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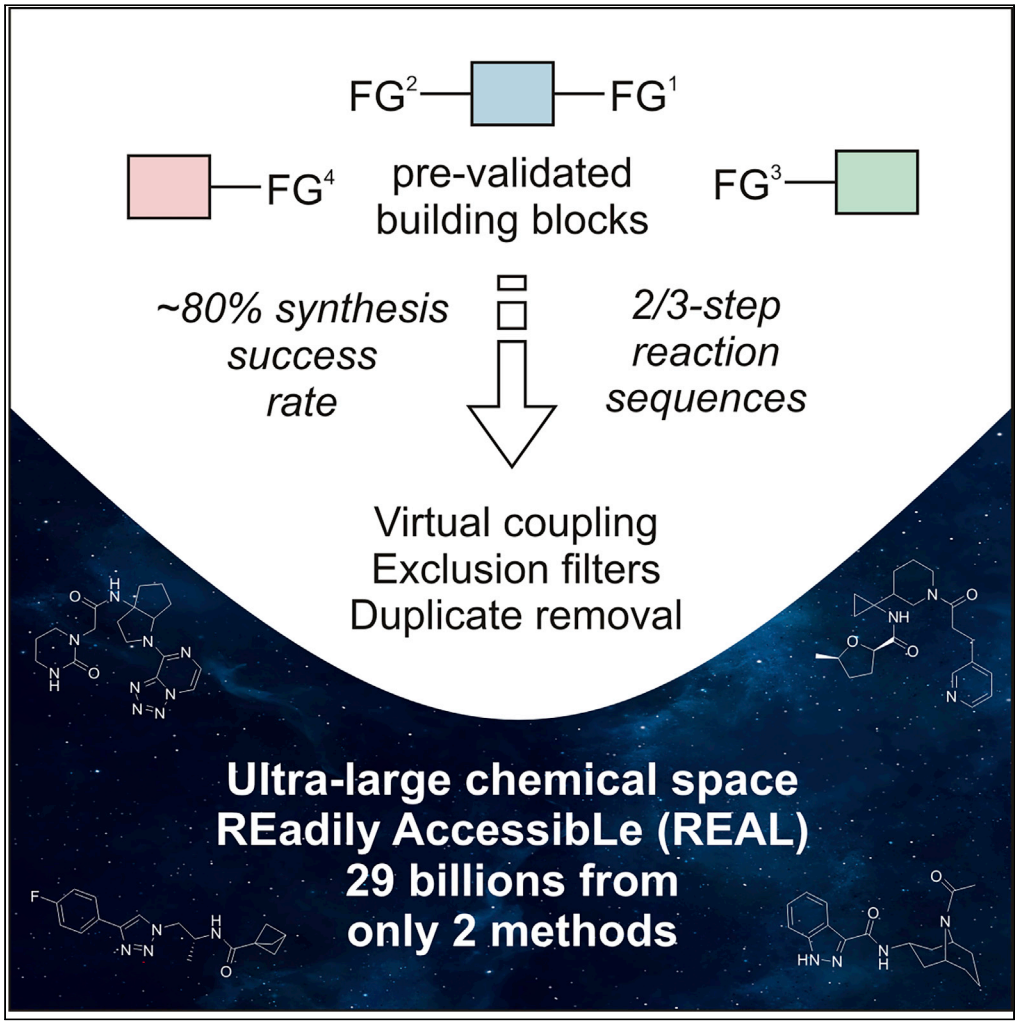

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HIGHLIGHTS

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

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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 [Nicolaou 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

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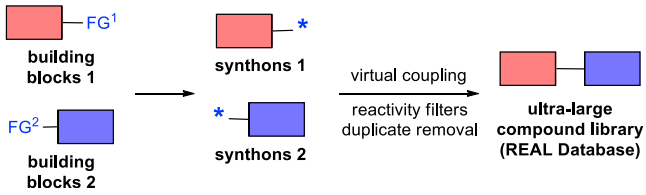


Figure 1. A General Principle of the REAL Database Generation Using One-Step Two-Component Reactions

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 β-lactamase (AmpC) inhibitors, D_4 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 × 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 arylation/alkylation of *N*-hydroxybenzotriazole (formed from HATU, a coupling reagent from the acylation step) might be a major problem lowering the efficiency of the latter reaction sequences.

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

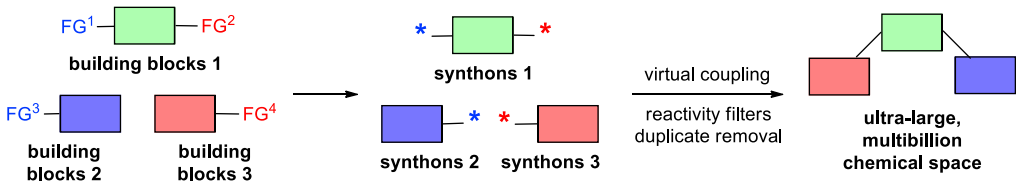
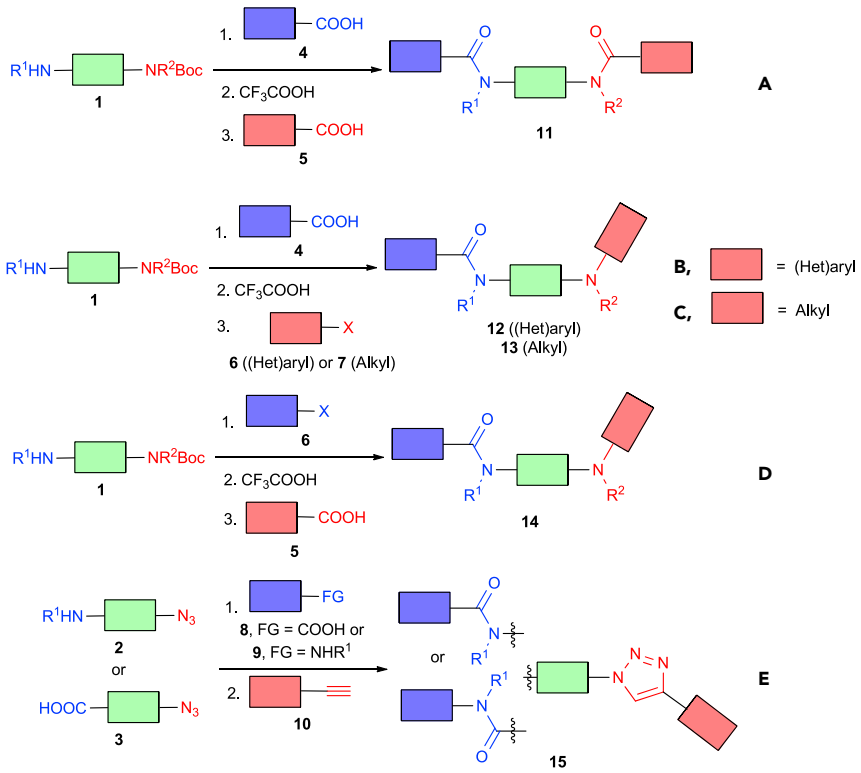


Figure 2. An Approach to the Generation of Ultra-large Chemical Space Described in this Work



Scheme 1. Parallel Reaction Sequences Studied in This Work.
See also Tables S1 and S2, Figures S1 and S2.

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.

#	Method	Conditions	Library	Success Rate, %[a]	Average Yield, %	
					All Experiments	Successful Experiments
1	*A*	1. HATU, *i*-Pr_2NEt, DMSO, rt, 16 h 2. CF_3COOH, *i*-Pr_3SiH, H_2O, rt, 6 h 3. HATU, *i*-Pr_2NEt, DMSO, rt, 16 h	**11**	77	34	44
2	*B*	1-2. Same as for *A* 3. *i*-Pr_2NEt, NMP,[b] 100°C, 16 h	**12**	60	26	43
3	*C*	1-2. Same as for *A* 3. *i*-Pr_2NEt, DMF, 80°C, 16 h	**13**	53	16	31
4	*D*	1. *i*-Pr_2NEt, NMP,[b] 100°C, 16 h 2-3. Same as for *A*	**14**	81	30	38
5	*E*	1. HATU, *i*-Pr_2NEt, DMF, rt, 16 h 2. *i*-Pr_2NEt, $Cu(OAc)_2$, 80°C, 16 h	**15**	80	41	51

Table 1. Validation Experiments for the Parallel Synthesis of Libraries 11–15

See Also Tables S1 and S2, Figures S1 and S2.

[a]Fraction of 400 experiments that allowed for the preparation of the target product.

[b]NMP, *N*-methyl-2-pyrrolidone.

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

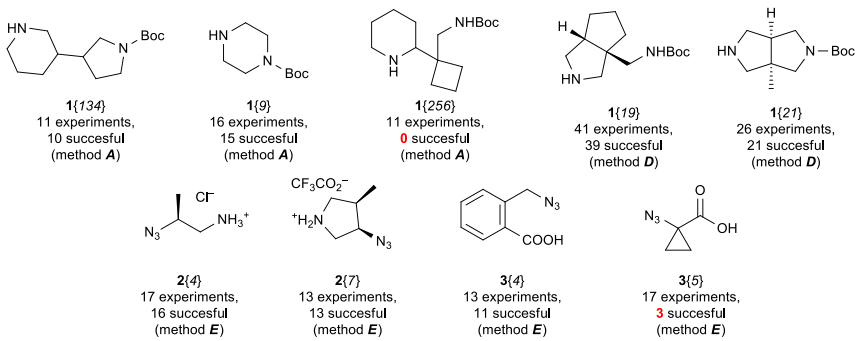


Figure 3. Examples of Reagents 1–3 Showing Excellent and Poor Efficiency in the Methods Studied (Relative Configurations are Shown)

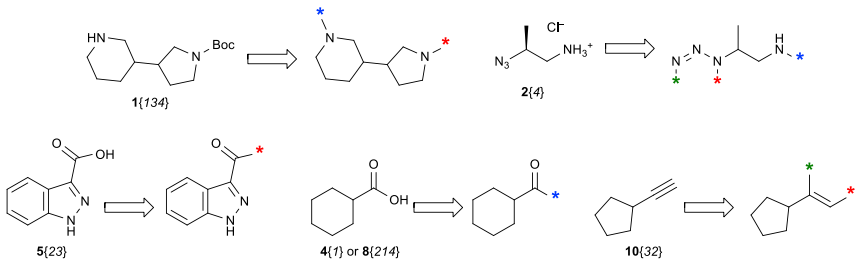


Figure 4. Examples of Synthons Generated from Reagents 1, 2, 4, 5, 8, and 10 (in the Corresponding SMILES Representations, Uncommon ["Dummy"] Atoms are Used Instead of the Colored Asterisks [*] to Denote Different Types of the Variation Points)

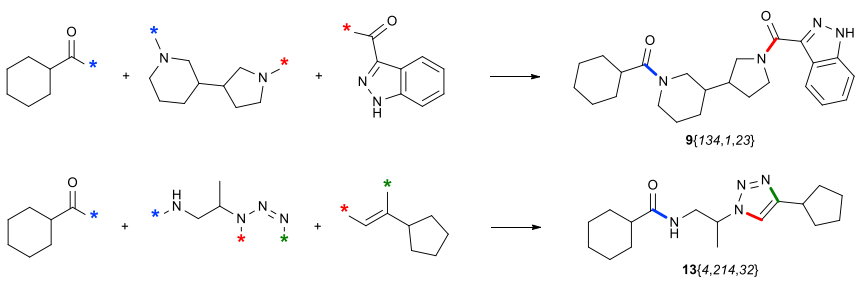
mentioned in the Introduction, this chemical space can be accessed either directly as a pre-enumerated database or through a feature-tree based search engine that performs generation of the corresponding structures upon a query. The current versions of the REAL Database and REAL Space include 0.27 and 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 (Fsp^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



Scheme 2. Virtual Coupling of the Synthons Shown in Figure 4 (the Variation Points [*] Are Connected according to Their Types)

#	Method	Reagents	Number of Synthons		
			No Reactivity Features	With Steric Features	Total
1	*A*	1	467	196[a]	663
2		4	6,706	1,271	7,977
3		5	5,451	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

Table 2. Number of Various Synthons Types Generated for Reaction Sequences *A* and *E*

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

an obvious consequence of the chemical methodology used (Table 4 and Figure 6). They are also more sp^3 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 7).

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 8A). 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 8B).

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 Boström, 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,

Figure 5. The Workflow of the Multibillion Chemical Space Generation

#	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

the huge size of both DNA-encoded libraries and multibillion chemical spaces like the one described herein 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.

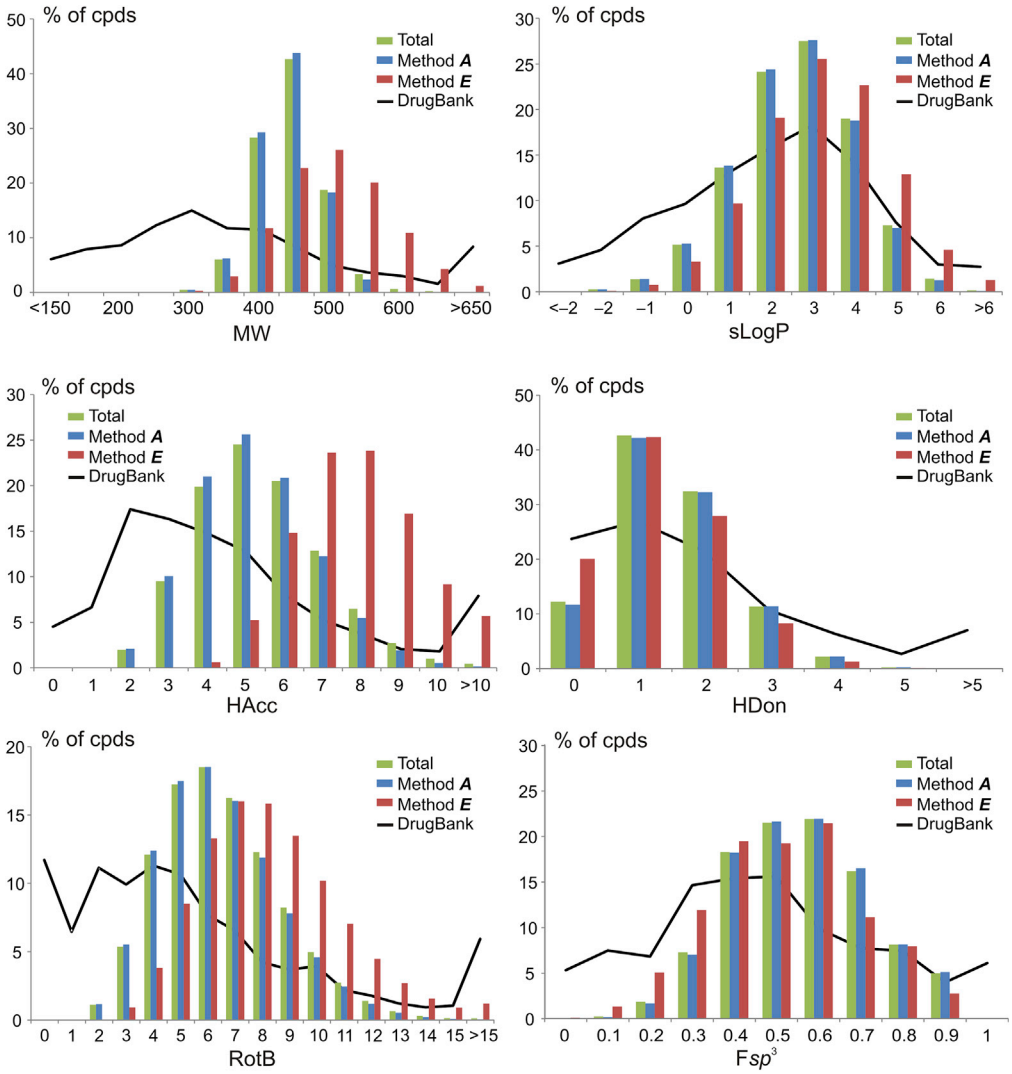


Figure 6. Distribution of Physico-Chemical Descriptors Predicted for the Generated Chemical Space and Approved Drugs

See also Table S3.

#	Method	MW	sLogP	HAcc	HDon	TPSA, Å^2	RotB	Fsp^3
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[a]	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

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

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 ~80% synthesis success rate (e.g., acylation – deprotection – acylation of monoprotected diamines, 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" reagents 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	Rule of 5[a]	+ Veber's Rules[b]	Rule of 4.5[c]	Rule of 4[d]	Churcher's Rules[e,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

[a]MW < 500, LogP<5, HAcc≤10, HDon≤5 (Lipinski et al., 1997).
[b]RotB ≤10, TPSA <140 (Veber et al., 2002).
[c]MW < 450, LogP<4.5 (Oprea et al., 2001).
[d]MW < 400, LogP<4 (Hann and Oprea, 2004).
[e]MW 200 … 350, LogP −1 … 3 (Nadin et al., 2012).
[f]Absolute numbers of the library members are given in brackets.

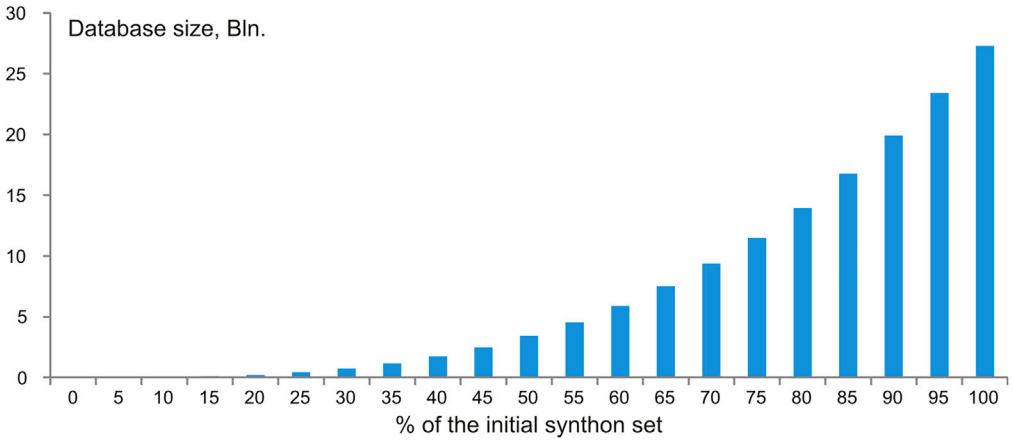


Figure 7. Relationship between the Size of the Generated Databases and the Size of the Synthon Subsets
Obtained by random selections from the initial synthon set for Method ***A***; average from three independent selections; see also Table S4.

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.

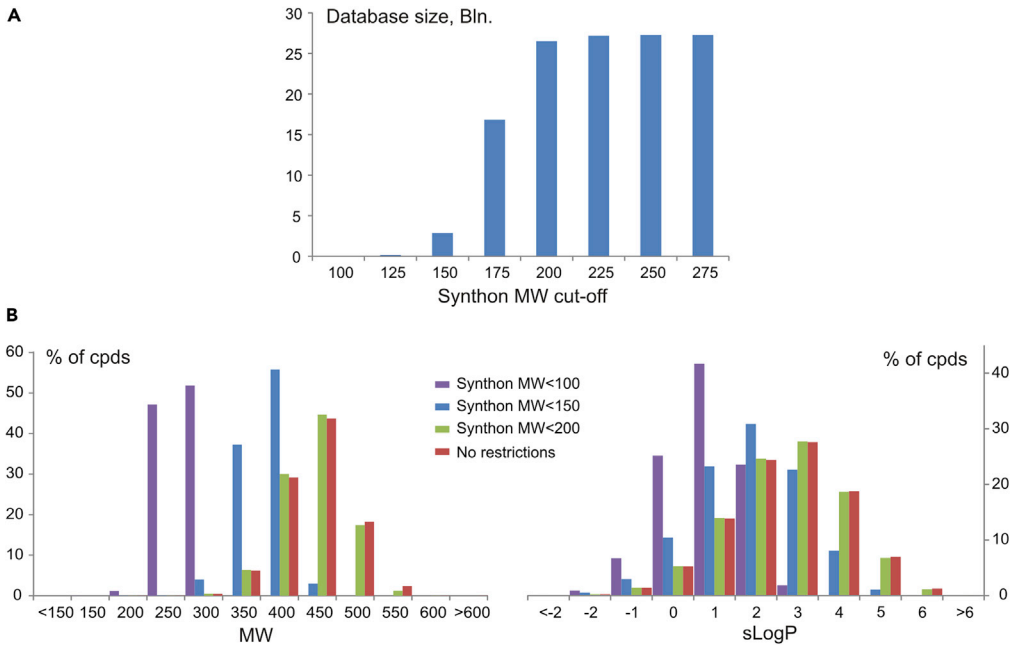


Figure 8. Properties of the Generated Chemical Space as a Function of the Molecular Weight Cut-offs Applied to the Initial Synthon Sets for Method *A*
(A and B) (A) The size of the generated databases. (B) Distribution of physico-chemical descriptors (MW and sLogP) for the generated chemical space.
See also Table S5.

Feature	Approach Described in This Work	Previous Feasibility-Based approaches[a]	Recent AI-Based approaches[b]
Virtual chemical space	Multibillion (over 3×10^{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

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

[b]The subject was reviewed and critically accessed in a number of recent publications (Schneider, 2018; Schwaller and Laino, 2019; Brown et al., 2020; Lemonick, 2020).

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.

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.

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.

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	126840477	0.465	4818124	0.308	131658601	0.456
350	1690324822	6.192	45585024	2.915	1735909846	6.015
400	7949008636	29.120	182488242	11.670	8131496878	28.178
450	11893243921	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	184500744	0.639
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	71464639	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	1491880134	5.171
1	3783279941	13.859	151434129	9.684	3934714070	13.638
2	6666422497	24.421	298753963	19.105	6965176460	24.142
3	7536160005	27.608	399412101	25.542	7935572106	27.505
4	5124595911	18.773	354665763	22.680	5479261674	18.991
5	1906945290	6.986	201575452	12.890	2108520742	7.308
6	344499995	1.262	72158367	4.614	416658362	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	0.995
>10	37623018	0.138	88851620	5.682	126474638	0.438
All	27297397644	100	1563752616	100	28861150260	100

HDon	Method ***A***		Method ***E***		Total	
	No. of cpds	% of cpds	No. of cpds	% of cpds	No. of cpds	% of cpds
0	3187748954	11.6778	313693134	20.06028	3501442088	12.26534
1	11514063585	42.1801	661866465	42.32552	12175930050	42.65154
2	8814595589	32.2910	436524642	27.9152	9251120231	32.40611
3	3107816412	11.3850	129777225	8.299089	3237593637	11.34109
4	602113896	2.2058	20101362	1.285457	622215258	2.179582
5	66845429	0.2449	1703616	0.108944	68549045	0.240123
>5	4213779	0.0154	86172	0.005511	4299951	0.015062
All	27297397644	100	1250059482	100	28547457126	100

RotB	Method ***A***		Method ***E***		Total	
	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	318002912	1.118
3	1508875367	5.528	14538387	0.930	1523413754	5.356
4	3381280817	12.387	59564079	3.809	3440844896	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	2342337457	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

Fsp^3	Method ***A***		Method ***E***		Total	
	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	7381387637
35	1167189585	1170624550	1171458018	1169757384
40	1747577364	1747527058	1740846423	1745316948
45	2480899801	2486719501	2487750229	2485123177
50	3417793869	3416799399	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	0	0	0
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	37.191	6.375	6.192
400	0	55.673	29.960	29.120
450	0	3.006	44.520	43.569
500	0	0	17.388	18.227
550	0	0	1.267	2.361
600	0	0	0.000	0.053
>600	0	0	0	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	8.073	18.662	18.773
5	0	1.075	6.780	6.986
6	0	0.036	1.160	1.262
>6	0	0.000	0.082	0.100

Transparent methods

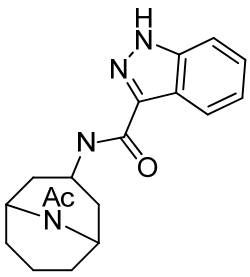
General. All chemicals and solvents were obtained from Enamine Ltd. and used without further purification. ^{1}H, ^{13}C, and ^{19}F NMR spectra were acquired on Bruker Advance DRX 400, Bruker Avance DRX 500, and Agilent ProPulse 600 spectrometers using DMSO-d_6 as a solvent (unless noted otherwise). 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_2NEt (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.

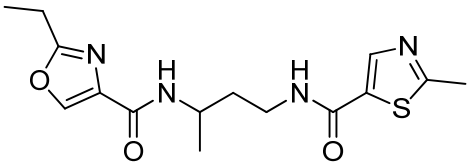
General procedure for the reaction sequence *A*. *N*-Boc-diamine **1** (0.5 mmol), carboxylic acid **4** (0.6 mmol), *i*-Pr_2NEt (1.25 mmol*), and 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) (0.575 mmol) were mixed in dry DMSO (appr. 1.4 mL). 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)-1*H*-indazole-3-carboxamide (11{*52*,*55*,*23*})**



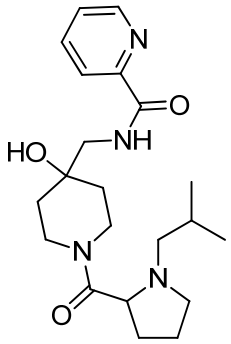
Beige solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.56 (s, 1H), 8.24 (d, J = 8.8 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.40 (t, J = 7.2 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 4.97 – 4.74 (m, 1H), 4.34 – 4.07 (m, 1H), 3.93 – 3.59 (m, 1H), 2.36 – 2.04 (m, 3H), 2.03 (s, 3H), 1.72 – 1.58 (m, 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 $C_{18}H_{22}N_4O_2$: 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*})



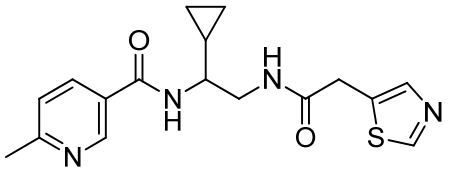
Yellowish oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.48 (t, J = 5.5 Hz, 1H), 8.42 (s, 1H), 8.12 (s, 1H), 7.95 (d, J = 8.8 Hz, 1H), 4.07 – 3.98 (m, 1H), 3.28 – 3.20 (m, 1H), 3.19 – 3.12 (m, 1H), 2.76 (q, J = 7.6 Hz, 2H), 2.63 (s, 3H), 1.81 – 1.67 (m, 2H), 1.23 (t, J = 7.6 Hz, 3H), 1.14 (d, J = 6.5 Hz, 3H). ^{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 $C_{15}H_{20}N_4O_3S$: C 53.56; H 5.99; N 16.65; S 9.53. Found: C 53.80; H 5.91; N 16.65; S 9.32.

