constructed from at least three building blocks, which increases the lower MW limit. In our opinion,

| # | Method | Reagents | Number of Synthons | No Reactivity Features | With Steric Features | Total |
|---|---|---|---|---|---|---|
| 1 | A | 1 | 467 | 196* | 663 |
| 2 | 4 | 6,706 | 6,277 | 7,977 |
| 3 | 5 | 4,511 | 1,063 | 6,514 |
| 4 | E | 2 | 41 | 0 | 41 |
| 5 | 3 | 52 | 0 | 52 |
| 6 | 8 | 17,944 | 550 | 18,494 |
| 7 | 9 | 26,434 | 646 | 27,080 |
| 8 | 10 | 807 | 0 | 807 |

*With steric hindrance at the free amino group (103), the protected amino group (82), or both (11).

Table 2. Number of Various Synthons Types Generated for Reaction Sequences A and E
the huge size of both DNA-encoded libraries and multibillion chemical spaces like the one described here-in can be considered as compensation for the increased molecular complexity (provided that efficient in vitro or in silico screening technologies are available to mine these ultra-large libraries). The success stories available in the literature for both technologies (Goodnow et al., 2017; Kunig et al., 2018; Lyu et al., 2019; Gorgulla et al., 2020) can serve as a justification for the above hypothesis.

| # | Method | No. of Synthons | No. of Library Members after |
|---|---|---|---|
|   |   | Virtual Coupling | Exclusion Filters | Duplicate Removal |
| 1 | A  | 15,154 | 34,450,924,014 | 32,733,348,058 | 27,297,397,644 |
| 2 | E  | 46,474 | 1,748,296,098 | 1,748,296,098 | 1,563,752,616 |
| 3 | Total | 60,431 | 36,199,220,112 | 34,481,644,156 | 28,861,150,260 |

**Table 3. Results of the Multibillion Chemical Space Generation**

Figure 6. Distribution of Physico-Chemical Descriptors Predicted for the Generated Chemical Space and Approved Drugs
See also Table S3.
Conclusions

Combined with the modern virtual screening tools, ultra-large libraries of readily accessible (“REAL”) compounds have proven their utility for the identification of highly potent hits against various biological targets. Herein, it is shown that a nearly 29-billion chemical space covering such synthetically feasible representatives can be easily generated using two- or three-step three-component reaction sequences and available starting materials with the chemical reactivity validated in one-step parallel reactions. Only the methods with at least \( \geq 80\% \) synthesis success rate (e.g., acylation – deprotection – acylation of monoprotected di-amines, as well as amide formation – click reaction with amino azides or azido acids) are acceptable to generate the target chemical space with sufficient synthetic confidence. It is shown that diversity of the “core” (bifunctional) building blocks, as well as nearly equal (but sufficient) accessibility of the “capping” re-agents are essential to obtain the largest numbers of the library members. Analysis of physico-chemical descriptors reveals that the generated chemical space contains large fractions of both drug-like and “beyond rule-of-five” members, whereas the strictest lead-likeness criteria (i.e., Churcher’s rules) are met for the lesser part (which still exceeds 22 million compounds). In our opinion, a combination of ultra-large REAL libraries and modern virtual screening tools is similar to DNA-encoded libraries (that have gained momentum in recent years) in terms of physico-chemical properties and chemical space coverage.

The approach proposed in this work is a substantial extension of the previous methodology that was based mainly on the two-component parallel reactions. It is also distinct from recent approaches relying heavily on artificial intelligence (Hoffmann and Gastreich, 2019) since it relies on the very robust and straightforward algorithm (Table 6).

Limitations of the Study

Possible limitations of the study include: (1) difficulties with handling of the full generated chemical space owing to the current hardware capabilities; this can be overcome by pre-selection of its part according to some criteria (like molecular weight) or by using special search engines like those mentioned in the Introduction; (2) a ca. 20% probability for the particular library member to be not produced according to the proposed synthetic methodology; a possible solution is to make a larger selection of the library members of interest (e.g., at least 100–200 representatives) to be synthesized with ca. 80% confidence; (3) impossibility to provide more or less precise synthetic feasibility for a particular compound—only an average value

| # | Method | MW  | sLogP | HAcc | HDon | TPSA, Å² | RotB | Fsp³ |
|---|--------|-----|-------|------|------|----------|------|------|
| 1 | A      | 440 | 2.61  | 5.3  | 1.5  | 93.7     | 6.4  | 0.56 |
| 2 | E      | 502 | 3.15  | 7.8  | 1.3  | 112.1    | 8.3  | 0.51 |
| 3 | Total  | 444 | 2.64  | 5.4  | 1.5  | 94.6     | 6.5  | 0.55 |
| 4 | DrugBank* | 395 | 2.05  | 5.1  | 2.4  | 96.9     | 6.4  | 0.47 |

Table 4. Average Values of Physico-Chemical Descriptors Predicted for the Generated Chemical Space and Approved Drugs

*Data for 2,470 drugs deposited in DrugBank (as of September 2020).

| # | Method | Rule of 5a | + Veber’s Rulesb | Rule of 4.5c | Rule of 4d | Churcher’s Rules²e,f |
|---|--------|------------|-------------------|-------------|----------|----------------------|
| 1 | A      | 89.1       | 82.6              | 56.9        | 16.9     | 0.08 (21,167,934)    |
| 2 | E      | 48.4       | 40.4              | 24.3        | 7.4      | 0.06 (952,402)       |
| 3 | Total  | 86.9       | 80.3              | 55.1        | 16.5     | 0.08 (22,120,336)    |

Table 5. Fractions of the Generated Chemical Space (%) Compliant with the Drug- and Lead-likeness Rules

*MW < 500, LogP<5, HAcc ≤ 10, HDon ≤ 5 (Lipinski et al., 1997).
²RotB ≤ 10, TPSA < 140 (Veber et al., 2002).
³MW < 450, LogP<4.5 (Oprea et al., 2001).
⁴MW < 400, LogP<4 (Hann and Oprea, 2004).
⁵MW 200 .. 350, LogP – 1 .. 3 (Nadin et al., 2012).
²Absolute numbers of the library members are given in brackets.
can be predicted for the method as a whole; (4) dynamic nature of the generated space due to the changes in the availability of the starting materials or information on their reactivity; this can be addressed by its regular periodic updates, as well as by applying cut-offs for the amounts of the stock reagents.

**Resource Availability**

**Lead Contact**

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Dr. Yurii S. Moroz, ysmoroz@gmail.com.

**Figure 7.** Relationship between the Size of the Generated Databases and the Size of the Synthon Subsets

Obtained by random selections from the initial synthon set for Method A, average from three independent selections; see also Table S4.

**Figure 8.** Properties of the Generated Chemical Space as a Function of the Molecular Weight Cut-offs Applied to the Initial Synthon Sets for Method A

(A and B) (A) The size of the generated databases. (B) Distribution of physico-chemical descriptors (MW and sLogP) for the generated chemical space.

See also Table S5.
Materials Availability

Compound library members generated in this study will be made available on request, but we shall require payment and/or a completed Materials Transfer Agreement if there is potential for commercial application.

Data and Code Availability

The complete lists of reagents used to construct the chemical space supporting the current study have not been deposited in a public repository owing to the company’s policy but are available from the corresponding author on request. There are restrictions on the availability of the in-house code and the synthon lists with the reactivity features that have been used to generate the chemical space owing to commercial confidentiality reasons.

METHODS

All methods can be found in the accompanying Transparent Methods supplemental file.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.isci.2020.101681.

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AUTHOR CONTRIBUTIONS

Conceptualization, O.O.G. and D.S.R.; Methodology, D.S.R. and A.C.; Software, I.D. and A.C.; Validation, D.S.R., I.D., and A.C.; Formal Analysis, O.O.G. and D.S.R.; Investigation, D.S.R., I.D., and K.E.G.; Data Curation, D.S.R., Y.S.M., and K.E.G.; Writing – Original Draft, O.O.G.; Writing – Review & Editing, O.O.G., D.S.R., and Y.S.M.; Visualization, O.O.G.; Supervision, O.O.G. and Y.S.M.; Project Administration, D.S.R. and Y.S.M.; Funding Acquisition, Y.S.M.

| Feature                                  | Approach Described in This Work                                      | Previous Feasibility-Based approachesa | Recent AI-Based approachesb |
|------------------------------------------|---------------------------------------------------------------------|---------------------------------------|-------------------------------|
| Virtual chemical space                   | Multibillion (over 3 x 10^10)                                       | Large (≈10^9)                         | Varied but typically less than 10^9 |
| Synthetic methods                        | Experimentally validated three-component two- or three-step reaction sequences | Experimentally validated two-component one-step reactions (mostly) | Various; typically based on the literature data (not always validated experimentally) |
| Algorithm                                | Very straightforward                                                |                                       | Sophisticated                 |
| Synthetic feasibility                    | Average value for each method or synthon, described as average synthesis success rate | Varied; from unknown to predicted for each particular member |                                       |
| Building block reactivity assessment     | Semi-qualitative; by a chemical expert aided by a computer         |                                       | Typically quantitative; by AI |

Table 6. Selected Approaches to Generate (Ultra-)large Virtual Chemical Space

aPrevious version of our REAL methodology is referred here; much larger datasets were also generated internally within big pharma companies (Hoffmann and Gastreich, 2019).

bThe subject was reviewed and critically accessed in a number of recent publications (Schneider, 2018; Schwaller and Laino, 2019; Brown et al., 2020; Lemonick, 2020).
DECLARATION OF INTERESTS
The authors declare no competing interests.

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Supplemental Information

Generating Multibillion Chemical Space
of Readily Accessible Screening Compounds

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**Figure S1.** The parallel reactions set up (related to Scheme 1 and Table 1). Reprinted with permission from: Bogolubsky, A. V., Moroz, Y. S. et al. (2018) *ACS Comb. Sci.* 20, 35–43.

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**Figure S2.** A laboratory oven with a shaker (related to Scheme 1 and Table 1). Reprinted with permission from: Bogolubsky, A. V., Moroz, Y. S. et al. (2018) *ACS Comb. Sci.* 20, 35–43.

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Table S3. Data used to build the diagrams in Figure 6.

| MW   | Method A | Method E | Total |
|------|----------|----------|-------|
|      | No. of cpds | % of cpds | No. of cpds | % of cpds | No. of cpds | % of cpds |
| <150 | 0          | 0        | 0      | 0        | 0          | 0         |
| 150  | 81         | 0.000    | 2      | 0.000    | 83         | 0.000     |
| 200  | 24865      | 0.000    | 1506   | 0.000    | 26371      | 0.000     |
| 250  | 2928095    | 0.011    | 146677 | 0.009    | 3074772    | 0.011     |
| 300  | 12684077   | 0.465    | 4818124| 0.308    | 131658601  | 0.456     |
| 350  | 16903248   | 6.192    | 45585024| 2.915    | 1735909846| 6.015     |
| 400  | 7949008636 | 2.361    | 182488242| 11.670   | 8131496878| 28.178    |
| 450  | 1189324321| 43.569   | 354039102| 22.640   | 12247283023| 42.440    |
| 500  | 4975547385 | 18.227   | 405752895| 25.947   | 5381300280| 18.647    |
| 550  | 644594878 | 2.361    | 312759436| 20.000   | 957354314 | 3.317     |
| 600  | 14483114   | 0.053    | 170017630| 10.872   | 184507744 | 0.739     |
| 650  | 400282     | 0.001    | 66893317 | 4.278    | 67293599 | 0.233     |
| >650 | 1088       | 0.000    | 18214639 | 1.165    | 18215727 | 0.063     |
| All  | 27297397644| 100      | 1560716594| 100     | 28858114238| 100      |

| sLogP | Method A | Method E | Total |
|-------|----------|----------|-------|
|      | No. of cpds | % of cpds | No. of cpds | % of cpds | No. of cpds | % of cpds |
| <-2  | 9680365 | 0.035  | 151552 | 0.010  | 9680365 | 0.034 |
| -2   | 71466439 | 0.262  | 1726477 | 0.110  | 73191116 | 0.254 |
| -1   | 387167997 | 1.418  | 12021028 | 0.769  | 399189025 | 1.384 |
| 0    | 1439959065 | 5.275  | 51921069 | 3.320  | 195117014 | 6.595 |
| 1    | 3783279941 | 13.859 | 151434129 | 9.684  | 3937623160 | 13.638 |
| 2    | 6666422497 | 24.421 | 298753963 | 19.105 | 6666422497 | 24.142 |
| 3    | 7536160005 | 27.608 | 399412101 | 25.542 | 7536160005 | 27.050 |
| 4    | 5124595911 | 18.773 | 354665763 | 22.680 | 5124595911 | 18.991 |
| 5    | 1906945290 | 6.986  | 201575452 | 12.890 | 1906945290 | 6.791  |
| 6    | 344999995  | 1.262  | 72158367 | 4.614  | 344999995  | 1.444  |
| >6   | 27221939 | 0.100  | 19932715 | 1.275  | 47154654 | 0.163  |
| All  | 27287717279 | 100   | 1563601064 | 100    | 28851318343 | 100    |

| HAcc | Method A | Method E | Total |
|------|----------|----------|-------|
|      | No. of cpds | % of cpds | No. of cpds | % of cpds | No. of cpds | % of cpds |
| 0    | 0         | 0        | 0      | 0        | 0          | 0         |
| 1    | 0         | 0        | 0      | 0        | 0          | 0         |
| 2    | 572147399 | 2.096    | 0      | 0        | 572147399 | 1.982     |
| 3    | 2747814751 | 10.066   | 0      | 0        | 2747814751 | 9.521     |
| 4    | 5737303319 | 21.018   | 9610832 | 0.615    | 5746914151 | 19.912    |
| 5    | 7004112548 | 25.659   | 81854862 | 5.235    | 7085967410 | 24.552    |
| 6    | 5696047963 | 20.867   | 232148220 | 14.846  | 5928196183 | 20.540    |
| 7    | 3345554738 | 12.256   | 369738217 | 23.644  | 3715292955 | 12.873    |
| 8    | 1493257821 | 5.470    | 372963949 | 23.851  | 1866221770 | 6.466     |
| 9    | 520065936 | 1.905    | 265014059 | 16.947  | 785079995 | 2.720     |
| 10   | 143470151 | 0.526    | 143570857 | 9.181   | 287041008 | 0.95      |
| >10  | 37623018 | 0.138    | 88851620 | 5.682   | 126474638 | 0.438     |
| All  | 27297397644 | 100   | 1563752616 | 100     | 28861150260 | 100      |
### HDon Method

| No. of cpds | % of cpds | No. of cpds | % of cpds | No. of cpds | % of cpds |
|-------------|-----------|-------------|-----------|-------------|-----------|
| 0           | 3187748954 | 11.677      | 313693134 | 20.060      | 3501442088 | 12.265     |
| 1           | 11514063585 | 42.180      | 661866465 | 42.325      | 12175930050 | 42.651     |
| 2           | 8814595589  | 32.291      | 436524642 | 27.915      | 9251120231  | 32.406     |
| 3           | 3107816412  | 11.385      | 129777225 | 8.299       | 3237593637  | 11.341     |
| 4           | 602113896   | 2.205       | 20101362  | 1.285       | 622215258   | 2.179      |
| 5           | 66845429    | 0.244       | 1703616   | 0.109       | 68549045    | 0.240      |
| >5          | 4213779     | 0.015       | 86172     | 0.005       | 4299951     | 0.015      |
| All         | 27297397644 | 100         | 1250059482| 100         | 28445767201 | 100        |

### RotB Method

| No. of cpds | % of cpds | No. of cpds | % of cpds | No. of cpds | % of cpds |
|-------------|-----------|-------------|-----------|-------------|-----------|
| 0           | 29957     | 0.000       | 0         | 0.000       | 29957     | 0.000     |
| 1           | 6028530   | 0.022       | 104       | 0.000       | 6028634   | 0.021     |
| 2           | 317910606 | 1.165       | 92306     | 0.006       | 310800972 | 1.076     |
| 3           | 1508875367 | 5.528      | 14538387  | 0.930       | 1523413754 | 5.356     |
| 4           | 3381280817 | 12.387     | 59564079  | 3.809       | 3440984896 | 12.096     |
| 5           | 4774360963 | 17.490     | 133246511 | 8.521       | 4907607474 | 17.253     |
| 6           | 5056521442 | 18.524     | 207941672 | 13.298      | 5264463114 | 18.507     |
| 7           | 4374782280 | 16.026     | 250341558 | 16.009      | 4625123838 | 16.259     |
| 8           | 3246990992 | 11.895     | 247807164 | 15.847      | 3494798156 | 12.286     |
| 9           | 2131540056 | 7.809      | 210797401 | 13.480      | 2342374574 | 8.234      |
| 10          | 1255491384 | 4.599      | 159490637 | 10.199      | 1414982021 | 4.974      |
| 11          | 670246782  | 2.455      | 109918272 | 7.029       | 780165054  | 2.743      |
| 12          | 326795259  | 1.197      | 70088476  | 4.482       | 396883735  | 1.395      |
| 13          | 146403645  | 0.536      | 42137017  | 2.695       | 188540662  | 0.663      |
| 14          | 61249058   | 0.224      | 24518316  | 1.568       | 85767374   | 0.302      |
| 15          | 24370304   | 0.089      | 14243016  | 0.911       | 38613320   | 0.136      |
| >15         | 14520202   | 0.053      | 19027700  | 1.217       | 33547902   | 0.118      |
| All         | 27297397644 | 100        | 1148369557| 100         | 28445767201| 100        |

### Fsp³ Method

| No. of cpds | % of cpds | No. of cpds | % of cpds | No. of cpds | % of cpds |
|-------------|-----------|-------------|-----------|-------------|-----------|
| 0           | 602496    | 0.002       | 1442908   | 0.092       | 2045404   | 0.007     |
| 0.1         | 47724123  | 0.175       | 20483171  | 1.310       | 68207294  | 0.236     |
| 0.2         | 453879381 | 1.663       | 79048294  | 5.055       | 532927675 | 1.847     |
| 0.3         | 1904676513| 6.978       | 185528454 | 11.864      | 2090204967| 7.242     |
| 0.4         | 4954266113| 18.149      | 303197434 | 19.389      | 5257463547| 18.216     |
| 0.5         | 5884585398| 21.557      | 299512055 | 19.153      | 6184097453| 21.427     |
| 0.6         | 5967794224| 21.862      | 334194659 | 21.371      | 6301988883| 21.836     |
| 0.7         | 4483237975| 16.424      | 173555288 | 11.099      | 4656793263| 16.135     |
| 0.8         | 2213453075| 8.109       | 123783792 | 7.916       | 2337236867| 8.098      |
| 0.9         | 1387178346| 5.082       | 43006561  | 2.750       | 1430184907| 4.955      |
| All         | 27297397644 | 100        | 1563752616| 100         | 28861150260| 100        |
### Table S4. Data used to build the diagram in Figure 7.

| % of the initial synthon set | Database size |
|-----------------------------|---------------|
|                            | Selection 1   | Selection 2   | Selection 3   | Average   |
| 0                           | 0             | 0             | 0             | 0         |
| 5                           | 3403925       | 3428214       | 3390057       | 3407399   |
| 10                          | 27110556      | 27394230      | 27186189      | 27230325  |
| 15                          | 91840658      | 91732904      | 91402990      | 91658851  |
| 20                          | 218527689     | 218963333     | 218703739     | 218731587 |
| 25                          | 425632157     | 426936973     | 426736465     | 426435198 |
| 30                          | 738353634     | 737414660     | 738647994     | 738138763 |
| 35                          | 1167189585    | 1170624550    | 1171458018    | 1169757384 |
| 40                          | 1747577364    | 1747527058    | 1740846423    | 1745316948 |
| 45                          | 2480899801    | 2486719501    | 2487750229    | 2485123177 |
| 50                          | 3417793869    | 341799399     | 3419592448    | 3418061905 |
| 55                          | 4537339006    | 4550268732    | 4543764987    | 4543790908 |
| 60                          | 5906370545    | 5900799500    | 5911540359    | 5906236801 |
| 65                          | 7486457003    | 7501975505    | 7499292741    | 7495908416 |
| 70                          | 9357690180    | 9370507250    | 9356875950    | 9361691127 |
| 75                          | 11508760458   | 11507498938   | 11504122179   | 11506793858 |
| 80                          | 13948650520   | 13949995515   | 13962963245   | 13953869760 |
| 85                          | 16773978528   | 16766934320   | 16776040301   | 16772317716 |
| 90                          | 19909715437   | 19905994815   | 19912856421   | 19909522224 |
| 95                          | 23416800942   | 23390466947   | 23412827679   | 23406698523 |
| 100                         | 27297397644   | 27297397644   | 27297397644   | 27297397644 |
Table S5. Data used to build the diagrams in Figure 8.

| Synthon MW cut-off | Database size     |
|--------------------|-------------------|
| 100                | 1619048           |
| 125                | 159135441         |
| 150                | 2880024222        |
| 175                | 16838150263       |
| 200                | 26512675168       |
| 225                | 27163855694       |
| 250                | 27287325628       |
| 275                | 27297397644       |
| 300                | 27297397644       |

| Database member MW | % of the database with the synthon MW cut-off |
|--------------------|----------------------------------------------|
|                    | <100  | <150  | <200  | <300  |
| <150               | 0.00  | 0.00  | 0.00  | 0.00  |
| 150                | 0.005 | 0.000 | 0.000 | 0.000 |
| 200                | 1.229 | 0.001 | 0.000 | 0.000 |
| 250                | 47.054| 0.101 | 0.011 | 0.011 |
| 300                | 51.712| 4.027 | 0.478 | 0.465 |
| 350                | 0.00  | 37.191| 6.375 | 6.192 |
| 400                | 0.00  | 55.673| 29.960| 29.120|
| 450                | 0.00  | 3.006 | 44.520| 43.569|
| 500                | 0.00  | 0.00  | 17.388| 18.227|
| 550                | 0.00  | 0.00  | 1.267 | 2.361 |
| 600                | 0.00  | 0.00  | 0.000 | 0.053 |
| >600               | 0.00  | 0.00  | 0.001 |       |

| Database member LogP | % of the database with the synthon MW cut-off |
|----------------------|----------------------------------------------|
|                      | <100 | <150  | <200  | <300  |
| <-2                  | 0.063| 0.065 | 0.035 | 0.035 |
| -2                   | 0.904| 0.534 | 0.259 | 0.262 |
| -1                   | 6.737| 2.978 | 1.417 | 1.418 |
| 0                    | 25.170| 10.439| 5.299 | 5.275 |
| 1                    | 41.718| 23.251| 13.966| 13.859|
| 2                    | 23.541| 30.885| 24.615| 24.421|
| 3                    | 1.866 | 22.663| 27.724| 27.608|
| 4                    | 0.00  | 8.073 | 18.662| 18.773|
| 5                    | 0.00  | 1.075 | 6.780 | 6.986 |
| 6                    | 0.00  | 0.036 | 1.160 | 1.262 |
| >6                   | 0.00  | 0.000 | 0.082 | 0.100 |
Transparent methods

General. All chemicals and solvents were obtained from Enamine Ltd. and used without further purification. $^1$H, $^{13}$C, and $^{19}$F NMR spectra were acquired on Bruker Advance DRX 400, Bruker Avance DRX 500, and Agilent ProPulse 600 spectrometers using DMSO-$d_6$ as a solvent (unless noted otherwise). Melting points were determined on a Buchi melting point apparatus. LCMS data were recorded on Agilent 1100 HPLC equipped with diode-matrix and mass-selective detector Agilent LC/MSD SL instrument, column: Zorbax SB-C18, 4.6 mm × 15 mm; eluent, A, acetonitrile – water with 0.1% of TFA (95:5), B, water with 0.1% of TFA; flow rate: 1.8 mL/min. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Kyiv National Taras Shevchenko University.

The transformation of the reagents into the synthons was performed by our proprietary software; this can be also easily done using an open-source software e.g. ChemAxon tools (www.chemaxon.com). Virtual coupling, InChi key generation and duplicate removal, calculation of descriptor values, filtering by physico-chemical parameters and structural features were performed using RDKit (www.rdkit.org) in Python (www.python.org).

Syntheses of the libraries were typically performed in 8 mL vials (Figure S1); loading of the reagents, as well as work-up of the reaction mixtures was performed manually in a parallel fashion. If any of the reagents 1–10 was used as a salt, an additional amount of i-Pr$_2$NEt (0.55 mmol per each equivalent of acid was added to the reaction mixture to convert the reagent into a free form at the corresponding step of the procedure indicated by an asterisk (*). The reactions were performed in ultrasonic baths or laboratory ovens with a shaker (Figure S2); up to 1,000 vials could be used simultaneously. Centrifugal evaporators were used to remove the solvents from the vials in a parallel fashion.

General procedure for the reaction sequence A. N-Boc-diamine 1 (0.5 mmol), carboxylic acid 4 (0.6 mmol), i-Pr$_2$NEt (1.25 mmol*), and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.575 mmol) were mixed in dry DMSO (appr. 1.4 mL). The reaction mixture was sealed and left at ambient temperature for 16 h, then evaporated under reduced pressure. Then the cleavage cocktail containing trifluoroacetic acid, triisopropylsilane, and water (93:5:2) (appr. 2 mL) was added in one portion. The mixture was stirred at ambient temperature for 6 h and evaporated under reduced pressure. The residue was taken up in DMSO (appr. 1.4 mL). Carboxylic acid 5 (0.6 mmol), i-PrNEt$_2$ (3 mmol*), and HATU (0.6 mmol) were added in one portion, the reaction mixture was sealed and left at ambient temperature for 16 h, then cooled and evaporated under reduced pressure. The residue was dissolved in DMSO (appr. 1 mL), filtered, analyzed by LCMS, and transferred for the HPLC purification.

$N$-(9-Acetyl-9-azabicyclo[3.3.1]nonan-3-yl)-1H-indazole-3-carboxamide (11{52,55,23})
Beige solid. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 13.56 (s, 1H), 8.24 (d, $J = 8.8$ Hz, 1H), 8.16 (d, $J = 8.1$ Hz, 1H), 7.60 (d, $J = 8.4$ Hz, 1H), 7.40 (t, $J = 7.2$ Hz, 1H), 7.23 (t, $J = 7.5$ Hz, 1H), 4.97 – 4.74 (m, 1H), 4.34 – 4.07 (m, 1H), 3.93 – 3.59 (m, 1H), 2.36 – 2.04 (m, 3H), 2.03 (s, 3H), 1.72 – 1.58 (m, 2H), 1.58 – 1.18 (m, 5H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 168.0, 162.0, 141.6, 138.8, 126.9, 122.4, 122.1, 122.0, 111.1, 47.8, 41.9, 40.9, 32.0, 31.5, 31.0, 21.5, 13.9. LC/MS (CI): $m/z = 327$ [M+H]$^+$. Anal. calcd. for C$_{18}$H$_{22}$N$_4$O$_2$: C 66.24; H 6.79; N 17.17. Found: C 65.89; H 6.97; N 16.96.

2-Ethyl-$N$-(4-(2-methylthiazole-5-carboxamido)butan-2-yl)oxazole-4-carboxamide (11{25,19,9})

![Chemical structure]

Yellowish oil. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.48 (t, $J = 5.5$ Hz, 1H), 8.42 (s, 1H), 8.12 (s, 1H), 7.95 (d, $J = 8.8$ Hz, 1H), 4.07 – 3.98 (m, 1H), 3.28 – 3.20 (m, 1H), 3.19 – 3.12 (m, 1H), 2.76 (q, $J = 7.6$ Hz, 2H), 2.63 (s, 3H), 1.81 – 1.67 (m, 2H), 1.23 (t, $J = 7.6$ Hz, 3H), 1.14 (d, $J = 6.5$ Hz, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 169.7, 165.6, 160.2, 160.0, 142.9, 141.7, 136.5, 135.5, 42.9, 37.1, 35.8, 21.4, 20.9, 19.6, 11.4. LC/MS (CI): $m/z = 337$ [M+H]$^+$. Anal. calcd. for C$_{15}$H$_{20}$N$_4$O$_3$S: C 53.56; H 5.99; N 16.65; S 9.32.

$N$-((4-Hydroxy-1-(isobutylprolyl)piperidin-4-yl)methyl)picolinamide (11{24,21,10})

![Chemical structure]

Yellowish solid. The compound existed as a ca. 1:1 mixture of rotamers. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.63 (d, $J = 4.7$ Hz, 1H), 8.58 (q, $J = 7.1$, 6.5 Hz, 1H), 8.03 (d, $J = 7.6$ Hz, 1H), 7.98 (td, $J = 7.6$, 1.7 Hz, 1H), 7.59 (ddd, $J = 6.9$, 4.8, 1.5 Hz, 1H), 4.86 (s, 1H), 4.10 – 3.78 (m, 2H), 3.33 (s, 2H), 3.31 – 3.10 (m, 3H), 3.09 – 2.86 (m, 2H), 2.37 – 1.81 (m, 4H), 1.75 – 1.54 (m, 3H), 1.52 – 1.25 (m, 4H), 0.79 (t, $J = 6.9$ Hz, 3H), 0.74 (d, $J = 5.7$ Hz, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 170.9, 164.3, 150.1, 148.9, 138.3, 127.0, 122.3, 69.4 and 69.3, 67.1 and 66.7, 63.0 and 63.0, 52.9 and 52.8, 49.1, 41.1 and 40.8, 38.2 and 37.9, 35.7 and 35.6, 35.0 and 34.8, 28.4 and 28.3, 27.4, 23.0, 21.5 and 21.4, 21.0. LC/MS (CI): $m/z = 389$ [M+H]$^+$. Anal. calcd. for C$_{21}$H$_{32}$N$_4$O$_3$: C 64.92; H 8.3; N 14.42. Found: C 64.84; H 8.02; N 14.25.

$N$-(1-Cyclopropyl-2-(2-(thiazol-5-yl)acetamido)ethyl)-6-methylnicotinamide (11{30,17,13})

![Chemical structure]
Beige solid. The compound existed as a ca. 3:1 mixture of rotamers. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.12 – 8.61 (m, 2H), 8.53 (t, $J = 5.7$ Hz, 0.25H) and 8.35 (d, $J = 8.3$ Hz, 0.75H) and 8.23 (t, $J = 5.7$ Hz, 0.75H) and 8.14 (d, $J = 8.3$ Hz, 0.25H), 8.01 (dd, $J = 8.1$, 2.2 Hz, 0.75H) and 7.96 (dd, $J = 8.1$, 2.2 Hz, 0.25H), 7.64 (s, 0.25H) and 7.62 (s, 0.75H), 7.36 – 7.23 (m, 1H), 3.68 (s, 2H), 3.51 – 3.36 (m, 2H), 3.32 – 3.21 (m, 1H), 2.49 – 2.47 (m, 3H), 0.98 – 0.85 (m, 1H), 0.50 – 0.38 (m, 1H), 0.38 – 0.29 (m, 1H), 0.29 – 0.12 (m, 2H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 169.4 and 168.9, 165.5 and 165.1, 161.0, 154.0, 148.4 and 148.3, 141.9 and 141.8, 135.7 and 135.5, 132.8 and 132.6, 127.8 and 127.8, 123.0 and 122.9, 53.9 and 53.2, 43.7 and 43.2, 33.8 and 33.6, 24.5, 14.1 and 14.0, 3.7, 2.7 and 2.4. LC/MS (CI): $m/z = 345$ [M+H]$^+$. Anal. calcd. for C$_{17}$H$_{20}$N$_4$O$_2$S: C 59.28; H 5.85; N 16.27; S 9.31. Found: C 59.64; H 5.7; N 16.05; S 9.62.

(2-(Cyclobutanecarbonyl)-2,8-diazaspiro[4.5]decan-8-yl)(tetrahydro-2H-pyran-4-yl)methanone (11{50,64,26})

Beige solid. The compound existed as a ca. 1:1 mixture of rotamers. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 3.82 (dt, $J = 10.7$, 3.2 Hz, 2H), 3.61 – 3.33 (m, 8H), 3.26 – 3.15 (m, 3H), 2.86 (ddt, $J = 11.3$, 7.4, 3.6 Hz, 1H), 2.18 – 2.01 (m, 4H), 1.88 (ddt, $J = 17.4$, 8.9, 5.8 Hz, 1H), 1.82 – 1.66 (m, 3H), 1.64 – 1.53 (m, 2H), 1.53 – 1.28 (m, 6H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 172.6 and 172.5, 172.5 and 172.4, 66.8, 55.3, 44.0 and 43.9, 42.8 and 42.6, 41.5, 39.1 and 39.1, 37.9 and 37.6, 36.7, 35.9, 35.4 and 35.1, 34.2 and 34.0, 34.0, 29.5, 24.6, 18.0 and 17.9. LC/MS (CI): $m/z = 335$ [M+H]$^+$. Anal. calcd. for C$_{19}$H$_{30}$N$_2$O$_3$: C 68.23; H 9.04; N 8.38. Found: C 67.86; H 8.77; N 8.41.

Oxazol-5-yl(2-picolinoyl-2,8-diazaspiro[4.5]decan-8-yl)methanone (11{50,69,10})

Yellowish oil. The compound existed as a ca. 1:1 mixture of rotamers. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.58 (t, $J = 4.2$ Hz, 1H), 8.53 (s, 0.5H) and 8.50 (s, 0H), 7.93 – 7.89 (m, 0.5H), 7.72 – 7.68 (m, 1H), 7.67 (s, 0.5H) and 7.63 (s, 0.5H), 7.47 (ddd, $J = 7.9$, 4.9, 1.5 Hz, 1H), 3.73 – 3.56 (m, 6H), 3.51 (s, 1H) and 3.45 (s, 1H), 1.86 – 1.80 (m, 2H), 1.66 – 1.45 (m, 5H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 166.3 and 166.2, 157.1 and 154.5, 154.5 and 153.4, 148.6 and 148.5, 144.8 and 144.7, 137.7 and 137.6, 130.3 and 130.2, 125.4 and 123.8, 58.6, 56.3, 47.2, 45.2, 41.8, 39.3, 36.2, 33.1. LC/MS (CI): $m/z = 341$ [M+H]$^+$. Anal. calcd. for C$_{18}$H$_{20}$N$_4$O$_3$: C 63.52; H 5.92; N 16.46. Found: C 63.52; H 6.20; N 16.36.

(2-(Furan-3-carbonyl)-2,7-diazaspiro[3.5]nonan-7-yl)(o-toly)methanone (11{60,73,32})
Yellowish solid. \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 8.10 (s, 1H), 7.73 – 7.17 (m, 3H), 7.13 (d, \(J = 7.5\) Hz, 1H), 6.73 – 6.64 (m, 1H), 4.15 – 4.07 (m, 1H), 4.07 – 3.99 (m, 1H), 3.77 – 3.69 (m, 2H), 3.68 – 3.43 (m, 2H), 3.13 – 3.00 (m, 2H), 2.18 (s, 3H), 1.77 (t, \(J = 5.6\) Hz, 2H), 1.67 – 1.53 (m, 2H). \(^{13}\)C NMR (126 MHz, DMSO-\(d_6\)) \(\delta\) 168.9, 163.2, 145.5, 144.3, 137.0, 134.0, 130.6, 129.0, 126.2, 125.9, 120.8, 110.1, 61.3, 43.8, 38.3, 35.5, 34.9, 34.4, 19.0. LC/MS (CI): \(m/z = 339\) [M+H]\(^+\). Anal. calcd. for C\(_{20}\)H\(_{22}\)N\(_2\)O\(_3\): C 70.99; H 6.55; N 8.28. Found: C 71.16; H 6.62; N 8.56.

\(N\)-(2-Isobutyramidopropyl)-\(N\)-methylbenzofuran-3-carboxamide (11\{67,81,37\})

Brownish oil. The compound existed as a ca. 3:2 mixture of rotamers. \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 8.49 (d, \(J = 1.6\) Hz, 0.4H) and 8.44 (d, \(J = 1.6\) Hz, 0.6H), 8.17 (d, \(J = 8.7\) Hz, 0.4H) and 8.08 – 7.99 (m, 1.6H), 7.64 – 7.57 (m, 1H), 7.39 – 7.28 (m, 2H), 4.37 – 4.29 (m, 1H), 3.51 (ddd, \(J = 13.4, 8.8, 1.6\) Hz, 0.6H) and 3.48 – 3.42 (m, 0.4H), 3.30 (dd, \(J = 5.5, 1.6\) Hz, 1.6H) and 3.02 – 2.96 (m, 0.4H) and 2.83 (d, \(J = 1.6\) Hz, 1.2H) and 2.78 – 2.73 (m, 0.6H), 1.17 (dd, \(J = 6.8, 1.6\) Hz, 1.2H) and 1.10 (dd, \(J = 6.7, 1.6\) Hz, 1.8H), 0.97 (dd, \(J = 6.8, 1.6\) Hz, 1.2H) and 0.93 (dd, \(J = 6.7, 1.6\) Hz, 1.8H), 0.86 (dd, \(J = 6.7, 1.6\) Hz, 1.2H) and 0.80 (dd, \(J = 6.8, 1.6\) Hz, 1.8H). \(^{13}\)C NMR (126 MHz, DMSO-\(d_6\)) \(\delta\) 176.8 and 176.6, 162.0 and 161.9, 155.1, 147.7 and 147.5, 125.6 and 125.6, 125.6 and 125.4, 124.2 and 124.1, 122.4 and 122.4, 117.6 and 117.4, 112.0 and 111.9, 54.3 and 52.3, 43.9 and 43.3, 36.0 and 34.6, 29.8 and 29.3, 20.2 and 20.1 and 19.6 and 19.5, 18.5 and 18.3. LC/MS (Cl): \(m/z = 303\) [M+H]\(^+\). Anal. calcd. for C\(_{17}\)H\(_{22}\)N\(_2\)O\(_3\): C 67.53; H 7.33; N 9.26. Found: C 67.61; H 7.22; N 8.97.

1-(2-(1-Methylcyclopropane-1-carbonyl)-2,7-diazaspiro[3.5]nonan-7-yl)-3-phenylbutan-1-one (11\{50,102,51\})

Yellowish oil. \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.32 – 7.19 (m, 4H), 7.18 – 7.09 (m, 1H), 4.10 – 3.88 (m, 2H), 3.67 – 3.33 (m, 5H), 3.19 – 3.12 (m, 1H), 2.59 (dd, \(J = 17.7, 6.5\) Hz, 1H), 2.52 (dd, \(J = 15.2, 7.8\) Hz, 1H), 1.80 – 1.31 (m, 5H), 1.20 (s, 3H), 1.18 (d, \(J = 7.0\) Hz, 3H), 0.90 – 0.79 (m, 2H), 0.48 – 0.38 (m, 2H). \(^{13}\)C NMR (151 MHz, DMSO-\(d_6\)) \(\delta\) 174.5, 169.7, 147.1, 128.7, 127.3, 126.4, 42.7, 40.7, 38.7, 36.5, 35.7, 35.0, 33.9, 22.4, 20.5, 19.2, 14.2. LC/MS (Cl): \(m/z = 355\) [M+H]\(^+\). Anal. calcd. for C\(_{22}\)H\(_{30}\)N\(_2\)O\(_2\): C 74.54; H 8.87; N 7.65. Found: C 74.67; H 8.87; N 7.65.

3-Chloro-\(N\)-(4-(2-(1-ethyl-1H-pyrazol-4-yl)acetamido)pentan-2-yl)-4-methylbenzamide (11\{70,84,38\})
Yellowish solid. The compound existed as a ca. 3:2 mixture of rotamers. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.27 (d, $J = 8.2$ Hz, 0.6H) and 8.20 (d, $J = 8.2$ Hz, 0.4H), 7.91 – 7.83 (m, 1H), 7.81 (d, $J = 8.2$ Hz, 0.6H) and 7.74 – 7.64 (m, 1.4H), 7.52 (s, 0.6H) and 7.48 (s, 0.4H), 7.44 – 7.37 (m, 1H), 7.24 (s, 0.6H) and 7.22 (s, 0.4H), 4.20 – 3.97 (m, 3H), 3.83 – 3.74 (m, 1H), 3.16 (s, 1.2H) and 3.14 (s, 0.8H), 2.35 (s, 3H), 1.69 – 1.46 (m, 2H), 1.30 (t, $J = 7.3$ Hz, 3H), 1.09 (d, $J = 6.6$ Hz, 3H), 1.02 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 169.9 and 169.9, 164.5 and 164.3, 139.0 and 138.9, 138.6 and 138.6, 134.8 and 134.6, 133.6 and 133.6, 131.5 and 131.4, 128.3, 127.9 and 127.9, 126.5, 115.1 and 115.1, 46.4, 43.4 and 43.0, 43.0 and 42.4, 42.4 and 42.3, 32.1, 21.5 and 21.4 and 21.2 and 21.2, 20.0, 16.0. LC/MS (Cl): $m/z = 391$ [M+H]$^+$. Anal. calcd. for C$_{20}$H$_{27}$ClN$_4$O$_2$: C 61.45; H 6.96; N 14.33; Cl 9.07. Found: C 61.47; H 6.62; N 14.33; Cl 9.02.