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



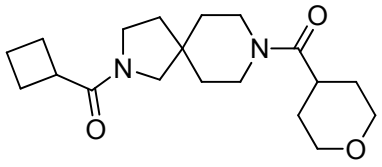
Yellowish solid. The compound existed as a ca. 1:1 mixture of rotamers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (d, J = 4.7 Hz, 1H), 8.58 (q, J = 7.1, 6.5 Hz, 1H), 8.03 (d, J = 7.6 Hz, 1H), 7.98 (td, J = 7.6, 1.7 Hz, 1H), 7.59 (ddd, J = 6.9, 4.8, 1.5 Hz, 1H), 4.86 (s, 1H), 4.10 – 3.78 (m, 2H), 3.33 (s, 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 $C_{21}H_{32}N_4O_3$: 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*})**



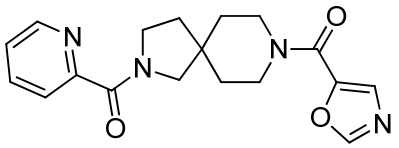
Beige solid. The compound existed as a ca. 3:1 mixture of rotamers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.12 – 8.61 (m, 2H), 8.53 (t, *J* = 5.7 Hz, 0.25H) and 8.35 (d, *J* = 8.3 Hz, 0.75H) and 8.23 (t, *J* = 5.7 Hz, 0.75H) and 8.14 (d, *J* = 8.3 Hz, 0.25H), 8.01 (dd, *J* = 8.1, 2.2 Hz, 0.75H) and 7.96 (dd, *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) δ 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 $C_{17}H_{20}N_4O_2S$: 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-2*H*-pyran-4-yl)methanone (11{*50*,*64*,*26*})



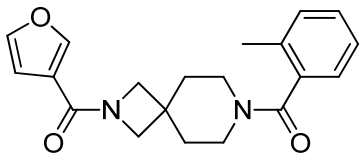
Beige solid. The compound existed as a ca. 1:1 mixture of rotamers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.82 (dt, *J* = 10.7, 3.2 Hz, 2H), 3.61 – 3.33 (m, 8H), 3.26 – 3.15 (m, 3H), 2.86 (ddt, *J* = 11.3, 7.4, 3.6 Hz, 1H), 2.18 – 2.01 (m, 4H), 1.88 (dtd, *J* = 17.4, 8.9, 5.8 Hz, 1H), 1.82 – 1.66 (m, 3H), 1.64 – 1.53 (m, 2H), 1.53 – 1.28 (m, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 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 $C_{19}H_{30}N_2O_3$: 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*})



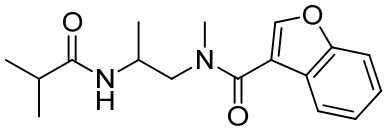
Yellowish oil. The compound existed as a ca. 1:1 mixture of rotamers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (t, *J* = 4.2 Hz, 1H), 8.53 (s, 0.5H) and 8.50 (s, 0H), 7.93 – 7.89 (m, 0.5H), 7.72 – 7.68 (m, 1H), 7.67 (s, 0.5H) and 7.63 (s, 0.5H), 7.47 (ddd, *J* = 7.9, 4.9, 1.5 Hz, 1H), 3.73 – 3.56 (m, 6H), 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) δ 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 $C_{18}H_{20}N_4O_3$: 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*-tolyl)methanone (11{*60*,*73*,*32*})



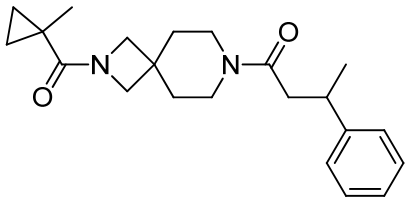
Yellowish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.73 (d, J = 1.6 Hz, 1H), 7.33 – 7.17 (m, 3H), 7.13 (d, J = 7.5 Hz, 1H), 6.73 – 6.64 (m, 1H), 4.15 – 4.07 (m, 1H), 4.07 – 3.99 (m, 1H), 3.77 – 3.69 (m, 2H), 3.68 – 3.43 (m, 2H), 3.13 – 3.00 (m, 2H), 2.18 (s, 3H), 1.77 (t, J = 5.6 Hz, 2H), 1.67 – 1.53 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 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, 58.0, 43.8, 38.3, 35.5, 34.9, 34.4, 19.0. LC/MS (CI): *m/z* = 339 $[M+H]^+$. Anal. calcd. for $C_{20}H_{22}N_2O_3$: 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*})



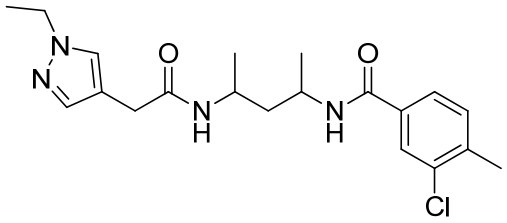
Brownish oil. The compound existed as a ca. 3:2 mixture of rotamers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.49 (d, J = 1.6 Hz, 0.4H) and 8.44 (d, J = 1.6 Hz, 0.6H), 8.17 (d, J = 8.7 Hz, 0.4H) and 8.08 – 7.99 (m, 1.6H), 7.64 – 7.57 (m, 1H), 7.39 – 7.28 (m, 2H), 4.37 – 4.29 (m, 1H), 3.51 (ddd, J = 13.4, 8.8, 1.6 Hz, 0.6H) and 3.48 – 3.42 (m, 0.4H), 3.30 (dd, J = 5.5, 1.6 Hz, 0.6H) and 3.27 (dd, J = 5.5, 1.6 Hz, 0.4H), 3.03 (d, J = 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) δ 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 (CI): *m/z* = 303 $[M+H]^+$. Anal. calcd. for $C_{17}H_{22}N_2O_3$: 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{*60*,*102*,*51*})



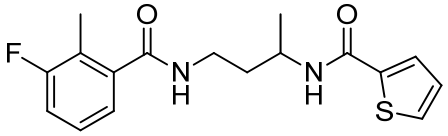
Yellowish oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.32 – 7.19 (m, 4H), 7.18 – 7.09 (m, 1H), 4.10 – 3.88 (m, 2H), 3.67 – 3.33 (m, 5H), 3.19 – 3.12 (m, 1H), 2.59 (dd, J = 17.7, 6.5 Hz, 1H), 2.52 (dd, J = 15.2, 7.8 Hz, 1H), 1.80 – 1.31 (m, 5H), 1.20 (s, 3H), 1.18 (d, J = 7.0 Hz, 3H), 0.90 – 0.79 (m, 2H), 0.48 – 0.38 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 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 (CI): *m/z* = 355 $[M+H]^+$. Anal. calcd. for $C_{22}H_{30}N_2O_2$: C 74.54; H 8.53; N 7.90. Found: C 74.67; H 8.87; N 7.65.

3-Chloro-_N_-(4-(2-(1-ethyl-1_H_-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) δ 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) δ 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 (CI): m/z = 391 $[M+H]^+$. Anal. calcd. for $C_{20}H_{27}ClN_4O_2$: C 61.45; H 6.96; N 14.33; Cl 9.07. Found: C 61.47; H 6.62; N 14.39; Cl 9.02.

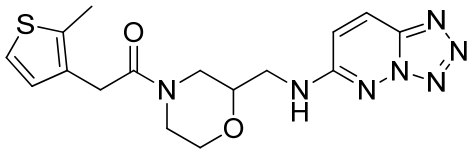
***N*-(4-(3-Fluoro-2-methylbenzamido)butan-2-yl)thiophene-2-carboxamide (11{*83*,*105*,*54*})**



Beige solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 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) δ 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) δ –116.9. LC/MS (CI): m/z = 335 $[M+H]^+$. Anal. calcd. for $C_{17}H_{19}FN_2O_2S$: C 61.06; H 5.73; N 8.38; S 9.59. Found: C 60.95; H 6.11; N 8.16; S 9.98.

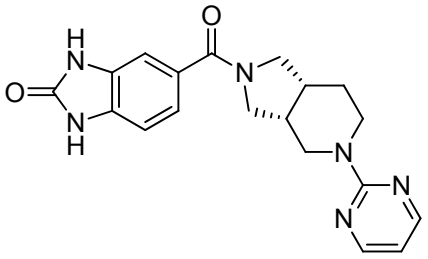
General procedure for the reaction sequence *B*. *N*-Boc-diamine **1** (0.5 mmol), carboxylic acid **4** (0.6 mmol), and *i*-Pr_2NEt (1.25 mmol*), and HATU (0.575 mmol) were mixed in dry DMSO (appr. 1.4 mL). The reaction mixture was sealed and left at ambient temperature for 16 h, then evaporated under 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*})



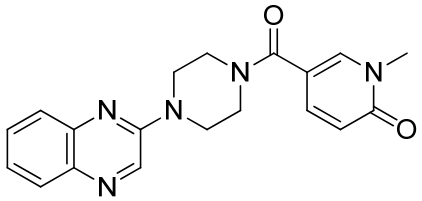
Brownish solid. The compound existed as a *ca.* 1:1 mixture of rotamers. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.22 (t, *J* = 9.5 Hz, 1H), 8.06 – 7.95 (m, 1H), 7.26 – 7.16 (m, 1H), 7.14 (d, *J* = 5.2 Hz, 0.5H) and 7.05 (d, *J* = 5.2 Hz, 0.5H), 6.77 (dd, *J* = 9.4, 5.2 Hz, 1H), 4.32 (d, *J* = 13.3 Hz, 0.5H) 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) δ 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 $C_{16}H_{19}N_7O_2S$: 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-((3a*R*,7a*R*)-5-(Pyrimidin-2-yl)octahydro-1*H*-pyrrolo[3,4-*c*]pyridine-2-carbonyl)-1*H*-benzo[*d*]imidazol-2(3*H*)-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) δ 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) δ 169.7 and 169.5, 162.0 and 161.9, 158.4, 158.4, 155.8, 131.6 and 131.5, 129.7 and 129.7, 129.6 and 129.4, 120.8 and 120.7, 110.2 and 110.1, 108.3 and 108.1, 108.1, 62.5, 53.9, 50.9 and 47.8, 42.7 and 41.3, 37.5 and 36.7, 35.6 and 34.5, 26.0 and 25.0. LC/MS (CI): *m/z* = 365 $[M+H]^+$. Anal. calcd. for $C_{19}H_{20}N_6O_2$: C 62.62; H 5.53; N 23.06. Found: C 62.69; H 5.23; N 23.24.

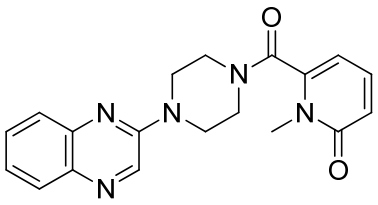
1-Methyl-5-(4-(quinoxalin-2-yl)piperazine-1-carbonyl)pyridin-2(1*H*)-one (12{*9*,*26*,*3*})



Yellowish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 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) δ 166.8, 161.9, 152.3, 141.9, 141.4, 139.5, 137.4,

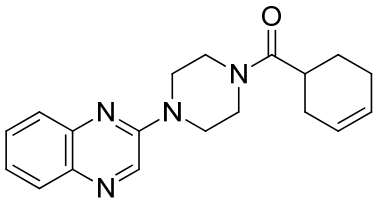
136.8, 130.5, 128.9, 126.5, 125.1, 118.7, 113.2, 44.6, 40.3, 37.6. LC/MS (CI): *m/z* = 350 $[M+H]^+$. Anal. calcd. for $C_{19}H_{19}N_5O_2$: C 65.32; H 5.48; N 20.04. Found: C 64.95; H 5.33; N 19.74.

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



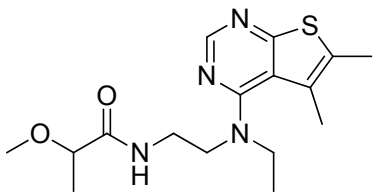
Yellowish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.83 (s, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.64 – 7.57 (m, 2H), 7.45 (dd, *J* = 9.1, 6.8 Hz, 1H), 7.43 – 7.39 (m, 1H), 6.46 (dd, *J* = 9.1, 1.4 Hz, 1H), 6.29 (dd, *J* = 6.8, 1.4 Hz, 1H), 3.96 – 3.88 (m, 2H), 3.86 – 3.73 (m, 4H), 3.53 – 3.43 (m, 2H), 3.32 (s, 3H). ^{13}C 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 $C_{19}H_{19}N_5O_2$: 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*})



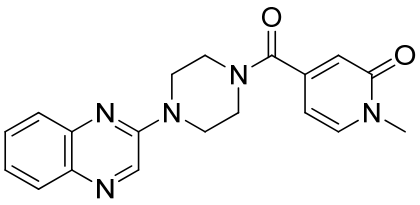
Brownish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.83 (s, 1H), 7.84 (d, *J* = 8.3 Hz, 1H), 7.67 – 7.57 (m, 2H), 7.42 (ddd, *J* = 8.3, 6.2, 2.2 Hz, 1H), 5.77 – 5.63 (m, 2H), 3.88 – 3.74 (m, 4H), 3.72 – 3.58 (m, 4H), 2.93 – 2.80 (m, 1H), 2.24 – 2.01 (m, 4H), 1.77 (dd, *J* = 12.1, 4.7 Hz, 1H), 1.59 – 1.46 (m, 1H). ^{13}C 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 (CI): *m/z* = 323 $[M+H]^+$. Anal. calcd. for $C_{19}H_{22}N_4O$: 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*})**



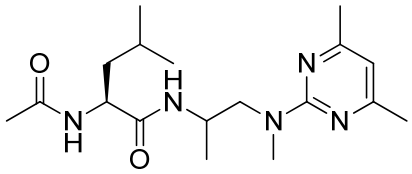
Yellowish oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.73 (t, *J* = 5.9 Hz, 1H), 3.56 – 3.48 (m, 3H), 3.42 (qd, *J* = 6.9, 2.3 Hz, 2H), 3.30 – 3.22 (m, 2H), 3.13 (s, 3H), 2.40 (s, 3H), 2.34 (s, 3H), 1.06 (d, *J* = 6.7 Hz, 3H), 1.01 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.6, 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 (CI): *m/z* = 337 $[M+H]^+$. Anal. calcd. for $C_{16}H_{24}N_4O_2S$: 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(1*H*)-one (12{*9*,*48*,*3*})



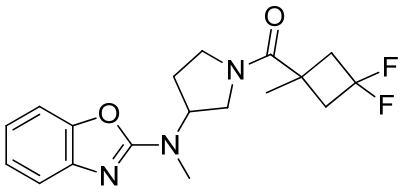
Yellowish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.81 (s, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.79 (d, J = 6.8 Hz, 1H), 7.68 – 7.53 (m, 2H), 7.40 (ddd, J = 8.2, 5.8, 2.4 Hz, 1H), 6.38 (d, J = 1.6 Hz, 1H), 6.22 (dt, J = 6.8, 1.6 Hz, 1H), 4.04 – 3.60 (m, 6H), 3.57 – 3.46 (m, 2H), 3.44 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.8, 161.9, 152.3, 147.4, 141.3, 141.2, 137.3, 136.7, 130.5, 128.8, 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 $C_{19}H_{19}N_5O_2$: C 65.32; H 5.48; N 20.04. Found: C 65.27; H 5.56; N 19.93.

(2*S*)-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) δ 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) δ 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 $C_{18}H_{31}N_5O_2$: C 61.86; H 8.94; N 20.04. Found: C 61.64; H 8.82; N 19.94.

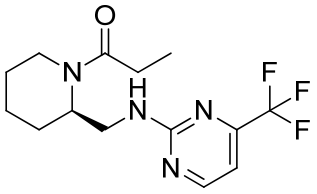
(3-(Benzo[*d*]oxazol-2-yl(methyl)amino)pyrrolidin-1-yl)(3,3-difluoro-1-methylcyclobutyl)methanone (12{*81*,*39*,*30*})



Brownish solid. The compound existed as a *ca.* 1:1 mixture of rotamers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 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) δ 172.8 and 172.8, 162.7 and 162.5, 148.7, 143.4 and 143.4, 124.4, 120.8 and 120.8, 116.1 and 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) δ –83.3 (dd, J = 194, 30.4 Hz), –91.7 (dd,

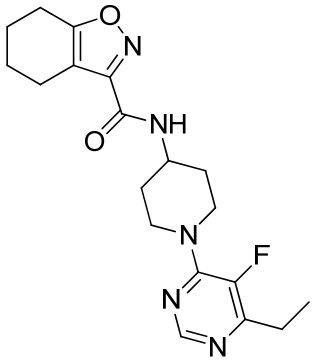
J = 194, 17.3 Hz). LC/MS (CI): *m/z* = 350 $[M+H]^+$. Anal. calcd. for $C_{18}H_{21}F_2N_3O_2$: C 61.88; H 6.06; N 12.03. Found: C 61.86; H 5.8; N 12.24.

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



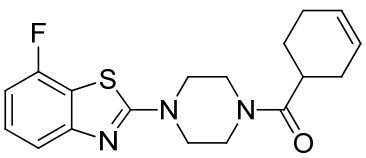
Yellowish solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.58 (d, *J* = 4.8 Hz, 1H), 7.70 (t, *J* = 6.4 Hz, 1H), 6.88 (d, *J* = 4.8 Hz, 1H), 5.01 – 4.86 (m, 1H), 4.54 (d, *J* = 13.7 Hz, 1H), 3.42 – 3.31 (m, 1H), 3.29 – 3.20 (m, 1H), 3.02 (td, *J* = 14.2, 13.7, 2.6 Hz, 1H), 1.87 (q, *J* = 7.6 Hz, 2H), 1.75 – 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) δ 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) δ –70.0. LC/MS (CI): *m/z* = 317 $[M+H]^+$. Anal. calcd. for $C_{14}H_{19}F_3N_4O$: 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) δ 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) δ 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) δ –146.5. LC/MS (CI): *m/z* = 374 $[M+H]^+$. Anal. calcd. for $C_{19}H_{24}FN_5O_2$: C 61.11; H 6.48; N 18.75. Found: C 61.26; H 6.60; N 18.78.

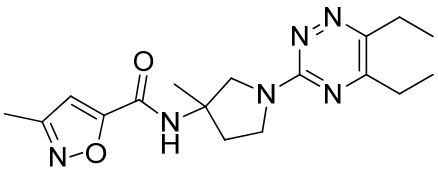
Cyclohex-3-en-1-yl(4-(7-fluorobenzo[*d*]thiazol-2-yl)piperazin-1-yl)methanone (12{*9*,*28*,*43*})



Yellowish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 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,

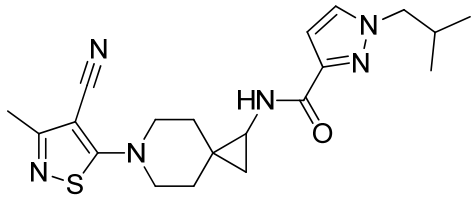
1H), 1.51 (qd, *J* = 12.0, 5.6 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.0, 168.7, 156.6 (d, *J* = 245 Hz), 155.8 (d, *J* = 2.7 Hz), 127.8 (d, *J* = 8.0 Hz), 126.9, 126.2, 116.7 (d, *J* = 15.8 Hz), 115.4, 107.8 (d, *J* = 18.7 Hz), 49.0 and 48.5, 44.6 and 40.9, 35.7, 28.1, 25.9, 24.8. ^{19}F NMR (376 MHz, DMSO-d_6) δ –113.7. LC/MS (CI): *m/z* = 346 $[M+H]^+$. Anal. calcd. for $C_{18}H_{20}FN_3OS$: 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*})



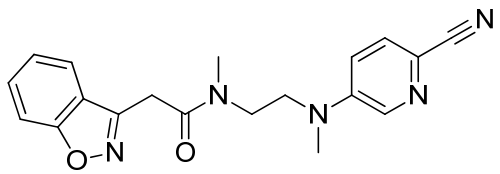
Yellowish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.76 (s, 1H), 6.92 (s, 1H), 4.05 (d, *J* = 11.6 Hz, 1H), 3.78 – 3.47 (m, 3H), 2.76 (q, *J* = 7.4 Hz, 2H), 2.66 (q, *J* = 7.4 Hz, 2H), 2.58 – 2.52 (m, 1H), 2.27 (s, 3H), 2.22 – 1.96 (m, 1H), 1.51 (s, 3H), 1.28 – 1.16 (m, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) 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 $C_{17}H_{24}N_6O_2$: 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-1*H*-pyrazole-3-carboxamide (12{*31*,*29*,*13*})



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). ^{13}C 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 $C_{20}H_{26}N_6O_S$: 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*})

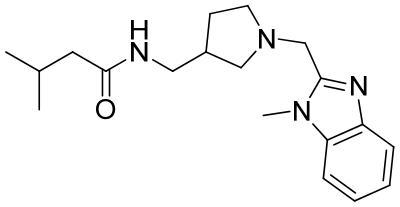


Brownish solid. The compound existed as a *ca.* 3:1 mixture of rotamers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (d, *J* = 2.9 Hz, 0.25H) and 8.18 (d, *J* = 2.9 Hz, 0.75H), 7.78 – 7.47 (m, 4H), 7.38 – 7.28 (m, 1H), 7.18 (dd, *J* = 9.0, 3.0 Hz, 0.25H) and 7.08 (dd, *J* = 9.0, 3.0 Hz, 0.75H), 4.10 (s, 2H), 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, 1.5H), 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 (CI): *m/z* = 350 $[M+H]^+$. Anal. calcd. for $C_{19}H_{19}N_5O_2$: C 65.32; H 5.48; N 20.04. Found: C 65.53; H 5.42; N 20.16.

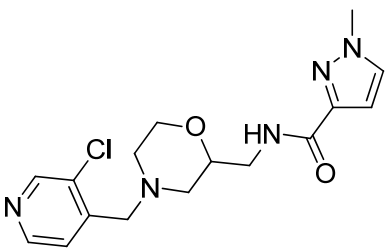
General procedure for the reaction sequence *C*. *N*-Boc-diamine **1** (0.5 mmol), carboxylic acid **4** (0.6 mmol), *i*-Pr_2NEt (1.25 mmol*), and HATU (0.575 mmol) were mixed in dry DMSO (appr. 1.4 mL). The reaction mixture was sealed and left at ambient temperature for 16 h, then evaporated under reduced 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-1*H*-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 (CI): *m/z* = 329 $[M+H]^+$. Anal. calcd. for $C_{19}H_{28}N_4O$: C 69.48; H 8.59; N 17.06. Found: C 69.29; H 8.87; N 17.07.

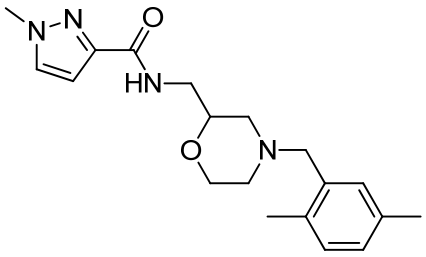
***N*-((4-((3-Chloropyridin-4-yl)methyl)morpholin-2-yl)methyl)-1-methyl-1*H*-pyrazole-3-carboxamide (13{*74*,*107*,*20*})**



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,

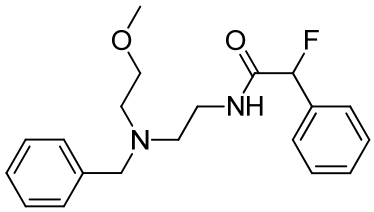
148.5, 146.5, 145.0, 133.0, 131.6, 125.2, 106.4, 74.5, 66.2, 58.2, 56.6, 53.1, 41.5, 39.4. LC/MS (CI): *m/z* = 350/352 $[M+H]^+$. Anal. calcd. for $C_{16}H_{20}ClN_5O_2$: C 54.94; H 5.76; N 20.02; Cl 10.13. Found: C 54.60; H 6.14; N 20.35; Cl 9.80.

_N_-((4-(2,5-Dimethylbenzyl)morpholin-2-yl)methyl)-1-methyl-1_H_-pyrazole-3-carboxamide (13{*74*,*107*,*21*}).



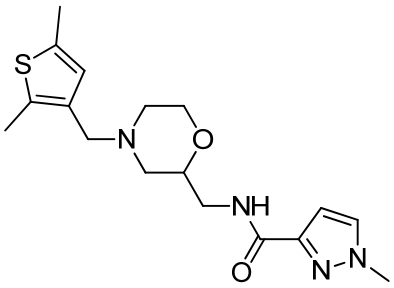
Yellowish oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90 (t, *J* = 6.0 Hz, 1H), 7.73 (d, *J* = 2.2 Hz, 1H), 7.06 – 6.96 (m, 2H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.57 (d, *J* = 2.2 Hz, 1H), 3.86 (s, 3H), 3.75 (d, *J* = 11.3 Hz, 1H), 3.57 – 3.50 (m, 1H), 3.47 – 3.33 (m, 3H), 3.24 (t, *J* = 6.2 Hz, 2H), 2.68 (d, *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) δ 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 $C_{19}H_{26}N_4O_2$: 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*})



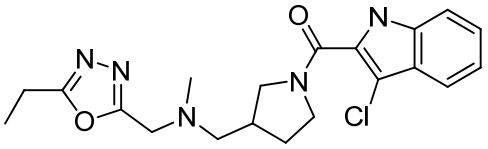
Yellowish oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.23 (t, *J* = 5.7 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.41 – 7.35 (m, 3H), 7.32 – 7.23 (m, 4H), 7.23 – 7.18 (m, 1H), 5.84 (d, *J* = 47.8 Hz, 1H), 3.59 (s, 2H), 3.33 (t, *J* = 5.8 Hz, 2H), 3.28 – 3.20 (m, 2H), 3.17 (s, 3H), 2.64 – 2.52 (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 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) δ –175.2. LC/MS (CI): *m/z* = 345 $[M+H]^+$. Anal. calcd. for $C_{20}H_{25}FN_2O_2$: 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-1_H_-pyrazole-3-carboxamide (13{*74*,*107*,*27*})



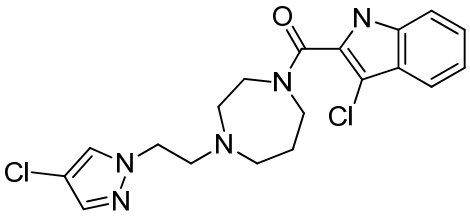
Yellowish oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.91 (t, *J* = 6.1 Hz, 1H), 7.74 (d, *J* = 2.5 Hz, 1H), 6.64 – 6.54 (m, 1H), 6.53 (s, 1H), 3.87 (s, 3H), 3.74 (d, *J* = 11.3 Hz, 1H), 3.51 (ddt, *J* = 8.7, 6.2, 3.7 Hz, 1H), 3.41 (td, *J* = 11.3, 2.5 Hz, 1H), 3.28 – 3.20 (m, 4H), 2.67 (d, *J* = 11.3 Hz, 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). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.8, 146.5, 134.6, 133.8, 133.3, 133.0, 128.4, 106.4, 74.5, 66.3, 56.5, 55.4, 52.9, 41.6, 39.4, 15.2, 13.1. LC/MS (CI): *m/z* = 349 $[M+H]^+$. Anal. calcd. for $C_{17}H_{24}N_4O_2S$: 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-1*H*-indol-2-yl)(3-((((5-ethyl-1,3,4-oxadiazol-2-yl)methyl)(methyl)amino)methyl)-pyrrolidin-1-yl)methanone (13{*44*,*129*,*33*})



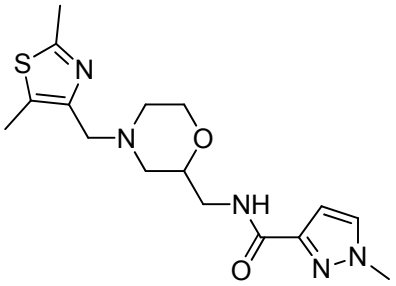
Yellowish oil. The compound existed as a ca. 11:9 mixture of rotamers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.83 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.44 – 7.36 (m, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 7.17 – 7.10 (m, 1H), 3.82 (s, 0.95H) and 3.72 (s, 1.1H), 3.65 – 3.46 (m, 3H), 3.27 – 3.20 (m, 1H), 2.83 (q, *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). ^{13}C NMR (126 MHz, DMSO-d_6) 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 (CI): *m/z* = 402/404 $[M+H]^+$. Anal. calcd. for $C_{20}H_{24}ClN_5O_2$: 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-1*H*-indol-2-yl)(4-(2-(4-chloro-1*H*-pyrazol-1-yl)ethyl)-1,4-diazepan-1-yl)methanone (13{*23*,*129*,*34*})



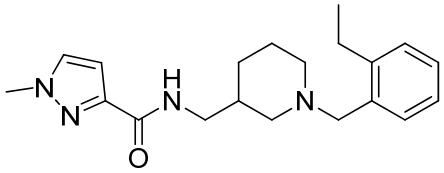
Yellowish oil. The compound existed as a ca. 1:1 mixture of rotamers.^{1}H NMR (500 MHz, DMSO-d_6) δ 11.88 (s, 1H), 7.97 (s, 0.5H) and 7.87 (s, 0.5H) and 7.61 – 7.41 (m, 2H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 4.16 (t, *J* = 6.5 Hz, 1H) and 4.08 (t, *J* = 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). ^{13}C NMR (126 MHz, DMSO-d_6) 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, 55.2 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 (CI): *m/z* = 406/408 $[M+H]^+$. Anal. calcd. for $C_{19}H_{21}Cl_2N_5O$: 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-1*H*-pyrazole-3-carboxamide (13{*74*,*107*,*35*})**



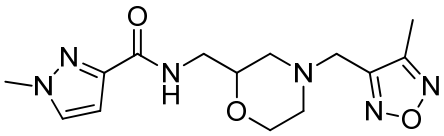
Brownish oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.91 (t, J = 5.3 Hz, 1H), 7.74 (t, J = 2.3 Hz, 1H), 6.58 (q, J = 2.3 Hz, 1H), 3.87 (s, 3H), 3.76 – 3.71 (m, 1H), 3.55 – 3.48 (m, 1H), 3.45 – 3.35 (m, 4H), 3.26 – 3.19 (m, 2H), 2.72 – 2.66 (m, 1H), 2.60 – 2.54 (m, 1H), 2.49 – 2.46 (m, 2H), 2.31 (s, 3H), 2.07 (t, J = 11.0 Hz, 1H), 1.83 (t, J = 10.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 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 (CI): m/z = 350 $[M+H]^+$. Anal. calcd. for $C_{16}H_{23}N_5O_2S$: 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*})



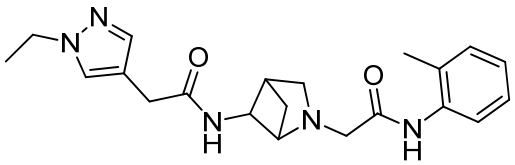
Yellowish oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.01 (t, J = 6.2 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 7.17 – 7.10 (m, 2H), 7.07 (td, J = 6.9, 2.5 Hz, 1H), 6.55 (d, J = 1.7 Hz, 1H), 3.95 – 3.77 (m, 3H), 3.44 – 3.34 (m, 2H), 3.13 – 3.02 (m, 2H), 2.75 – 2.67 (m, 1H), 2.64 (q, J = 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 (126 MHz, DMSO-d_6) δ 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 (CI): m/z = 341 $[M+H]^+$. Anal. calcd. for $C_{20}H_{28}N_4O$: 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_H_-pyrazole-3-carboxamide (13{*74*,*107*,*38*})



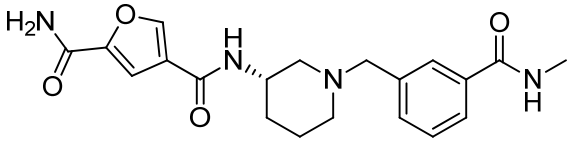
Yellowish oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.95 (t, J = 6.0 Hz, 1H), 7.74 (d, J = 1.8 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 3.87 (s, 3H), 3.79 – 3.72 (m, 1H), 3.70 (s, 2H), 3.59 – 3.49 (m, 1H), 3.43 (td, J = 11.4, 2.1 Hz, 1H), 3.25 (t, J = 6.1 Hz, 2H), 2.74 – 2.63 (m, 1H), 2.58 – 2.51 (m, 1H), 2.36 (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) δ 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 (CI): m/z = 321 $[M+H]^+$. Anal. calcd. for $C_{14}H_{20}N_6O_3$: 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*})



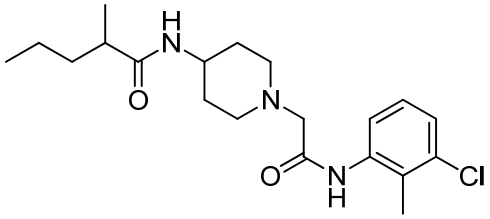
Yellowish oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.58 (s, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.50 (s, 1H), 7.36 – 7.21 (m, 2H), 7.19 (t, J = 7.6 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 4.03 (q, J = 7.3 Hz, 2H), 3.85 – 3.77 (m, 1H), 3.46 – 3.39 (m, 2H), 3.31 – 3.24 (m, 3H), 3.12 (d, J = 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 $C_{21}H_{27}N_5O_2$: 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*})



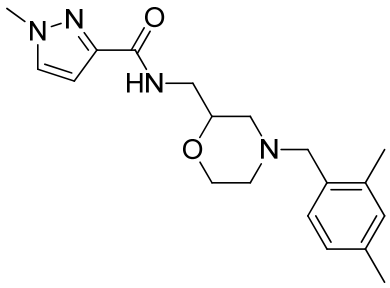
Yellowish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.39 (q, J = 4.4 Hz, 1H), 8.24 (s, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.85 (s, 1H), 7.74 (s, 1H), 7.71 – 7.66 (m, 1H), 7.46 (s, 1H), 7.44 – 7.39 (m, 2H), 7.37 (t, J = 7.5 Hz, 1H), 3.91 – 3.82 (m, 1H), 3.51 (s, 2H), 2.84 – 2.78 (m, 1H), 2.76 (d, J = 4.4 Hz, 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 $C_{20}H_{24}N_4O_4$: C 62.49; H 6.29; N 14.57. Found: C 62.30; H 5.97; N 14.95.

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



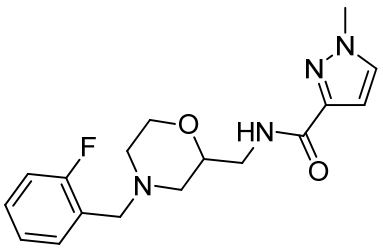
Beige solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.53 (s, 1H), 7.75 – 7.58 (m, 2H), 7.28 – 7.12 (m, 2H), 3.59 – 3.49 (m, 1H), 3.10 (s, 2H), 2.91 – 2.74 (m, 2H), 2.42 – 2.04 (m, 6H), 1.81 – 1.63 (m, 2H), 1.58 – 1.36 (m, 3H), 1.30 – 1.09 (m, 3H), 0.94 (d, J = 6.7 Hz, 3H), 0.83 (t, J = 6.8 Hz, 3H). ^{13}C NMR (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 $C_{20}H_{30}ClN_3O_2$: C 63.23; H 7.96; N 11.06; Cl 9.33. Found: C 63.4; H 7.92; N 10.70; 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) δ 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), 3.77 – 3.72 (m, 1H), 3.54 – 3.49 (m, 1H), 3.40 (td, *J* = 11.2, 2.5 Hz, 1H), 3.36 – 3.33 (m, 2H), 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) δ 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 (CI): *m/z* = 343 $[M+H]^+$. Anal. calcd. for $C_{19}H_{26}N_4O_2$: C 66.64; H 7.65; N 16.36. Found: C 66.76; H 7.99; N 16.46.

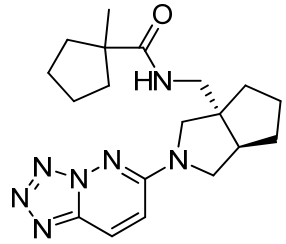
_N_-((4-(2-Fluorobenzyl)morpholin-2-yl)methyl)-1-methyl-1_H_-pyrazole-3-carboxamide (13{*74*,*107*,*25*})



Brownish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 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) δ 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) δ –118.6. LC/MS (CI): *m/z* = 333 $[M+H]^+$. Anal. calcd. for $C_{17}H_{21}FN_4O_2$: C 61.43; H 6.37; N 16.86. Found: C 61.60; H 6.62; N 16.65.

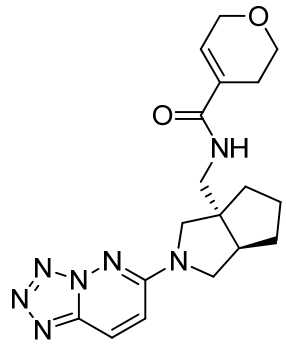
General procedure for the reaction sequence *D*. *N*-Boc-diamine **1** (0.5 mmol), aryll halide **6** (0.6 mmol), and *i*-Pr_2NEt (1.25 mmol*), were mixed in dry NMP (appr. 2 mL). The reaction mixture was sealed and heated at 100 °C for 16 h, then evaporated under reduced pressure. Then the cleavage 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*-(((3*aR*,6*aS*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)hexahydrocyclopenta[*c*]pyrrol-3*a*(1*H*)-yl)methyl)cyclopentane-1-carboxamide (14{*19*,*35*,*360*})**



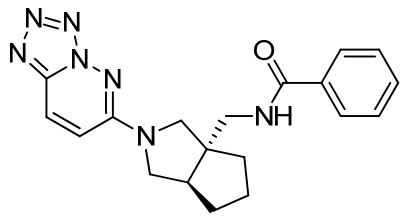
Brownish solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.32 (d, J = 9.9 Hz, 1H), 7.62 (t, J = 6.3 Hz, 1H), 7.32 (d, J = 9.9 Hz, 1H), 3.79 – 3.70 (m, 1H), 3.66 (d, J = 11.6 Hz, 1H), 3.32 – 3.26 (m, 3H), 3.12 (dd, J = 13.5, 5.9 Hz, 1H), 2.55 – 2.50 (m, 1H), 1.95 – 1.84 (m, 3H), 1.73 – 1.55 (m, 4H), 1.54 – 1.39 (m, 5H), 1.38 – 1.22 (m, 2H), 1.08 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 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 (CI): m/z = 370 $[M+H]^+$. Anal. calcd. for $C_{19}H_{27}N_7O$: C 61.77; H 7.37; N 26.54. Found: C 62.11; H 7.24; N 26.69.

rac-_N_-(((3a_R_,6a_S_)-2-(Tetrazolo[1,5-_b_]pyridazin-6-yl)hexahydrocyclopenta[_c_]pyrrol-3a(1_H_)-yl)methyl)-3,6-dihydro-2_H_-pyran-4-carboxamide (14{_19_,_35_,_361_})



Brownish oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 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) δ 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 (CI): m/z = 370 $[M+H]^+$. Anal. calcd. for $C_{18}H_{23}N_7O_2$: C 58.52; H 6.28; N 26.54. Found: C 58.61; H 6.13; N 26.42.

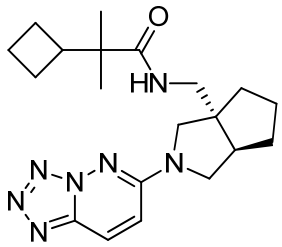
rac-_N_-(((3a_R_,6a_S_)-2-(Tetrazolo[1,5-_b_]pyridazin-6-yl)hexahydrocyclopenta[_c_]pyrrol-3a(1_H_)-yl)methyl)benzamide (14{_19_,_35_,_367_})



Yellowish solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.58 (t, J = 6.3 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) δ 167.5, 154.6, 140.0, 135.0, 131.6, 128.6, 127.7, 123.6, 119.3,

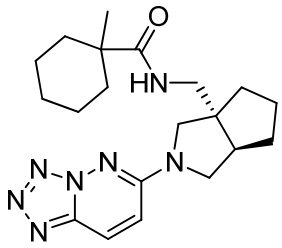
56.5, 55.8, 53.7, 45.7, 45.4, 35.2, 31.9, 24.4. LC/MS (CI): *m/z* = 364 $[M+H]^+$. Anal. calcd. for $C_{19}H_{21}N_7O$: C 62.79; H 5.82; N 26.98. Found: C 63.02; H 5.99; N 27.26.

rac-2-Cyclobutyl-2-methyl-_N_-(((3a_R_,6a_S_)-2-(tetrazolo[1,5-_b_]pyridazin-6-yl)hexahydrocyclopenta[_c_]pyrrol-3a(1_H_)-yl)methyl)propanamide (14{_19_,_35_,_369_})



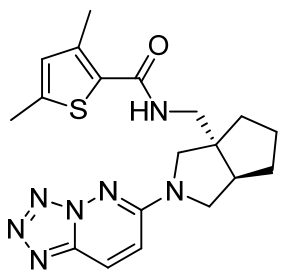
Brownish solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.33 (d, *J* = 9.9 Hz, 1H), 7.43 (t, *J* = 6.3 Hz, 1H), 7.32 (d, *J* = 9.9 Hz, 1H), 3.73 (dd, *J* = 11.1, 8.3 Hz, 1H), 3.64 (d, *J* = 11.6 Hz, 1H), 3.31 – 3.29 (m, 1H), 3.26 (dd, *J* = 13.5, 6.6 Hz, 1H), 3.11 (dd, *J* = 13.5, 6.0 Hz, 1H), 2.51 (td, *J* = 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), 1.51 – 1.26 (m, 2H), 0.93 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 177.1, 154.5, 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, 22.1, 16.9. LC/MS (CI): *m/z* = 384 $[M+H]^+$. Anal. calcd. for $C_{20}H_{29}N_7O$: C 62.64; H 7.62; N 25.57. Found: C 62.93; H 7.43; N 25.31.

rac-1-Methyl-_N_-(((3a_R_,6a_S_)-2-(tetrazolo[1,5-_b_]pyridazin-6-yl)hexahydrocyclopenta[_c_]pyrrol-3a(1_H_)-yl)methyl)cyclohexane-1-carboxamide (14{19,35,373})



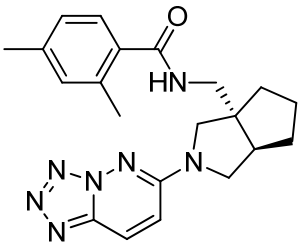
Brownish solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.32 (d, *J* = 9.8 Hz, 1H), 7.59 (t, *J* = 6.3 Hz, 1H), 7.32 (d, *J* = 9.8 Hz, 1H), 3.75 (t, *J* = 9.6 Hz, 1H), 3.68 (d, *J* = 11.6 Hz, 1H), 3.38 – 3.34 (m, 1H), 3.32 – 3.26 (m, 2H), 3.11 (dd, *J* = 13.5, 5.8 Hz, 1H), 2.54 (tt, *J* = 8.5, 4.6 Hz, 1H), 1.96 – 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) δ 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 (CI): *m/z* = 384 $[M+H]^+$. Anal. calcd. for $C_{20}H_{29}N_7O$: C 62.64; H 7.62; N 25.57. Found: C 62.77; H 7.37; N 25.52.

rac-3,5-Dimethyl-_N_-(((3a_R_,6a_S_)-2-(tetrazolo[1,5-_b_]pyridazin-6-yl)octahydrocyclopenta[_c_]-pyrrol-3a-yl)methyl)thiophene-2-carboxamide (14{_19_,_35_,_375_})



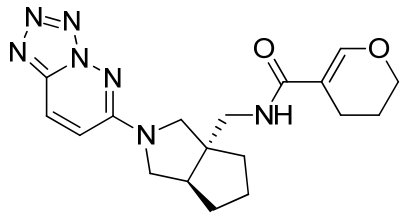
Brownish solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.31 (d, *J* = 9.9 Hz, 1H), 7.94 (t, *J* = 6.3 Hz, 1H), 7.33 (d, *J* = 9.8 Hz, 1H), 6.58 (s, 1H), 3.78 (dd, *J* = 11.2, 8.1 Hz, 1H), 3.71 (d, *J* = 11.5 Hz, 1H), 3.45 – 3.34 (m, 3H), 3.32 – 3.28 (m, 1H), 2.56 (tt, *J* = 8.4, 4.9 Hz, 1H), 2.32 (s, 3H), 2.25 (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) δ 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 (CI): *m/z* = 398 $[M+H]^+$. Anal. calcd. for $C_{19}H_{23}N_7OS$: 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_-(((3a_R_,6a_S_)-2-(tetrazolo[1,5-_b_]pyridazin-6-yl)octahydrocyclopenta[_c_]-pyrrol-3a-yl)methyl)benzamide (14{_19_,_35_,_377_})



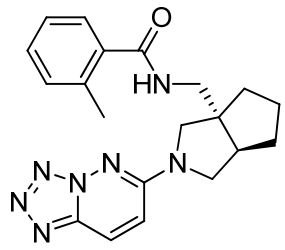
Brownish solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.36 (t, *J* = 6.3 Hz, 1H), 8.33 (d, *J* = 9.9 Hz, 1H), 7.34 (d, *J* = 9.9 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 6.99 (s, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 3.86 – 3.76 (m, 1H), 3.73 (d, *J* = 11.6 Hz, 1H), 3.43 – 3.36 (m, 3H), 3.32 – 3.28 (m, 1H), 2.58 (tt, *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) δ 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 (CI): *m/z* = 392 $[M+H]^+$. Anal. calcd. for $C_{21}H_{25}N7O$: C 64.43; H 6.44; N 25.05. Found: C 64.66; H 6.12; N 24.75.

_N_-(((3a_S_,6a_R_)-2-(tetrazolo[1,5-_b_]pyridazin-6-yl)octahydrocyclopenta[_c_]pyrrol-3a-yl)methyl)-3,4-dihydro-2_H_-pyran-5-carboxamide (14{_19_,_35_,_378_})



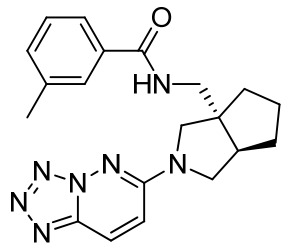
Brownish solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.31 (d, *J* = 9.9 Hz, 1H), 7.57 (t, *J* = 6.0 Hz, 1H), 7.31 (d, *J* = 9.9 Hz, 1H), 7.25 (s, 1H), 3.86 (t, *J* = 5.2 Hz, 2H), 3.74 (dd, *J* = 11.2, 8.3 Hz, 1H), 3.65 (d, *J* = 11.6 Hz, 1H), 3.35 (s, 1H), 3.32 – 3.26 (m, 2H), 3.20 (dd, *J* = 13.6, 6.1 Hz, 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) δ 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 (CI): *m/z* = 370 $[M+H]^+$. Anal. calcd. for $C_{18}H_{23}N_7O_2$: C 58.52; H 6.28; N 26.54. Found: C 58.67; H 6.26; N 26.86.

rac-2-Methyl-_N_-(((3a_R_,6a_S_)-2-(tetrazolo[1,5-_b_]pyridazin-6-yl)octahydrocyclopenta[_c_]pyrrol-3a-yl)methyl)benzamide (14{_19_,_35_,_384_})



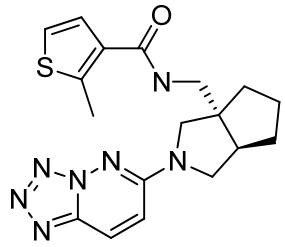
Brownish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.36 (d, *J* = 9.7 Hz, 1H), 7.37 (d, *J* = 9.7 Hz, 1H), 7.32 – 7.24 (m, 2H), 7.23 – 7.15 (m, 2H), 3.84 (dd, *J* = 10.4, 8.9 Hz, 1H), 3.76 (d, *J* = 11.6 Hz, 1H), 3.50 – 3.36 (m, 4H), 2.66 – 2.59 (m, 1H), 2.29 (s, 3H), 2.01 – 1.90 (m, 1H), 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 (CI): *m/z* = 378 $[M+H]^+$. Anal. calcd. for $C_{20}H_{23}N_7O$: C 63.64; H 6.14; N 25.98. Found: C 63.82; H 5.97; N 25.76.

rac-3-Methyl-_N_-(((3a_R_,6a_S_)-2-(tetrazolo[1,5-_b_]pyridazin-6-yl)octahydrocyclopenta[_c_]pyrrol-3a-yl)methyl)benzamide (14{*19*,*35*,*171*})



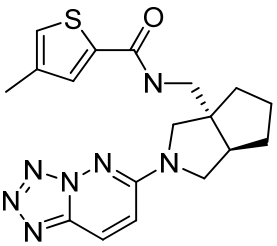
Brownish solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.52 (t, *J* = 6.2 Hz, 1H), 8.30 (d, *J* = 9.9 Hz, 1H), 7.69 – 7.47 (m, 2H), 7.32 (d, *J* = 9.9 Hz, 1H), 7.29 – 7.22 (m, 2H), 3.83 – 3.71 (m, 2H), 3.48 – 3.34 (m, 4H), 2.59 (tt, *J* = 8.5, 4.7 Hz, 1H), 1.96 – 1.88 (m, 1H), 1.79 – 1.72 (m, 2H), 1.69 – 1.61 (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 (CI): *m/z* = 378 $[M+H]^+$. Anal. calcd. for $C_{20}H_{23}N_7O$: C 63.64; H 6.14; N 25.98. Found: C 63.34; H 5.86; N 25.60.

rac-2-Methyl-_N_-(((3a_R_,6a_S_)-2-(tetrazolo[1,5-_b_]pyridazin-6-yl)octahydrocyclopenta[_c_]pyrrol-3a-yl)methyl)thiophene-3-carboxamide (14{*19*,*35*,*390*})



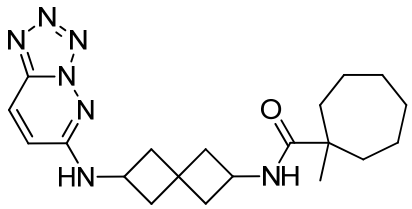
Brownish solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.31 (d, *J* = 9.8 Hz, 1H), 8.22 (t, *J* = 6.3 Hz, 1H), 7.33 (d, *J* = 9.8 Hz, 1H), 7.21 (s, 2H), 3.78 (dd, *J* = 11.1, 8.2 Hz, 1H), 3.71 (d, *J* = 11.6 Hz, 1H), 3.44 – 3.35 (m, 3H), 3.32 – 3.27 (m, 1H), 2.57 (tt, *J* = 8.6, 4.7 Hz, 1H), 2.47 (s, 3H), 1.97 – 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 (CI): *m/z* = 384 $[M+H]^+$. Anal. calcd. for $C_{18}H_{21}N_7OS$: 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*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)thiophene-2-carboxamide (14{*19*,*35*,*394*})**



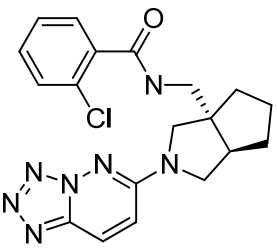
Brownish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (t, *J* = 6.3 Hz, 1H), 8.33 (d, *J* = 9.9 Hz, 1H), 7.56 (s, 1H), 7.34 (d, *J* = 9.9 Hz, 1H), 7.29 (s, 1H), 3.80 (dd, *J* = 11.2, 8.1 Hz, 1H), 3.73 (d, *J* = 11.6 Hz, 1H), 3.50 – 3.38 (m, 3H), 3.35 – 3.31 (m, 1H), 2.59 (tt, *J* = 8.4, 4.6 Hz, 1H), 2.17 (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) δ 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 $C_{18}H_{21}N_7OS$: 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) δ 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) δ 177.1, 155.1, 140.4, 123.5, 121.1, 45.0, 42.5, 42.4, 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 $C_{20}H_{29}N_7O$: C 62.64; H 7.62; N 25.57. Found: C 62.79; H 7.70; N 25.75.

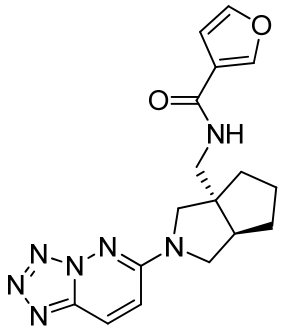
***rac*-2-Chloro-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)benzamide (14{*19*,*35*,*408*})**



Brownish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 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) δ 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,

32.2, 24.6. LC/MS (CI): *m/z* = 398/400 $[M+H]^+$. Anal. calcd. for $C_{19}H_{20}ClN_7O$: C 57.36; H 5.07; N 24.64; Cl 8.91. Found: C 57.48; H 4.96; N 24.62; Cl 8.64.

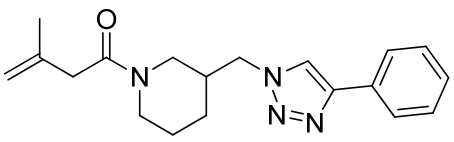
***rac*-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)furan-3-carboxamide (14{*19*,*35*,*32*})**



Brownish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.34 (d, *J* = 9.9 Hz, 1H), 8.29 (t, *J* = 6.3 Hz, 1H), 8.16 (s, 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) δ 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 $C_{17}H_{19}N_7O_2$: C 57.78; H 5.42; N 27.75. Found: C 58.07; H 5.29; N 28.08.