$N$-(4-(3-Fluoro-2-methylbenzamido)butan-2-yl)thiophene-2-carboxamide (11{83,105,54})

Beige solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.30 (t, $J = 5.5$ Hz, 1H), 8.26 (d, $J = 8.3$ Hz, 1H), 7.77 (d, $J = 3.6$ Hz, 1H), 7.71 (d, $J = 4.9$ Hz, 1H), 7.29 – 7.22 (m, 1H), 7.22 – 7.16 (m, 1H), 7.16 – 7.04 (m, 2H), 4.11 – 4.01 (m, 1H), 3.30 – 3.18 (m, 2H), 2.19 (d, $J = 2.2$ Hz, 3H), 1.80 – 1.67 (m, 2H), 1.17 (d, $J = 6.6$ Hz, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 168.1 (d, $J = 3.1$ Hz), 161.0 (d, $J = 243$ Hz), 160.9, 140.8, 140.3 (d, $J = 3.8$ Hz), 131.0, 128.2, 128.2, 127.6 (d, $J = 8.6$ Hz), 123.3 (d, $J = 3.2$ Hz), 122.5 (d, $J = 17.7$ Hz), 116.1 (d, $J = 22.8$ Hz), 43.4, 36.9, 36.1, 21.0, 11.5 (d, $J = 4.8$ Hz). $^{19}$F NMR (376 MHz, DMSO-$d_6$) $\delta$ –116.9. LC/MS (Cl): $m/z = 335$ [M+H]$^+$. Anal. calcd. for C$_{17}$H$_{19}$FN$_2$O$_2$S: C 61.05; H 5.73; N 8.38; S 9.59. Found: C 60.95; H 6.11; N 8.16; S 9.98.

General procedure for the reaction sequence B. N-Boc-diamine 1 (0.5 mmol), carboxylic acid 4 (0.6 mmol), and i-Pr$_2$NEt (1.25 mmol*), and HATU (0.575 mmol) were mixed in dry DMSO (appr. 1.4 mL). The reaction mixture was sealed and left at ambient temperature for 16 h, then evaporated under reduced pressure. Then the cleavage cocktail containing trifluoroacetic acid, triisopropylsilane, and water (93:5:2) (appr. 2 mL) was added in one portion. The mixture was stirred at ambient temperature for 6 h and evaporated under reduced pressure. The residue was taken up in N-methyl-2-pyrrolidone (NMP) (appr. 2 mL). Aryl halide 6 (0.6 mmol) and i-PrNEt$_2$ (3 mmol*) were added in one portion, the reaction mixture was sealed and heated at 100 °C for 16 h, then cooled and evaporated under reduced pressure. The residue was dissolved in DMSO (appr. 1 mL), filtered, analyzed by LCMS, and transferred for the HPLC purification.

2-(2-Methylthiophen-3-yl)-1-(2-((tetrazolo[1,5-b]pyridazin-6-ylamino)methyl)morpholino)ethanone (12{140,239,35})
Brownish solid. The compound existed as a ca. 1:1 mixture of rotamers. $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 8.22 (t, $J = 9.5$ Hz, 1H), 8.06 – 7.95 (m, 1H), 7.26 – 7.16 (m, 1H), 7.14 (d, $J = 5.2$ Hz, 0.5H) and 7.05 (d, $J = 5.2$ Hz, 0.5H), 6.77 (dd, $J = 9.4$, 5.2 Hz, 1H), 4.32 (d, $J = 13.3$ Hz, 0.5H) and 4.16 (d, $J = 13.3$ Hz, 0.5H), 3.95 – 3.85 (m, 1H), 3.83 (d, $J = 11.4$ Hz, 0.5H) and 3.76 (d, $J = 13.3$ Hz, 0.5H), 3.65 – 3.32 (m, 6H), 3.16 – 3.10 (m, 0.5H) and 2.95 (dd, $J = 13.3$, 10.3 Hz, 0.5H), 2.72 (dt, $J = 14.0$, 7.1 Hz, 0.5H) and 2.57 – 2.52 (m, 0.5H), 2.28 (s, 1.5H) and 2.28 (s, 1.5H). $^{13}$C NMR (151 MHz, DMSO-$d_6$) $\delta$ 169.2 and 169.2, 156.2, 140.5, 134.4 and 134.3, 131.5 and 131.4, 129.7 and 129.5, 123.6, 121.9 and 121.8, 121.2, 73.4, 66.2, 48.7 and 45.8, 44.5 and 43.6, 43.3 and 41.6, 33.2 and 33.1, 13.2. LC/MS (CI): $m/z$ = 374 [M+H$^+$]. Anal. calcd. for C$_{16}$H$_{19}$N$_7$O$_2$S: C 51.46; H 5.13; N 26.26; S 8.59. Found: C 51.20; H 5.08; N 26.20; S 8.89.

rac-5-((3aR,7aR)-5-(Pyrimidin-2-yl)octahydro-1H-pyrrolo[3,4-c]pyridine-2-carbonyl)-1H-benzo[d]imidazol-2(3H)-one (12{17,14,5})

Yellowish solid. The compound existed as a ca. 3:2 mixture of rotamers. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.79 (s, 1H), 10.70 (d, $J = 20.3$ Hz, 1H), 8.32 (dd, $J = 16.6$, 4.7 Hz, 2H), 7.17 – 7.00 (m, 2H), 6.95 – 6.85 (m, 1H), 6.58 (s, 1H), 4.17 – 3.74 (m, 2H), 3.68 – 3.54 (m, 2H), 3.47 (dd, $J = 12.0$, 7.8 Hz, 1H), 3.25 – 3.15 (m, 1H), 2.45 – 2.30 (m, 2H), 1.82 – 1.69 (m, 0.4H) and 1.68 – 1.41 (m, 1H) and 1.32 – 1.17 (m, 0.6H), 1.03 (d, $J = 6.1$ Hz, 2H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 169.7 and 169.5, 162.0 and 161.9, 158.4, 158.4, 155.8, 131.6 and 131.5, 129.7 and 129.5, 123.6, 121.9 and 121.8, 121.2, 73.4, 66.2, 48.7 and 45.8, 44.5 and 43.6, 43.3 and 41.6, 33.2 and 33.1, 13.2. LC/MS (CI): $m/z$ = 365 [M+H$^+$]. Anal. calcd. for C$_{19}$H$_{20}$N$_6$O$_2$: C 62.62; H 5.53; N 23.06. Found: C 62.69; H 5.23; N 23.24.

1-Methyl-5-(4-(quinoxalin-2-yl)piperazine-1-carbonyl)pyridin-2(1H)-one (12{9,26,3})

Yellowish solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.84 (s, 1H), 8.05 (d, $J = 2.5$ Hz, 1H), 7.85 (d, $J = 8.3$ Hz, 1H), 7.71 – 7.59 (m, 2H), 7.55 (dd, $J = 9.3$, 2.5 Hz, 1H), 7.42 (ddd, $J = 8.2$, 6.0, 2.5 Hz, 1H), 6.43 (d, $J = 9.3$ Hz, 1H), 3.85 (dd, $J = 6.7$, 3.8 Hz, 4H), 3.69 (dd, $J = 6.7$, 3.8 Hz, 4H), 3.48 (s, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 166.8, 161.9, 152.3, 141.9, 141.4, 139.5, 137.4,
136.8, 130.5, 128.9, 126.5, 125.1, 118.7, 113.2, 44.6, 40.3, 37.6. LC/MS (CI): m/z = 350 [M+H]+.
Anal. calcd. for C_{19}H_{19}N_{5}O_{2}: C 65.32; H 5.48; N 20.04. Found: C 64.95; H 5.33; N 19.74.

1-Methyl-6-(4-(quinoxalin-2-yl)piperazine-1-carbonyl)pyridin-2(1H)-one (12{9,27,3})

Yellowish solid. 1H NMR (500 MHz, DMSO-d$_6$) δ 8.83 (s, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.64 – 7.57 (m, 2H), 7.45 (dd, J = 9.1, 6.8 Hz, 1H), 7.43 – 7.39 (m, 1H), 6.64 (dd, J = 9.1, 1.4 Hz, 1H), 6.29 (dd, J = 6.8, 1.4 Hz, 1H), 3.96 – 3.88 (m, 2H), 3.86 – 3.73 (m, 4H), 3.53 – 3.43 (m, 2H), 3.32 (s, 3H). 13C NMR (126 MHz, DMSO-d$_6$) δ 162.4, 161.9, 152.2, 143.8, 141.2, 139.5, 137.4, 136.8, 130.6, 128.8, 126.5, 125.2, 120.2, 104.1, 46.3 and 44.7, 44.1 and 41.4, 33.0. LC/MS (CI): m/z = 350 [M+H]+. Anal. calcd. for C_{19}H_{19}N_{5}O_{2}: C 65.32; H 5.48; N 20.04. Found: C 65.69; H 5.28; N 19.64.

Cyclohex-3-en-1-yl(4-(quinoxalin-2-yl)piperazin-1-yl)methanone (12{9,28,3})

Brownish solid. 1H NMR (500 MHz, DMSO-d$_6$) δ 8.83 (s, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.67 – 7.57 (m, 2H), 7.42 (ddd, J = 8.3, 6.2, 2.2 Hz, 1H), 5.77 – 5.63 (m, 2H), 3.88 – 3.74 (m, 4H), 3.67 – 3.58 (m, 4H), 2.93 – 2.80 (m, 1H), 2.24 – 2.01 (m, 4H), 1.77 (dd, J = 12.1, 4.7 Hz, 1H), 1.59 – 1.46 (m, 1H). 13C NMR (126 MHz, DMSO-d$_6$) δ 174.0, 152.3, 141.4, 137.3, 136.8, 130.5, 128.9, 126.9, 126.5, 126.3, 125.0, 45.0 and 44.9, 44.5 and 41.3, 35.7, 28.1, 25.9, 24.8. LC/MS (Cl): m/z = 323 [M+H]+. Anal. calcd. for C_{19}H_{22}N_{4}O: C 70.78; H 6.88; N 17.38. Found: C 70.99; H 7.03; N 17.44.

N-(2-((5,6-Dimethylthieno[2,3-d]pyrimidin-4-yl)(ethyl)amino)ethyl)-2-methoxypropanamide (12{45,44,24})

Yellowish oil. 1H NMR (500 MHz, DMSO-d$_6$) δ 8.39 (s, 1H), 7.73 (t, J = 5.9 Hz, 1H), 3.56 – 3.48 (m, 3H), 3.42 (qd, J = 6.9, 2.3 Hz, 2H), 3.30 – 3.22 (m, 2H), 3.13 (s, 3H), 2.40 (s, 3H), 2.34 (s, 3H), 1.06 (d, J = 6.7 Hz, 3H), 1.01 (t, J = 6.9 Hz, 3H). 13C NMR (126 MHz, DMSO-d$_6$) δ 172.6, 166.8, 161.7, 151.1, 131.1, 125.4, 121.6, 77.8, 57.2, 48.1, 46.5, 36.6, 18.5, 14.1, 14.0, 12.6. LC/MS (Cl): m/z = 337 [M+H]+. Anal. calcd. for C_{18}H_{22}N_{4}O_{2}S: C 57.12; H 7.19; N 16.65; S 9.53. Found: C 57.29; H 7.35; N 16.50; S 9.59.

1-Methyl-4-(4-(quinoxalin-2-yl)piperazine-1-carbonyl)pyridin-2(1H)-one (12{9,48,3})
Yellowish solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.81 (s, 1H), 7.83 (d, $J = 8.2$ Hz, 1H), 7.79 (d, $J = 6.8$ Hz, 1H), 7.68 – 7.53 (m, 2H), 7.40 (ddd, $J = 8.2, 5.8, 2.4$ Hz, 1H), 6.38 (d, $J = 1.6$ Hz, 1H), 6.22 (dt, $J = 6.8, 1.6$ Hz, 1H), 4.04 – 3.60 (m, 6H), 3.57 – 3.46 (m, 2H), 3.44 (s, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 166.8, 162.9, 152.3, 147.4, 143.1, 142.1, 137.3, 136.7, 130.5, 126.5, 125.1, 116.6, 103.5, 46.6 and 44.7, 44.1 and 41.4, 37.3. LC/MS (CI): $m/z = 350$ [M+H]$^+$. Anal. calcd. for C$_{19}$H$_{19}$N$_5$O$_2$: C 65.32; H 5.48; N 20.04. Found: C 65.27; H 5.56; N 19.93.

(2S)-2-Acetamido-N-(1-((4,6-dimethylpyrimidin-2-yl)(methyl)amino)propan-2-yl)-4-methylpentanamide (12{68,82,32})

Beige solid. The compound existed as a ca. 11:9 mixture of rotamers. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.89 – 7.79 (m, 1.45H) and 7.67 (d, $J = 8.3$ Hz, 0.55H), 6.35 (s, 0.45H) and 6.33 (s, 0.55H), 4.20 (q, $J = 7.9$ Hz, 0.45H) and 4.17 – 4.06 (m, 1.55H), 3.81 – 3.69 (m, 1H), 3.44 (dd, $J = 13.7$, 5.0 Hz, 0.55H) and 3.39 (dd, $J = 13.7$, 7.5 Hz, 0.45H), 3.05 (s, 1.35H) and 3.03 (s, 1.65H), 2.24 – 2.18 (m, 6H), 1.80 (s, 1.35H) and 1.78 (s, 1.65H), 1.57 – 1.47 (m, 0.45H) and 1.46 – 1.38 (m, 0.55H), 1.34 (t, $J = 7.3$ Hz, 1H), 1.19 (ddd, $J = 14.7, 10.3, 5.1$ Hz, 0.55H) and 1.03 (d, $J = 6.6$ Hz, 2H) and 0.99 – 0.95 (m, 1.45H), 0.86 (d, $J = 6.6$ Hz, 1.35H) and 0.81 (d, $J = 6.6$ Hz, 1.35H) and 0.74 (d, $J = 2.6$ Hz, 1.65H) and 0.73 (d, $J = 2.6$ Hz, 1.65H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 172.0 and 171.8, 169.3, 166.7 and 166.7, 162.2 and 162.1, 108.5 and 108.5, 53.4 and 53.2, 51.6 and 51.3, 44.3 and 43.8, 41.6 and 41.4, 36.2 and 35.8, 24.7 and 24.5, 24.3 and 24.3, 23.4 and 23.4, 22.9 and 22.9, 22.2 and 21.9, 18.7 and 18.6. LC/MS (CI): $m/z = 350$ [M+H]$^+$. Anal. calcd. for C$_{18}$H$_{31}$N$_5$O$_2$: C 61.86; H 8.94; N 20.04. Found: C 61.64; H 8.82; N 19.94.

(3-(Benzo[d]oxazol-2-yl(methyl)amino)pyrrolidin-1-yl)(3,3-difluoro-1-methylcyclobutyl)methanone (12{81,39,30})

Brownish solid. The compound existed as a ca. 1:1 mixture of rotamers. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.39 (dd, $J = 7.8$, 2.5 Hz, 1H), 7.27 (dd, $J = 7.8$, 2.5 Hz, 1H), 7.16 – 7.10 (m, 1H), 6.99 (t, $J = 7.7$ Hz, 1H), 4.92 – 4.78 (m, 1H), 3.70 – 3.51 (m, 2H), 3.49 – 3.33 (m, 2H), 3.17 – 2.90 (m, 5H), 2.48 – 2.41 (m, 2H), 2.25 – 2.14 (m, 1H), 2.09 (q, $J = 7.7$ Hz, 1H), 1.40 (d, $J = 10.6$ Hz, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 172.8 and 172.7, 169.3, 166.7, 162.1, 116.1, 116.1, 109.3 and 109.3, 57.3 and 55.0, 48.0 and 47.3, 45.5 and 45.1, 45.0 – 44.0 (m), 33.5 (t, $J = 15.3$ Hz) and 33.5 (t, $J = 15.3$ Hz), 31.0 and 30.8, 29.1, 25.8, 23.2. $^{19}$F NMR (376 MHz, DMSO-$d_6$) $\delta$ –83.3 (dd, $J = 194$, 30.4 Hz), –91.7 (dd,
J = 194, 17.3 Hz). LC/MS (Cl): m/z = 350 [M+H]+. Anal. calcd. for C_{18}H_{21}F_{2}N_{3}O_{2}: C 61.88; H 6.06; N 12.03. Found: C 61.86; H 5.8; N 12.24.

(R)-1-(2-(((4-(Trifluoromethyl)pyrimidin-2-yl)amino)methyl)piperidin-1-yl)propan-1-one (12{84,40,34})

Yellowish solid. \(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \(\delta\) 8.58 (d, \(J = 4.8\) Hz, 1H), 7.70 (t, \(J = 6.4\) Hz, 1H), 6.88 (d, \(J = 4.8\) Hz, 1H), 5.01 – 4.86 (m, 1H), 4.54 (d, \(J = 13.7\) Hz, 1H), 3.42 – 3.31 (m, 1H), 3.29 – 3.20 (m, 1H), 3.02 (td, \(J = 14.2, 13.7, 2.6\) Hz, 1H), 1.87 (q, \(J = 7.6\) Hz, 2H), 1.75 – 1.58 (m, 3H), 1.56 – 1.42 (m, 2H), 1.35 – 1.25 (m, 1H), 0.80 (t, \(J = 7.6\) Hz, 3H). \(^{13}\)C NMR (151 MHz, DMSO-\(d_6\)) \(\delta\) 173.2, 161.7, 161.4, 154.9 (q, \(J = 34.6\) Hz), 121.1 (q, \(J = 275\) Hz), 104.3 (d, \(J = 2.9\) Hz), 49.9, 39.0, 37.5, 28.8, 26.0, 25.3, 19.3, 10.2. \(^{19}\)F NMR (376 MHz, DMSO-\(d_6\)) \(\delta\) –70.0. LC/MS (Cl): m/z = 317 [M+H]+. Anal. calcd. for C_{14}H_{19}F_{3}N_{4}O: C 53.16; H 6.05; N 17.71. Found: C 52.90; H 5.91; N 18.09.

N-(1-(6-Ethyl-5-fluoropyrimidin-4-yl)piperidin-4-yl)-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide (12{79,130,39})

Yellowish oil. \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 8.57 (d, \(J = 8.2\) Hz, 1H), 8.27 (d, \(J = 2.5\) Hz, 1H), 4.36 (d, \(J = 13.4\) Hz, 2H), 4.14 – 3.97 (m, 1H), 3.11 (t, \(J = 12.8\) Hz, 2H), 2.70 (t, \(J = 6.3\) Hz, 2H), 2.64 (qd, \(J = 7.5, 4.7\) Hz, 2H), 2.57 – 2.52 (m, 2H), 1.89 – 1.82 (m, 2H), 1.81 – 1.72 (m, 2H), 1.71 – 1.65 (m, 2H), 1.65 – 1.51 (m, 2H), 1.17 (t, \(J = 7.5\) Hz, 3H). \(^{13}\)C NMR (126 MHz, DMSO-\(d_6\)) \(\delta\) 170.1, 159.3, 156.1, 156.0 (d, \(J = 15.2\) Hz), 152.9 (d, \(J = 9.7\) Hz), 151.2 (d, \(J = 4.6\) Hz), 144.4 (d, \(J = 257\) Hz), 113.0, 46.6, 45.6, 45.5, 31.5, 23.6, 22.4, 22.2, 21.9, 20.0, 12.3. \(^{19}\)F NMR (376 MHz, DMSO-\(d_6\)) \(\delta\) –146.5. LC/MS (Cl): m/z = 374 [M+H]+. Anal. calcd. for C_{19}H_{24}F_{3}N_{5}O_{2}: C 61.11; H 6.48; N 18.75. Found: C 61.26; H 6.60; N 18.78.

Cyclohex-3-en-1-yl(4-(7-fluorobenzo[d]thiazol-2-yl)piperazin-1-yl)methanone (12{9,28,43})

Yellowish solid. \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.38 – 7.29 (m, 2H), 7.02 – 6.93 (m, 1H), 5.73 – 5.63 (m, 2H), 3.73 – 3.53 (m, 8H), 2.92 – 2.79 (m, 1H), 2.22 – 1.99 (m, 4H), 1.83 – 1.70 (m,
1H), 1.51 (qd, J = 12.0, 5.6 Hz, 1H). 13C NMR (126 MHz, DMSO-d$_6$) δ 174.0, 168.7, 156.6 (d, J = 3.7 Hz), 155.8 (d, J = 2.7 Hz), 127.8 (d, J = 8.0 Hz), 126.9, 126.2, 116.7 (d, J = 15.8 Hz), 115.4, 107.8 (d, J = 18.7 Hz), 49.0 and 48.5, 44.6 and 40.9, 35.7, 28.1, 25.9, 24.8. 19F NMR (376 MHz, DMSO-d$_6$) δ −113.7. LC/MS (CI): m/z = 346 [M+H]$^+$. Anal. calcd. for C$_{18}$H$_{20}$FN$_3$OS: C 62.59; H 5.84; N 12.16; S 9.28. Found: C 62.36; H 6.05; N 12.29; S 9.35.

**N-(1-(5,6-Diethyl-1,2,4-triazin-3-yl)-3-methylpyrrolidin-3-yl)-3-methylisoxazole-5-carboxamide (12{49,150,31})**

![Chemical structure](image)

Yellowish solid. $^1$H NMR (500 MHz, DMSO-d$_6$) δ 8.76 (s, 1H), 6.92 (s, 1H), 4.05 (d, J = 11.6 Hz, 1H), 3.78 – 3.47 (m, 3H), 2.76 (q, J = 7.4 Hz, 2H), 2.66 (q, J = 7.4 Hz, 2H), 2.58 – 2.52 (m, 1H), 2.27 (s, 3H), 2.22 – 1.96 (m, 1H), 1.51 (s, 3H), 1.28 – 1.16 (m, 6H). 13C NMR (126 MHz, DMSO-d$_6$) δ 163.7, 162.0, 160.8, 159.1, 156.4, 150.6, 107.6, 59.3, 56.8, 44.9, 36.7, 26.5, 24.6, 23.0, 13.2, 11.4, 11.2. LC/MS (CI): m/z = 345 [M+H]$^+$. Anal. calcd. for C$_{17}$H$_{24}$N$_6$O$_2$: C 59.28; H 7.02; N 24.4. Found: C 59.68; H 6.97; N 24.11.

**N-(6-(4-Cyano-3-methylisothiazol-5-yl)-6-azaspiro[2.5]octan-1-yl)-1-isobutyl-1H-pyrazole-3-carboxamide (12{31,29,13})**

![Chemical structure](image)

Yellowish solid. $^1$H NMR (500 MHz, DMSO-d$_6$) δ 8.14 (d, J = 3.4 Hz, 1H), 7.78 (d, J = 1.5 Hz, 1H), 6.63 (d, J = 1.5 Hz, 1H), 3.95 (d, J = 7.3 Hz, 2H), 3.74 – 3.64 (m, 2H), 3.61 – 3.52 (m, 1H), 3.44 (ddd, J = 12.6, 9.0, 3.6 Hz, 1H), 2.69 (dt, J = 8.3, 4.2 Hz, 1H), 2.29 (s, 3H), 2.14 (hept, J = 6.5 Hz, 1H), 1.74 – 1.61 (m, 2H), 1.52 – 1.41 (m, 2H), 0.90 (t, J = 5.1 Hz, 1H), 0.88 – 0.81 (m, 6H), 0.79 (dd, J = 8.3, 5.5 Hz, 1H). 13C NMR (126 MHz, DMSO-d$_6$) δ 179.4, 167.9, 163.8, 146.4, 132.5, 116.6, 106.1, 84.9, 59.3, 51.2, 51.0, 33.5, 33.3, 29.6, 28.4, 22.3, 20.1, 20.0, 19.2, 16.5. LC/MS (CI): m/z = 399 [M+H]$^+$. Anal. calcd. for C$_{20}$H$_{26}$N$_6$O$_5$: C 60.28; H 6.58; N 21.09; S 8.04. Found: C 60.10; H 6.71; N 21.17; S 8.35.

**2-(Benzo[d]isoxazol-3-yl)-N-(2-((6-cyanopyridin-3-yl)(methyl)amino)ethyl)-N-methylacetamide (12{2,23,11})**

![Chemical structure](image)

Brownish solid. The compound existed as a ca. 3:1 mixture of rotamers. $^1$H NMR (500 MHz, DMSO-d$_6$) δ 8.27 (d, J = 2.9 Hz, 0.25H) and 8.18 (d, J = 2.9 Hz, 0.75H), 7.78 – 7.47 (m, 4H), 7.38 – 7.28 (m, 1H), 7.18 (dd, J = 9.0, 3.0 Hz, 0.25H) and 7.08 (dd, J = 9.0, 3.0 Hz, 0.75H), 4.10 (s, 2H), 3.77 (t, J = 6.3 Hz, 0.5H) and 3.66 (t, J = 6.3 Hz, 0.5H) and 3.58 (t, J = 6.5 Hz, 1.5H)}
and 3.48 (t, J = 6.5 Hz, 1H), 3.14 (s, 2.25H) and 3.06 (s, 0.75H), 2.98 (s, 2.25H) and 2.89 (s, 0.75H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 168.3 and 167.5, 162.6, 155.0 and 154.8, 147.1 and 146.9, 136.0 and 135.8, 130.5, 129.8 and 129.6, 123.9 and 123.8, 123.1, 122.2 and 122.1, 119.5 and 119.4, 118.3 and 117.8, 117.4 and 117.0, 109.9, 49.4 and 48.4, 47.1 and 45.0, 38.5 and 38.1, 36.6 and 34.1, 30.6 and 30.1. LC/MS (Cl): m/z = 350 [M+H]$^+$. Anal. calcd. for C$_{19}$H$_{19}$N$_5$O$_2$: C 65.32; H 5.48; N 20.04. Found: C 65.53; H 5.42; N 20.16.

**General procedure for the reaction sequence C.** N-Boc-diamine 1 (0.5 mmol), carboxylic acid 4 (0.6 mmol), i-Pr$_2$NEt (1.25 mmol$^*$), and HATU (0.575 mmol) were mixed in dry DMSO (appr. 1.4 mL). The reaction mixture was sealed and left at ambient temperature for 16 h, then evaporated under reduced pressure. Then the cleavage cocktail containing trifluoroacetic acid, triisopropylsilane, and water (93:5:2) (appr. 2 mL) was added in one portion. The mixture was stirred at ambient temperature for 6 h and evaporated under reduced pressure. The residue was taken up in DMF (appr. 2 mL). Alkylating agent 7 (0.6 mmol) and i-PrNEt$_2$ (3 mmol$^*$) were added in one portion, the reaction mixture was sealed and heated at 80 °C for 16 h, then cooled and evaporated under reduced pressure. The residue was dissolved in DMSO (appr. 1 mL), filtered, analyzed by LCMS, and transferred for the HPLC purification.

3-Methyl-N-((1-((1-methyl-1H-benzo[d]imidazol-2-yl)methyl)pyrrolidin-3-yl)methyl)butanamide (13{125,197,36}).

Brownish oil. $^1$H NMR (600 MHz, DMSO-$d_6$) δ 7.76 (t, J = 5.7 Hz, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 3.81 (d, J = 2.5 Hz, 2H), 3.79 (s, 3H), 3.02 – 2.93 (m, 2H), 2.57 – 2.50 (m, 2H), 2.46 – 2.42 (m, 1H), 2.26 – 2.18 (m, 2H), 1.91 – 1.85 (m, 3H), 1.84 – 1.77 (m, 1H), 1.39 – 1.32 (m, 1H), 0.79 (d, J = 6.3 Hz, 3H), 0.77 (d, J = 6.3 Hz, 3H). $^{13}$C NMR (151 MHz, DMSO-$d_6$) δ 171.8, 152.6, 142.3, 136.5, 122.3, 121.6, 119.1, 110.2, 58.0, 53.8, 52.4, 45.2, 43.3, 37.6, 30.2, 28.4, 25.9, 22.7, 22.6. LC/MS (Cl): m/z = 329 [M+H]$^+$. Anal. calcd. for C$_{19}$H$_{28}$N$_4$O: C 69.48; H 8.59; N 17.06. Found: C 69.29; H 8.87; N 17.07.

$N$-((4-((3-Chloropyridin-4-yl)methyl)morpholin-2-yl)methyl)-1-methyl-1H-pyrazole-3-carboxamide (13{74,107,20})

Yellowish oil. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.55 (s, 1H), 8.46 (d, J = 4.9 Hz, 1H), 7.93 (t, J = 6.0 Hz, 1H), 7.73 (d, J = 2.3 Hz, 1H), 7.50 (d, J = 4.9 Hz, 1H), 6.58 (dt, J = 2.3, 1.0 Hz, 1H), 3.86 (s, 3H), 3.79 (d, J = 11.3 Hz, 1H), 3.64 – 3.59 (m, 1H), 3.57 (s, 2H), 3.50 (td, J = 11.3, 2.5 Hz, 1H), 3.26 (t, J = 5.7 Hz, 2H), 2.73 (d, J = 11.3 Hz, 1H), 2.59 (d, J = 11.3 Hz, 1H), 2.17 (td, J = 11.3, 3.2 Hz, 1H), 1.95 (t, J = 10.5 Hz, 1H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 161.8, 149.2,
148.5, 146.5, 145.0, 133.0, 131.6, 125.2, 106.4, 74.5, 66.2, 58.2, 56.6, 53.1, 41.5, 39.4. LC/MS (CI): $m/z = 350/352 \ [M+H]^+$. Anal. calcd. for C$_{16}$H$_{20}$ClN$_5$O$_2$: C 54.94; H 5.76; N 20.02; Cl 10.13. Found: C 54.60; H 6.14; N 20.35; Cl 9.80.

$N$-((4-(2,5-Dimethylbenzyl)morpholin-2-yl)methyl)-1-methyl-1H-pyrazole-3-carboxamide (13{74,107,21}).

![Structure](image1)

Yellowish oil. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.90 (t, $J = 6.0$ Hz, 1H), 7.73 (d, $J = 2.2$ Hz, 1H), 7.06 – 6.96 (m, 2H), 6.92 (d, $J = 7.7$ Hz, 1H), 6.57 (d, $J = 2.2$ Hz, 1H), 3.86 (s, 3H), 3.75 (d, $J = 11.3$ Hz, 1H), 3.57 – 3.50 (m, 1H), 3.47 – 3.33 (m, 3H), 3.24 (t, $J = 6.2$ Hz, 2H), 2.68 (d, $J = 11.3$ Hz, 1H), 2.55 – 2.50 (m, 1H), 2.23 (s, 3H), 2.20 (s, 3H), 2.04 (td, $J = 11.3, 3.1$ Hz, 1H), 1.82 (t, $J = 10.6$ Hz, 1H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 161.8, 146.5, 136.0, 134.6, 134.4, 133.0, 130.9, 130.5, 128.0, 106.4, 74.6, 66.3, 61.0, 56.8, 53.2, 41.6, 39.3, 21.1, 18.9. LC/MS (CI): $m/z = 343 \ [M+H]^+$. Anal. calcd. for C$_{19}$H$_{26}$N$_4$O$_2$: C 66.64; H 7.65; N 16.36. Found: C 67.03; H 7.45; N 16.05.

$N$-(2-(Benzyl(2-methoxyethyl)amino)ethyl)-2-fluoro-2-phenylacetamide (13{107,152,23})

![Structure](image2)

Yellowish oil. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.23 (t, $J = 5.7$ Hz, 1H), 7.46 – 7.41 (m, 2H), 7.41 – 7.35 (m, 3H), 7.32 – 7.23 (m, 4H), 7.23 – 7.18 (m, 1H), 5.84 (d, $J = 47.8$ Hz, 1H), 3.59 (s, 2H), 3.33 (t, $J = 5.8$ Hz, 2H), 3.28 – 3.20 (m, 2H), 3.17 (s, 3H), 2.64 – 2.52 (m, 4H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 168.0 (d, $J = 23.0$ Hz), 139.9, 136.3 (d, $J = 19.4$ Hz), 129.6 (d, $J = 2.4$ Hz), 129.0, 128.9, 128.5, 127.4 (d, $J = 5.9$ Hz), 127.2, 91.4 (d, $J = 183$ Hz), 70.9, 58.8, 58.5, 53.2, 52.7, 36.9. $^{19}$F NMR (376 MHz, DMSO-$d_6$) $\delta$ -175.2. LC/MS (CI): $m/z = 345 \ [M+H]^+$. Anal. calcd. for C$_{20}$H$_{25}$FN$_2$O$_2$: C 69.74; H 7.32; N 8.13. Found: C 69.47; H 7.39; N 8.50.

$N$-((4-((2,5-Dimethylthiophen-3-yl)methyl)morpholin-2-yl)methyl)-1-methyl-1H-pyrazole-3-carboxamide (13{74,107,27})

![Structure](image3)
(3-Chloro-1H-indol-2-yl)(3-(((5-ethyl-1,3,4-oxadiazol-2-yl)methyl)(methyl)amino)methyl)pyrrolidin-1-yl)methanone (13{44,129,33})

Yellowish oil. The compound existed as a ca. 11:9 mixture of rotamers. ¹H NMR (500 MHz, DMSO-d₆) δ 7.91 (t, J = 6.1 Hz, 1H), 7.74 (d, J = 2.5 Hz, 1H), 6.64 – 6.54 (m, 1H), 6.53 (s, 1H), 3.87 (s, 3H), 3.74 (d, J = 11.3 Hz, 1H), 3.51 (ddt, J = 8.7, 6.2, 3.7 Hz, 1H), 3.41 (td, J = 11.3, 2.5 Hz, 1H), 3.28 – 3.20 (m, 4H), 2.67 (d, J = 11.3 Hz, 1H), 2.53 (d, J = 11.3 Hz, 1H), 2.29 (s, 3H), 2.24 (s, 3H), 1.98 (td, J = 11.3, 3.2 Hz, 1H), 1.76 (t, J = 10.6 Hz, 1H). ¹³C NMR (126 MHz, DMSO-d₆) δ 161.8, 146.5, 134.6, 133.8, 133.3, 133.0, 128.4, 106.4, 74.5, 66.3, 55.6, 52.9, 41.6, 39.4, 15.2, 13.1. LC/MS (Cl): m/z = 349 [M+H]+. Anal. calcd. for C₁₇H₂₄N₄O₂S: C 58.6; H 6.94; N 16.08; S 9.20. Found: C 58.40; H 7.17; N 16.13; S 9.47.

(3-Chloro-1H-indol-2-yl)(3-(((5-ethyl-1,3,4-oxadiazol-2-yl)methyl)(methyl)amino)methyl)pyrrolidin-1-yl)methanone (13{23,129,34})

Yellowish oil. The compound existed as a ca. 11:9 mixture of rotamers. ¹H NMR (500 MHz, DMSO-d₆) δ 11.83 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.44 – 7.36 (m, 1H), 7.25 (t, J = 7.7 Hz, 1H), 7.17 – 7.10 (m, 1H), 3.82 (s, 0.95H) and 3.72 (s, 1.1H), 3.65 – 3.46 (m, 3H), 3.27 – 3.20 (m, 1H), 2.83 (q, J = 7.7 Hz, 0.9H) and 2.71 (q, J = 7.7 Hz, 1.1H), 2.47 – 2.29 (m, 3H), 2.27 (s, 1.35H) and 2.17 (s, 1.65H), 2.04 – 1.91 (m, 1H), 1.63 – 1.54 (m, 1H), 1.24 (t, J = 7.7 Hz, 1.35H) and 1.15 (t, J = 7.7 Hz, 1.65H). ¹³C NMR (126 MHz, DMSO-d₆) δ 168.4 and 168.3, 164.1 and 164.0, 161.0 and 160.9, 134.8, 129.2 and 129.1, 124.8, 124.4, 121.0, 118.4, 112.9, 103.2 and 103.1, 59.3 and 58.8, 52.1 and 51.0, 50.9 and 50.4, 47.2 and 45.6, 42.5, 37.1 and 35.4, 29.9 and 28.2, 18.8 and 18.7, 10.9 and 10.8. LC/MS (Cl): m/z = 402/404 [M+H]+. Anal. calcd. for C₂₀H₂₄ClN₅O₂: C 59.77; H 6.02; N 17.43; Cl 8.82. Found: C 59.95; H 5.71; N 17.12; Cl 8.47.

(3-Chloro-1H-indol-2-yl)(4-(2-(4-chloro-1H-pyrazol-1-yl)ethyl)-1,4-diazepan-1-yl)methanone

Yellowish oil. The compound existed as a ca. 11:9 mixture of rotamers. ¹H NMR (500 MHz, DMSO-d₆) δ 11.88 (s, 1H), 7.97 (s, 0.5H) and 7.87 (s, 0.5H) and 7.61 – 7.41 (m, 2H), 7.40 (d, J = 8.2 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 4.16 (t, J = 6.5 Hz, 1H) and 4.08 (t, J = 6.5 Hz, 1H), 3.68 – 3.55 (m, 2H), 3.54 – 3.43 (m, 2H), 2.86 (t, J = 6.5 Hz, 1H) and 2.84 – 2.73 (m, 2H) and 2.71 – 2.62 (m, 2H) and 2.62 – 2.55 (m, 1H), 1.86 – 1.77 (m, 1H) and 1.70 – 1.60 (m, 1H). ¹³C NMR (126 MHz, DMSO-d₆) δ 162.6, 137.1, 134.8, 128.9, 128.8, 128.8, 124.6, 124.1, 120.9, 118.2, 112.9, 108.0, 56.3 and 55.7, 55.5 and 55.0, 53.9 and 53.8, 50.7, 49.3 and 47.6, 45.9 and 44.9, 28.5 and 26.7. LC/MS (Cl): m/z = 406/408 [M+H]+. Anal. calcd. for C₁₉H₂₃ClN₂O₂: C 56.17; H 5.21; N 17.24; Cl 17.45. Found: C 56.21; H 5.58; N 17.12; Cl 17.35.

N-((4-((2,5-Dimethylthiazol-4-yl)methyl)morpholin-2-yl)methyl)-1-methyl-1H-pyrazole-3-carboxamide (13{74,107,35})
Brownish oil. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.91 (t, $J = 5.3$ Hz, 1H), 7.74 (t, $J = 2.3$ Hz, 1H), 6.58 (q, $J = 2.3$ Hz, 1H), 3.87 (s, 3H), 3.76 – 3.71 (m, 1H), 3.55 – 3.48 (m, 1H), 3.45 – 3.35 (m, 4H), 3.26 – 3.19 (m, 2H), 2.72 – 2.66 (m, 1H), 2.60 – 2.54 (m, 1H), 2.49 – 2.46 (m, 2H), 2.31 (s, 3H), 2.07 (t, $J = 11.0$ Hz, 1H), 1.83 (t, $J = 10.3$ Hz, 1H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 161.8, 160.9, 147.7, 146.6, 133.0, 130.1, 106.4, 74.5, 66.3, 56.4, 55.5, 52.9, 41.6, 39.4, 19.0, 11.4. LC/MS (Cl): $m/z$ = 350 [M+H]$^+$. Anal. calcd. for C$_{16}$H$_{23}$N$_5$O$_2$S: C 54.99; H 6.63; N 20.04; S 9.17. Found: C 55.01; H 6.41; N 19.89; S 9.53.

$N$-((1-(2-Ethylbenzyl)piperidin-3-yl)methyl)-1-methyl-$^1$H-pyrazole-3-carboxamide (13{102,107,29})

Yellowish oil. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.01 (t, $J = 6.2$ Hz, 1H), 7.72 (d, $J = 2.2$ Hz, 1H), 7.19 (d, $J = 7.5$ Hz, 1H), 7.17 – 7.10 (m, 2H), 7.07 (td, $J = 6.9$, 2.5 Hz, 1H), 6.55 (d, $J = 1.7$ Hz, 1H), 3.95 – 3.77 (m, 3H), 3.44 – 3.34 (m, 2H), 3.13 – 3.02 (m, 2H), 2.75 – 2.67 (m, 1H), 2.64 (q, $J = 7.5$ Hz, 2H), 2.60 – 2.53 (m, 1H), 1.90 (t, $J = 10.9$ Hz, 1H), 1.80 – 1.70 (m, 2H), 1.64 – 1.54 (m, 2H), 1.38 – 1.29 (m, 1H), 1.12 (t, $J = 7.5$ Hz, 3H), 0.98 – 0.88 (m, 1H). $^{13}$C NMR (151 MHz, DMSO-$d_6$) $\delta$ 161.8, 146.9, 143.4, 136.5, 132.9, 130.2, 128.8, 127.5, 125.7, 106.3, 60.9, 58.5, 54.2, 42.6, 39.3, 36.8, 28.6, 25.2, 24.9, 15.8. LC/MS (Cl): $m/z$ = 341 [M+H]$^+$. Anal. calcd. for C$_{20}$H$_{28}$N$_4$O: C 70.56; H 8.29; N 16.46. Found: C 70.80; H 7.94; N 16.15.

1-Methyl-$N$-((4-((4-methyl-1,2,5-oxadiazol-3-yl)methyl)morpholin-2-yl)methyl)-1$^1$H-pyrazole-3-carboxamide (13{74,107,38})

Yellowish oil. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.95 (t, $J = 6.0$ Hz, 1H), 7.74 (d, $J = 1.8$ Hz, 1H), 6.57 (d, $J = 1.8$ Hz, 1H), 3.87 (s, 3H), 3.79 – 3.72 (m, 1H), 3.70 (s, 2H), 3.59 – 3.49 (m, 1H), 3.43 (td, $J = 11.4$, 2.1 Hz, 1H), 3.25 (t, $J = 6.1$ Hz, 2H), 2.74 – 2.63 (m, 1H), 2.58 – 2.51 (m, 1H), 2.36 (s, 3H), 2.14 (td, $J = 11.2$, 3.2 Hz, 1H), 1.92 (t, $J = 10.5$ Hz, 1H). $^{13}$C NMR (151 MHz, DMSO-$d_6$) $\delta$ 161.7, 152.4, 152.4, 146.4, 133.0, 106.4, 74.4, 66.1, 56.2, 52.7, 50.0, 41.3, 39.3, 8.4. LC/MS (Cl): $m/z$ = 321 [M+H]$^+$. Anal. calcd. for C$_{16}$H$_{20}$N$_6$O$_3$: C 52.49; H 6.29; N 26.23. Found: C 52.83; H 6.22; N 26.56.