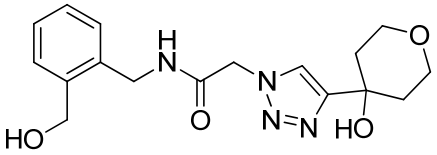
General procedure for the reaction sequence *E*. Amine **2** or **9** (0.5 mmol), carboxylic acid **8** or **3** (0.6 mmol), *i*-Pr_2NEt (1.25 mmol*), and 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo-[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) (0.575 mmol) were mixed in dry DMF (appr. 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 °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-1*H*-1,2,3-triazol-1-yl)methyl)piperidin-1-yl)but-3-en-1-one (15{*5*,*7*,*7*})



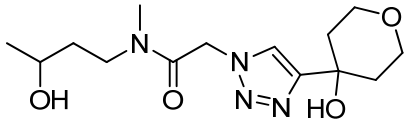
Yellowish liquid. The compound existed as a *ca.* 11:9 mixture of rotamers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56 (d, *J* = 7.1 Hz, 1H), 7.87 – 7.78 (m, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 4.81 (s, 0.55H) and 4.69 (s, 0.55H) and 4.68 (s, 0.45H) and 4.48 (s, 0.45H), 4.37 – 4.27 (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) δ 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 $C_{19}H_{24}N_4O$: 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-2*H*-pyran-4-yl)-1*H*-1,2,3-triazol-1-yl)acetamide (15{*3*,*17*,*38*})**



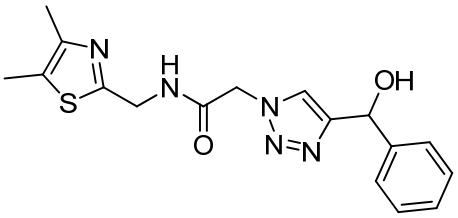
Yellowish oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.68 (t, *J* = 5.6 Hz, 1H), 7.91 (s, 1H), 7.43 – 7.37 (m, 1H), 7.29 – 7.20 (m, 3H), 5.23 (s, 1H), 5.15 (s, 1H), 5.13 (s, 2H), 4.56 (s, 2H), 4.36 (d, *J* = 5.5 Hz, 2H), 3.75 (td, *J* = 11.0, 2.5 Hz, 2H), 3.67 – 3.56 (m, 2H), 2.05 (ddd, *J* = 14.3, 10.5, 4.5 Hz, 2H), 1.74 – 1.63 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 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 $C_{17}H_{22}N_4O_4$: 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-2*H*-pyran-4-yl)-1*H*-1,2,3-triazol-1-yl)-*N*-methylacetamide (Z4180225403)**



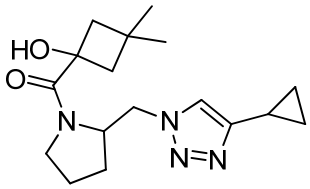
Yellowish solid. The compound existed as a *ca.* 11:9 mixture of rotamers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.81 (s, 0.45H) and 7.78 (s, 0.55H), 5.59 – 5.38 (m, 1H), 5.35 (s, 1H), 5.19 (s, 1H), 4.64 (d, *J* = 4.8 Hz, 0.45H) and 4.43 (d, *J* = 4.8 Hz, 0.55H), 3.77 – 3.69 (m, 2H), 3.67 – 3.50 (m, 3H), 3.50 – 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) δ 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 $C_{14}H_{24}N_4O_4$: 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)-1*H*-1,2,3-triazol-1-yl)-acetamide (15{*3*,*21*,*37*})**



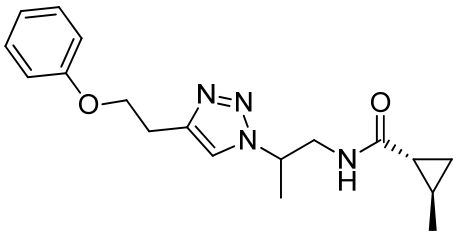
Yellowish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.09 (t, *J* = 6.1 Hz, 1H), 7.81 (s, 1H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.24 (t, *J* = 6.9 Hz, 1H), 5.99 (d, *J* = 3.9 Hz, 1H), 5.82 (d, *J* = 4.7 Hz, 1H), 5.11 (s, 2H), 4.46 (d, *J* = 5.9 Hz, 2H), 2.28 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 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 $C_{17}H_{19}N_5O_2S$: 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-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidin-1-yl)(1-hydroxy-3,3-dimethyl-cyclobutyl)methanone (15{*1*,*6*,*6*})



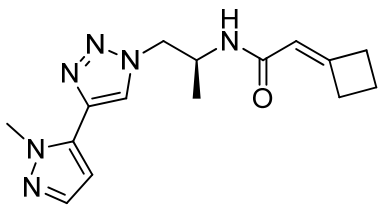
Yellowish oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.63 (s, 1H), 5.71 (s, 1H), 4.44 (d, *J* = 4.5 Hz, 2H), 4.22 (dq, *J* = 8.6, 4.5 Hz, 1H), 3.46 (dt, *J* = 10.8, 6.8 Hz, 1H), 3.16 – 3.07 (m, 1H), 2.47 – 2.42 (m, 1H), 2.36 (dd, *J* = 12.8, 2.6 Hz, 1H), 1.89 (tt, *J* = 8.6, 5.0 Hz, 1H), 1.85 – 1.68 (m, 3H), 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) δ 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 $C_{17}H_{26}N_4O_2$: C 64.12; H 8.23; N 17.60. Found: C 64.07; H 8.13; N 17.64.

rac-(1*R*,2*R*)-2-Methyl-*N*-(2-(4-(2-phenoxyethyl)-1*H*-1,2,3-triazol-1-yl)propyl)cyclopropane-carboxamide (15{*4*,*4*,*4*})



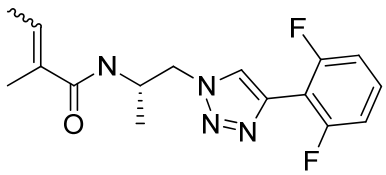
Yellowish oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.09 (q, *J* = 5.5 Hz, 1H), 7.95 (d, *J* = 3.0 Hz, 1H), 7.26 (t, *J* = 7.9 Hz, 2H), 7.00 – 6.80 (m, 3H), 4.75 – 4.64 (m, 1H), 4.19 (t, *J* = 6.8 Hz, 2H), 3.50 – 3.35 (m, 2H), 3.06 (t, *J* = 6.8 Hz, 2H), 1.41 (d, *J* = 6.9 Hz, 3H), 1.21 (dq, *J* = 7.9, 3.9 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) δ 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 (CI): *m/z* = 329 $[M+H]^+$. Anal. calcd. for $C_{18}H_{24}N_4O_2$: C 65.83; H 7.37; N 17.06. Found: C 65.75; H 7.34; N 16.96.

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



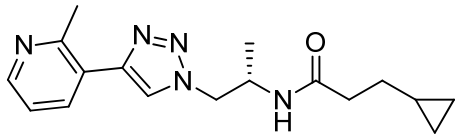
Yellowish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 1.8 Hz, 1H), 6.54 (d, *J* = 1.5 Hz, 1H), 5.55 – 5.45 (m, 1H), 4.50 – 4.34 (m, 2H), 4.31 – 4.21 (m, 1H), 4.01 (d, *J* = 1.3 Hz, 3H), 3.01 – 2.85 (m, 2H), 2.70 (t, *J* = 7.9 Hz, 2H), 2.02 – 1.86 (m, 2H), 1.06 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 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 (CI): *m/z* = 301 $[M+H]^+$. Anal. calcd. for $C_{15}H_{20}N_6O$: C 59.98; H 6.71; N 27.98. Found: C 60.18; H 6.75; N 27.72.

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



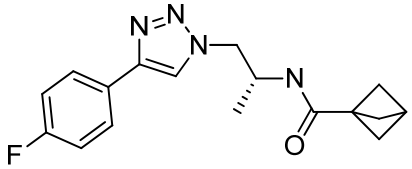
Yellowish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.33 (d, J = 1.5 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.46 (tt, J = 8.4, 6.4 Hz, 1H), 7.21 (t, J = 8.4 Hz, 2H), 6.20 (q, J = 6.4 Hz, 1H), 4.53 (dd, J = 13.6, 5.4 Hz, 1H), 4.47 (dd, J = 13.6, 7.9 Hz, 1H), 4.38 – 4.28 (m, 1H), 1.91 – 1.39 (m, 6H), 1.11 (d, J = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.7, 159.8 (dd, J = 251, 7.1 Hz), 135.1 (t, J = 2.7 Hz), 132.3, 130.6 (t, J = 10.5 Hz), 129.6, 126.2 (t, J = 4.2 Hz), 112.6 (dd, J = 20.7, 5.0 Hz), 108.8 (t, J = 17.4 Hz), 53.9, 45.5, 18.3, 14.0, 12.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ –111.9. LC/MS (CI): m/z = 321 $[M+H]^+$. Anal. calcd. for $C_{16}H_{18}F_2N_4O$: C 59.99; H 5.66; N 17.49. Found: C 59.81; H 5.97; N 17.62.

(*S*)-3-Cyclopropyl-*N*-(1-(4-(2-methylpyridin-3-yl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)propanamide (15{*6*,*27*,*27*})



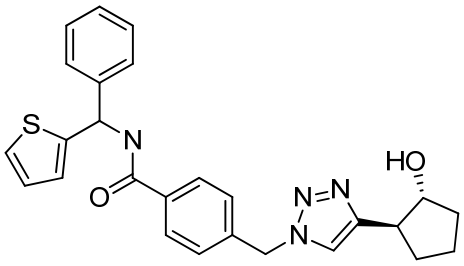
Beige solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 – 8.42 (m, 1H), 8.38 (d, J = 1.5 Hz, 1H), 8.08 (dd, J = 7.9, 1.8 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.32 (dd, J = 7.9, 4.8 Hz, 1H), 4.49 (dd, J = 13.6, 5.2 Hz, 1H), 4.40 (dd, J = 13.6, 7.5 Hz, 1H), 4.35 – 4.25 (m, 1H), 2.63 (s, 3H), 2.08 (t, J = 7.4 Hz, 2H), 1.39 – 1.24 (m, 2H), 1.10 (d, J = 6.7 Hz, 3H), 0.60 – 0.49 (m, 1H), 0.32 – 0.22 (m, 2H), –0.04 – –0.13 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.1, 155.0, 148.5, 144.0, 135.8, 126.0, 124.8, 121.9, 54.2, 45.0, 36.0, 30.7, 24.7, 18.2, 10.8, 4.7, 4.7. LC/MS (CI): m/z = 314 $[M+H]^+$. Anal. calcd. for $C_{17}H_{23}N_5O$: C 65.15; H 7.40; N 22.35. Found: C 65.41; H 7.03; N 22.24.

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



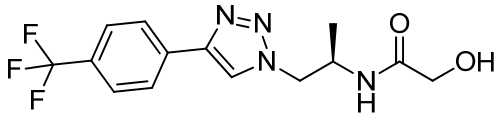
Colorless soild. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.84 (dd, J = 8.7, 5.6 Hz, 2H), 7.63 (d, J = 8.4 Hz, 1H), 7.26 (t, J = 8.7 Hz, 2H), 4.42 (dd, J = 13.6, 5.6 Hz, 1H), 4.33 (dd, J = 13.6, 7.4 Hz, 1H), 4.24 – 4.15 (m, 1H), 2.33 (s, 1H), 1.84 (s, 6H), 1.06 (d, J = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.9, 162.1 (d, J = 244 Hz), 145.5, 127.8 (d, J = 3.1 Hz), 127.5 (d, J = 8.2 Hz), 122.1, 116.2 (d, J = 21.7 Hz), 53.9, 50.8, 45.0, 44.6, 26.7, 18.0. ^{19}F NMR (376 MHz, DMSO-d_6) δ –114.8. LC/MS (CI): m/z = 315 $[M+H]^+$. Anal. calcd. for $C_{17}H_{19}FN_4O$: C 64.95; H 6.09; N 17.82. Found: C 65.06; H 6.17; N 17.48.

***rac*-4-((4-((1*R*,2*S*)-2-Hydroxycyclopentyl)-1*H*-1,2,3-triazol-1-yl)methyl)-N-(phenyl(thiophen-2-yl)methyl)benzamide (15{*1*,*2*,*17*})**



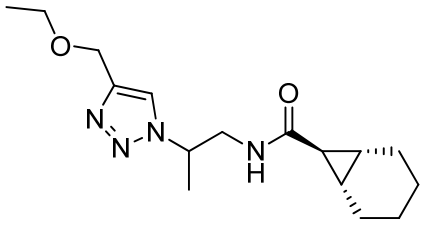
Beige solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.46 (d, J = 8.7 Hz, 1H), 7.98 – 7.87 (m, 3H), 7.48 (d, J = 7.4 Hz, 2H), 7.46 – 7.42 (m, 1H), 7.42 – 7.34 (m, 4H), 7.31 (t, J = 7.4 Hz, 1H), 6.97 (t, J = 4.2 Hz, 1H), 6.87 – 6.79 (m, 1H), 6.58 (d, J = 8.7 Hz, 1H), 5.60 (s, 2H), 4.74 (d, J = 4.8 Hz, 1H), 4.08 – 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, 127.9, 127.3, 126.1, 125.9, 122.1, 78.0, 52.8, 52.8, 45.2, 34.4, 30.5, 22.1. LC/MS (CI): m/z = 459 $[M+H]^+$. Anal. calcd. for $C_{26}H_{26}N_4O_2S$: 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)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)acetamide (15{*2*,*30*,*29*})



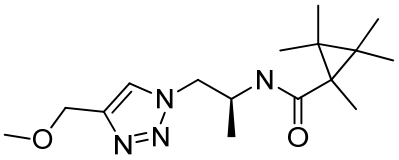
Beige solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.04 (d, J = 8.2 Hz, 2H), 7.84 (d, J = 8.6 Hz, 1H), 7.78 (d, J = 8.2 Hz, 2H), 5.47 (t, J = 5.8 Hz, 1H), 4.53 – 4.44 (m, 2H), 4.37 – 4.31 (m, 1H), 3.78 – 3.67 (m, 2H), 1.10 (d, J = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.0, 145.2, 135.2, 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 (CI): m/z = 329 $[M+H]^+$. Anal. calcd. for $C_{26}H_{26}N_4O_2S$: 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.

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



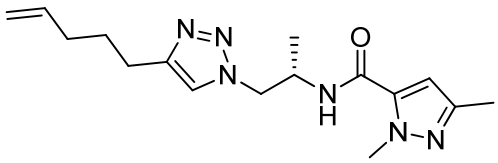
Yellowish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.08 (s, 1H), 8.01 (t, J = 5.0 Hz, 1H), 4.77 – 4.67 (m, 1H), 4.47 (s, 2H), 3.53 – 3.41 (m, 4H), 1.86 – 1.76 (m, 2H), 1.53 (s, 2H), 1.43 (d, J = 6.9 Hz, 3H), 1.32 – 1.17 (m, 5H), 1.17 – 1.04 (m, 5H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.4, 144.3, 122.8, 65.3, 63.7, 56.4, 44.5, 26.6, 22.8, 21.2, 19.5, 19.5, 19.1, 15.5. LC/MS (CI): m/z = 307 $[M+H]^+$. Anal. calcd. for $C_{16}H_{26}N_4O_2$: C 62.72; H 8.55; N 18.29. Found: C 62.96; H 8.58; N 18.06.

(*S*)-*N*-(1-(4-(Methoxymethyl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)-1,2,2,3,3-pentamethylcyclopropanecarboxamide (15{*6*,*14*,*13*})



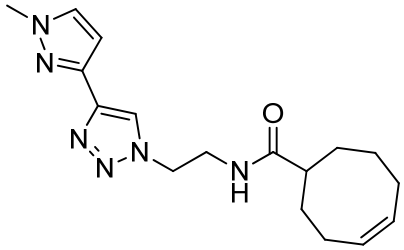
Yellowish oil. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.33 (d, J = 8.4 Hz, 1H), 4.38 (s, 2H), 4.35 – 4.29 (m, 2H), 4.26 – 4.20 (m, 1H), 3.20 (d, J = 1.2 Hz, 3H), 1.02 (d, J = 6.7 Hz, 3H), 0.98 (s, 3H), 0.89 (s, 6H), 0.87 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.8, 143.9, 124.6, 65.3, 57.6, 53.8, 44.8, 34.6, 23.6, 23.6, 20.9, 20.9, 18.4, 18.1, 17.9, 15.6. LC/MS (CI): *m/z* = 309 $[M+H]^+$. Anal. calcd. for $C_{16}H_{28}N_4O_2$: C 62.31; H 9.15; N 18.17. Found: C 61.98; H 8.85; N 18.51.

(*S*)-1,3-Dimethyl-*N*-(1-(4-(pent-4-en-1-yl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)-1*H*-pyrazole-5-carboxamide (15{*6*,*9*,*9*})



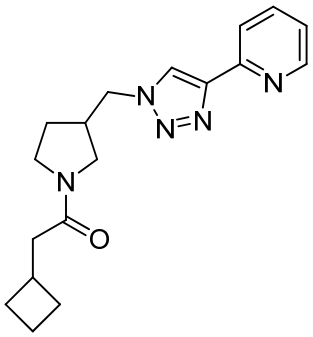
Yellowish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.26 (d, J = 7.3 Hz, 1H), 7.77 (s, 1H), 6.53 (s, 1H), 5.78 (ddt, J = 17.0, 10.3, 6.6 Hz, 1H), 4.96 (t, J = 13.9 Hz, 2H), 4.50 – 4.30 (m, 3H), 3.87 (s, 3H), 2.58 (t, J = 7.5 Hz, 2H), 2.00 (q, J = 7.2 Hz, 2H), 1.62 (p, J = 7.5 Hz, 2H), 1.14 (d, J = 5.9 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.4, 146.8, 145.7, 138.8, 136.1, 122.9, 115.5, 106.9, 53.7, 45.5, 38.7, 32.9, 28.6, 24.8, 18.1, 13.5. LC/MS (CI): *m/z* = 317 $[M+H]^+$. Anal. calcd. for $C_{16}H_{24}N_6O$: C 60.74; H 7.65; N 26.56. Found: C 60.46; H 7.62; N 26.76.

***N*-(2-(4-(1-Methyl-1*H*-pyrazol-3-yl)-1*H*-1,2,3-triazol-1-yl)ethyl)cyclooct-4-enecarboxamide (15{*3*,*3*,*3*})**

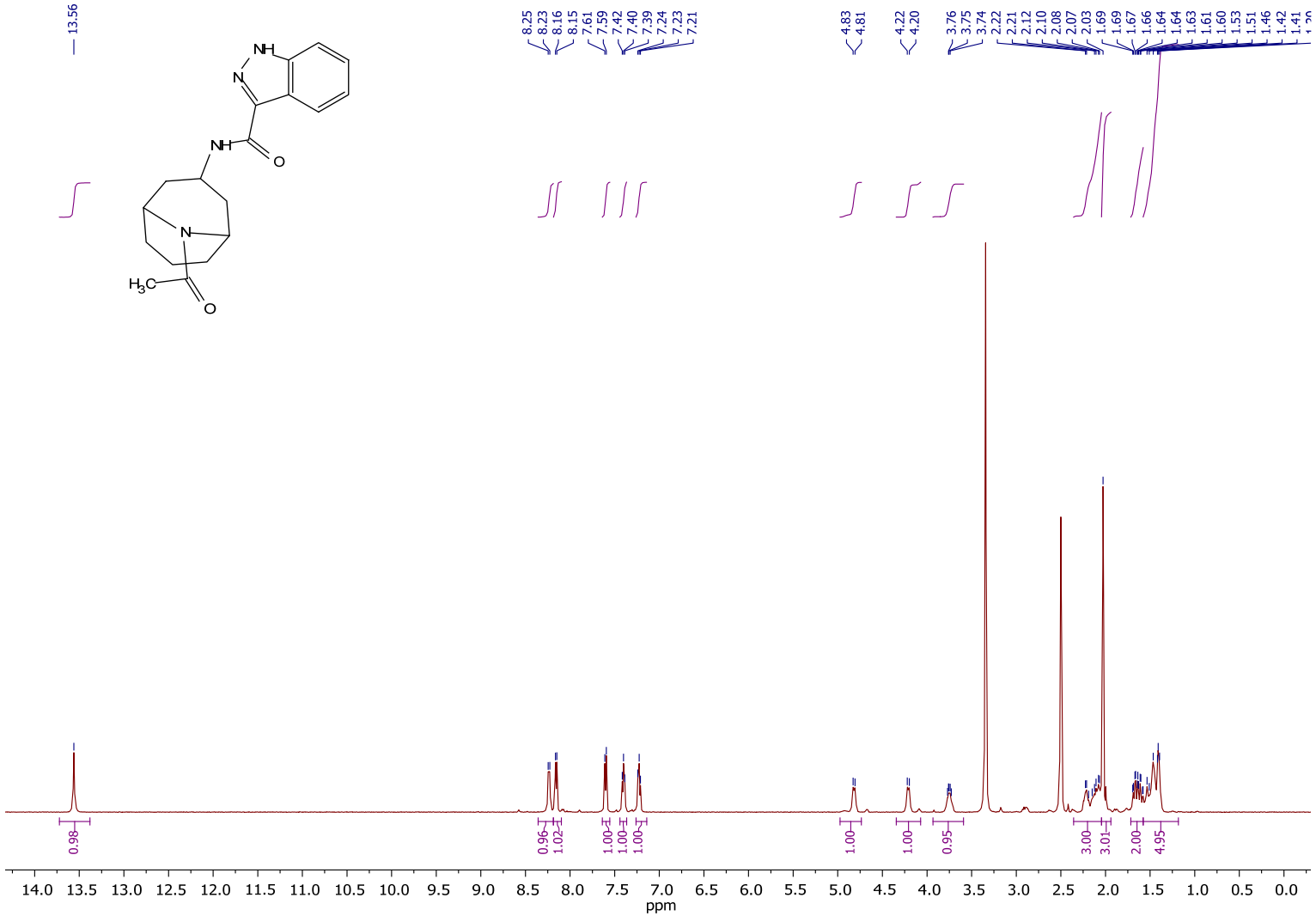


Yellowish oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.84 (t, J = 5.7 Hz, 1H), 7.71 (d, J = 2.3 Hz, 1H), 6.54 (dd, J = 2.3, 0.8 Hz, 1H), 5.66 – 5.49 (m, 2H), 4.40 (t, J = 6.0 Hz, 2H), 3.84 (s, 3H), 3.54 – 3.38 (m, 2H), 2.30 – 2.21 (m, 1H), 2.13 (ddd, J = 11.5, 6.9, 4.1 Hz, 1H), 2.10 – 2.00 (m, 2H), 2.00 – 1.89 (m, 1H), 1.66 (dt, J = 14.6, 4.1 Hz, 1H), 1.62 – 1.34 (m, 4H), 1.31 – 1.21 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 177.6, 143.5, 142.0, 132.3, 130.4, 130.2, 121.4, 103.3, 49.3, 44.3, 39.1, 39.0, 32.4, 30.2, 27.9, 25.9, 24.4. LC/MS (CI): *m/z* = 329 $[M+H]^+$. Anal. calcd. for $C_{17}H_{24}N_6O$: C 62.17; H 7.37; N 25.59. Found: C 62.28; H 7.23; N 25.23.

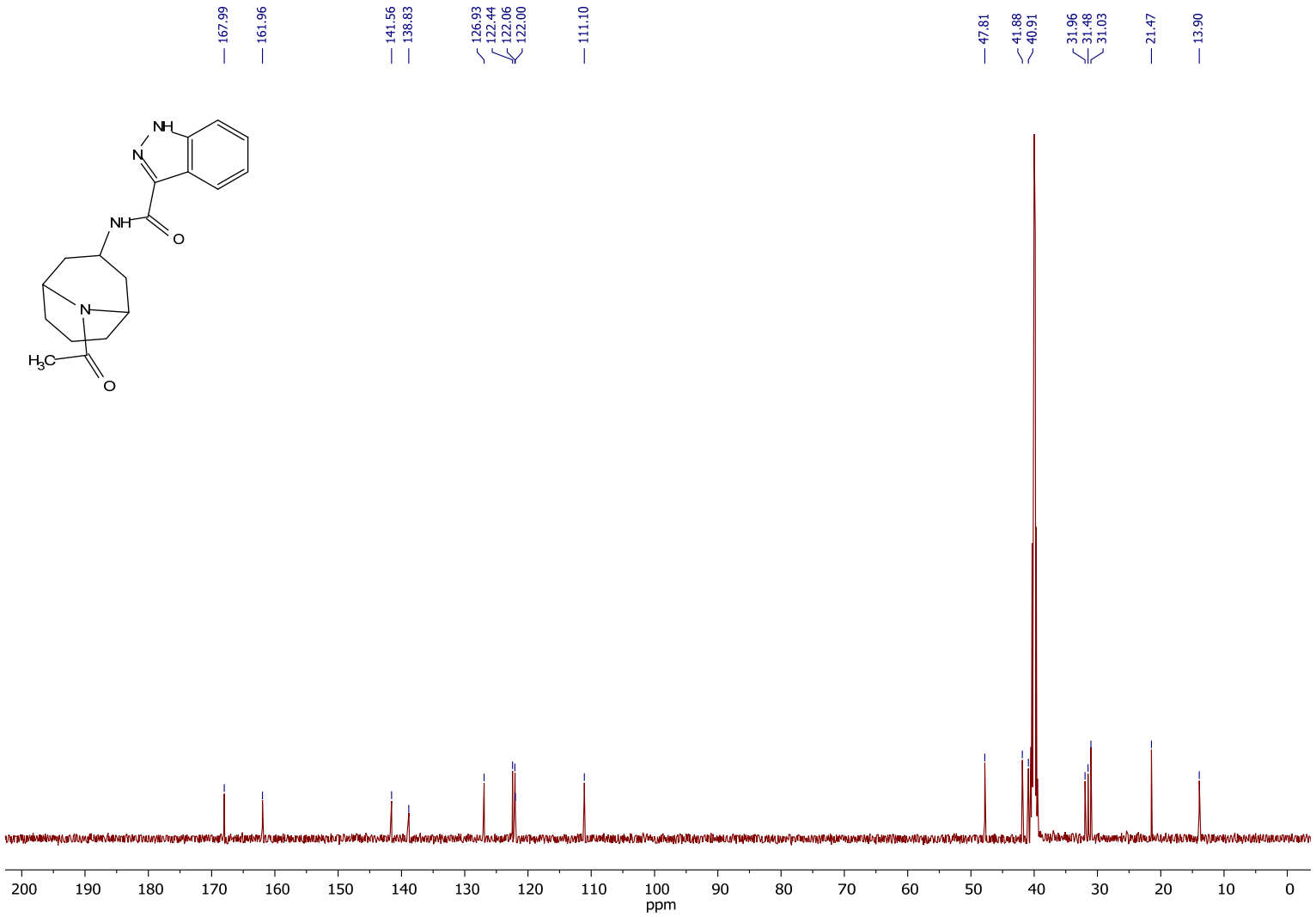
2-Cyclobutyl-1-(3-((4-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidin-1-yl)ethanone (15{*8*,*10*,*10*})



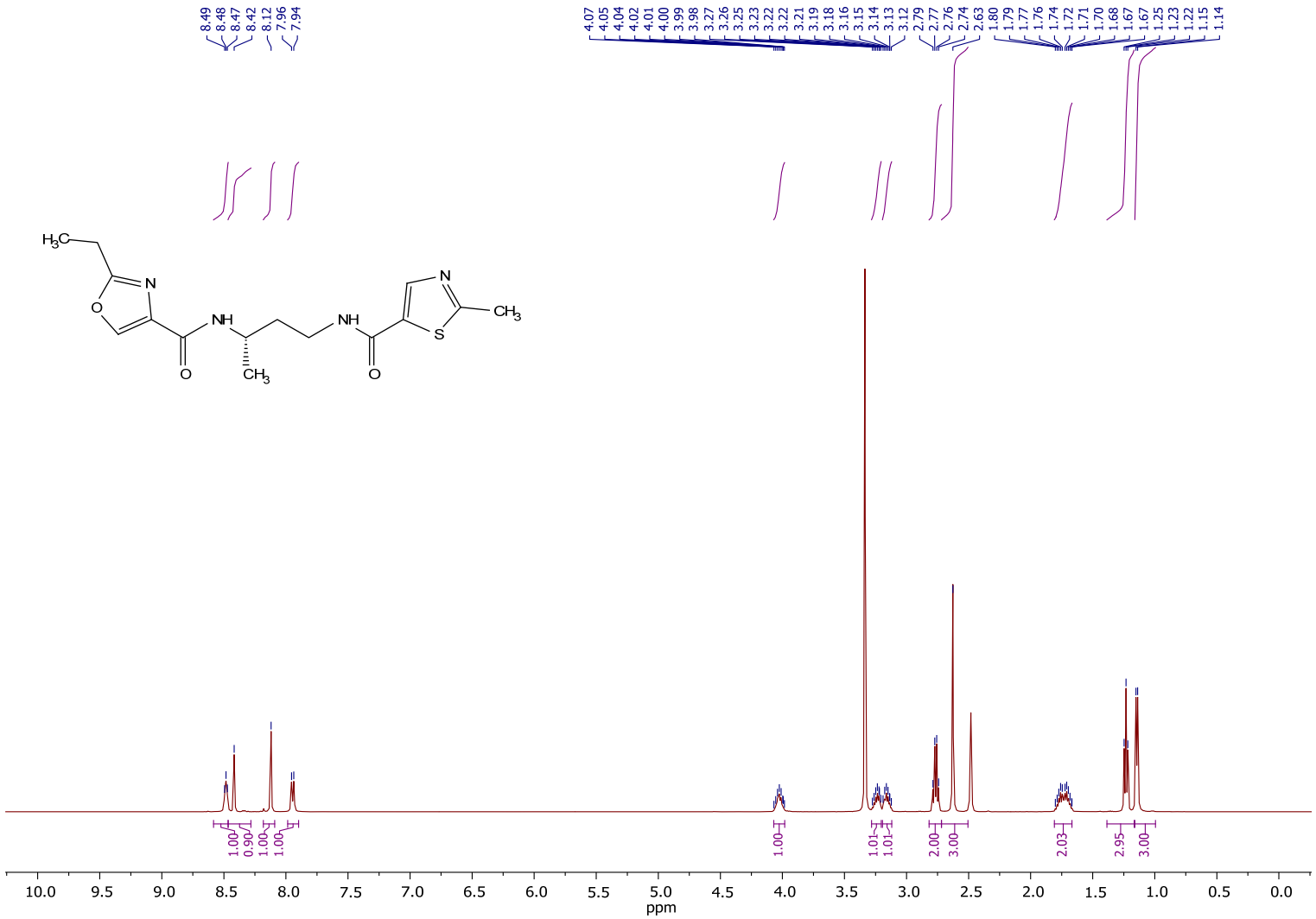
Brownish solid. The compound existed as a ca. 1:1 mixture of rotamers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.76 – 8.64 (m, 1H), 8.60 (s, 1H), 8.04 (s, 1H), 7.89 (t, *J* = 7.8 Hz, 1H), 7.35 (s, 1H), 4.54 – 4.47 (m, 2H), 3.58 – 3.49 (m, 1H), 3.46 – 3.37 (m, 1.5H) and 3.28 – 3.17 (m, 1H) and 3.09 (dd, *J* = 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) δ 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 (CI): *m/z* = 326 $[M+H]^+$. Anal. calcd. for $C_{18}H_{23}N_5O$: C 66.44; H 7.12; N 21.52. Found: C 66.43; H 7.34; N 21.40.



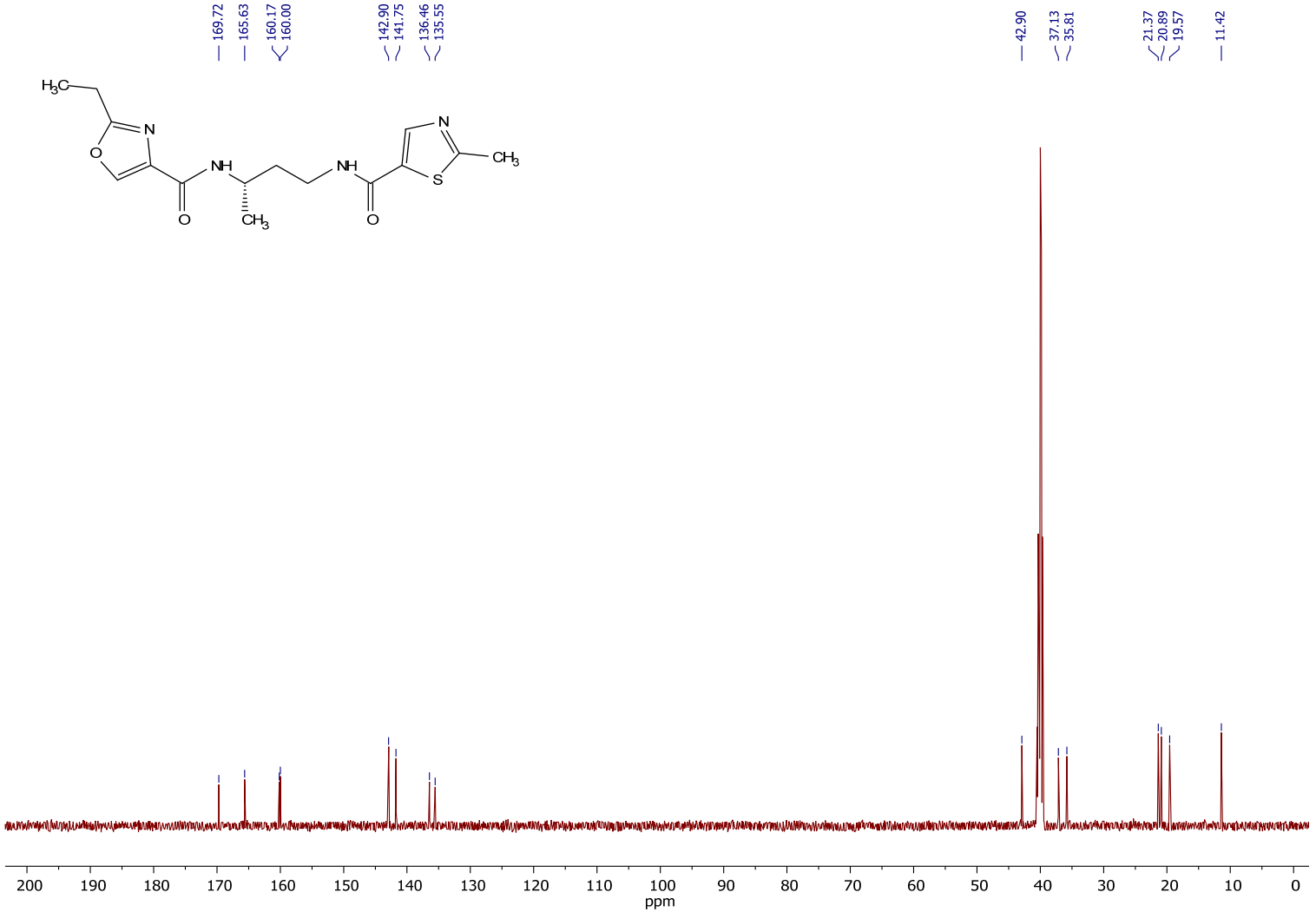
N-(9-Acetyl-9-azabicyclo[3.3.1]nonan-3-yl)-1*H*-indazole-3-carboxamide (**11**{*52*,*55*,*23*}), ^{1}H NMR (500 MHz, DMSO-d_6)



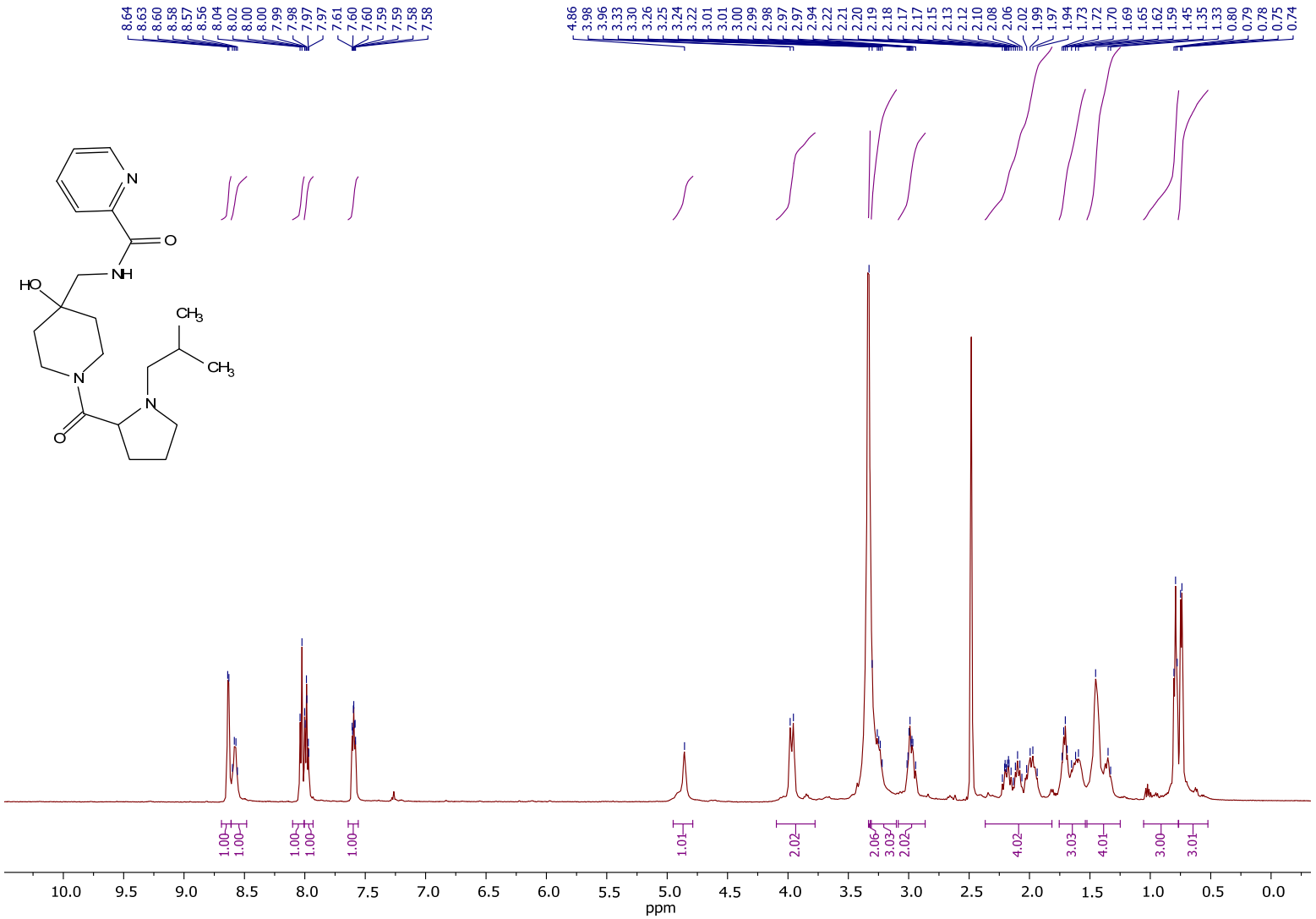
N-(9-Acetyl-9-azabicyclo[3.3.1]nonan-3-yl)-1*H*-indazole-3-carboxamide (**11**{*52*,*55*,*23*}), ^{13}C NMR (126 MHz, DMSO-d_6)



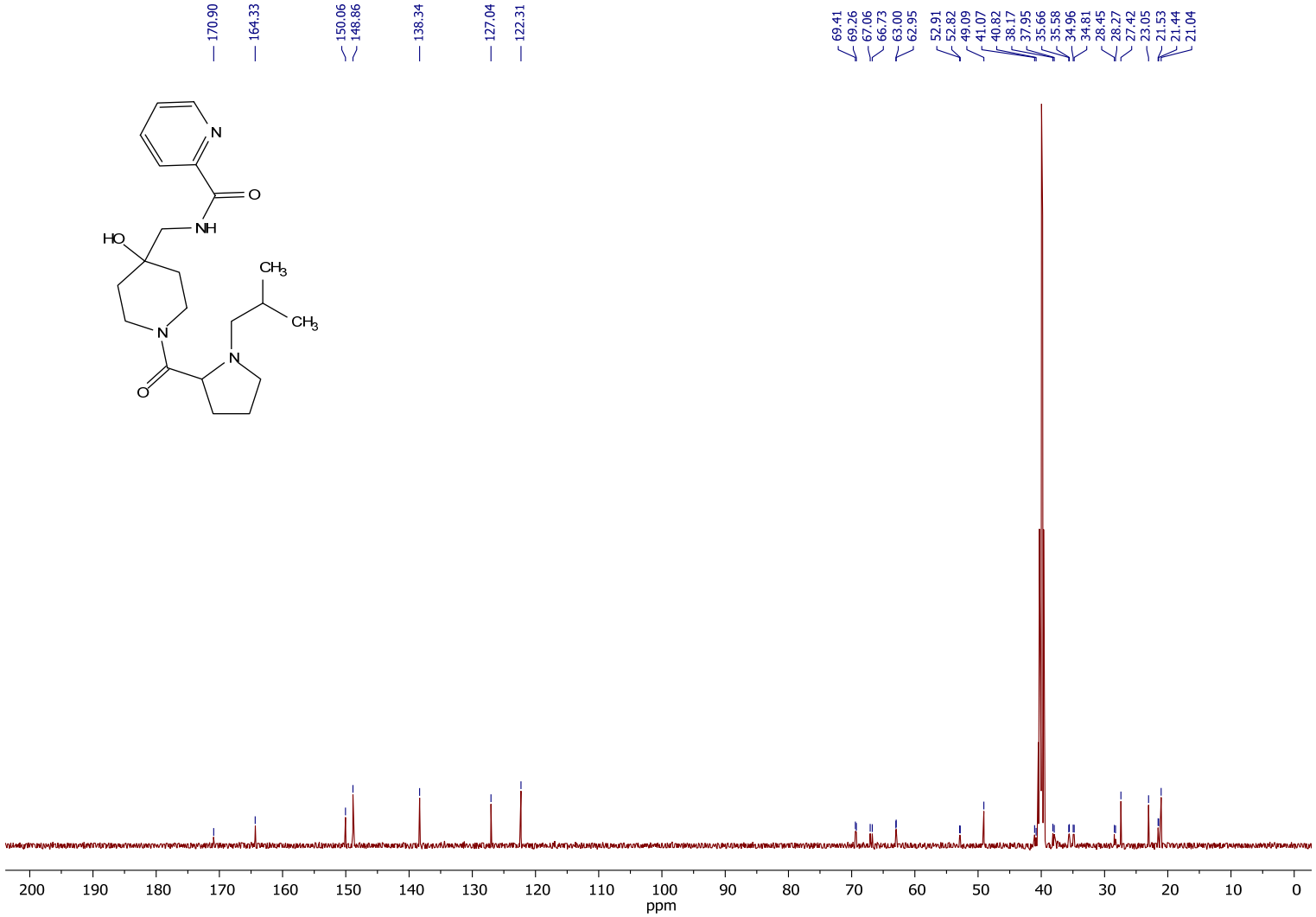
(*S*)-2-Ethyl-*N*-(4-(2-methylthiazole-5-carboxamido)butan-2-yl)oxazole-4-carboxamide (**11**{*25*,*19*,*9*}), ^{1}H NMR (500 MHz, DMSO-d_6)



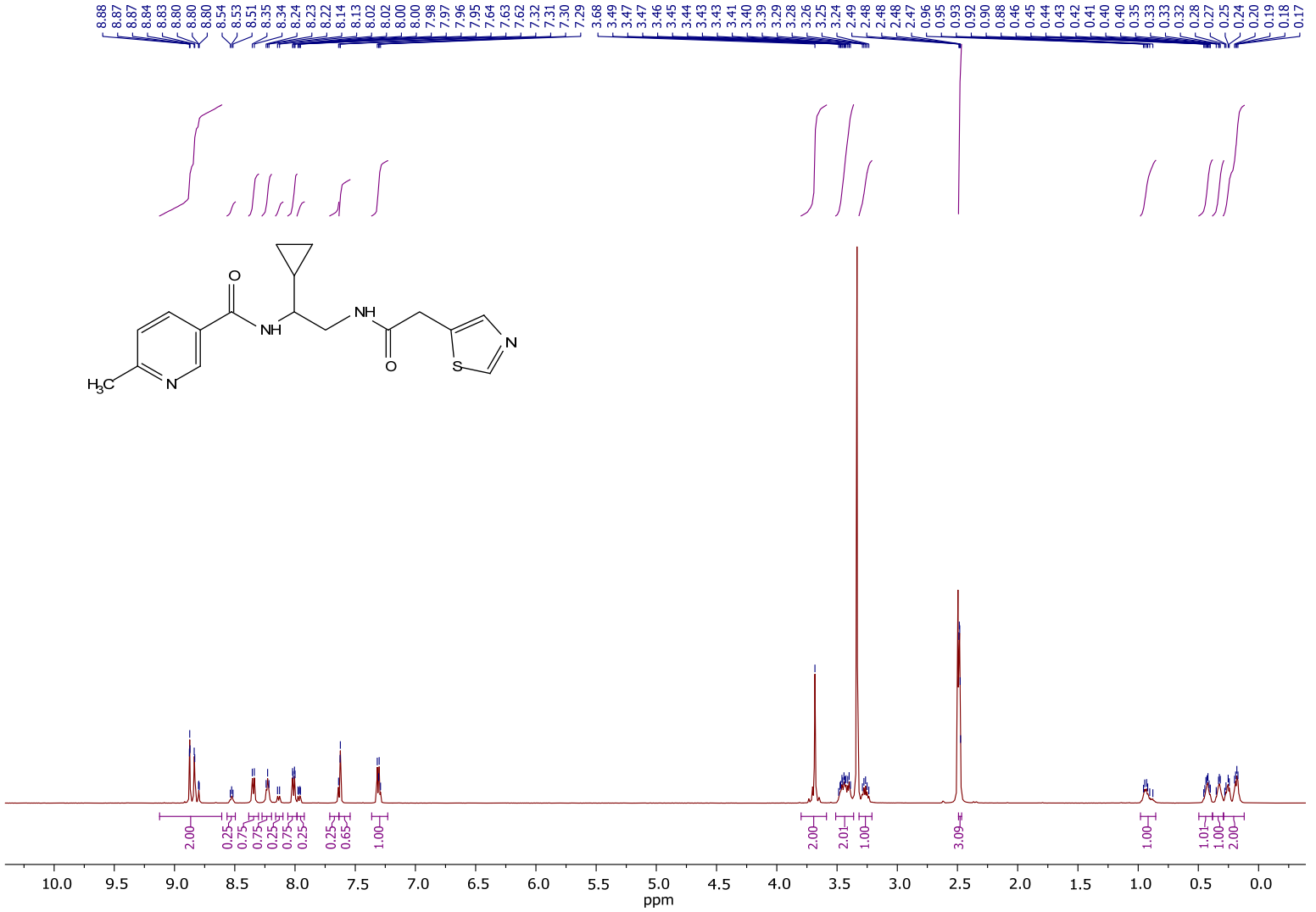
(*S*)-2-Ethyl-*N*-(4-(2-methylthiazole-5-carboxamido)butan-2-yl)oxazole-4-carboxamide (**11**{*25*,*19*,*9*}), ^{13}C NMR (126 MHz, DMSO-d_6)



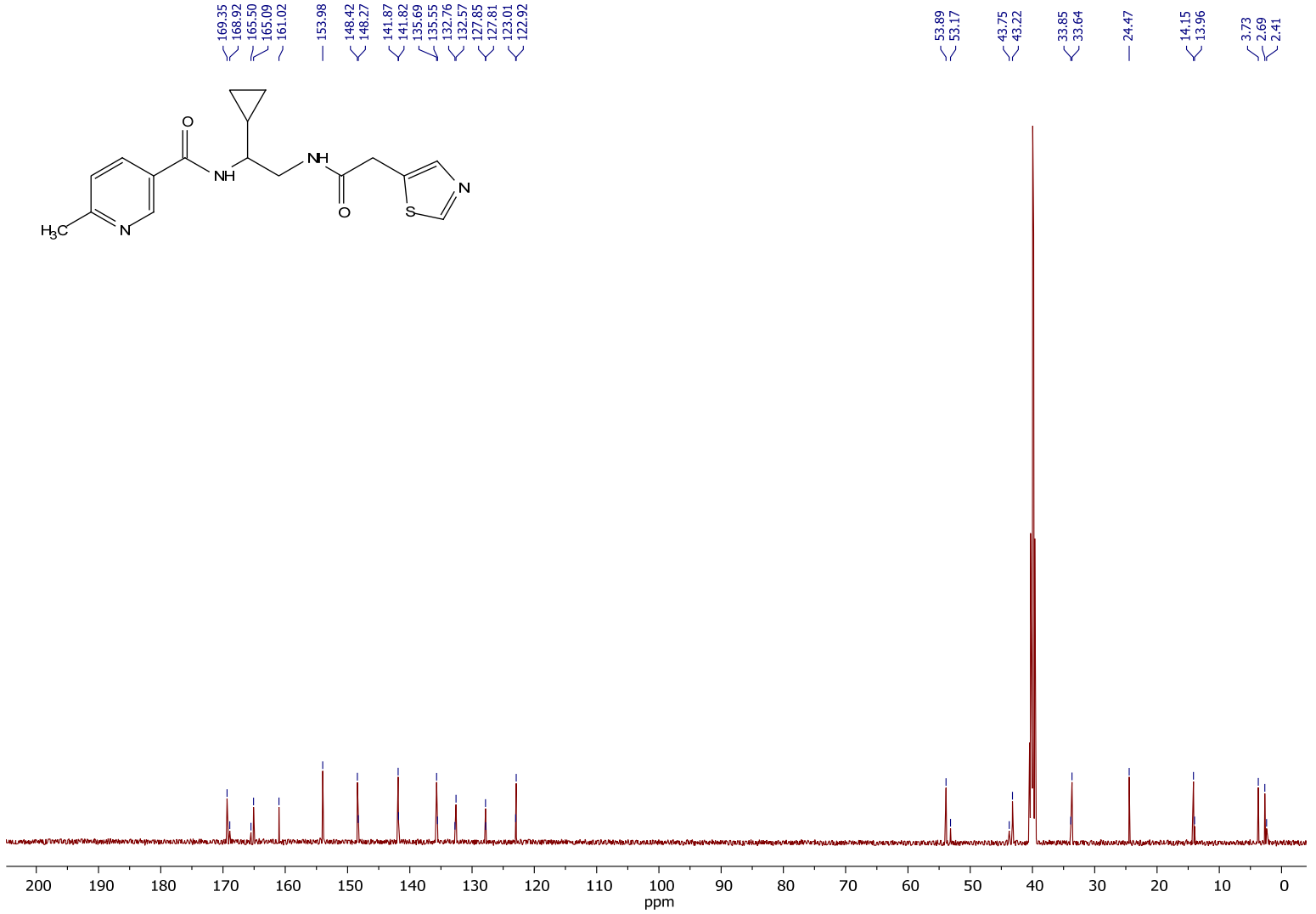
N-((4-Hydroxy-1-(isobutylprolyl)piperidin-4-yl)methyl)picolinamide (**11**{*24*,*21*,*10*}), ^{1}H NMR (500 MHz, DMSO-d_6)



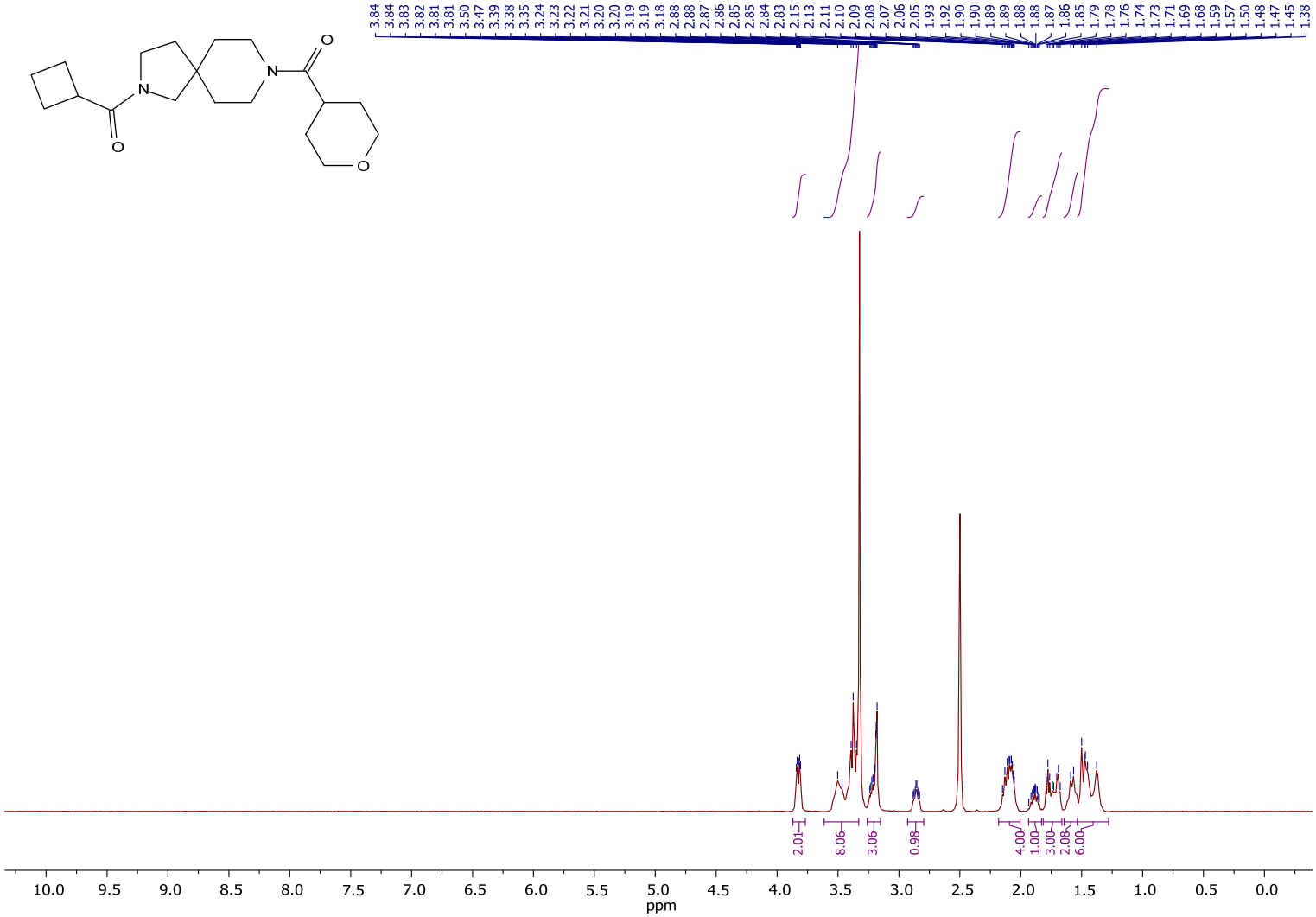
N-((4-Hydroxy-1-(isobutylprolyl)piperidin-4-yl)methyl)picolinamide (**11**{*24*,*21*,*10*}), ^{13}C NMR (126 MHz, DMSO-d_6)