2-(1-Ethyl-$^1$H-pyrazol-4-yl)-$N$-(2-(2-oxo-2-(o-tolylamino)ethyl)-2-azabicyclo[2.1.1]hexan-5-yl)acetamide (13{7,7,1})
Yellowish oil. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.58 (s, 1H), 7.94 (d, $J = 7.6$ Hz, 1H), 7.55 (d, $J = 7.9$ Hz, 1H), 7.50 (s, 1H), 7.36 – 7.21 (m, 2H), 7.19 (t, $J = 7.6$ Hz, 1H), 7.09 (t, $J = 7.4$ Hz, 1H), 4.03 (q, $J = 7.3$ Hz, 2H), 3.85 – 3.77 (m, 1H), 3.46 – 3.39 (m, 2H), 3.31 – 3.24 (m, 3H), 3.12 (d, $J = 8.4$ Hz, 1H), 2.68 – 2.61 (m, 1H), 2.34 (d, $J = 8.4$ Hz, 1H), 2.20 (s, 3H), 1.31 (t, $J = 7.3$ Hz, 3H), 1.28 (s, 2H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 170.8, 169.4, 138.6, 136.5, 131.8, 130.7, 128.4, 126.6, 125.6, 125.0, 114.8, 66.1, 58.9, 52.9, 52.6, 46.4, 43.1, 31.5, 28.7, 18.1, 16.0. LC/MS (CI): $m/z = 382$ [M+H]$^+$. Anal. calcd. for C$_{21}$H$_{27}$N$_5$O$_2$: C 66.12; H 7.13; N 18.36. Found: C 66.18; H 6.91; N 18.38.

(S)-N$^4$-(1-(3-(Methylcarbamoyl)benzyl)piperidin-3-yl)furan-2,4-dicarboxamide (13{139,243,50})

Yellowish solid. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.39 (q, $J = 4.4$ Hz, 1H), 8.24 (s, 1H), 8.01 (d, $J = 4.4$ Hz, 1H), 7.85 (s, 1H), 7.74 (s, 1H), 7.71 – 7.66 (m, 1H), 7.46 (s, 1H), 7.44 – 7.39 (m, 2H), 7.37 (t, $J = 7.5$ Hz, 1H), 3.91 – 3.82 (m, 1H), 3.51 (s, 2H), 2.84 – 2.78 (m, 1H), 2.76 (d, $J = 4.4$ Hz, 3H), 2.70 – 2.65 (m, 1H), 1.90 (t, $J = 10.7$ Hz, 1H), 1.83 (t, $J = 10.2$ Hz, 1H), 1.80 – 1.74 (m, 1H), 1.70 – 1.62 (m, 1H), 1.54 – 1.45 (m, 1H), 1.25 (qd, $J = 11.9$, 4.0 Hz, 1H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 167.1, 160.7, 159.4, 148.8, 146.8, 138.8, 134.9, 131.9, 128.5, 128.0, 126.1, 124.6, 112.8, 62.3, 58.5, 53.2, 46.4, 30.3, 26.7, 24.3. LC/MS (CI): $m/z = 385$ [M+H]$^+$. Anal. calcd. for C$_{20}$H$_{24}$N$_4$O$_4$: C 62.49; H 6.29; N 14.57. Found: C 62.30; H 5.97; N 14.95.

N-(1-((3-Chloro-2-methylphenyl)amino)-2-oxoethyl)piperidin-4-yl)-2-methylpentanamide (13{79,95,11})

Beige solid. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.53 (s, 1H), 7.75 – 7.58 (m, 2H), 7.28 – 7.12 (m, 2H), 3.59 – 3.49 (m, 1H), 3.10 (s, 2H), 2.91 – 2.74 (m, 2H), 2.42 – 2.04 (m, 6H), 1.81 – 1.63 (m, 2H), 1.58 – 1.36 (m, 3H), 1.30 – 1.09 (m, 3H), 0.94 (d, $J = 6.7$ Hz, 3H), 0.83 (t, $J = 6.8$ Hz, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 175.3, 168.9, 138.1, 134.0, 128.1, 127.5, 125.6, 122.3, 62.1, 52.8, 45.6, 39.7, 36.6, 32.3, 32.1, 20.5, 18.4, 14.9, 14.4. LC/MS (CI): $m/z = 380$ [M+H]$^+$. Anal. calcd. for C$_{20}$H$_{20}$ClN$_3$O$_2$: C 63.23; H 7.96; Cl 9.33. Found: C 63.4; H 7.92; Cl 8.97.

N-((4-(2,4-Dimethylbenzyl)morpholin-2-yl)methyl)-1-methyl-1$^H$-pyrazole-3-carboxamide (13{74,107,12})
Yellowish oil. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.91 (t, $J = 6.0$ Hz, 1H), 7.73 (d, $J = 2.2$ Hz, 1H), 7.05 (d, $J = 7.6$ Hz, 1H), 6.93 (s, 1H), 6.91 – 6.87 (m, 1H), 6.63 – 6.50 (m, 1H), 3.86 (d, $J = 1.0$ Hz, 3H), 3.54 – 3.49 (m, 1H), 3.40 (td, $J = 11.2$, 2.5 Hz, 1H), 3.36 – 3.33 (m, 1H), 3.23 (td, $J = 6.2$, 2.5 Hz, 2H), 2.66 (d, $J = 11.2$ Hz, 1H), 2.51 (d, $J = 3.2$ Hz, 1H), 2.20 (s, 3H), 2.02 (td, $J = 11.3$, 3.2 Hz, 1H), 1.80 (t, $J = 10.6$ Hz, 1H). $^{13}$C NMR (151 MHz, DMSO-$d_6$) $\delta$ 161.7, 146.5, 137.4, 136.4, 133.2, 133.0, 131.3, 130.2, 126.3, 106.3, 74.5, 66.3, 60.7, 56.7, 53.1, 41.5, 39.3, 21.0, 19.2. LC/MS (Cl): $m/z$ = 343 [M+H]$^+$. Anal. calcd. for C$_{19}$H$_{26}$N$_4$O$_2$: C 66.64; H 7.65; N 16.36. Found: C 66.76; H 7.99; N 16.46.

$N$-((4-(2-Fluorobenzyl)morpholin-2-yl)methyl)-1-methyl-1$H$-pyrazole-3-carboxamide (13{$74,107,25$})

Brownish solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.91 (t, $J = 6.0$ Hz, 1H), 7.73 (d, $J = 2.2$ Hz, 1H), 7.38 (td, $J = 7.7$, 1.8 Hz, 1H), 7.33 – 7.25 (m, 1H), 7.19 – 7.08 (m, 2H), 6.66 – 6.53 (m, 1H), 3.86 (s, 3H), 3.79 – 3.70 (m, 1H), 3.61 – 3.37 (m, 4H), 3.23 (td, $J = 6.2$, 2.3 Hz, 2H), 2.71 (d, $J = 11.3$ Hz, 1H), 2.56 (d, $J = 11.3$ Hz, 1H), 2.06 (td, $J = 11.3$, 3.2 Hz, 1H), 1.84 (t, $J = 10.6$ Hz, 1H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 161.7, 161.2 (d, $J = 245$ Hz), 146.5, 133.0, 132.0 (d, $J = 4.6$ Hz), 129.6 (d, $J = 8.3$ Hz), 124.6 (d, $J = 14.5$ Hz), 124.6 (d, $J = 3.4$ Hz), 115.6 (d, $J = 21.9$ Hz), 106.3, 74.5, 66.2, 56.4, 55.3, 52.8, 41.5, 39.3. $^{19}$F NMR (376 MHz, DMSO-$d_6$) $\delta$ – 118.6. LC/MS (Cl): $m/z$ = 333 [M+H]$^+$. Anal. calcd. for C$_{17}$H$_{21}$FN$_4$O$_2$: C 66.64; H 7.65; N 16.36. Found: C 66.60; H 6.62; N 16.65.

General procedure for the reaction sequence D. $N$-Boc-diamine 1 (0.5 mmol), aryll halide 6 (0.6 mmol), and $i$-Pr$_2$NEt (1.25 mmol$^*$), were mixed in dry NMP (appr. 2 mL). The reaction mixture was sealed and heated at 100 °C for 16 h, then evaporated under reduced pressure. Then the cleavage cocktail containing trifluoroacetic acid, triisopropylsilane, and water (93:5:2) (appr. 2 mL) was added in one portion. The mixture was stirred at ambient temperature for 6 h and evaporated under reduced pressure. The residue was taken up in DMSO (appr. 1.4 mL). Carboxylic acid 5 (0.6 mmol), $i$-PrNEt$_2$ (3 mmol$^*$), and HATU (0.6 mmol) were added in one portion, the reaction mixture was sealed and left at ambient temperature for 16 h, then cooled and evaporated under reduced pressure. The residue was dissolved in DMSO (appr. 1 mL), filtered, analyzed by LCMS, and transferred for the HPLC purification.

rac-1-Methyl-$N$-((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)hexahydrocyclopenta[c]pyrrol-3a(1H)-yl)methyl)cyclopentane-1-carboxamide (14{$19,35,360$})
Brownish solid. $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 8.32 (d, $J = 9.9$ Hz, 1H), 7.62 (t, $J = 6.3$ Hz, 1H), 7.32 (d, $J = 9.9$ Hz, 1H), 3.79 – 3.70 (m, 1H), 3.66 (d, $J = 11.6$ Hz, 1H), 3.32 – 3.26 (m, 3H), 3.12 (dd, $J = 13.5, 5.9$ Hz, 1H), 2.55 – 2.50 (m, 1H), 1.95 – 1.84 (m, 3H), 1.73 – 1.55 (m, 4H), 1.54 – 1.39 (m, 5H), 1.38 – 1.22 (m, 2H), 1.08 (s, 3H). $^{13}$C NMR (151 MHz, DMSO-$d_6$) $\delta$ 178.3, 154.5, 140.0, 123.6, 119.3, 56.5, 55.8, 53.8, 50.1, 45.6, 45.2, 37.5, 37.4, 35.2, 32.2, 25.6, 24.5, 24.5. LC/MS (Cl): $m/z = 370$ [M+H]$^+$. Anal. calcd. for C$_{19}$H$_{27}$N$_7$O: C 61.77; H 7.37; N 26.54. Found: C 62.11; H 7.24; N 26.69.

$^{rac}$-$N$-(((3aR,6aS)-2-(Tetrazolo[1,5-b]pyridazin-6-yl)hexahydrocyclopenta[c]pyrrol-3a(1H)-yl)methyl)-3,6-dihydro-2H-pyran-4-carboxamide (14{19,35,361})

Brownish oil. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.34 (d, $J = 9.9$ Hz, 1H), 7.99 (t, $J = 6.2$ Hz, 1H), 7.35 (d, $J = 9.7$ Hz, 1H), 6.51 (s, 1H), 4.18 – 4.03 (m, 2H), 3.78 (t, $J = 9.8$ Hz, 1H), 3.70 – 3.59 (m, 3H), 3.48 – 3.37 (m, 2H), 3.25 (dd, $J = 13.5, 6.0$ Hz, 1H), 2.57 – 2.51 (m, 2H), 2.25 – 2.14 (m, 2H), 1.95 – 1.84 (m, 1H), 1.77 – 1.60 (m, 4H), 1.56 – 1.49 (m, 1H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 167.4, 154.6, 140.0, 131.3, 131.1, 123.7, 119.3, 64.7, 63.6, 56.5, 55.8, 53.7, 45.7, 45.0, 35.1, 31.9, 24.8, 24.4. LC/MS (Cl): $m/z = 370$ [M+H]$^+$. Anal. calcd. for C$_{18}$H$_{23}$N$_7$O$_2$: C 58.52; H 6.28; N 26.54. Found: C 58.61; H 6.13; N 26.42.

$^{rac}$-$N$-(((3aR,6aS)-2-(Tetrazolo[1,5-b]pyridazin-6-yl)hexahydrocyclopenta[c]pyrrol-3a(1H)-yl)methyl)benzamide (14{19,35,367})

Yellowish solid. $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 8.58 (t, $J = 9.8$ Hz, 1H), 8.30 (d, $J = 9.8$ Hz, 1H), 7.87 – 7.71 (m, 2H), 7.46 (t, $J = 7.4$ Hz, 1H), 7.39 (t, $J = 7.4$ Hz, 2H), 7.32 (d, $J = 10.1$ Hz, 1H), 3.84 – 3.76 (m, 1H), 3.74 (d, $J = 11.6$ Hz, 1H), 3.49 – 3.35 (m, 4H), 2.59 (tt, $J = 8.5, 4.8$ Hz, 1H), 1.96 – 1.88 (m, 1H), 1.86 – 1.72 (m, 2H), 1.71 – 1.59 (m, 2H), 1.56 – 1.48 (m, 1H). $^{13}$C NMR (151 MHz, DMSO-$d_6$) $\delta$ 167.5, 154.6, 140.0, 135.0, 131.6, 128.6, 127.7, 123.6, 119.3,
rac-2-Cyclobutyl-2-methyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)hexahydrocyclopenta[c]pyrrol-3a(1H)-yl)methyl)propanamide (14{19,35,369})

Brownish solid. \(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \(\delta\) 8.33 (d, \(J = 9.9\) Hz, 1H), 7.43 (t, \(J = 6.3\) Hz, 1H), 7.30 – 7.31 (m, 1H), 7.23 (dd, \(J = 8.9\) Hz, 1H), 3.73 (dd, \(J = 11.1\), 8.3 Hz, 1H), 3.64 (d, \(J = 11.6\) Hz, 1H), 3.31 – 3.32 (m, 1H), 3.26 (dd, \(J = 13.5\), 6.6 Hz, 1H), 3.11 (dd, \(J = 13.5\), 6.0 Hz, 1H), 2.51 (td, \(J = 8.3\), 4.2 Hz, 1H), 2.44 (d, \(J = 8.9\) Hz, 1H), 1.91 – 1.83 (m, 1H), 1.83 – 1.50 (m, 10H), 0.93 (s, 3H), 0.92 (s, 3H). \(^{13}\)C NMR (151 MHz, DMSO-\(d_6\)) \(\delta\) 177.1, 154.0, 140.0, 123.7, 119.2, 56.5, 55.8, 53.8, 45.5, 44.9, 43.7, 43.3, 35.2, 32.0, 24.4, 23.4, 23.3, 22.1, 21.6. LC/MS (Cl): \(m/z\) = 384 [M+H]\(^+\). Anal. calcd. for C\(_{20}\)H\(_{29}\)N\(_7\)O: C 62.64; H 7.62; N 25.57. Found: C 62.77; H 7.37; N 25.52.

rac-1-Methyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)hexahydrocyclopenta[c]pyrrol-3a(1H)-yl)methyl)cyclohexane-1-carboxamide (14{19,35,373})

Brownish solid. \(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \(\delta\) 8.32 (d, \(J = 9.8\) Hz, 1H), 7.59 (t, \(J = 6.3\) Hz, 1H), 7.30 (d, \(J = 9.8\) Hz, 1H), 3.75 (t, \(J = 9.6\) Hz, 1H), 3.68 (d, \(J = 11.6\) Hz, 1H), 3.38 – 3.34 (m, 1H), 3.32 – 3.26 (m, 2H), 3.11 (dd, \(J = 13.5\), 5.8 Hz, 1H), 2.54 (tt, \(J = 8.5\), 4.6 Hz, 1H), 1.96 – 1.82 (m, 3H), 1.74 – 1.56 (m, 4H), 1.52 – 1.45 (m, 1H), 1.40 – 1.31 (m, 2H), 1.27 – 1.04 (m, 6H), 0.95 (s, 3H). \(^{13}\)C NMR (151 MHz, DMSO-\(d_6\)) \(\delta\) 177.5, 154.5, 139.9, 123.7, 119.2, 56.6, 55.9, 53.8, 45.6, 45.1, 42.6, 35.5, 35.4, 32.2, 27.2, 25.8, 24.5, 23.1. LC/MS (Cl): \(m/z\) = 384 [M+H]\(^+\). Anal. calcd. for C\(_{20}\)H\(_{29}\)N\(_7\)O: C 62.64; H 7.62; N 25.57. Found: C 62.77; H 7.37; N 25.52.

rac-3,5-Dimethyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)thiophene-2-carboxamide (14{19,35,375})
Brownish solid. $^1$H NMR (600 MHz, DMSO-d$_6$) $\delta$ 8.31 (d, $J = 9.9$ Hz, 1H), 7.94 (t, $J = 6.3$ Hz, 1H), 7.33 (d, $J = 9.8$ Hz, 1H), 6.58 (s, 1H), 3.78 (dd, $J = 11.2$, 8.1 Hz, 1H), 3.71 (d, $J = 11.5$ Hz, 1H), 3.45 – 3.34 (m, 3H), 3.32 – 3.28 (m, 1H), 2.56 (tt, $J = 8.4$, 4.9 Hz, 1H), 2.32 (s, 3H), 2.25 (s, 3H), 1.95 – 1.87 (m, 1H), 1.81 – 1.58 (m, 4H), 1.54 – 1.47 (m, 1H). $^{13}$C NMR (151 MHz, DMSO-d$_6$) $\delta$ 163.4, 154.6, 140.9, 140.2, 140.0, 130.5, 129.5, 123.6, 119.3, 56.5, 55.7, 53.8, 45.7, 45.3, 35.3, 32.1, 24.5, 15.7, 15.3. LC/MS (Cl): $m/z$ = 398 [M+H]$^+$. Anal. calcd. for C$_{19}$H$_{23}$N$_7$O$_8$: C 57.41; H 5.83; N 24.67; S 8.07. Found: C 57.16; H 5.53; N 24.47; S 8.13.

rac-2,4-Dimethyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)benzamide (14{19,35,377})

Brownish solid. $^1$H NMR (600 MHz, DMSO-d$_6$) $\delta$ 8.36 (t, $J = 6.3$ Hz, 1H), 8.33 (d, $J = 9.9$ Hz, 1H), 7.34 (d, $J = 7.7$ Hz, 1H), 6.99 (s, 1H), 6.95 (d, $J = 7.7$ Hz, 1H), 3.86 – 3.76 (m, 1H), 3.73 (d, $J = 11.6$ Hz, 1H), 3.43 – 3.36 (m, 3H), 3.32 – 3.28 (m, 1H), 2.58 (tt, $J = 8.5$, 4.7 Hz, 1H), 2.23 (s, 6H), 1.95 – 1.86 (m, 1H), 1.79 – 1.71 (m, 2H), 1.71 – 1.63 (m, 2H), 1.57 – 1.48 (m, 1H). $^{13}$C NMR (151 MHz, DMSO-d$_6$) $\delta$ 170.2, 154.6, 140.0, 139.1, 135.5, 134.8, 131.4, 127.5, 126.3, 123.7, 119.3, 56.6, 55.6, 53.8, 45.7, 45.3, 35.4, 32.1, 24.5, 21.2, 19.8. LC/MS (Cl): $m/z$ = 392 [M+H]$^+$. Anal. calcd. for C$_{21}$H$_{25}$N$_7$O: C 64.43; H 6.44; N 25.05. Found: C 64.66; H 6.12; N 24.75.

$N$-(((3aS,6aR)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)-3,4-dihydro-2H-pyran-5-carboxamide (14{19,35,378})

Brownish solid. $^1$H NMR (600 MHz, DMSO-d$_6$) $\delta$ 8.31 (d, $J = 9.9$ Hz, 1H), 7.57 (t, $J = 6.0$ Hz, 1H), 7.31 (d, $J = 9.9$ Hz, 1H), 7.25 (s, 1H), 3.86 (t, $J = 5.2$ Hz, 2H), 3.74 (dd, $J = 11.2$, 8.3 Hz, 1H), 3.65 (d, $J = 11.6$ Hz, 1H), 3.35 (s, 1H), 3.32 – 3.26 (m, 2H), 3.20 (dd, $J = 13.6$, 6.1 Hz, 1H), 2.53 – 2.49 (m, 1H), 2.13 – 2.06 (m, 2H), 1.92 – 1.84 (m, 1H), 1.77 – 1.67 (m, 4H), 1.65 – 1.56 (m, 2H), 1.51 – 1.45 (m, 1H). $^{13}$C NMR (151 MHz, DMSO-d$_6$) $\delta$ 167.9, 154.5, 150.4, 140.0, 123.6, 119.3, 109.3, 66.0, 56.5, 55.8, 53.6, 45.6, 44.7, 35.1, 31.8, 24.4, 21.2, 19.6. LC/MS (Cl): $m/z$ = 370 [M+H]$^+$. Anal. calcd. for C$_{18}$H$_{23}$N$_7$O$_2$: C 58.52; H 6.28; N 26.54. Found: C 58.67; H 6.26; N 26.86.

rac-2-Methyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)benzamide (14{19,35,384})
Brownish solid. $^1$H NMR (500 MHz, DMSO-d$_6$) δ 8.47 (s, 1H), 8.36 (d, $J$ = 9.7 Hz, 1H), 7.37 (d, $J$ = 9.7 Hz, 1H), 7.32 – 7.24 (m, 2H), 7.23 – 7.15 (m, 2H), 3.84 (dd, $J$ = 10.4, 8.9 Hz, 1H), 3.76 (d, $J$ = 11.6 Hz, 1H), 3.50 – 3.36 (m, 4H), 2.66 – 2.59 (m, 1H), 2.29 (s, 3H), 2.01 – 1.90 (m, 1H), 1.83 – 1.75 (m, 2H), 1.73 – 1.65 (m, 2H), 1.60 – 1.52 (m, 1H). $^{13}$C NMR (126 MHz, DMSO-d$_6$) δ 170.2, 154.7, 140.0, 137.8, 135.4, 130.8, 129.6, 127.4, 125.9, 123.8, 119.3, 56.7, 55.7, 53.8, 45.8, 45.4, 35.5, 32.1, 24.6, 19.8. LC/MS (Cl): $m/z$ = 378 [M+H]$^+$. Anal. calcd. for C$_{20}$H$_{23}$N$_7$O: C 63.64; H 6.14; N 25.98. Found: C 63.82; H 5.97; N 25.76.

$^{rac}$-3-Methyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)benzamide (14{19,35,171})

Brownish solid. $^1$H NMR (600 MHz, DMSO-d$_6$) δ 8.52 (t, $J$ = 6.2 Hz, 1H), 8.30 (d, $J$ = 9.9 Hz, 1H), 7.69 – 7.47 (m, 2H), 7.32 (d, $J$ = 9.9 Hz, 1H), 7.29 – 7.22 (m, 2H), 3.83 – 3.71 (m, 2H), 3.48 – 3.34 (m, 4H), 2.59 (tt, $J$ = 8.5, 4.7 Hz, 1H), 1.96 – 1.88 (m, 1H), 1.79 – 1.72 (m, 2H), 1.69 – 1.61 (m, 2H), 1.55 – 1.48 (m, 1H). $^{13}$C NMR (151 MHz, DMSO-d$_6$) δ 167.6, 154.5, 140.0, 137.9, 135.0, 132.1, 128.5, 128.1, 124.8, 123.6, 119.3, 56.5, 55.8, 53.7, 45.8, 45.4, 35.2, 31.9, 24.4, 21.3. LC/MS (Cl): $m/z$ = 378 [M+H]$^+$. Anal. calcd. for C$_{20}$H$_{23}$N$_7$O: C 63.64; H 6.14; N 25.98. Found: C 63.34; H 5.86; N 25.60.

$^{rac}$-2-Methyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)thiophene-3-carboxamide (14{19,35,390})

Brownish solid. $^1$H NMR (600 MHz, DMSO-d$_6$) δ 8.31 (d, $J$ = 9.8 Hz, 1H), 8.22 (t, $J$ = 6.3 Hz, 1H), 7.33 (d, $J$ = 9.8 Hz, 1H), 7.21 (s, 2H), 3.78 (dd, $J$ = 11.1, 8.2 Hz, 1H), 3.71 (d, $J$ = 11.6 Hz, 1H), 3.44 – 3.35 (m, 3H), 3.32 – 3.27 (m, 1H), 2.57 (tt, $J$ = 8.6, 4.7 Hz, 1H), 2.47 (s, 3H), 1.97 – 1.86 (m, 1H), 1.81 – 1.71 (m, 2H), 1.69 – 1.60 (m, 2H), 1.55 – 1.47 (m, 1H). $^{13}$C NMR (151 MHz, DMSO-d$_6$) δ 164.8, 154.6, 143.3, 140.0, 133.0, 127.7, 123.6, 122.3, 119.3, 56.5, 55.7, 53.7, 45.7, 45.0, 35.3, 31.9, 24.4, 14.9. LC/MS (Cl): $m/z$ = 384 [M+H]$^+$. Anal. calcd. for C$_{18}$H$_{23}$N$_7$OS: C 56.38; H 5.52; N 25.57; S 8.36. Found: C 55.99; H 5.81; N 25.78; S 8.00.
rac-4-Methyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)thiophene-2-carboxamide (14{19,35,394})

Brownish solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.51 (t, $J = 6.3$ Hz, 1H), 8.33 (d, $J = 9.9$ Hz, 1H), 7.56 (s, 1H), 7.34 (d, $J = 9.9$ Hz, 1H), 7.29 (s, 1H), 3.80 (dd, $J = 11.2$, 8.1 Hz, 1H), 3.73 (d, $J = 11.6$ Hz, 1H), 3.50 – 3.38 (m, 3H), 3.35 – 3.31 (m, 1H), 2.59 (tt, $J = 8.4$, 4.6 Hz, 1H), 2.17 (s, 3H), 1.99 – 1.88 (m, 1H), 1.83 – 1.73 (m, 2H), 1.71 – 1.63 (m, 2H), 1.57 – 1.50 (m, 1H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 162.3, 154.6, 140.0, 139.8, 138.1, 130.5, 126.5, 123.7, 119.3, 56.5, 55.8, 53.7, 45.8, 45.3, 35.2, 31.8, 24.4, 15.8. LC/MS (CI): $m/z$ = 384 [M+H]$^+$. Anal. calcd. for C$_{18}$H$_{21}$N$_7$OS: C 56.38; H 5.52; N 25.57; S 8.36. Found: C 56.09; H 5.52; N 25.53; S 8.13.

1-Methyl-N-(6-(tetrazolo[1,5-b]pyridazin-6-ylamino)spiro[3.3]heptan-2-yl)cycloheptane-carboxamide (14{114,35,399})

Brownish solid. $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 8.17 (d, $J = 9.7$ Hz, 1H), 8.10 (d, $J = 6.4$ Hz, 1H), 7.36 (d, $J = 7.3$ Hz, 1H), 7.03 (d, $J = 9.7$ Hz, 1H), 4.14 – 4.05 (m, 2H), 2.54 – 2.50 (m, 1H), 2.39 – 2.32 (m, 2H), 2.15 (ddd, $J = 12.0$, 7.5, 4.9 Hz, 1H), 2.05 (dd, $J = 10.7$, 8.8 Hz, 1H), 2.00 – 1.90 (m, 5H), 1.45 – 1.36 (m, 8H), 1.29 – 1.24 (m, 2H), 0.99 (s, 3H). $^{13}$C NMR (151 MHz, DMSO-$d_6$) $\delta$ 177.1, 155.1, 140.4, 123.5, 121.1, 45.0, 42.5, 42.4, 42.3, 41.9, 37.9, 37.9, 31.4, 29.9, 27.7, 23.7. LC/MS (CI): $m/z$ = 384 [M+H]$^+$. Anal. calcd. for C$_{20}$H$_{29}$N$_7$O: C 62.64; H 7.62; N 25.57; S 8.13. Found: C 62.79; H 7.70; N 25.75.

rac-2-Chloro-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)benzamide (14{19,35,408})

Brownish solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.67 (t, $J = 5.9$ Hz, 1H), 8.36 (d, $J = 9.7$ Hz, 1H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.44 – 7.40 (m, 1H), 7.39 – 7.33 (m, 3H), 3.84 (dd, $J = 10.6$, 8.5 Hz, 1H), 3.75 (d, $J = 11.7$ Hz, 1H), 3.50 – 3.36 (m, 4H), 2.68 – 2.61 (m, 1H), 2.00 – 1.91 (m, 1H), 1.82 – 1.67 (m, 4H), 1.58 – 1.52 (m, 1H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 167.5, 154.7, 140.0, 137.6, 131.1, 130.1, 130.0, 129.2, 127.5, 123.8, 119.3, 56.7, 55.6, 53.8, 45.7, 45.4, 35.6,
rac-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)furan-3-carboxamide (14{19,35,32})

Brownish solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.34 (d, $J$ = 9.9 Hz, 1H), 8.29 (t, $J$ = 6.3 Hz, 1H), 7.68 (d, $J$ = 2.0 Hz, 1H), 7.35 (d, $J$ = 9.8 Hz, 1H), 6.83 (d, $J$ = 2.0 Hz, 1H), 3.79 (dd, $J$ = 11.4, 8.1 Hz, 1H), 3.70 (d, $J$ = 11.4 Hz, 1H), 3.47 – 3.36 (m, 4H), 2.61 – 2.54 (m, 1H), 1.97 – 1.89 (m, 1H), 1.81 – 1.73 (m, 2H), 1.70 – 1.62 (m, 2H), 1.57 – 1.50 (m, 1H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 162.7, 154.6, 145.6, 144.4, 140.0, 123.7, 123.1, 119.3, 109.5, 56.5, 55.7, 53.7, 45.7, 44.7, 35.2, 31.8, 24.4. LC/MS (CI): $m/z$ = 354 [M+H]$^+$. Anal. calcd. for C$_{17}$H$_{19}$N$_7$O$_2$: C 57.78; H 5.42; N 27.75. Found: C 58.07; H 5.29; N 28.08.

**General procedure for the reaction sequence E.** Amine 2 or 9 (0.5 mmol), carboxylic acid 8 or 3 (0.6 mmol), i-Pr$_2$NEt (1.25 mmol$^*$), and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (0.575 mmol) were mixed in dry DMF (appr. 1.4 mL). The reaction mixture was sealed and left at ambient temperature for 16 h, Alkyne 10 (0.6 mmol), i-PrNEt$_2$ (1.5 mmol$^*$), and Cu(OAc)$_2$ (0.05 mmol) were added in one portion, the reaction mixture was sealed and heated at 80 $^\circ$C for 16 h, then cooled and evaporated under reduced pressure. The residue was dissolved in DMSO (appr. 1 mL), filtered, analyzed by LCMS, and transferred for the HPLC purification.

3-Methyl-1-(3-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)piperidin-1-yl)but-3-en-1-one (15{5,7,7})

Yellowish liquid. The compound existed as a ca. 11:9 mixture of rotamers. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.56 (d, $J$ = 7.1 Hz, 1H), 7.87 – 7.78 (m, 2H), 7.43 (t, $J$ = 7.5 Hz, 2H), 7.31 (t, $J$ = 7.5 Hz, 1H), 4.81 (s, 0.55H) and 4.69 (s, 0.55H) and 4.68 (s, 0.45H) and 4.48 (s, 0.45H), 4.37 – 4.27 (m, 2H), 4.19 – 4.10 (m, 1H), 3.70 – 3.63 (m, 0.55H) and 3.58 – 3.53 (m, 0.45H), 3.09 – 2.93 (m, 2H), 2.91 – 2.80 (m, 1H), 2.66 – 2.60 (m, 0.45H) and 2.55 (dd, $J$ = 12.9, 10.2 Hz, 0.55H), 2.04 – 1.92 (m, 1H), 1.72 – 1.52 (m, 5H), 1.37 – 1.19 (m, 2H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 168.6 and 168.4, 146.9 and 146.7, 140.7 and 140.3, 131.2, 129.3, 128.3, 125.6 and 125.6, 122.2 and 122.2, 113.1 and 113.0, 52.8 and 52.5, 49.2 and 46.4, 44.6 and 43.0, 42.8 and 41.9, 37.7 and 36.9, 28.0 and 27.9, 25.0 and 24.4, 22.9 and 22.7. LC/MS (CI): $m/z$ = 325 [M+H]$^+$. Anal. calcd. for C$_{19}$H$_{24}$N$_4$O: C 70.34; H 7.46; N 17.27. Found: C 70.63; H 7.43; N 17.24.
**N-(2-(Hydroxymethyl)benzyl)-2-(4-(4-hydroxytetrahydro-2H-pyran-4-yl)-1H-1,2,3-triazol-1-yl)acetamide (15{3,17,38})**

Yellowish oil. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.68 (t, $J = 5.6$ Hz, 1H), 7.91 (s, 1H), 7.43 – 7.37 (m, 1H), 7.29 – 7.20 (m, 3H), 5.23 (s, 1H), 5.15 (s, 1H), 5.13 (s, 2H), 4.56 (s, 2H), 4.36 (d, $J = 5.5$ Hz, 2H), 3.75 (td, $J = 11.0$, 2.5 Hz, 2H), 3.67 – 3.56 (m, 2H), 2.05 (ddd, $J = 14.3$, 10.5, 4.5 Hz, 2H), 1.74 – 1.63 (m, 2H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 165.9, 155.1, 140.3, 136.1, 128.3, 127.7, 127.4, 127.3, 123.1, 66.1, 63.5, 61.0, 52.0, 40.0, 38.4. LC/MS (CI): $m/z = 347$ [M+H]$^+$. Anal. calcd. for C$_{17}$H$_{22}$N$_4$O$_4$: C 58.95; H 6.4; N 16.17. Found: C 59.25; H 6.19; N 16.43.

**N-(3-Hydroxybutyl)-2-(4-(4-hydroxytetrahydro-2H-pyran-4-yl)-1H-1,2,3-triazol-1-yl)-N-methylacetamide (Z4180225403)**

Yellowish solid. The compound existed as a ca. 11:9 mixture of rotamers. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.81 (s, 0.45H) and 7.78 (s, 0.55H), 5.59 – 5.38 (m, 1H), 5.35 (s, 1H), 5.19 (s, 1H), 4.64 (d, $J = 4.8$ Hz, 0.45H) and 4.43 (d, $J = 4.8$ Hz, 0.55H), 3.77 – 3.69 (m, 2H), 3.67 – 3.50 (m, 3H), 3.50 – 3.33 (m, 2H), 3.02 (s, 1.65H) and 2.81 (s, 1.35H), 2.03 (ddd, $J = 14.2$, 10.4, 4.3 Hz, 2H), 1.74 – 1.65 (m, 2.2H) and 1.60 – 1.42 (m, 1.8H), 1.11 (d, $J = 6.2$ Hz, 1.35H) and 1.04 (d, $J = 6.2$ Hz, 1.65H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 165.9 and 165.7, 154.9 and 154.9, 123.3 and 123.2, 66.1 and 66.0, 64.2 and 63.7, 63.5, 51.1 and 50.7, 45.8 and 45.4, 38.5, 37.1 and 36.7, 34.6 and 33.4, 24.4 and 24.1. LC/MS (CI): $m/z = 313$ [M+H]$^+$. Anal. calcd. for C$_{14}$H$_{24}$N$_4$O$_4$: C 53.83; H 7.74; N 17.94. Found: C 53.81; H 7.50; N 17.56.

**N-((4,5-Dimethylthiazol-2-yl)methyl)-2-(4-(hydroxy(phenyl)methyl)-1H-1,2,3-triazol-1-yl)acetamide (15{3,17,38})**

Yellowish solid. 1H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.09 (t, $J = 6.1$ Hz, 1H), 7.81 (s, 1H), 7.41 (d, $J = 7.6$ Hz, 2H), 7.33 (t, $J = 7.6$ Hz, 2H), 7.24 (t, $J = 6.9$ Hz, 1H), 5.99 (d, $J = 3.9$ Hz, 1H), 5.82 (d, $J = 4.7$ Hz, 1H), 5.11 (s, 2H), 4.46 (d, $J = 5.9$ Hz, 2H), 2.28 (s, 3H), 2.21 (s, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 166.2, 163.3, 151.7, 147.6, 144.6, 128.5, 127.5, 126.9, 126.6, 124.0, 68.4, 51.9, 40.8, 14.9, 11.3. LC/MS (CI): $m/z = 358$ [M+H]$^+$. Anal. calcd. for C$_{17}$H$_{19}$N$_5$O$_2$S: C 57.13; H 5.36; N 19.59; S 8.97. Found: C 56.82; H 5.03; N 19.58; S 9.24.

**N-(4,5-Dimethylthiazol-2-yl)methyl)-2-(4-(hydroxy(phenyl)methyl)-1H-1,2,3-triazol-1-yl)-acetamide (15{3,21,37})**

Yellowish solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.09 (t, $J = 6.1$ Hz, 1H), 7.81 (s, 1H), 7.41 (d, $J = 7.6$ Hz, 2H), 7.33 (t, $J = 7.6$ Hz, 2H), 7.24 (t, $J = 6.9$ Hz, 1H), 5.99 (d, $J = 3.9$ Hz, 1H), 5.82 (d, $J = 4.7$ Hz, 1H), 5.11 (s, 2H), 4.46 (d, $J = 5.9$ Hz, 2H), 2.28 (s, 3H), 2.21 (s, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 166.2, 163.3, 151.7, 147.6, 144.6, 128.5, 127.5, 126.9, 126.6, 124.0, 68.4, 51.9, 40.8, 14.9, 11.3. LC/MS (CI): $m/z = 358$ [M+H]$^+$. Anal. calcd. for C$_{17}$H$_{19}$N$_5$O$_2$S: C 57.13; H 5.36; N 19.59; S 8.97. Found: C 56.82; H 5.03; N 19.58; S 9.24.

**2-((4-Cyclopropyl-1H-1,2,3-triazol-1-yl)methyl)pyrrolidin-1-yl)(1-hydroxy-3,3-dimethyl-cyclobutyl)methanone (15{1,6,6})**
rac-(1R,2R)-2-Methyl-N-(2-(4-(2-phenoxyethyl)-1H-1,2,3-triazol-1-yl)propyl)cyclopropanecarboxamide (15{4,4,4})

Yellowish oil. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.63 (s, 1H), 5.71 (s, 1H), 4.44 (d, $J = 4.5$ Hz, 2H), 4.22 (dq, $J = 8.6$, 4.5 Hz, 1H), 3.46 (dt, $J = 10.8$, 6.8 Hz, 1H), 3.16 – 3.07 (m, 1H), 2.47 – 2.42 (m, 1H), 2.36 (dd, $J = 12.8$, 2.6 Hz, 1H), 1.89 (tt, $J = 8.6$, 5.0 Hz, 1H), 1.85 – 1.68 (m, 3H), 1.65 – 1.52 (m, 2H), 1.33 – 1.23 (m, 1H), 1.17 (s, 3H), 0.98 (s, 3H), 0.92 – 0.81 (m, 2H), 0.71 – 0.59 (m, 2H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 172.7, 149.6, 121.8, 70.5, 57.3, 50.4, 47.0, 45.8, 31.1, 29.8, 27.0, 26.9, 24.1, 8.2, 8.1, 7.0. LC/MS (CI): $m/z = 319$ [M+H]$^+$. Anal. calcd. for C$_{17}$H$_{26}$N$_4$O$_2$: C 64.12; H 8.23; N 17.60. Found: C 64.07; H 8.13; N 17.64.

(S)-2-Cyclobutylidene-N-(1-(4-(1-methyl-1H-pyrazol-5-yl)-1H-1,2,3-triazol-1-yl)propan-2-yl)acetamide (15{6,11,11})

Yellowish solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.09 (q, $J = 5.5$ Hz, 1H), 7.95 (d, $J = 3.0$ Hz, 1H), 7.26 (t, $J = 7.9$ Hz, 2H), 7.00 – 6.80 (m, 3H), 4.75 – 4.64 (m, 1H), 4.19 (t, $J = 6.8$ Hz, 2H), 3.50 – 3.35 (m, 2H), 3.06 (t, $J = 6.8$ Hz, 2H), 1.41 (d, $J = 6.9$ Hz, 3H), 1.21 (dq, $J = 7.9$, 3.9 Hz, 1H), 1.12 – 1.01 (m, 1H), 0.97 (dd, $J = 6.0$, 2.2 Hz, 3H), 0.85 – 0.76 (m, 1H), 0.42 (ddd, $J = 8.8$, 5.8, 3.4 Hz, 1H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 173.1, 158.8, 143.5, 129.9, 121.8, 121.1, 114.9, 66.9, 56.2, 56.2, 44.6, 26.1, 22.4, 19.0, 19.0, 18.0, 14.9, 14.9, 14.9, 14.9. LC/MS (Cl): $m/z = 329$ [M+H]$^+$. Anal. calcd. for C$_{18}$H$_{24}$N$_6$O$_2$: C 65.83; H 7.37; N 17.06. Found: C 65.75; H 7.34; N 16.96.