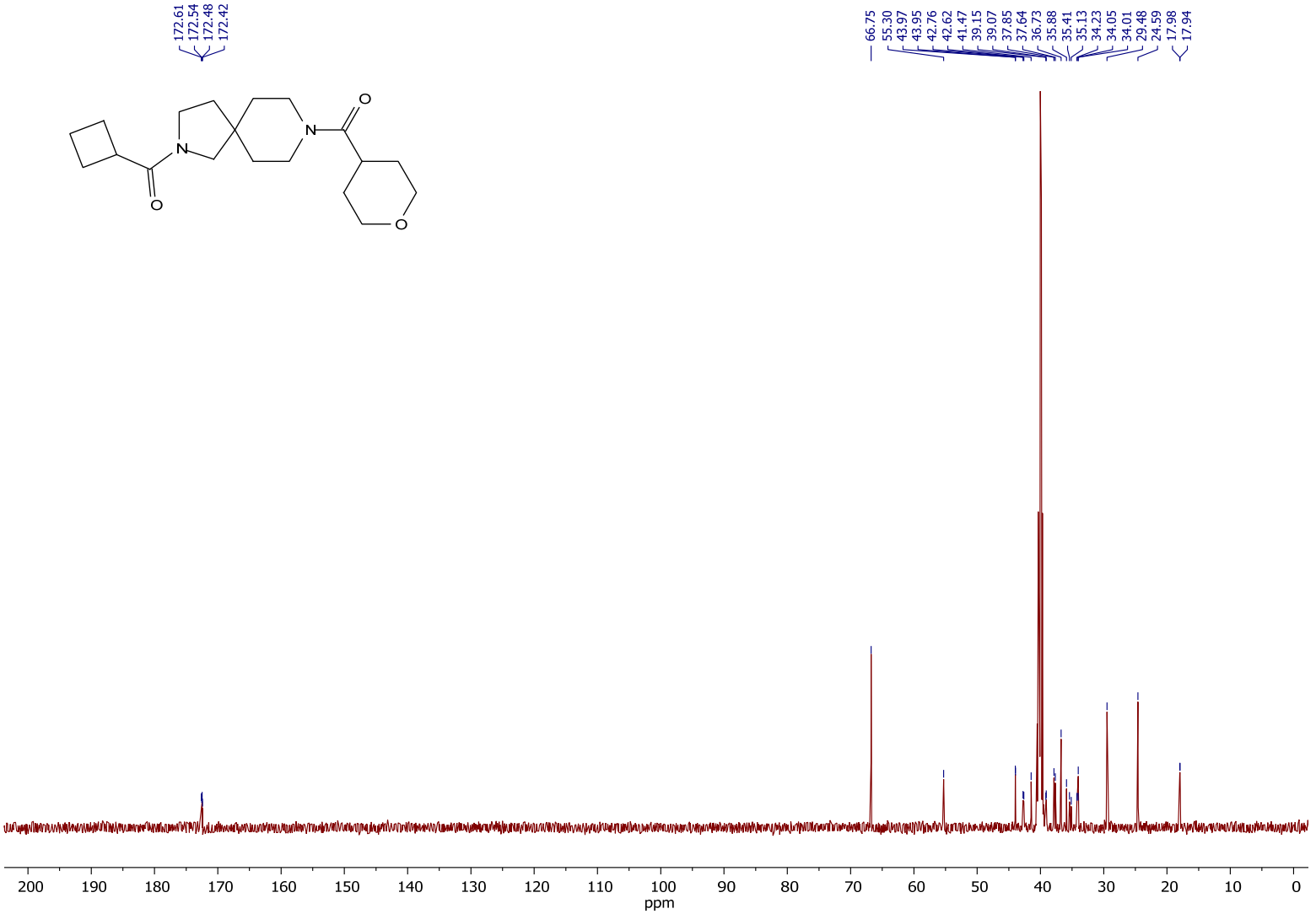
N-(1-Cyclopropyl-2-(2-(thiazol-5-yl)acetamido)ethyl)-6-methylnicotinamide (**11**{*30*,*17*,*13*}), ^{1}H NMR (500 MHz, DMSO-d_6)



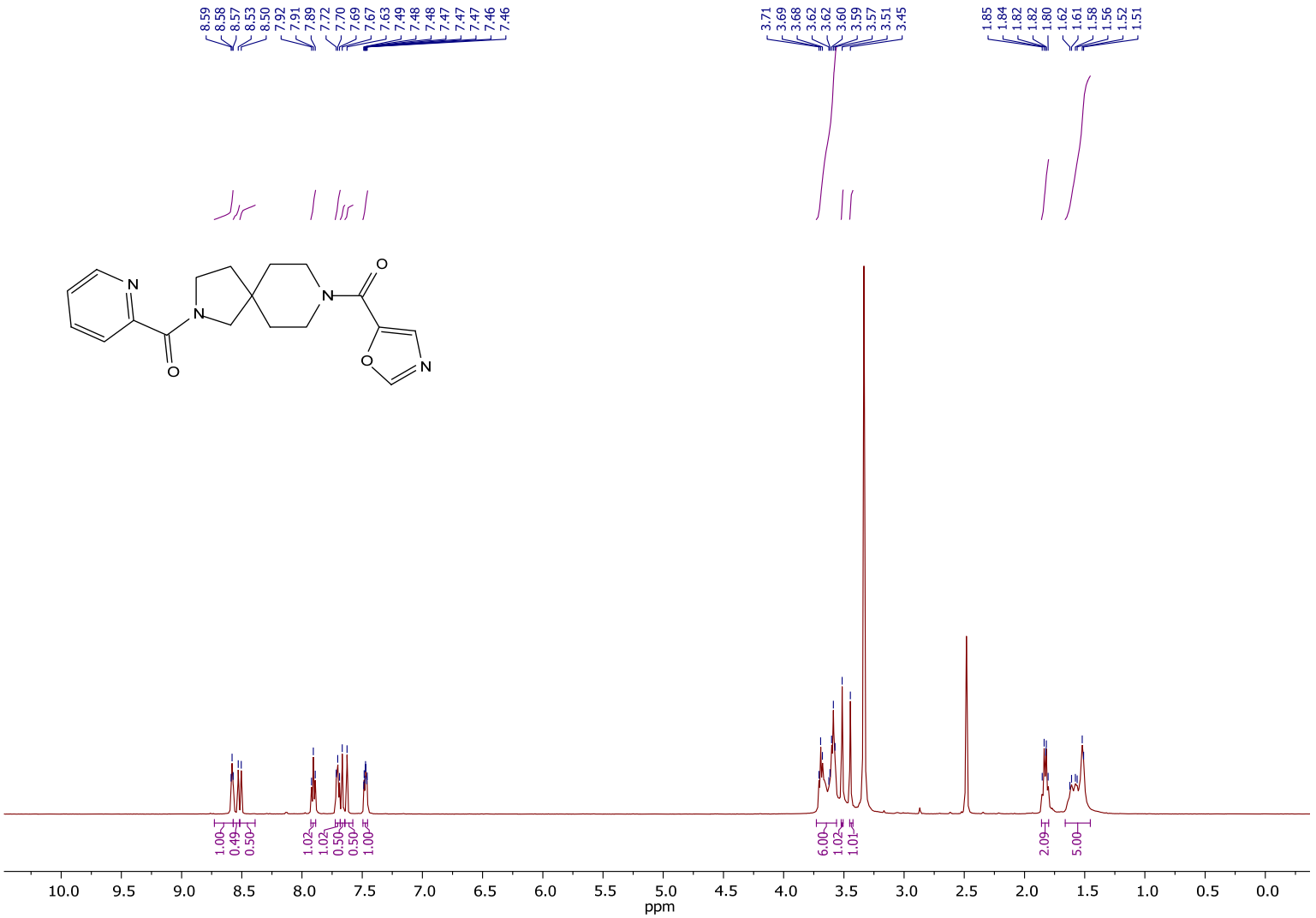
N-(1-Cyclopropyl-2-(2-(thiazol-5-yl)acetamido)ethyl)-6-methylnicotinamide (**11**{*30*,*17*,*13*}), ^{13}C NMR (126 MHz, DMSO-d_6)



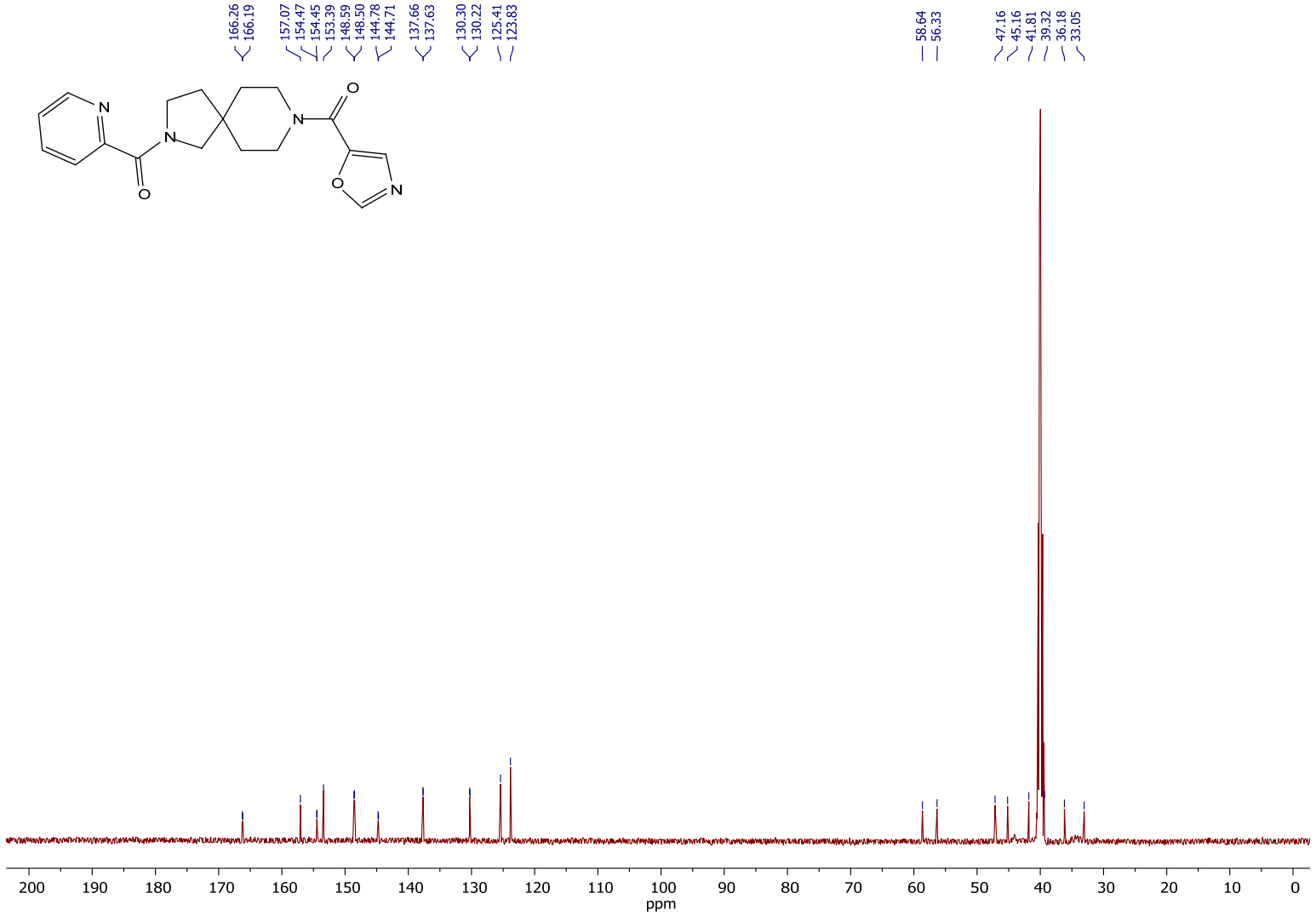
(2-(Cyclobutanecarbonyl)-2,8-diazaspiro[4.5]decan-8-yl)(tetrahydro-2*H*-pyran-4-yl)methanone (**11**{*50*,*64*,*26*}), ^{1}H NMR (500 MHz, DMSO-d_6)



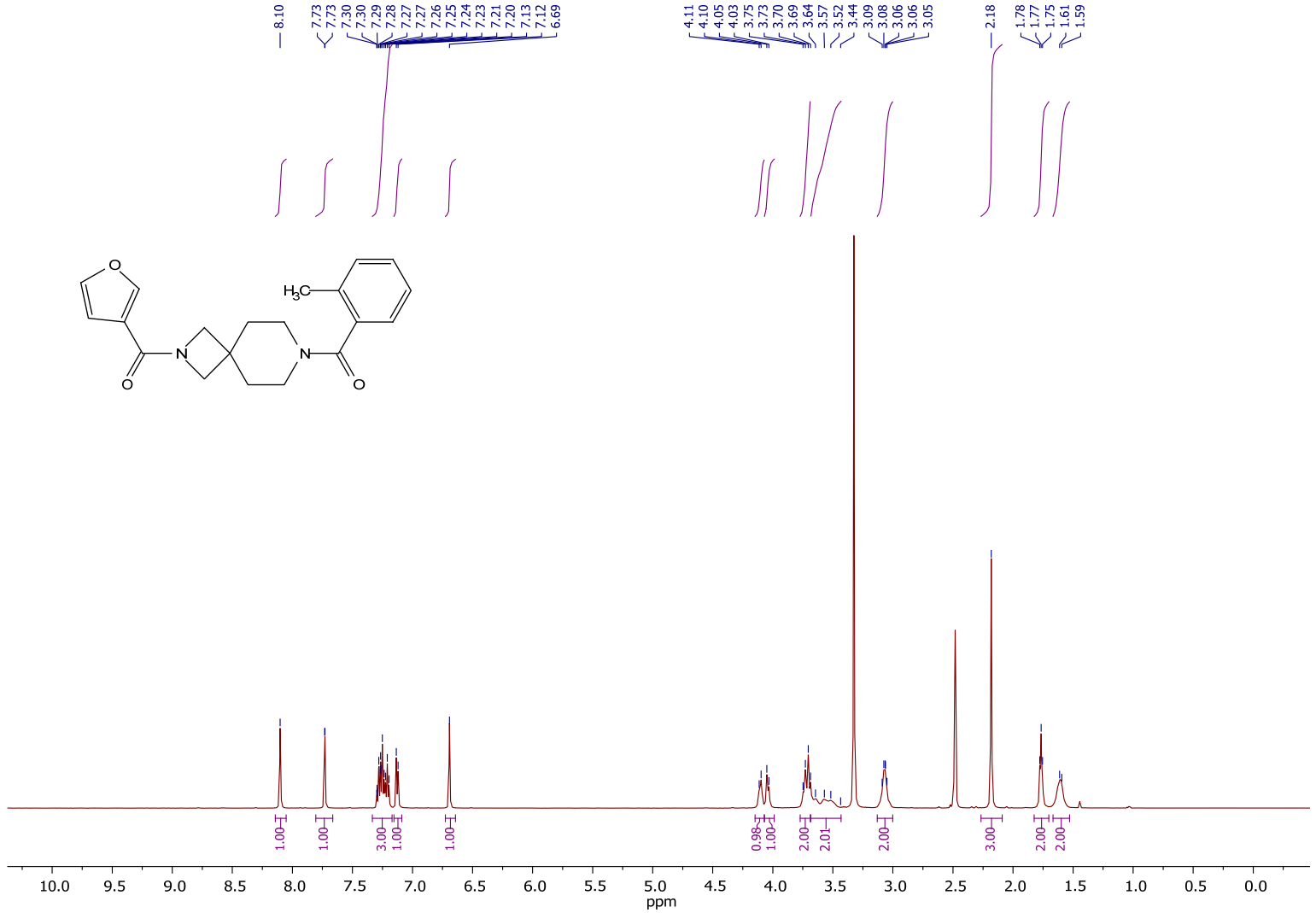
(2-(Cyclobutanecarbonyl)-2,8-diazaspiro[4.5]decan-8-yl)(tetrahydro-2*H*-pyran-4-yl)methanone (**11**{*50*,*64*,*26*}), ^{13}C NMR (126 MHz, DMSO-d_6)



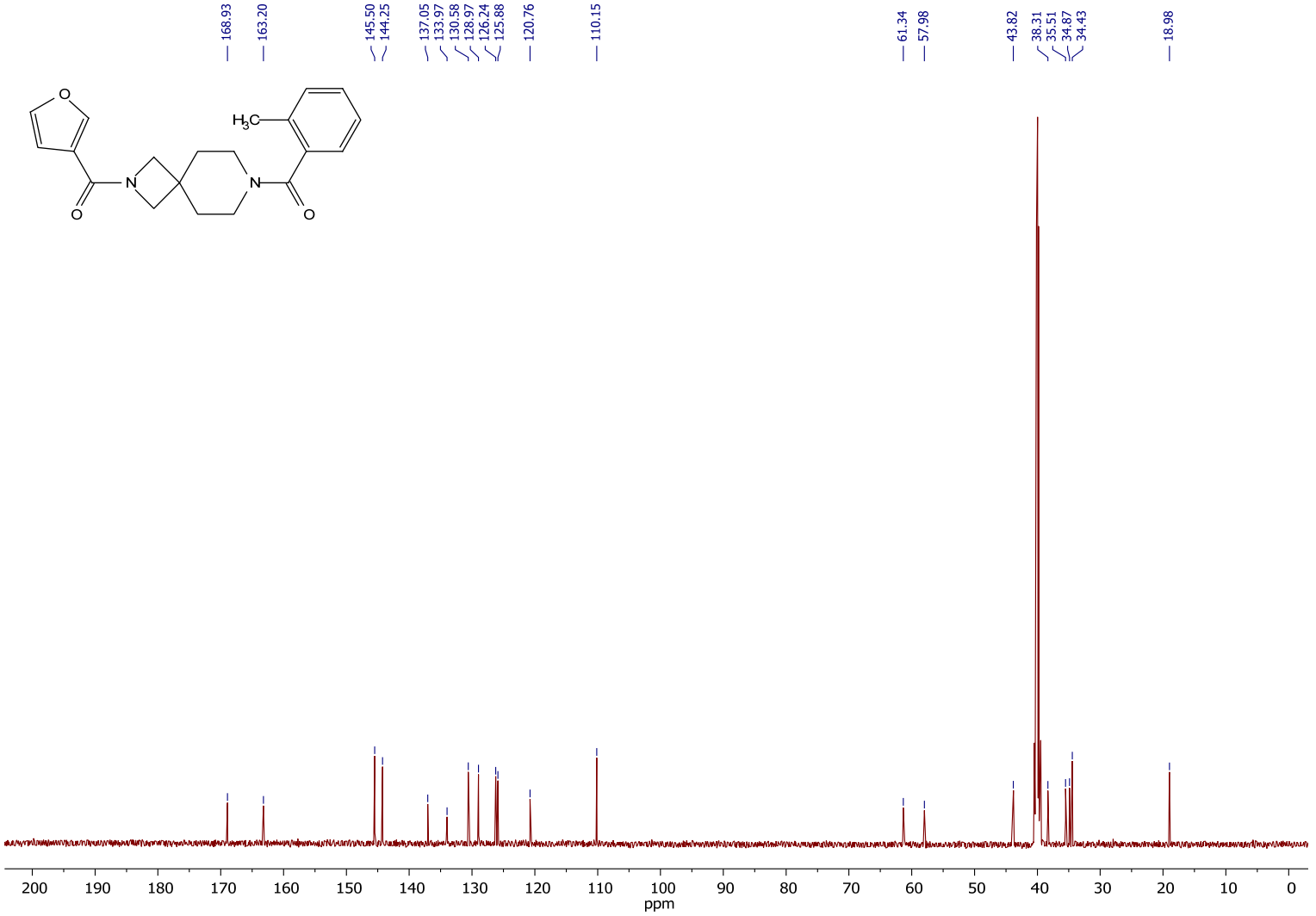
Oxazol-5-yl(2-picolinoyl-2,8-diazaspiro[4.5]decan-8-yl)methanone (**11**{*50*,*69*,*10*}), ^{1}H NMR (500 MHz, DMSO-d_6)



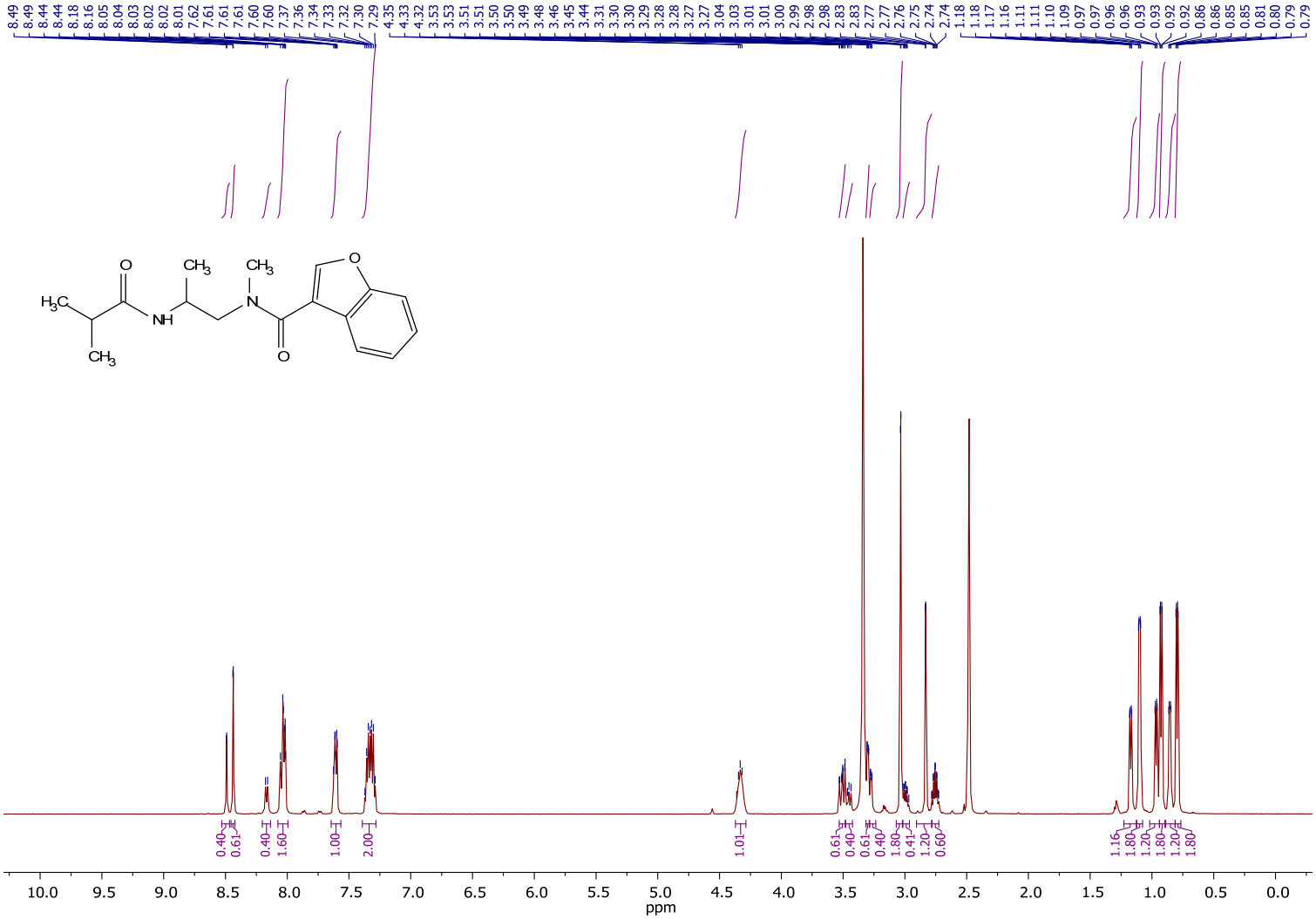
Oxazol-5-yl(2-picolinoyl-2,8-diazaspiro[4.5]decan-8-yl)methanone (**11**{*50*,*69*,*10*}), ^{13}C NMR (126 MHz, DMSO-d_6)



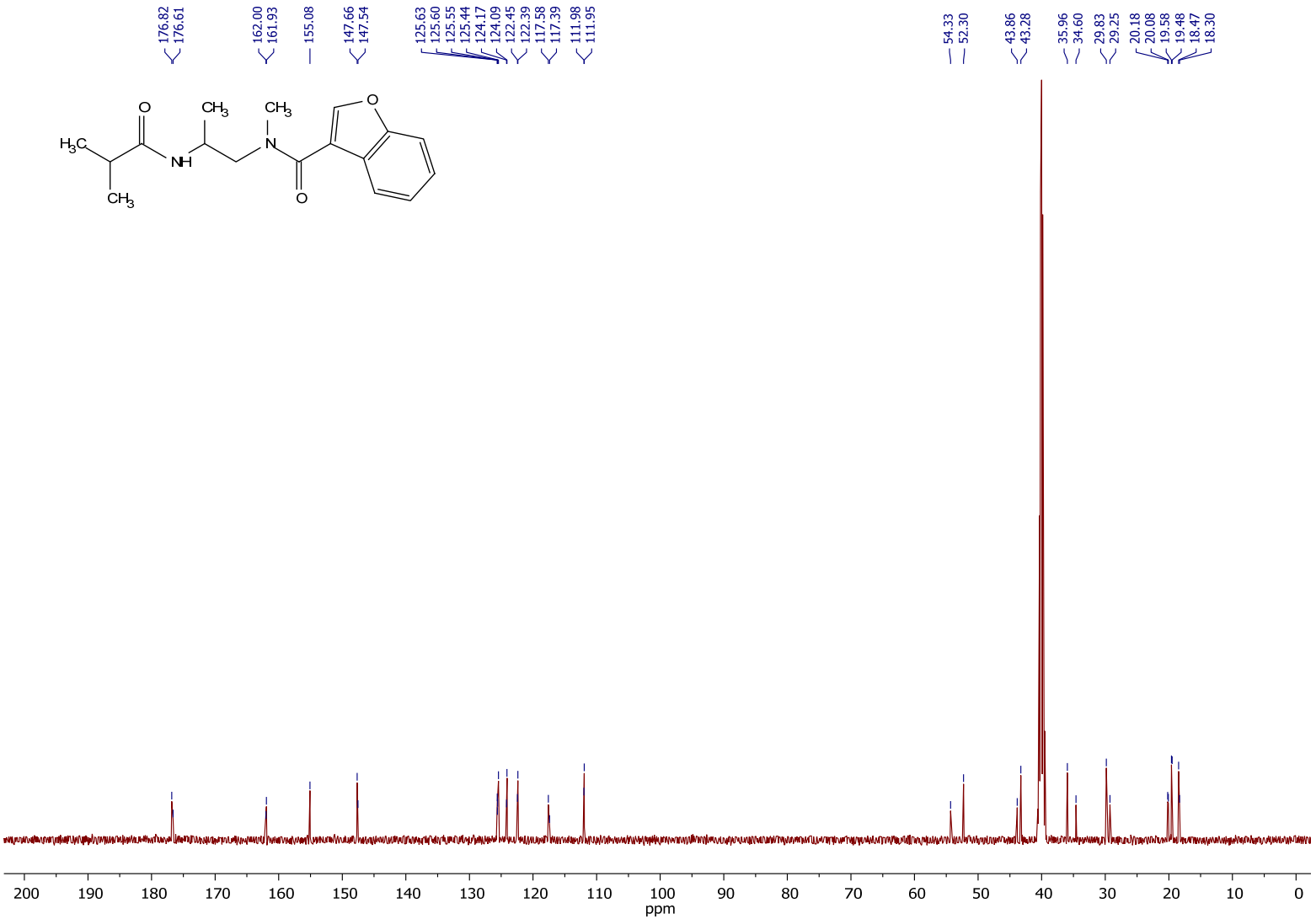
(2-(Furan-3-carbonyl)-2,7-diazaspiro[3.5]nonan-7-yl)(*o*-tolyl)methanone (**11**{*60*,*73*,*32*}), ^{1}H NMR (500 MHz, DMSO-d_6)



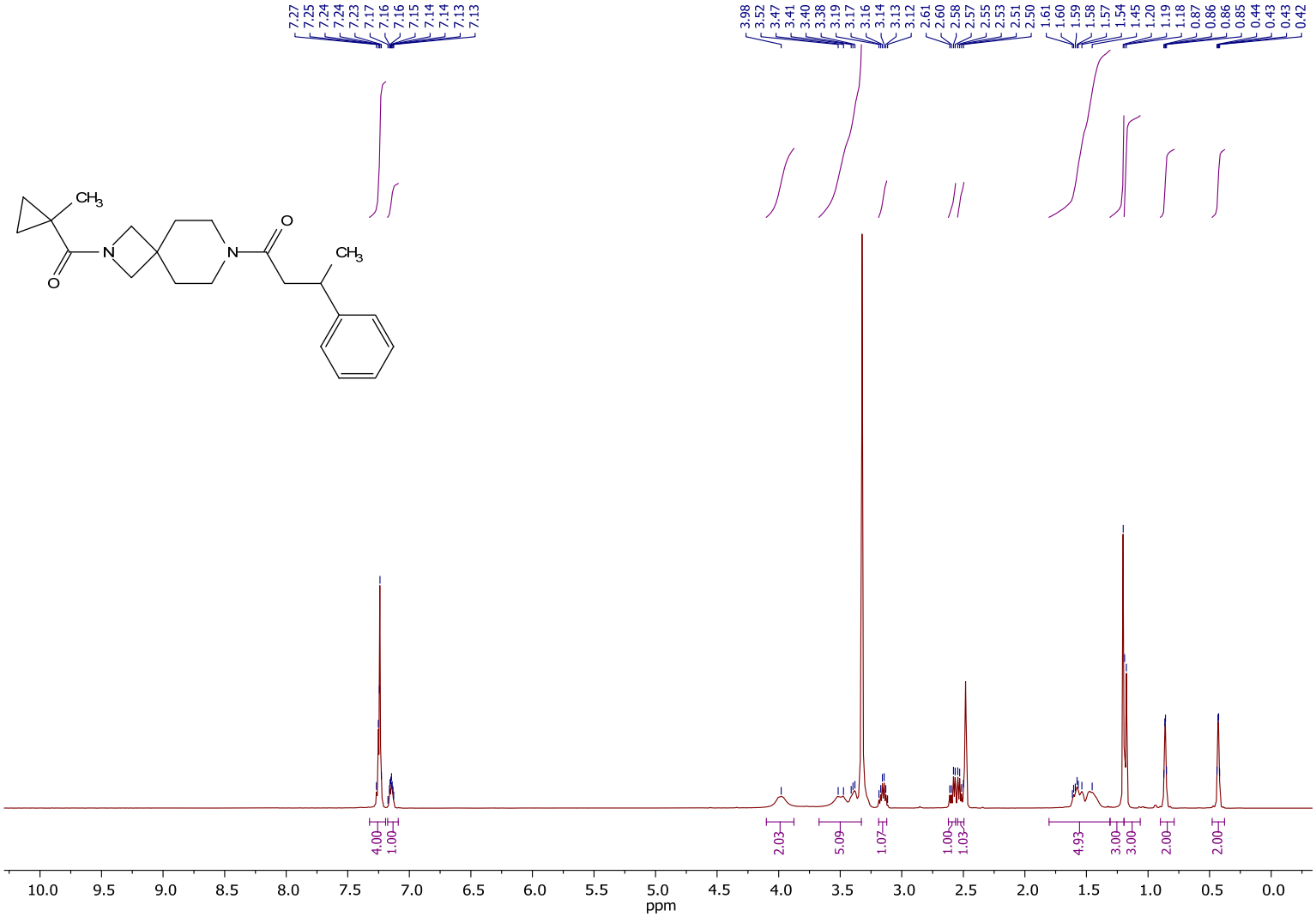
(2-(Furan-3-carbonyl)-2,7-diazaspiro[3.5]nonan-7-yl)(*o*-tolyl)methanone (**11**{*60*,*73*,*32*}), ^{13}C NMR (126 MHz, DMSO-d_6)



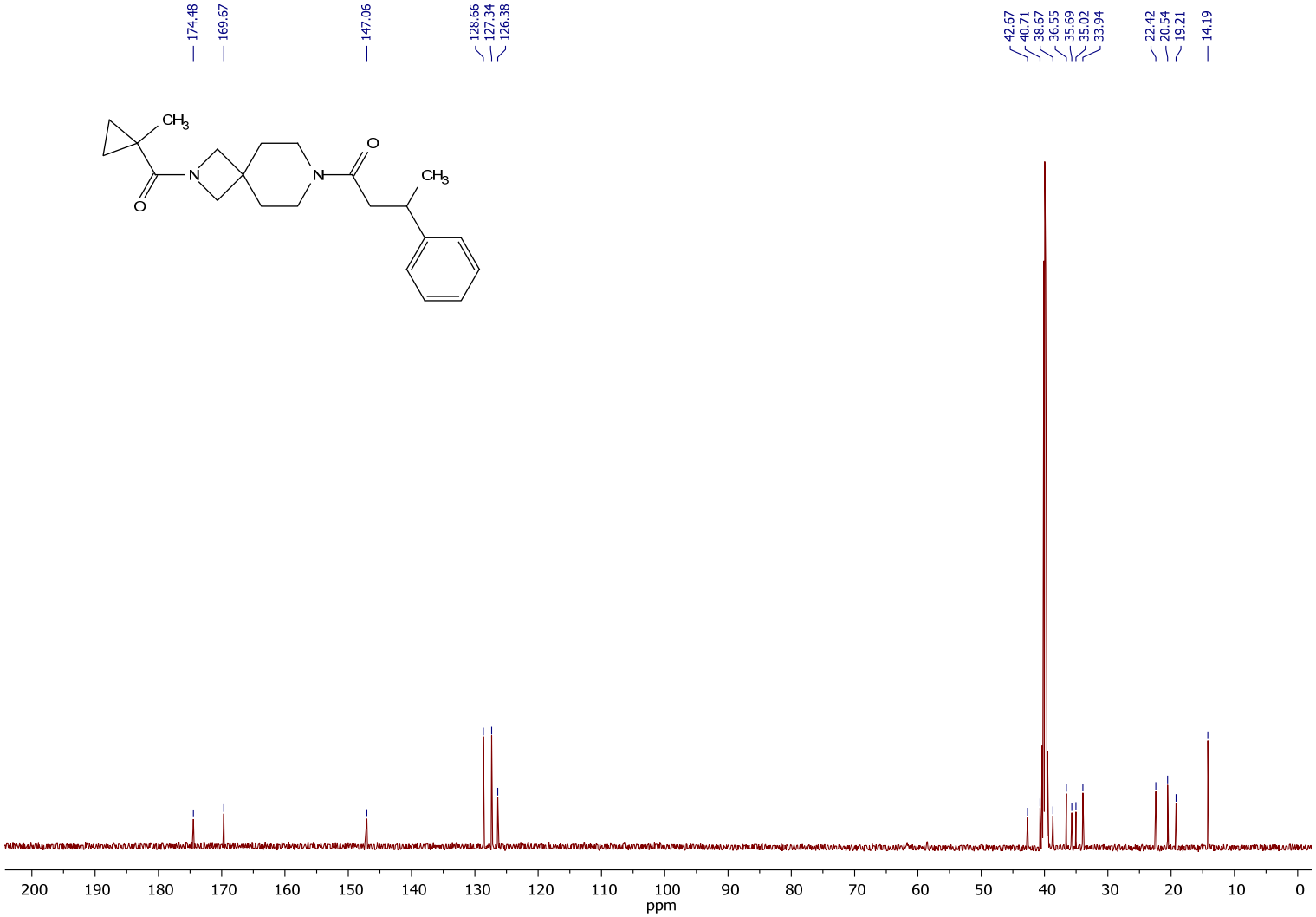
N-(2-Isobutyramidopropyl)-*N*-methylbenzofuran-3-carboxamide (**11**{*67*,*81*,*37*}), ^{1}H NMR (500 MHz, DMSO-d_6)



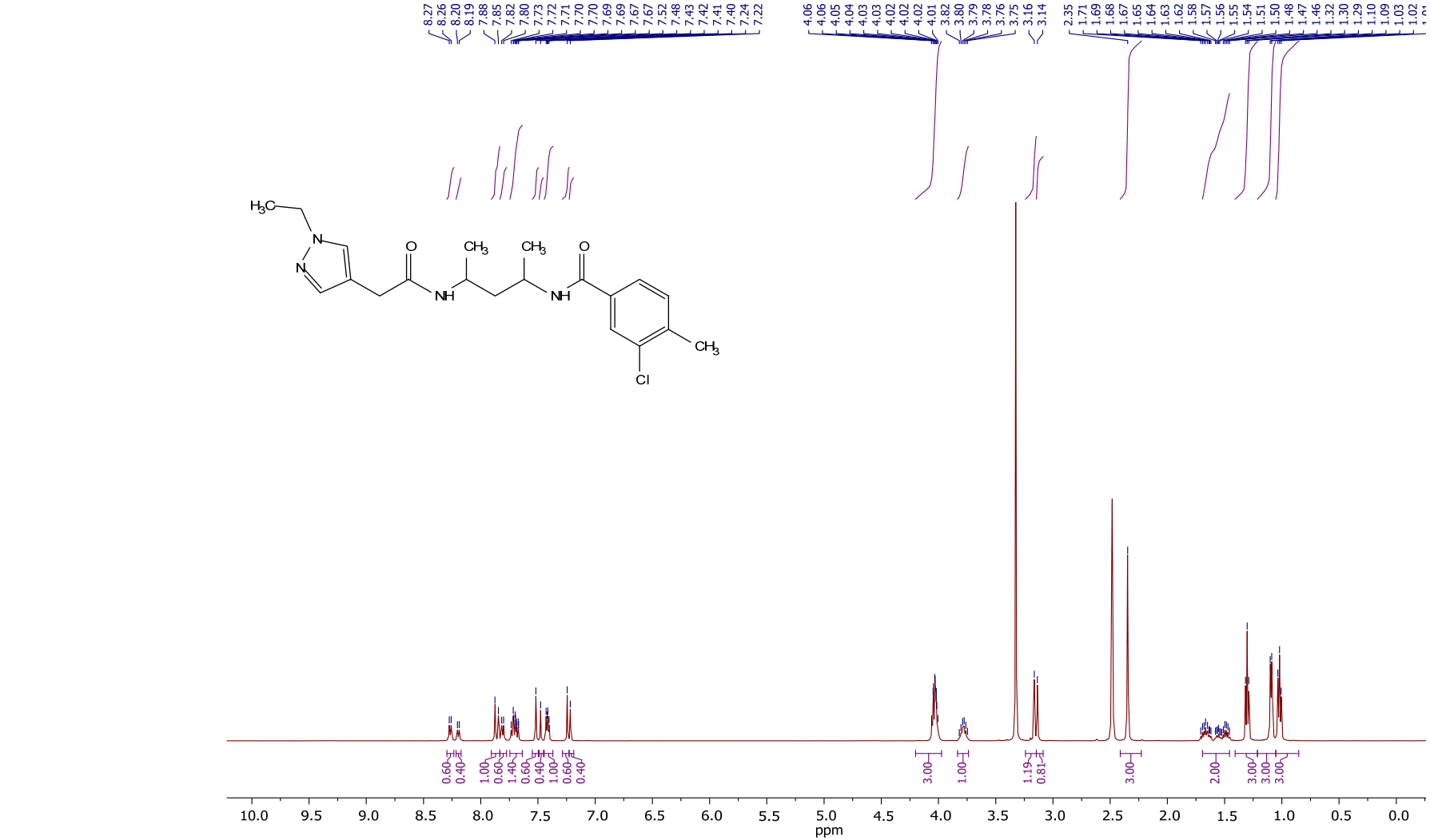
N-(2-Isobutyramidopropyl)-*N*-methylbenzofuran-3-carboxamide (**11**{*67*,*81*,*37*}), ^{13}C NMR (126 MHz, DMSO-d_6)



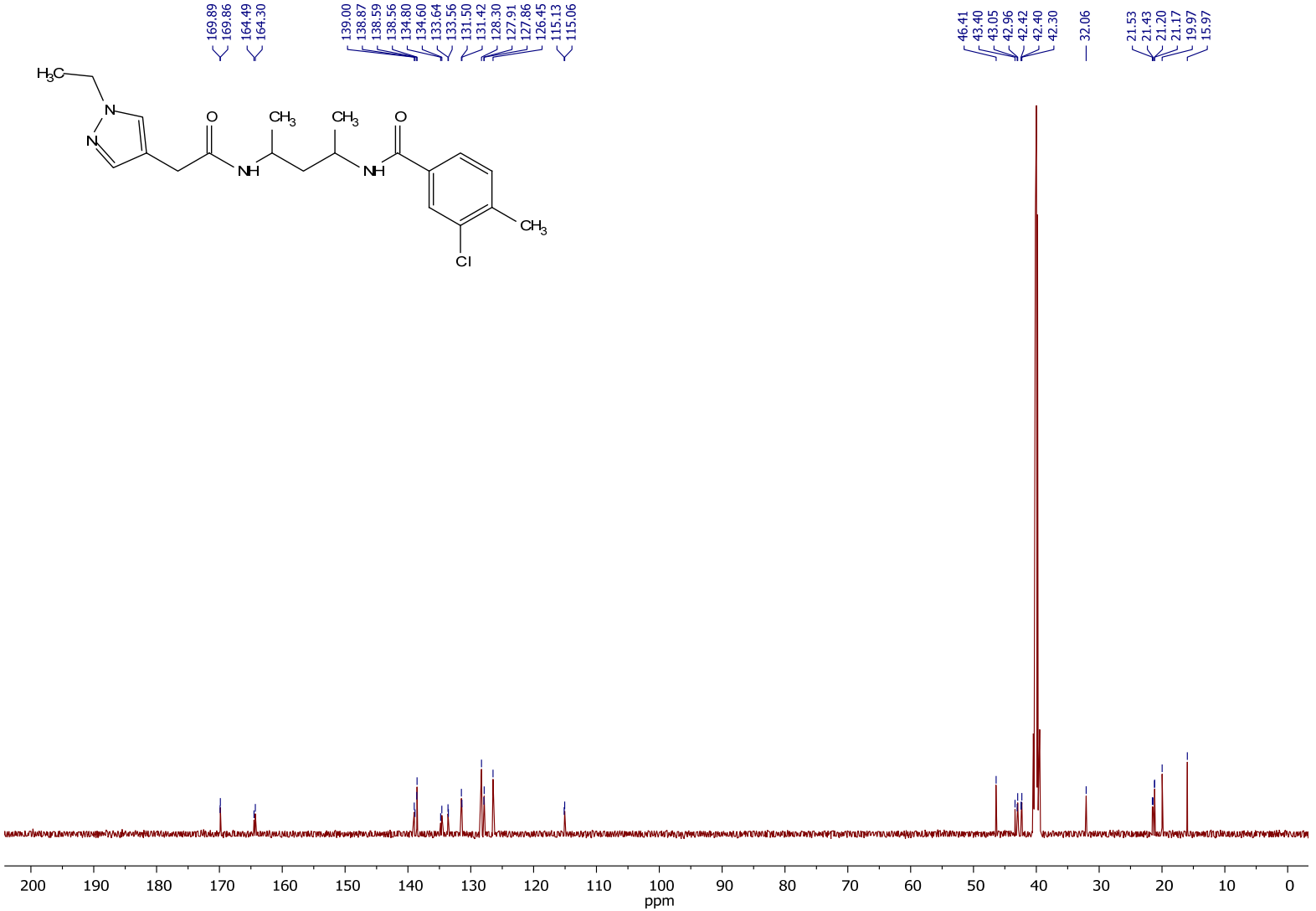
1-(2-(1-Methylcyclopropane-1-carbonyl)-2,7-diazaspiro[3.5]nonan-7-yl)-3-phenylbutan-1-one (**11**{*60*,*102*,*51*}), ^{1}H NMR (500 MHz, DMSO-d_6)



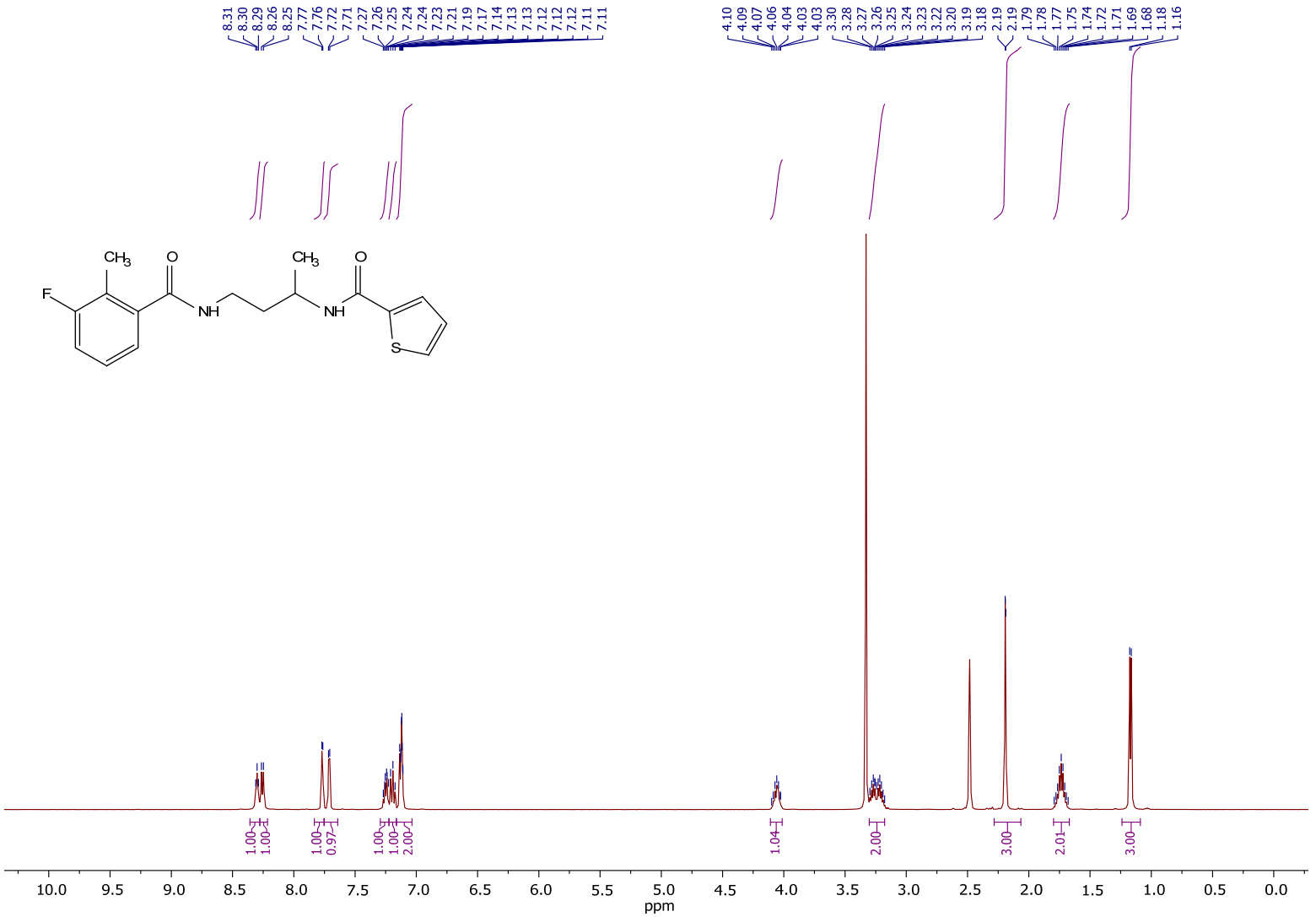
1-(2-(1-Methylcyclopropane-1-carbonyl)-2,7-diazaspiro[3.5]nonan-7-yl)-3-phenylbutan-1-one (**11**{*60*,*102*,*51*}), ^{13}C NMR (151 MHz, DMSO-d_6)



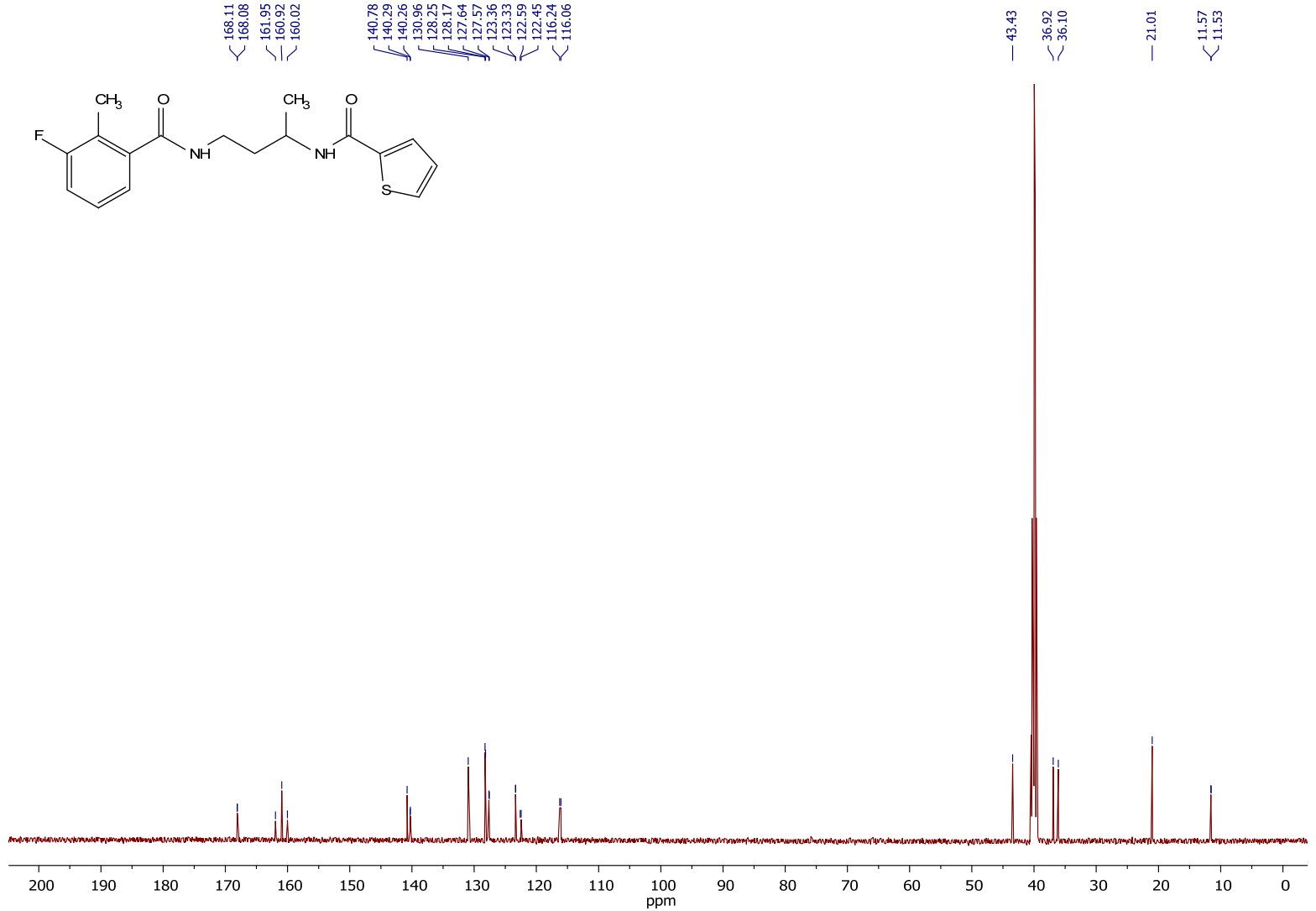
3-Chloro-*N*-(4-(2-(1-ethyl-1*H*-pyrazol-4-yl)acetamido)pentan-2-yl)-4-methylbenzamide (**11**{*70*,*84*,*38*}), ^{1}H NMR (500 MHz, DMSO-d_6)



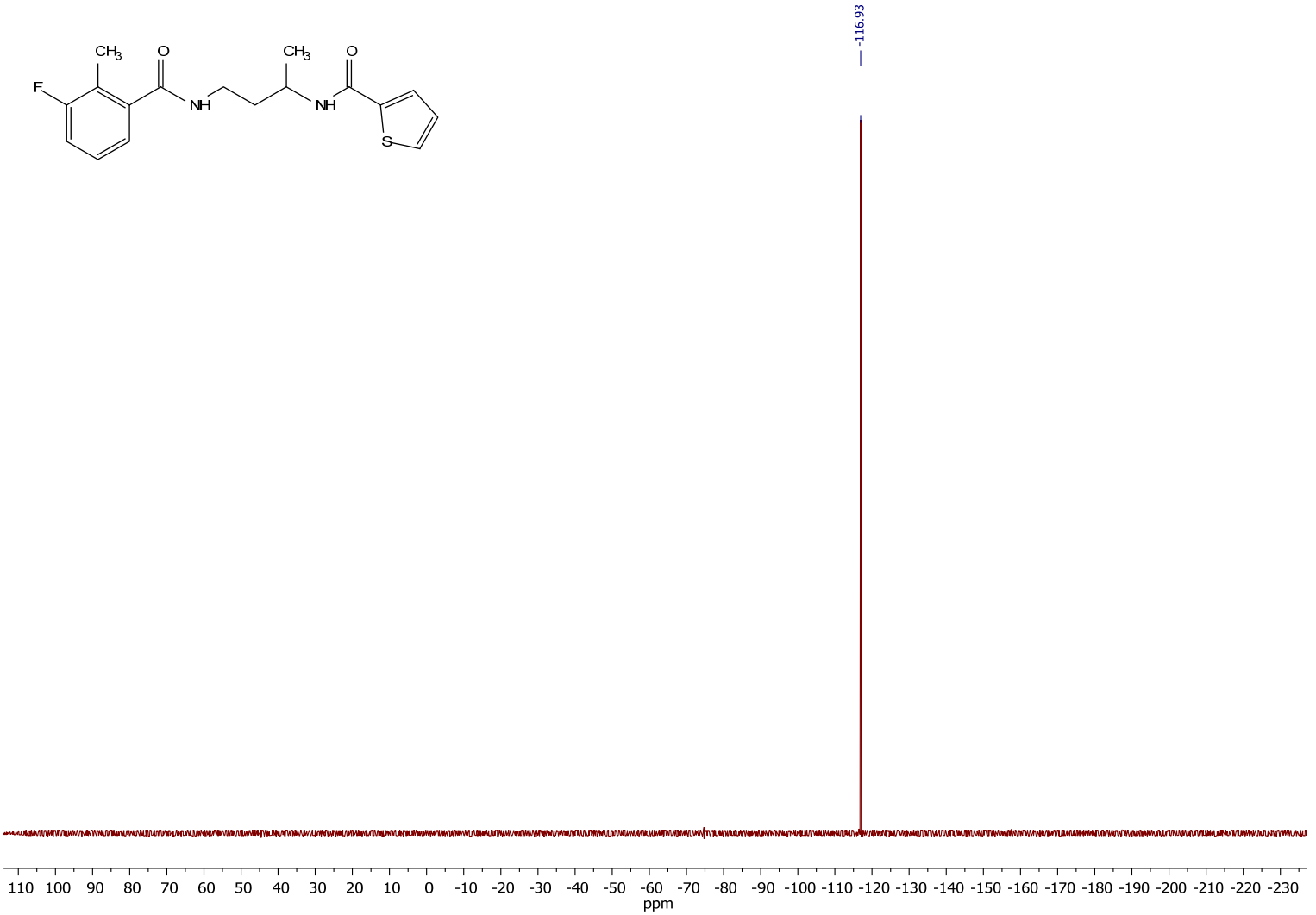
3-Chloro-*N*-(4-(2-(1-ethyl-1*H*-pyrazol-4-yl)acetamido)pentan-2-yl)-4-methylbenzamide (**11**{*70*,*84*,*38*}), ^{13}C NMR (126 MHz, DMSO-d_6