(S)-N-(1-(4-(2,6-Difluorophenyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)-2-methylbut-2-enamide (15{6,1,8})

Yellowish solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.42 (s, 1H), 7.71 (d, $J = 8.0$ Hz, 1H), 7.45 (d, $J = 1.8$ Hz, 1H), 6.54 (d, $J = 1.5$ Hz, 1H), 5.55 – 5.45 (m, 1H), 4.50 – 4.34 (m, 2H), 4.31 – 4.21 (m, 1H), 4.01 (d, $J = 1.3$ Hz, 3H), 3.01 – 2.85 (m, 2H), 2.70 (t, $J = 7.9$ Hz, 2H), 2.02 – 1.86 (m, 2H), 1.06 (d, $J = 7.0$ Hz, 3H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 165.4, 160.3, 138.5, 137.7, 133.7, 124.2, 114.9, 105.6, 54.3, 44.7, 38.7, 33.4, 32.1, 18.2, 18.1. LC/MS (Cl): $m/z = 301$ [M+H]$^+$. Anal. calcd. for C$_{15}$H$_{20}$N$_6$O: C 59.98; H 6.71; N 27.98. Found: C 60.18; H 6.75; N 27.72.
(S)-3-Cyclopropyl-N-(1-(4-(2-methylpyridin-3-yl)-1H-1,2,3-triazol-1-yl)propan-2-yl)propanamide (15(6,27,27))

(R)-N-(1-(4-(4-Fluorophenyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)bicyclo[1.1.1]pentane-1-carboxamide (15(2,2,2))

rac-4-((4-((1R,2S)-2-Hydroxycyclopentyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(phenyl(thiophen-2-yl)methyl)benzamide (15(1,2,17))
Beige solid. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.46 (d, $J = 8.7$ Hz, 1H), 7.98 – 7.87 (m, 3H), 7.48 (d, $J = 7.4$ Hz, 2H), 7.46 – 7.42 (m, 1H), 7.42 – 7.34 (m, 4H), 7.31 (t, $J = 7.4$ Hz, 1H), 6.97 (t, $J = 4.2$ Hz, 1H), 6.87 – 6.79 (m, 1H), 6.58 (d, $J = 8.7$ Hz, 1H), 5.60 (s, 2H), 4.74 (d, $J = 4.8$ Hz, 1H), 4.08 – 3.98 (m, 1H), 2.98 – 2.89 (m, 1H), 2.12 – 2.02 (m, 1H), 1.88 – 1.80 (m, 1H), 1.76 – 1.60 (m, 3H), 1.55 – 1.48 (m, 1H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 165.8, 150.4, 146.7, 142.2, 140.0, 134.3, 128.8, 128.6, 128.2, 127.9, 127.3, 126.1, 125.9, 122.1, 78.0, 52.8, 52.8, 45.2, 34.4, 30.5, 22.1. LC/MS (Cl): m/z = 459 [M+H]$^+$. Anal. calcd. for C$_{26}$H$_{26}$N$_4$O$_2$S: C 68.10; H 5.72; N 12.22; S 6.99. Found: C 68.08; H 5.56; N 11.84; S 6.92.

(R)-2-Hydroxy-$N$-(1-(4-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)acetamide (15{2,30,29})

Beige solid. $^1$H NMR (600 MHz, DMSO-$d_6$) δ 8.63 (s, 1H), 8.04 (d, $J = 8.2$ Hz, 2H), 7.84 (d, $J = 8.6$ Hz, 1H), 7.78 (d, $J = 8.2$ Hz, 2H), 5.47 (t, $J = 5.8$ Hz, 1H), 4.53 – 4.44 (m, 2H), 4.37 – 4.31 (m, 1H), 3.78 – 3.67 (m, 2H), 1.10 (d, $J = 6.9$ Hz, 3H). $^{13}$C NMR (151 MHz, DMSO-$d_6$) δ 172.0, 145.2, 135.2, 128.4 (q, $J = 31.7$ Hz), 126.3 (q, $J = 4.0$ Hz), 126.1, 124.7 (q, $J = 272$ Hz), 123.5, 61.7, 54.1, 44.7, 18.1. $^{19}$F NMR (376 MHz, DMSO-$d_6$) δ –61.5. LC/MS (Cl): m/z = 329 [M+H]$^+$. Anal. calcd. for C$_{26}$H$_{26}$N$_4$O$_2$: C 68.10; H 5.72; N 12.22; S 6.99. Found: C 68.08; H 5.56; N 11.84; S 6.92.

(1R,6S,7r)-$N$-(2-(4-(Ethoxymethyl)-1H-1,2,3-triazol-1-yl)propyl)bicyclo[4.1.0]heptane-7-carboxamide (15{4,15,14})

Yellowish solid. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.08 (s, 1H), 8.01 (t, $J = 5.0$ Hz, 1H), 4.77 – 4.67 (m, 1H), 4.47 (s, 2H), 3.53 – 3.41 (m, 4H), 1.86 – 1.76 (m, 2H), 1.53 (s, 2H), 1.43 (d, $J = 6.9$ Hz, 3H), 1.32 – 1.17 (m, 5H), 1.17 – 1.04 (m, 5H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 173.4, 144.3, 122.8, 65.3, 63.7, 56.4, 44.5, 26.6, 22.8, 21.2, 19.5, 19.5, 19.1, 15.5. LC/MS (Cl): m/z = 307 [M+H]$^+$. Anal. calcd. for C$_{16}$H$_{26}$N$_4$O$_2$: C 62.72; H 8.55; N 18.29. Found: C 62.96; H 8.58; N 18.06.

(S)-$N$-(1-(4-(Methoxymethyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)-1,2,2,3,3-pentamethylcyclopropanecarboxamide (15{6,14,13})
(S)-1,3-Dimethyl-N-(1-(4-(pent-4-en-1-yl)-1H-1,2,3-triazol-1-yl)propan-2-yl)-1H-pyrazole-5-carboxamide (15(6,9,9))
Brownish solid. The compound existed as a ca. 1:1 mixture of rotamers. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.76 – 8.64 (m, 1H), 8.60 (s, 1H), 8.04 (s, 1H), 7.89 (t, $J = 7.8$ Hz, 1H), 7.35 (s, 1H), 4.54 – 4.47 (m, 2H), 3.58 – 3.49 (m, 1H), 3.46 – 3.37 (m, 1.5H) and 3.28 – 3.17 (m, 1H) and 3.09 (dd, $J = 11.8$, 7.1 Hz, 0.5H), 2.90 – 2.79 (m, 0.5H) and 2.77 – 2.70 (m, 0.5H), 2.63 – 2.54 (m, 1H), 2.39 – 2.27 (m, 2H), 2.05 – 1.95 (m, 2.5H) and 1.94 – 1.85 (m, 0.5H), 1.83 – 1.70 (m, 2.5H) and 1.66 – 1.56 (m, 2.5H). $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 170.1 and 170.0, 150.5, 150.0, 147.7, 137.6, 124.1, 123.5, 119.9, 52.0 and 52.0, 49.5 and 48.6, 45.6 and 44.7, 41.1 and 40.9, 38.1, 32.1 and 32.1, 29.4, 28.4 and 28.4, 28.4, 27.8, 18.8. LC/MS (Cl): $m/z = 326$ [M+H]$^+$. Anal. calcd. for C$_{18}$H$_{23}$N$_5$O: C 66.44; H 7.12; N 21.52. Found: C 66.43; H 7.34; N 21.40.
$N$-(9-Acetyl-9-azabicyclo[3.3.1]nonan-3-yl)-1$H$-indazole-3-carboxamide (11{52,55,23}), $^1$H NMR (500 MHz, DMSO-$d_6$)
N-(9-Acetyl-9-azabicyclo[3.3.1]nonan-3-yl)-1H-indazole-3-carboxamide (1 {52,55,23}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
(S)-2-Ethyl-N-(4-(2-methylthiazole-5-carboxamido)butan-2-yl)oxazole-4-carboxamide, \( \text{HMN} \) (500 MHz, DMSO-\( d_6 \))
(S)-2-Ethyl-N-(4-(2-methylthiazole-5-carboxamido)butan-2-yl)oxazole-4-carboxamide (11{25,19,9}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
$N$-((4-Hydroxy-1-(isobutylprolyl)piperidin-4-yl)methyl)picolinamide (11{24,21,10}), $^1$H NMR (500 MHz, DMSO-$d_6$)
$N-$((4-Hydroxy-1-(isobutylprolyl)piperidin-4-yl)methyl)picolinamide ($1\{24,21,10\}$), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
N-(1-Cyclopropyl-2-(2-thiazol-5-yl)acetamido)ethyl)-6-methylnicotinamide (11{30,17,13}), ^1H NMR (500 MHz, DMSO-d$_6$)
N-(1-Cyclopropyl-2-(2-(thiazol-5-yl)acetamido)ethyl)-6-methylnicotinamide (11{30,17,13}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
(2-(Cyclobutanecarbonyl)-2,8-diazaspiro[4.5]decan-8-yl)(tetrahydro-2H-pyran-4-yl)methanone (11{50,64,26}), $^1$H NMR (500 MHz, DMSO-$d_6$)
(2-(Cyclobutanecarbonyl)-2,8-diazaspiro[4.5]decan-8-yl)(tetrahydro-2$H$-pyran-4-yl)methanone (11\{50,64,26\}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
Oxazol-5-yl(2-picolinoyl-2,8-diazaspiro[4.5]decan-8-yl)methanone (11 \{50,69,10\}), $^1$H NMR (500 MHz, DMSO-$d_6$)
Oxazol-5-yl(2-picolinoyl-2,8-diazaspiro[4.5]decan-8-yl)methanone (11{50,69,10}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
(2-(Furan-3-carbonyl)-2,7-diazaspiro[3.5]nonan-7-yl)(o-tolyl)methanone (11{60,73,32}), $^1$H NMR (500 MHz, DMSO-$d_6$)
(2-(Furan-3-carbonyl)-2,7-diazaspiro[3.5]nonan-7-yl)(o-tolyl)methanone (11{60,73,32}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
N-(2-Isobutylamidopropyl)-N-methylbenzofuran-3-carboxamide (11\{67,81,37\}), $^1$H NMR (500 MHz, DMSO-$d_6$)
$N$-(2-Isobutyramidopropyl)-$N$-methylbenzofuran-3-carboxamide (11{67,81,37}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
1-(2-(1-Methylcyclopropane-1-carbonyl)-2,7-diazaspiro[3.5]nonan-7-yl)-3-phenylbutan-1-one (11\{60,102,51\}), \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}_6)
1-(2-(1-Methylocyclopropane-1-carbonyl)-2,7-diazaspiro[3.5]nonan-7-yl)-3-phenylbutan-1-one (11\{60,102,51\}), $^{13}$C NMR (151 MHz, DMSO-$d_6$)
3-Chloro-N-(4-(2-(1-ethyl-1H-pyrazol-4-yl)acetamido)pentan-2-yl)-4-methylbenzamide (11{70,84,38}), $^1$H NMR (500 MHz, DMSO-$d_6$)
3-Chloro-\(N\)-(4-(2-(1-ethyl-1H-pyrazol-4-yl)acetamido)pentan-2-yl)-4-methylbenzamide (11\{70,84,38\}), \(^{13}\)C NMR (126 MHz, DMSO-\(d_6\))
N-(4-(3-Fluoro-2-methylbenzamido)butan-2-yl)thiophene-2-carboxamide (11{83,105,54}), $^1$H NMR (500 MHz, DMSO-$d_6$)
$N-(4-(3\text{-Fluoro-2-methylbenzamido})\text{butan-2-yl})\text{thiophene-2-carboxamide (~11{83,105,54})}, ~^{13}\text{C NMR (126 MHz, DMSO-}d_6\text{)}}$
N-(4-(3-Fluoro-2-methylbenzamido)butan-2-yl)thiophene-2-carboxamide (11{83,105,54}), $^{19}$F NMR (376 MHz, DMSO-d$_6$)
2-(2-Methylthiophen-3-yl)-1-(2-((tetrazolo[1,5-b]pyridazin-6-ylamino)methyl)morpholino)ethanone (12{140,239,35}),
³¹H NMR (600 MHz, DMSO-d₆)
2-(2-Methylthiophen-3-yl)-1-(2-((tetrazolo[1,5-b]pyridazin-6-ylamino)methyl)morpholino)ethanone (12\{140,239,35\}), $^{13}$C NMR (151 MHz, DMSO-$d_6$)
rac-5-((3aR,7aR)-5-(Pyrimidin-2-yl)octahydro-1H-pyrrolo[3,4-c]pyridine-2-carbonyl)-1H-benzo[d]imidazol-2(3H)-one (12{17,14,5}),

$^1$H NMR (500 MHz, DMSO-$d_6$)
rac-5-((3aR,7aR)-5-(Pyrimidin-2-yl)octahydro-1H-pyrrolo[3,4-c]pyridine-2-carbonyl)-1H-benzo[d]imidazol-2(3H)-one (12{17,14,5}),
13C NMR (126 MHz, DMSO-d6)
1-Methyl-5-(4-(quinoxalin-2-yl)piperazine-1-carbonyl)pyridin-2(1H)-one (12\{9,26,3\}), $^1$H NMR (500 MHz, DMSO-$d_6$)
1-Methyl-5-(4-(quinoxalin-2-yl)piperazine-1-carbonyl)pyridin-2(1H)-one (12{9,26,3}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
1-Methyl-6-(4-(quinoxalin-2-yl)piperazine-1-carbonyl)pyridin-2(1H)-one \((12\{9,27,3\})\), \(^1\)H NMR (500 MHz, DMSO-\(d_6\))
1-Methyl-6-(4-(quinoxalin-2-yl)piperazine-1-carbonyl)pyridin-2(1H)-one (12\{9,27,3\}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
Cyclohex-3-en-1-yl(4-(quinoxalin-2-yl)piperazin-1-yl)methanone (129,28,3), $^1$H NMR (500 MHz, DMSO-$d_6$)
Cyclohex-3-en-1-yl(4-(quinoxalin-2-yl)piperazin-1-yl)methanone (12{9,28,3}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
$N\text{-}(2\text{-}((5,6\text{-dimethylthieno}\text{[2,3-d]}\text{pyrimidin-4-yl})(\text{ethyl}amino)\text{ethyl})\text{-}2\text{-methoxypropanamide} (\textbf{12}\{45,44,24\}), \textsuperscript{1}H\text{ NMR} (500 MHz, DMSO-}d_6)$
\[ N-(2-((5,6-\text{Dimethylthieno}[2,3-d]\text{pyrimidin}-4-\text{yl})(\text{ethyl})\text{amino})\text{ethyl})-2-\text{methoxypropanamide (12)\{45,44,24\}} \], \text{\textsuperscript{13}C NMR (126 MHz, DMSO-\textit{d}_{6})}
1-Methyl-4-(4-(quinoxalin-2-yl)piperazine-1-carbonyl)pyridin-2(1H)-one (12{9,48,3}), $^1$H NMR (500 MHz, DMSO-$d_6$)
1-Methyl-4-(4-(quinoxalin-2-yl)piperazine-1-carbonyl)pyridin-2(1H)-one (12{9,48,3}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
(2S)-2-Acetamido-N-(1-((4,6-dimethylpyrimidin-2-yl)(methyl)amino)propan-2-yl)-4-methylpentanamide (12\{68,82,32\}),
\(^1\)H NMR (500 MHz, DMSO-\(d_6\))
(2S)-2-Acetamido-N-(1-((4,6-dimethylpyrimidin-2-yl)(methyl)amino)propan-2-yl)-4-methylpentanamide (12{\delta_{88,82,32}}),
$^{13}$C NMR (126 MHz, DMSO-$d_6$)
(3-(Benzo[d]oxazol-2-yl(methyl)amino)pyrrolidin-1-yl)(3,3-difluoro-1-methylocyclobutyl)methanone (12{81,39,30}), \( ^1H \) NMR (500 MHz, DMSO-\( d_6 \))
(3-(Benzo[d]oxazol-2-yl(methyl)amino)pyrrolidin-1-yl)(3,3-difluoro-1-methylcyclobutyl)methanone (12{81,39,30}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
(3-(Benzo[d]oxazol-2-yl)(methyl)amino)pyrrolidin-1-yl)(3,3-difluoro-1-methylcyclobutyl)methanone (12\{81,39,30\}), $^{19}$F NMR (376 MHz, DMSO-$d_6$)
(R)-1-(2-(((4-(Trifluoromethyl)pyrimidin-2-yl)amino)methyl)piperidin-1-yl)propan-1-one (12{84,40,34}), $^1$H NMR (600 MHz, DMSO-$d_6$)
(R)-1-(2-(((4-(Trifluoromethyl)pyrimidin-2-yl)amino)methyl)piperidin-1-yl)propan-1-one (12\{84,40,34\}), $^{13}$C NMR (151 MHz, DMSO-$d_6$)
(R)-1-(2-(((4-(Trifluoromethyl)pyrimidin-2-yl)amino)methyl)piperidin-1-yl)propan-1-one (12\{84,40,34\}), $^{19}$F NMR (376 MHz, DMSO-$d_6$)
$N$-(1-(6-Ethyl-5-fluoropyrimidin-4-yl)piperidin-4-yl)-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide ($\textcolor{red}{12}$\textcolor{orange}{79,130,39}),

$^1$H NMR (500 MHz, DMSO-$d_6$)
$N$-(1-(6-Ethyl-5-fluoropyrimidin-4-yl)piperidin-4-yl)-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide (12,79,130,39),

$^{13}$C NMR (126 MHz, DMSO-$d_6$)
\[ N-(1-(6\text{-Ethyl-5-fluoropyrimidin-4-yl})piperidin-4-yl)-4,5,6,7\text{-tetrahydrobenzo}[d]\text{-isoxazole-3-carboxamide (12\{79,130,39\})}, \]

\[ ^{19}\text{F NMR (376 MHz, DMSO-}d_6\text{)} \]
Cyclohex-3-en-1-yl(4-(7-fluorobenzo[d]thiazol-2-yl)piperazin-1-yl)methanone (12{9,28,43}), $^1$H NMR (500 MHz, DMSO-$d_6$)
Cyclohex-3-en-1-yl(4-(7-fluorobenzo[d]thiazol-2-yl)piperazin-1-yl)methanone (12{9,28,43}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
Cyclohex-3-en-1-yl(4-(7-fluorobenzo[d]thiazol-2-yl)piperazin-1-yl)methanone (12{9,28,43}), $^{19}$F NMR (376 MHz, DMSO-$d_6$)
N-(1-(5,6-Diethyl-1,2,4-triazin-3-yl)-3-methylpyrrolidin-3-yl)-3-methylisoxazole-5-carboxamide 12 {49,150,31}, ¹H NMR (500 MHz, DMSO-d₆)
\[
N-(1-(5,6-Diethyl-1,2,4-triazin-3-yl)-3-methylpyrrolidin-3-yl)-3-methylisoxazole-5-carboxamide (12\{49,150,31\}), ^{13}\text{C} \text{ NMR} \text{ (126 MHz, DMSO-}d_6) 
\]
N-(6-(4-Cyano-3-methylisothiazol-5-yl)-6-azaspiro[2.5]octan-1-yl)-1-isobutyl-1H-pyrazole-3-carboxamide (12{31,29,13}),

\(^1\)H NMR (500 MHz, DMSO-\(d_6\))
$N$-(6-(4-Cyano-3-methylisothiazol-5-yl)-6-azaspiro[2.5]octan-1-yl)-1-isobutyl-$1H$-pyrazole-3-carboxamide (12{31,29,13}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
2-(Benzo[d]isoxazol-3-yl)-N-(2-((6-cyanopyridin-3-yl)(methyl)amino)ethyl)-N-methylacetamide (12{2,23,11}), ^1H NMR (500 MHz, DMSO-d$_6$)
2-(Benzo[d]isoxazol-3-yl)-N-(2-((6-cyanopyridin-3-yl)(methyl)amino)ethyl)-N-methylacetamide (12{2, 23, 11}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
3-Methyl-N-((1-((1-methyl-1H-benzo[d]imidazol-2-yl)methyl)pyrrolidin-3-yl)methyl)butanamide (13 {85,113,14}), $^1$H NMR (600 MHz, DMSO-$d_6$)
3-Methyl-N-((1-((1-methyl-1H-benzo[d]imidazol-2-yl)methyl)pyrrolidin-3-yl)methyl)butanamide (13{85,113,14}), $^{13}$C NMR (151 MHz, DMSO-$_d$$_6$)
$N$-((4-((3-Chloropyridin-4-yl)methyl)morpholin-2-yl)methyl)-1-methyl-1H-pyrazole-3-carboxamide (13\{74,107,20\}), $^1$H NMR (500 MHz, DMSO-$d_6$)
$N\text{-}\{(4\text{-}\{(3\text{-} Chloropyridin}\text{-}4\text{-}yl)\text{methyl}\}\text{morpholin}\text{-}2\text{-}yl)\text{methyl}\}\text{-}1\text{-methyl}\text{-}1H\text{-pyrazole}\text{-}3\text{-carboxamide}$

$^13$C NMR (126 MHz, DMSO-$d_6$)
N-((4-(2,5-Dimethylbenzyl)morpholin-2-yl)methyl)-1-methyl-1H-pyrazole-3-carboxamide (13{74,107,21}), $^1$H NMR (500 MHz, DMSO-$d_6$)
\textit{N-((4-(2,5-Dimethylbenzyl)morpholin-2-yl)methyl)-1-methyl-1H-pyrazole-3-carboxamide (13 \{74,107,21\}),} $^{13}$C NMR (126 MHz, DMSO-$d_6$)
$N$-(2-(Benzyl(2-methoxyethyl)amino)ethyl)-2-fluoro-2-phenylacetamide (13{107,152,23}), $^1$H NMR (500 MHz, DMSO-$d_6$)
$N$-(2-(Benzyl(2-methoxyethyl)amino)ethyl)-2-fluoro-2-phenylacetamide (13{107,152,23}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
$N$-(2-(Benzyl(2-methoxyethyl)amino)ethyl)-2-fluoro-2-phenylacetamide (13{107,152,23}), $^{19}$F NMR (376 MHz, DMSO-$d_6$)
N-((4-((2,5-Dimethylthiophen-3-yl)methyl)morpholin-2-yl)methyl)-1-methyl-1H-pyrazole-3-carboxamide (13{74,107,27}),
$^1$H NMR (500 MHz, DMSO-$d_6$)
N-((4-((2,5-Dimethylthiophen-3-yl)methyl)morpholin-2-yl)methyl)-1-methyl-1H-pyrazole-3-carboxamide (13\{74,107,27\}), \textsuperscript{13}C NMR (126 MHz, DMSO-d\textsubscript{6})
(3-Chloro-1H-indol-2-yl)(3-((((5-ethyl-1,3,4-oxadiazol-2-yl)methyl)(methyl)amino)methyl)pyrrolidin-1-yl)methanone (13 \{44,129,33\}), 
$^1$H NMR (500 MHz, DMSO-$d_6$)
(3-Chloro-1H-indol-2-yl)(3-(((5-ethyl-1,3,4-oxadiazol-2-yl)methyl)(methyl)amino)methyl)pyrrolidin-1-yl)methanone (13{44,129,33}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
(3-Chloro-1H-indol-2-yl)(4-(2-(4-chloro-1H-pyrazol-1-yl)ethyl)-1,4-diazepan-1-yl)methanone (13\{23, 29, 34\}), $^1$H NMR (500 MHz, DMSO-$d_6$)
(3-Chloro-1H-indol-2-yl)(4-(2-(4-chloro-1H-pyrazol-1-yl)ethyl)-1,4-diazepan-1-yl)methanone (13{23,29,34}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
$N\text{-}((4\text{-}((2,5\text{-Dimethylthiazol-4-yl})\text{methyl})\text{morpholin-2-yl})\text{methyl})\text{-}1\text{-methyl}\text{-}1H\text{-pyrazole-3-carboxamide (13\{74,107,35\})},$

$^1\text{H NMR (500 MHz, DMSO-$d_6$)}$
$N\textendash(4\textendash((2,5\textendash\text{Dimethylthiazol\textendash4\textendashyl})\text{methyl})\text{morpholin\textendash2\textendashyl})\text{methyl})\text{1\textendashmethyl\textendash1}H\textendash\text{pyrazole\textendash3\textendashcarboxamide\ (13\{74,107,35\}),}\ 
^{13}C\text{ NMR\ (126 MHz, DMSO-}d_6)$
\[ N-((1-(2\text{-Ethylbenzyl})piperidin-3-yl)methyl)-1\text{-methyl}-1H\text{-pyrazole-3-carboxamide (13{102,107,29})}, \text{ }^1H\text{ NMR (500 MHz, DMSO}-d_6) \]
$N\-((1\-{(2\-Ethybenzyl)piperidin\-3\-yl)methyl})\-1\-methyl\-1H\-pyrazole\-3\-carboxamide \(\text{13}\{J02,J07,29\}\), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
1-Methyl-N-((4-((4-methyl-1,2,5-oxadiazol-3-yl)methyl)morpholin-2-yl)methyl)-1H-pyrazole-3-carboxamide (13\{74,107,38\}), \[^1\text{H}\] NMR (500 MHz, DMSO-\textit{d}_6)
1-Methyl-N-((4-((4-methyl-1,2,5-oxadiazol-3-yl)methyl)morpholin-2-yl)methyl)-1H-pyrazole-3-carboxamide (13{74,107,38}), $^{13}$C NMR (151 MHz, DMSO-$d_6$)
(S)-N\textsuperscript{\textbeta}-(1-(3-(Methylcarbamoyl)benzyl)piperidin-3-yl)furan-2,4-dicarboxamide (13\{139,243,50\}), \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}\textsubscript{6})
(S)-N\textsuperscript{t}-(1-(3-(Methylcarbamoyl)benzyl)piperidin-3-yl)furan-2,4-dicarboxamide (13\{139,243,50\}), \textsuperscript{13}C NMR (126 MHz, DMSO-d\textsubscript{6})
$N\text{-}(1\text{-}((3\text{-}\text{Chloro}-2\text{-}\text{methylphenyl})\text{amino})\text{-}2\text{-}\text{oxoethyl})\text{piperidin}-4\text{-}y\text{l})\text{-}2\text{-}\text{methylpentanamide}$ (13\{79,95,11\}), $^1$H NMR (500 MHz, DMSO-$d_6$)
$N$-(1-(2-((3-Chloro-2-methylphenyl)amino)-2-oxoethyl)piperidin-4-yl)-2-methylpentanamide (13$^{79,95,11}$), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
\[ N-((4-(2,4-Dimethylbenzyl)morpholin-2-yl)methyl)-1-methyl-1H-pyrazole-3-carboxamide \ (13\{74,107,12\}), ^1\text{H} \text{NMR} \ (500 \text{ MHz, DMSO-}d_6) \]
$N-((4\text{-}(2,4\text{-Dimethylbenzyl})\text{morpholin}-2\text{-yl})\text{methyl})\text{-1-methyl-1H-pyrazole-3-carboxamide (13}$, $^{13}\text{C NMR (151 MHz, DMSO-}$d$_6$)
N-((4-(2-Fluorobenzyl)morpholin-2-yl)methyl)-1-methyl-1H-pyrazole-3-carboxamide (13\{74,107,25\}), $^1$H NMR (500 MHz, DMSO-$d_6$)
N-((4-(2-Fluorobenzyl)morpholin-2-yl)methyl)-1-methyl-1H-pyrazole-3-carboxamide (13\{74,107,25\}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
N-((4-(2-Fluorobenzyl)morpholin-2-yl)methyl)-1-methyl-1H-pyrazole-3-carboxamide (13\{74,107,25\}), $^{19}$F NMR (376 MHz, DMSO-$d_6$)
rac-1-Methyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)hexahydrocyclopenta[c]pyrrol-3a(1H)-yl)methyl)cyclopentane-1-carboxamide (14{19,35,360}), \textsuperscript{1}H NMR (600 MHz, DMSO-\textit{d}_6)
*rac*-1-Methyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridin-6-yl)hexahydrocyclopenta[c]pyrrolo-3a(1H)-yl)methyl)cyclopentane-1-carboxamide (14{19,35,360}), $^{13}$C NMR (151 MHz, DMSO-$d_6$)
rac-N-(((3aR,6aS)-2-(Tetrazolo[1,5-b]pyridazin-6-yl)hexahydrocyclopenta[c]pyrrol-3a(1H)-yl)methyl)-3,6-dihydro-2H-pyran-4-carboxamide (14{19,35,361}), ^1^H NMR (500 MHz, DMSO-d$_6$)
rac-N-(((3aR,6aS)-2-(Tetrazolo[1,5-b]pyrazin-6-yl)hexahydrocyclopenta[c]pyrrol-3a(1H)-yl)methyl)-3,6-dihydro-2H-pyran-4-carboxamide (14{19,35,361}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
rac-N-(((3aR,6aS)-2-(Tetrazolo[1,5-b]pyridin-6-yl)hexahydrocyclopenta[c]pyrrol-3a(1H)-yl)methyl)benzamide (14{19,35,367}),
$^1$H NMR (600 MHz, DMSO-$d_6$)
rac-N-(((3aR,6aS)-2-(Tetrazolo[1,5-b]pyridazin-6-yl)hexahydrocyclopenta[c]pyrrol-3a(1H)-yl)methyl)benzamide (14{19,35,367}),
^{15}C NMR (151 MHz, DMSO-d_6)
rac-2-Cyclobutyl-2-methyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)hexahydrocyclopenta[c]pyrrol-3a(1H)-yl)methyl)propanamide (14[19,35,369]), $^1$H NMR (600 MHz, DMSO-$d_6$)
rac-2-Cyclobutyl-2-methyl-N-((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)hexahydrocyclopenta[c]pyrrol-3a(1H)-yl)methyl)propanamide (14{19,35,369}), $^{13}$C NMR (151 MHz, DMSO-$d_6$)
rac-1-Methyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)hexahydrocyclopenta[c]pyrrol-3a(1H)-yl)methyl)cyclohexane-1-carboxamide (14\{19,35,373\}), \textsuperscript{1}H NMR (600 MHz, DMSO-\textit{d}_6)
rac-1-Methyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)hexahydrocyclopenta[c]pyrrol-3a(1H)-yl)methyl)cyclohexane-1-carboxamide (14{19,35,373}), $^{13}$C NMR (151 MHz, DMSO-$d_6$)
rac-3,5-Dimethyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)thiophene-2-carboxamide (14{19,35,375}), $^1$H NMR (600 MHz, DMSO-$_d_6$)
**rac-3,5-Dimethyl-N-(((3\text{a}R,6\text{a}S))-2-(tetrazolo[1,5-\text{b}]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)thiophene-2-carboxamide**

(14\{19,35,375\}), \textsuperscript{13}C NMR (151 MHz, DMSO-\textit{d}6)
rac-2,4-Dimethyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)benzamide (14{19,35,377}),
$^1$H NMR (600 MHz, DMSO-$d_6$)
rac-2,4-Dimethyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)benzamide (14\{19,35,377\}), $^{13}$C NMR (151 MHz, DMSO-$d_6$)
$N-\{(3aS,6aR)-2-\{\text{tetrazolo[1,5-b]}\text{pyridazin-6-yl}\}\text{octahydrocyclopenta}\{c\}\text{pyrro}-3a\text{-yl}methyl\}\text{-3,4-dihydro-2H-pyran-5-carboxamide (14) \{19,35,378\}}$, 
$^1\text{H NMR (600 MHz, DMSO-}d_6\)$
$N$-((3aS,6aR)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)-3,4-dihydro-2$H$-pyran-5-carboxamide (14\cite{19,35,378}),
\[ ^{13}C \text{ NMR} (151 \text{ MHz, DMSO-}d_6) \]
rac-2-Methyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)benzamide (14{19,35,384}),

$^1$H NMR (500 MHz, DMSO-$d_6$)
rac-2-Methyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)benzamide (14{19,35,384}),

$^{13}$C NMR (126 MHz, DMSO-$d_6$)
rac-3-Methyl-N-((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)benzamide (14\{19,35,171\}),
$^1$H NMR (600 MHz, DMSO-$d_6$)
rac-3-Methyl-N-(((3aR,6aS)-2-((tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)benzamide (14{19,35,171}),
$^{13}$C NMR (151 MHz, DMSO-$d_6$)
rac-2-Methyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)thiophene-3-carboxamide

$^{1}$H NMR (600 MHz, DMSO-$d_6$)
rac-2-Methyl-N-((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)thiophene-3-carboxamide 14{19,35,390},

$^{13}$C NMR (151 MHz, DMSO-$d_6$)
rac-4-Methyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)thiophene-2-carboxamide (14{19,35,394}),

$^1$H NMR (500 MHz, DMSO-$d_6$)
rac-4-Methyl-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)thiophene-2-carboxamide (14{19,35,394}),
\(^{13}\)C NMR (126 MHz, DMSO-\(d_6\))
1-Methyl-N-(6-(tetrazolo[1,5-b]pyridazin-6-ylamino)spiro[3.3]heptan-2-yl)cycloheptanecarboxamide (14\{114,35,399\}),

$^1$H NMR (600 MHz, DMSO-$d_6$)
1-Methyl-N-(6-(tetrazolo[1,5-\textit{b}]pyridazin-6-ylamino)spiro[3.3]heptan-2-yl)cycloheptanecarboxamide (14{114,35,399}),
$^{13}$C NMR (151 MHz, DMSO-$d_6$)
rac-2-Chloro-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)benzamide (14{19,35,408}),
\(^1\)H NMR (500 MHz, DMSO-\(d_6\))
rac-2-Chloro-N-(((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)benzamide (14\{19,35,408\}),
$^{13}$C NMR (126 MHz, DMSO-$_d_6$)
rac-N-((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)furan-3-carboxamide (14\{19,35,32}\)},

$^1$H NMR (500 MHz, DMSO-$d_6$)
\textit{rac}-N-((3aR,6aS)-2-(tetrazolo[1,5-b]pyridazin-6-yl)octahydrocyclopenta[c]pyrrol-3a-yl)methyl)furan-3-carboxamide (14\cite{19,35,32}),

$^1$C NMR (126 MHz, DMSO-$d_6$)
3-Methyl-1-(3-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)piperidin-1-yl)but-3-en-1-one (15{5,7,7}), $^1$H NMR (500 MHz, DMSO-$d_6$)
3-Methyl-1-(3-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)piperidin-1-yl)but-3-en-1-one (155{5,7}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
N-(3-Hydroxybutyl)-2-(4-(4-hydroxytetrahydro-2H-pyran-4-yl)-1H-1,2,3-triazol-1-yl)-N-methylacetamide (15{3,20,38}),

$^1$H NMR (500 MHz, DMSO-$d_6$)
$N$-(3-Hydroxybutyl)-2-(4-(4-hydroxytetrahydro-2$H$-pyran-4-yl)-1$H$-1,2,3-triazol-1-yl)-$N$-methylacetamide ($15\{3,20,38\}$),

$^{13}$C NMR (126 MHz, DMSO-$d_6$)

$N$-(3-Hydroxybutyl)-2-(4-(4-hydroxytetrahydro-2$H$-pyran-4-yl)-1$H$-1,2,3-triazol-1-yl)-$N$-methylacetamide ($15\{3,20,38\}$),

$^{13}$C NMR (126 MHz, DMSO-$d_6$)
N-(3-Hydroxybutyl)-2-(4-(4-hydroxytetrahydro-2H-pyran-4-yl)-1H-1,2,3-triazol-1-yl)-N-methylacetamide (15{3,20,38}),

$^1$H NMR (500 MHz, DMSO-$d_6$)
$N$-$(3\text{-Hydroxybutyl})$-$2$-$$(4\text{-}(4\text{-hydroxytetrahydro}-2H\text{-pyran}-4\text{-yl})$-$1H$-$1,2,3\text{-triazol}$-$1\text{-yl})$-$N$-$methylacetamide$ (15\{3,20,38\})$, $^{13}$C NMR (126 MHz, DMSO-$d_6$)
$N$-((4,5-Dimethylthiazol-2-yl)methyl)-2-(4-(hydroxy(phenyl)methyl)-1H-1,2,3-triazol-1-yl)acetamide (15\{3,21,37\}), $^1$H NMR (500 MHz, DMSO-$d_6$)
(N-((4,5-Dimethylthiazol-2-yl)methyl)-2-(4-(hydroxy(phenyl)methyl)-1H-1,2,3-triazol-1-yl)acetamide (15\{3,21,37\}),
$^{13}$C NMR (126 MHz, DMSO-$d_6$)
(2-((4-Cyclopropyl-1H-1,2,3-triazol-1-yl)methyl)pyrrolidin-1-yl)(1-hydroxy-3,3-dimethylcyclobutyl)methanone (15\{1,6,6\}),
$^1$H NMR (500 MHz, DMSO-$d_6$)
(2-((4-Cyclopropyl-1H-1,2,3-triazol-1-yl)methyl)pyrrolidin-1-yl)(1-hydroxy-3,3-dimethylcyclobutyl)methanone (15{1,6,6}), $^{13}C$ NMR (126 MHz, DMSO-$d_6$)
rac-(1R,2R)-2-Methyl-N-(2-(4-(2-phenoxyethyl)-1H-1,2,3-triazol-1-yl)propyl)cyclopropanecarboxamide (15{4,4,4}), $^1$H NMR (500 MHz, DMSO-$d_6$)
rac-(1R,2R)-2-Methyl-N-(2-(4-(2-phenoxyethyl)-1H-1,2,3-triazol-1-yl)propyl)cyclopropanecarboxamide (15{4,4,4}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
(S)-2-Cyclobutylidene-N-(1-(4-(1-methyl-1H-pyrazol-5-yl)-1H-1,2,3-triazol-1-yl)propan-2-yl)acetamide 15\{6,11,11\}, \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}_6)
(S)-2-Cyclobutylidene-N-(1-(4-(1-methyl-1H-pyrazol-5-yl)-1H-1,2,3-triazol-1-yl)propan-2-yl)acetamide 15 {6,11,11},

$^{13}$C NMR (126 MHz, DMSO-$d_6$)
(S)-N-(1-(4-(2,6-Difluorophenyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)-2-methylbut-2-enamide (15{6,1,8}), $^1$H NMR (500 MHz, DMSO-$d_6$)
(S)-N-(1-(4-(2,6-Difluorophenyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)-2-methyl-2-enamide (15{6,7,8}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
(S)-N-(1-(4-(2,6-Difluorophenyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)-2-methylbut-2-enamide (15{6,7,8}), $^{19}$F NMR (376 MHz, DMSO-$d_6$)
(S)-3-Cyclopropyl-N-(1-(4-(2-methylpyridin-3-yl)-1H-1,2,3-triazol-1-yl)propan-2-yl)propanamide (15{6,27,27}), $^1$H NMR (500 MHz, DMSO-$d_6$)
(S)-3-Cyclopropyl-N-(1-(4-(2-methylpyridin-3-yl)-1H-1,2,3-triazol-1-yl)propan-2-yl)propanamide (15{6,27,27}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
(R)-N-(1-(4-(4-Fluorophenyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)bicyclo[1.1.1]pentane-1-carboxamide (15\{2,2,2\}), \(^1\)H NMR (600 MHz, DMSO-\(d_6\))
(R)-N-(1-(4-(4-Fluorophenyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)bicyclo[1.1.1]pentane-1-carboxamide (15{2,2,2}), $^{13}$C NMR (151 MHz, DMSO-$d_6$)
(R)-N-((4-(4-Fluorophenyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)bicyclo[1.1.1]pentane-1-carboxamide (15{2,2,2}), $^{19}$F NMR (376 MHz, DMSO)
rac-4-((4-((1R,2S)-2-Hydroxycyclopentyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(phenyl(thiophen-2-yl)methyl)benzamide (15{1,2,17}),

$^1$H NMR (500 MHz, DMSO-$d_6$)
rac-4-((4-((1R,2S)-2-Hydroxycyclopentyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(phenyl(thiophen-2-yl)methyl)benzamide (15{1,2,17}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)
(R)-2-Hydroxy-N-(1-(4-(4-(trifluoromethyl)phenyl)-1H,2,3-triazol-1-yl)propan-2-yl)acetamide 15{2,30,29}, $^1$H NMR (600 MHz, DMSO-$d_6$)
(R)-2-Hydroxy-N-(1-(4-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)acetamide 15\{2,30,29\}, $^{13}$C NMR (151 MHz, DMSO-$d_6$)
(R)-2-Hydroxy-N-(1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)acetamide 15\{2,30,29\}, $^{19}$F NMR (376 MHz, DMSO-$d_6$)
(1R,6S,7r)-N-(2-(4-(Ethoxymethyl)-1H-1,2,3-triazol-1-yl)propyl)bicyclo[4.1.0]heptane-7-carboxamide (15{4,15,14}), $^1$H NMR (500 MHz, DMSO-$d_6$)
(1R,6S,7r)-N-(2-(4-(Ethoxymethyl)-1H-1,2,3-triazol-1-yl)propyl)bicyclo[4.1.0]heptane-7-carboxamide (15\{4,15,14\}),
$^{13}$C NMR (126 MHz, DMSO-$d_6$)
(S)-N-(1-(4-(Methoxymethyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)-1,2,2,3,3-pentamethylcyclopropanecarboxamide (15{6,14,13}),

$^1$H NMR (600 MHz, DMSO-$d_6$)
(S)-N-(1-(4-(Methoxymethyl)-1H-1,2,3-triazol-1-yl)propan-2-yl)-1,2,2,3,3-pentamethylcyclopropanecarboxamide (15{6,14,13}), $^{13}$C NMR (151 MHz, DMSO-$d_6$)
(S)-1,3-Dimethyl-N-(1-(4-(pent-4-en-1-yl)-1H-1,2,3-triazol-1-yl)propan-2-yl)-1H-pyrazole-5-carboxamide 15{6,9,9}, \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}_{6})
(S)-1,3-Dimethyl-N-(1-(4-(pent-4-en-1-yl)-1H-1,2,3-triazol-1-yl)propan-2-yl)-1H-pyrazole-5-carboxamide 15\{6,9,9\}, $^{13}$C NMR (126 MHz, DMSO-$d_6$)
N-(2-(4-(1-Methyl-1H-pyrazol-3-yl)-1H-1,2,3-triazol-1-yl)ethyl)cyclooct-4-enecarboxamide 15{3,3,3}, \(^1\)H NMR (500 MHz, DMSO-\(d_6\))
\(N-(2-(4-(1\text{-Methyl}-1H\text{-pyrazol-3-yl})-1H,1,2,3\text{-triazol-1-yl})\text{-ethyl})\text{cyclooct-4-enecarboxamide} \ 15\{3,3,3\}, \ ^{13}\text{C NMR} \ (126 \text{ MHz, DMSO-}d_6)\)
2-Cyclobutyl-1-(3-((4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl)methyl)pyrrolidin-1-yl)ethanone (15\{8,10,10\}), \textsuperscript{1}H NMR (500 MHz, DMSO-d\textsubscript{6})
2-Cyclobutyl-1-(3-((4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl)methyl)pyrrolidin-1-yl)ethanone (15{8,10,10}), $^{13}$C NMR (126 MHz, DMSO-$d_6$)