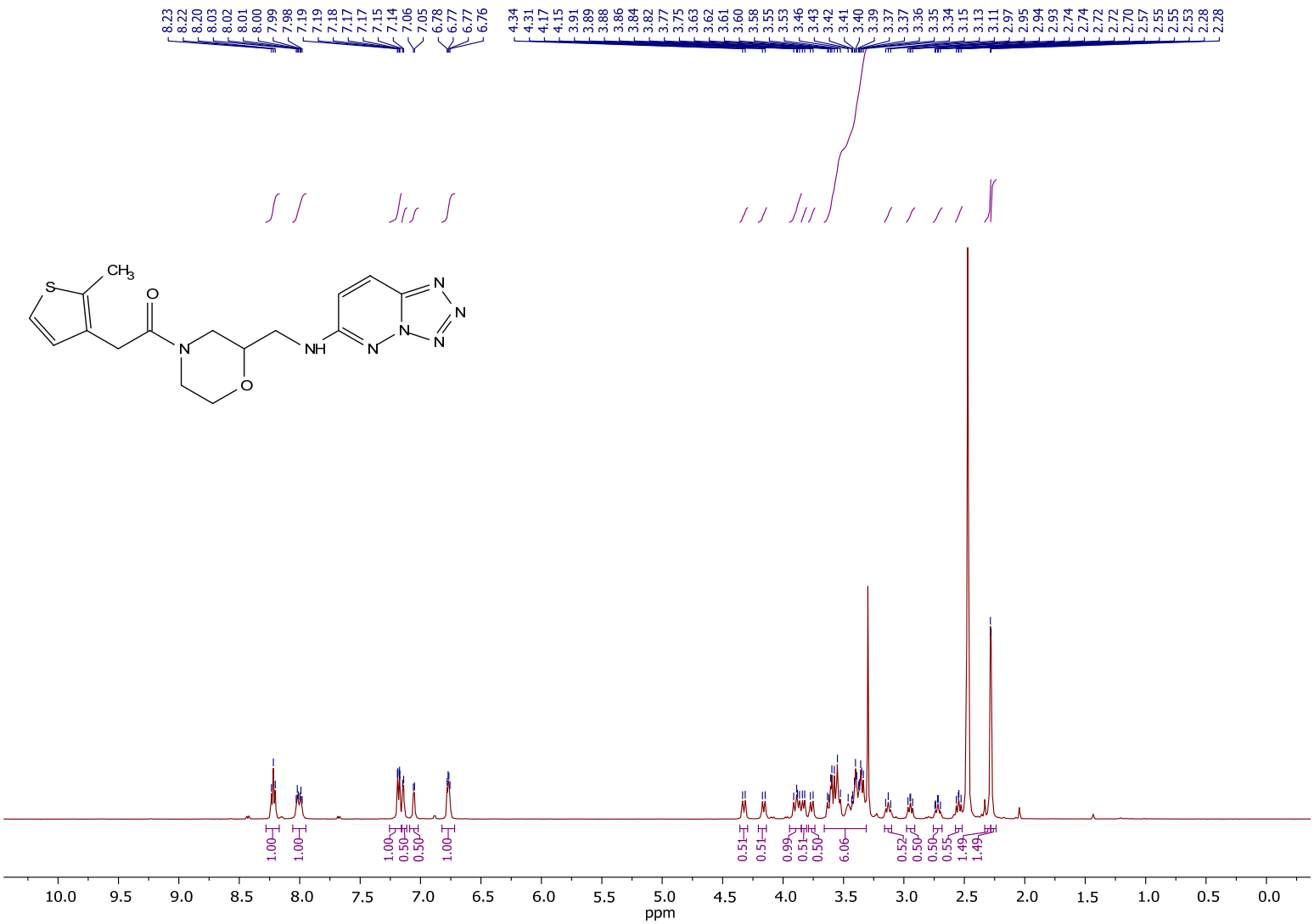
N-(4-(3-Fluoro-2-methylbenzamido)butan-2-yl)thiophene-2-carboxamide (**11**{*83*,*105*,*54*}), ^{1}H NMR (500 MHz, DMSO-d_6)



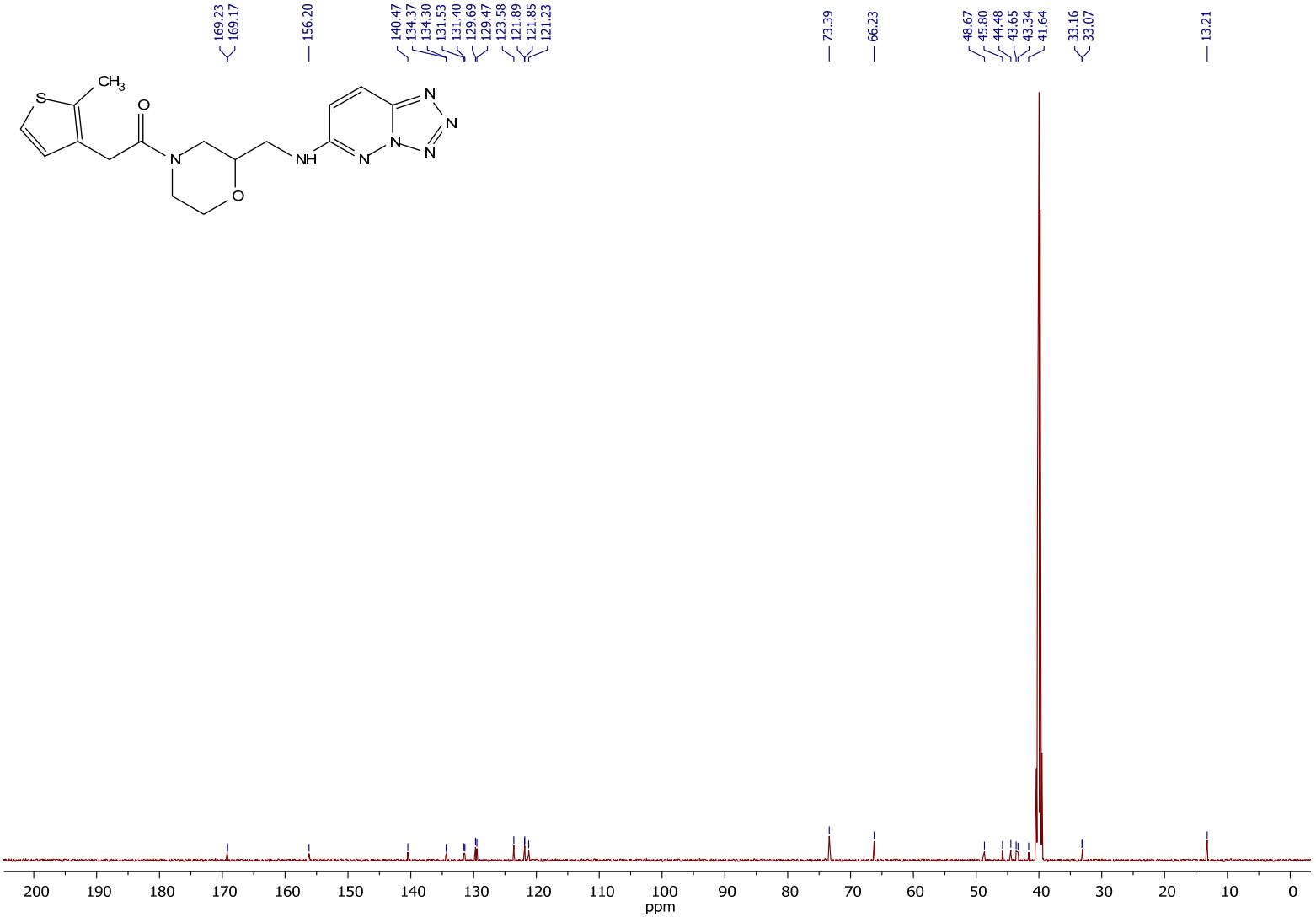
N-(4-(3-Fluoro-2-methylbenzamido)butan-2-yl)thiophene-2-carboxamide (**11**{*83*,*105*,*54*}), ^{13}C NMR (126 MHz, DMSO-d_6)



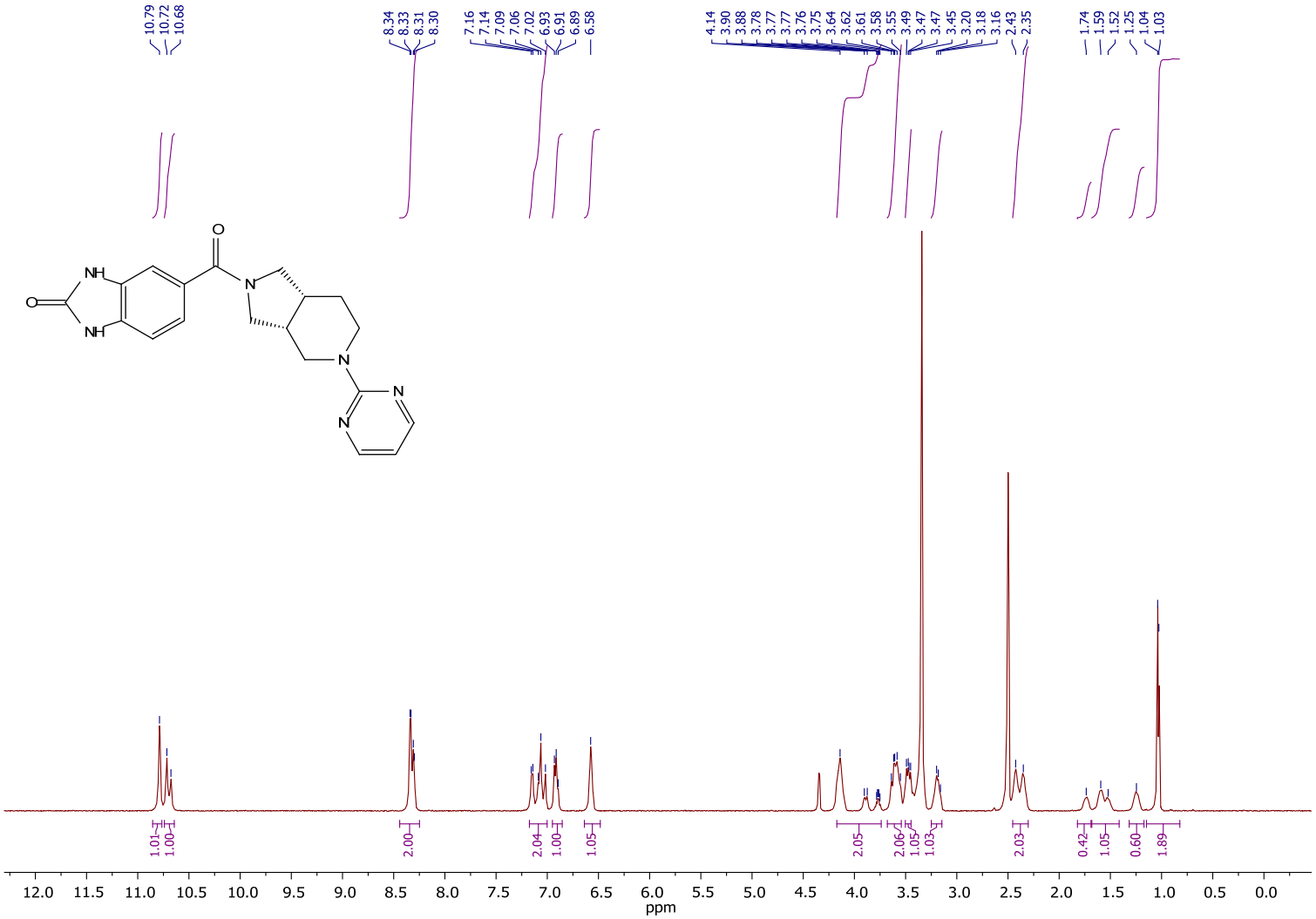
N-(4-(3-Fluoro-2-methylbenzamido)butan-2-yl)thiophene-2-carboxamide (**11**{*83*,*105*,*54*}), ^{19}F NMR (376 MHz, DMSO-d_6)



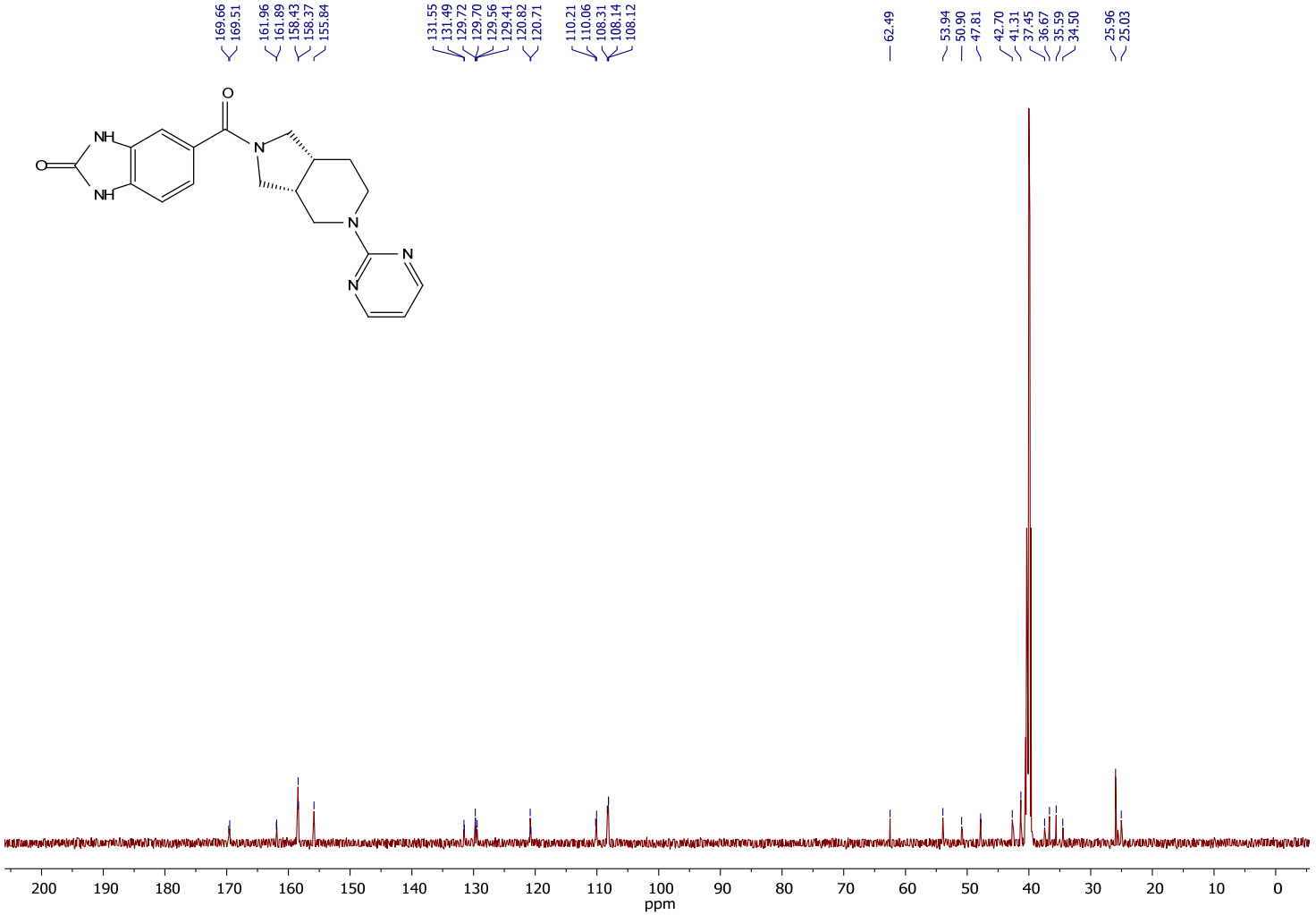
2-(2-Methylthiophen-3-yl)-1-(2-((tetrazolo[1,5-*b*]pyridazin-6-ylamino)methyl)morpholino)ethanone (**12**{*140*,*239*,*35*}), ^{1}H NMR (600 MHz, DMSO-d_6)



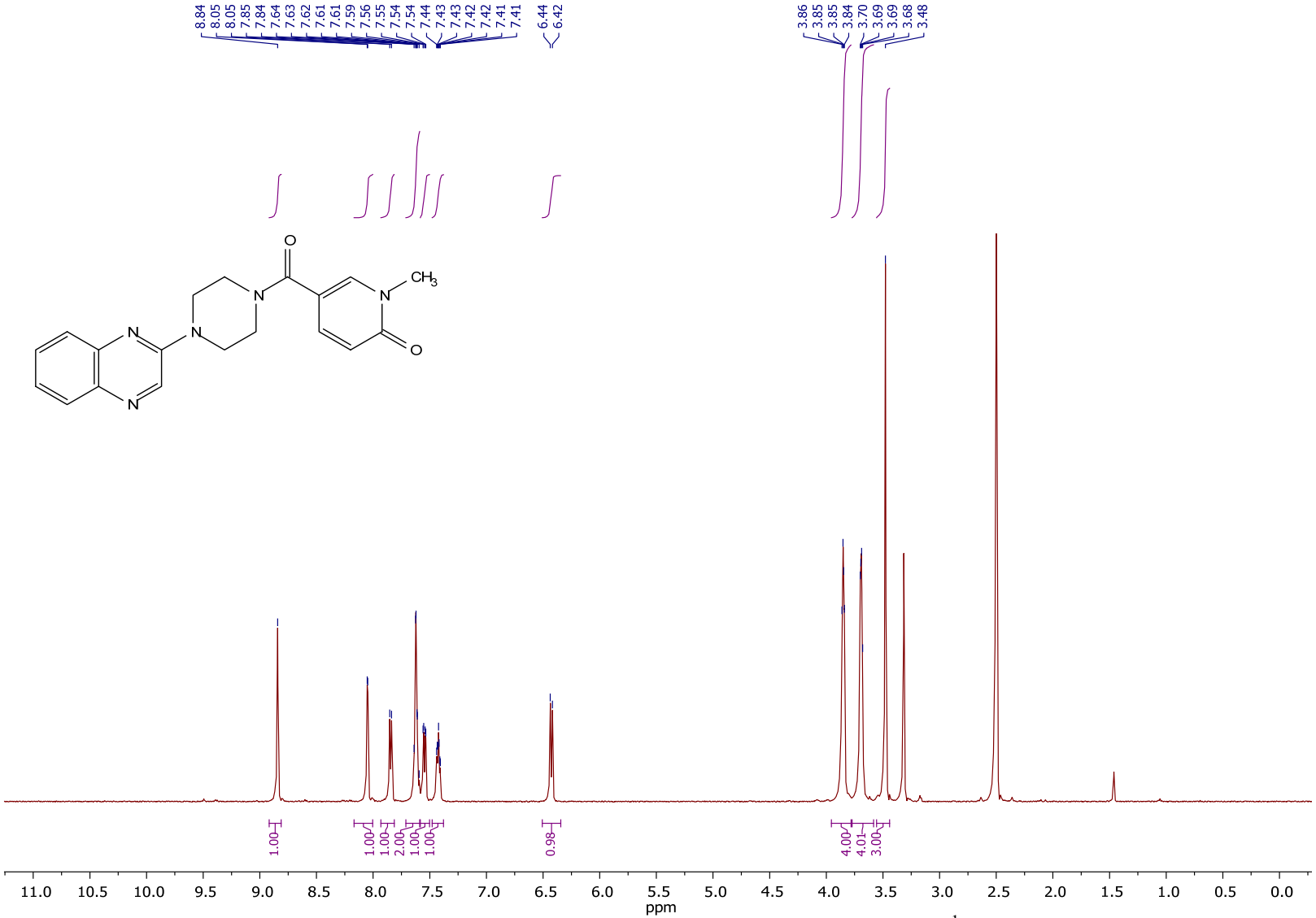
2-(2-Methylthiophen-3-yl)-1-(2-((tetrazolo[1,5-*b*]pyridazin-6-ylamino)methyl)morpholino)ethanone (**12**{*140*,*239*,*35*}), ^{13}C NMR (151 MHz, DMSO-d_6)



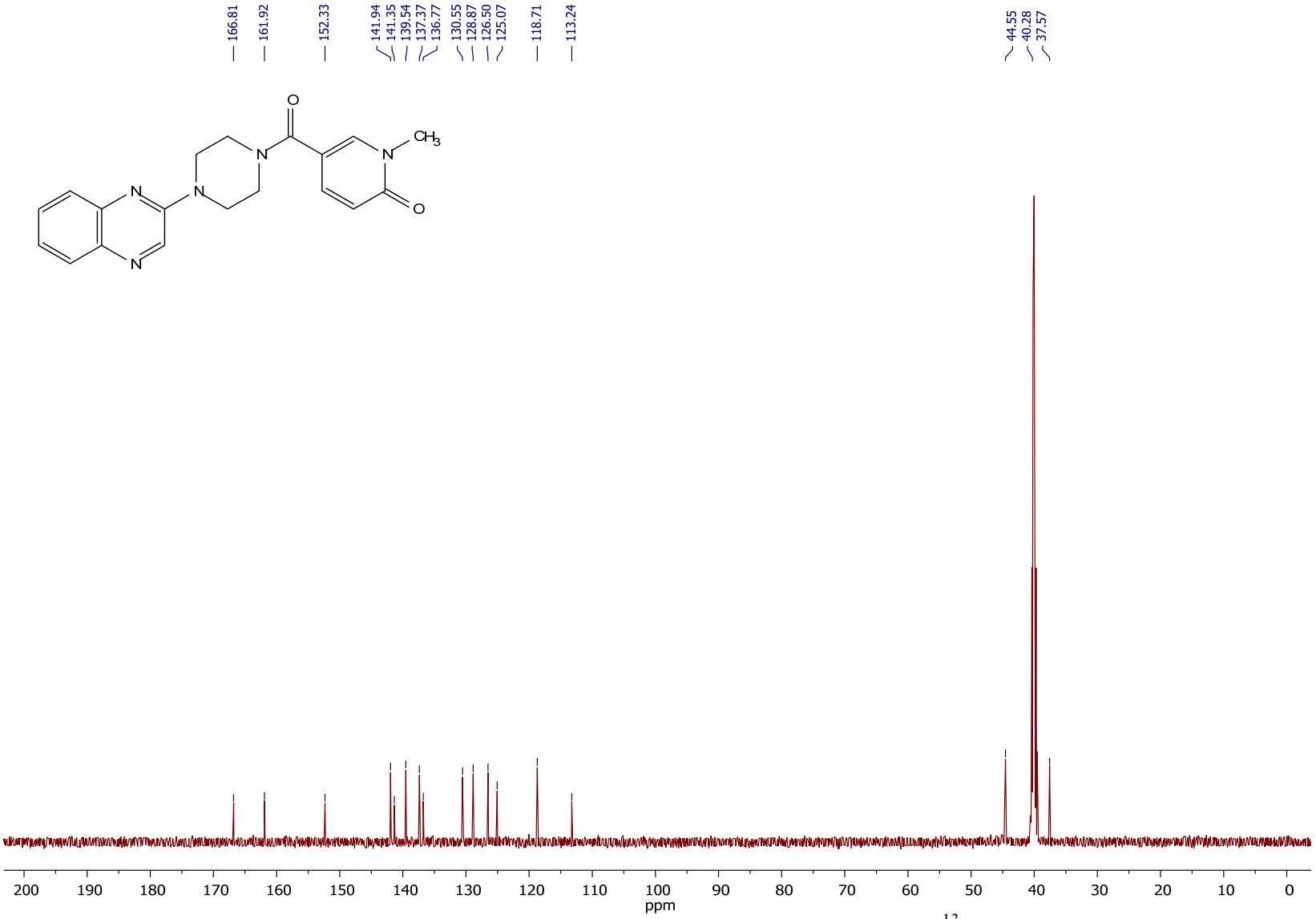
rac-5-((3a*R*,7a*R*)-5-(Pyrimidin-2-yl)octahydro-1*H*-pyrrolo[3,4-*c*]pyridine-2-carbonyl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one (**12**{*17*,*14*,*5*}), ^{1}H NMR (500 MHz, DMSO-d_6)



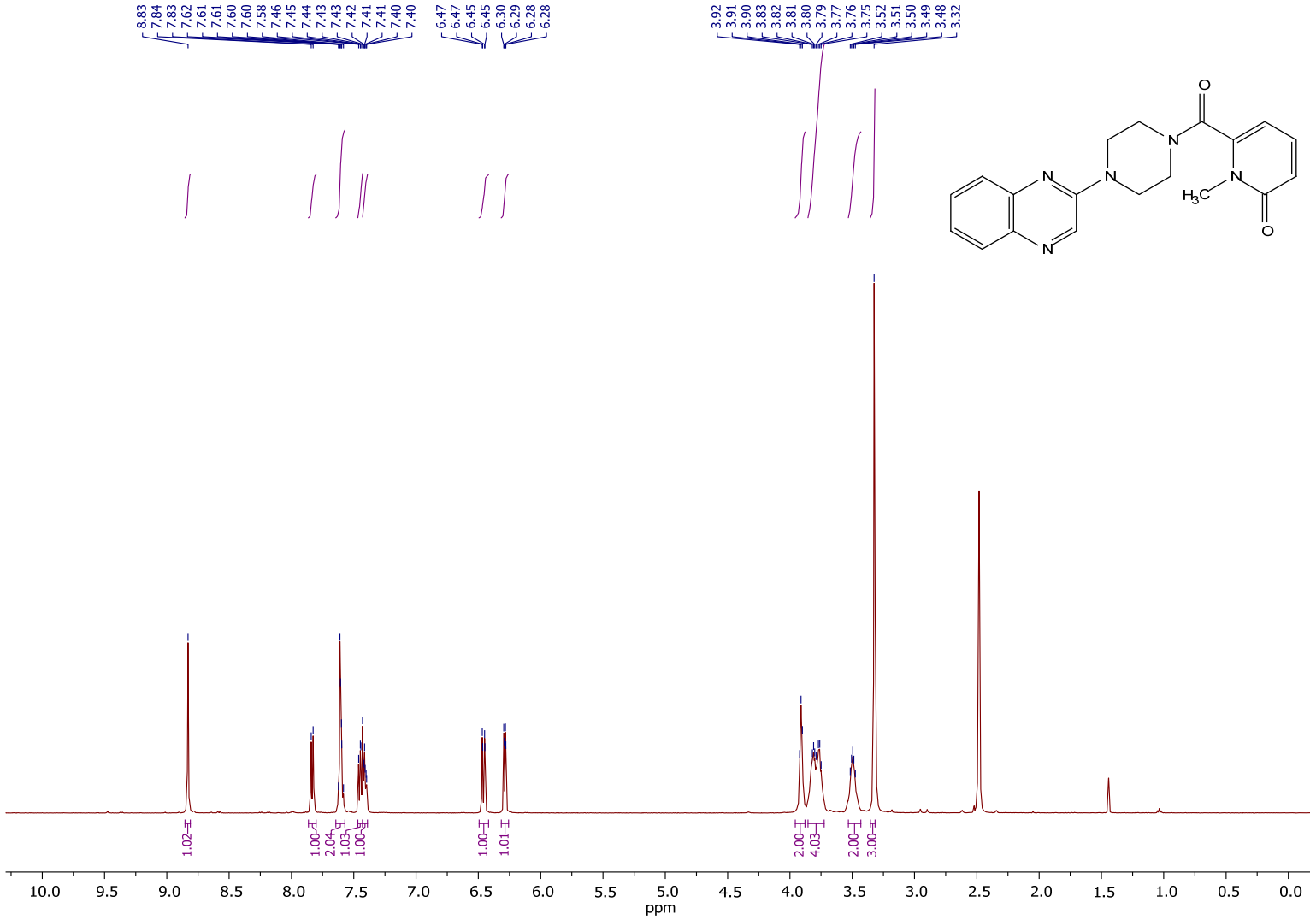
rac-5-((3a*R*,7a*R*)-5-(Pyrimidin-2-yl)octahydro-1*H*-pyrrolo[3,4-*c*]pyridine-2-carbonyl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one (**12**{*17*,*14*,*5*}), ^{13}C NMR (126 MHz, DMSO-d_6)



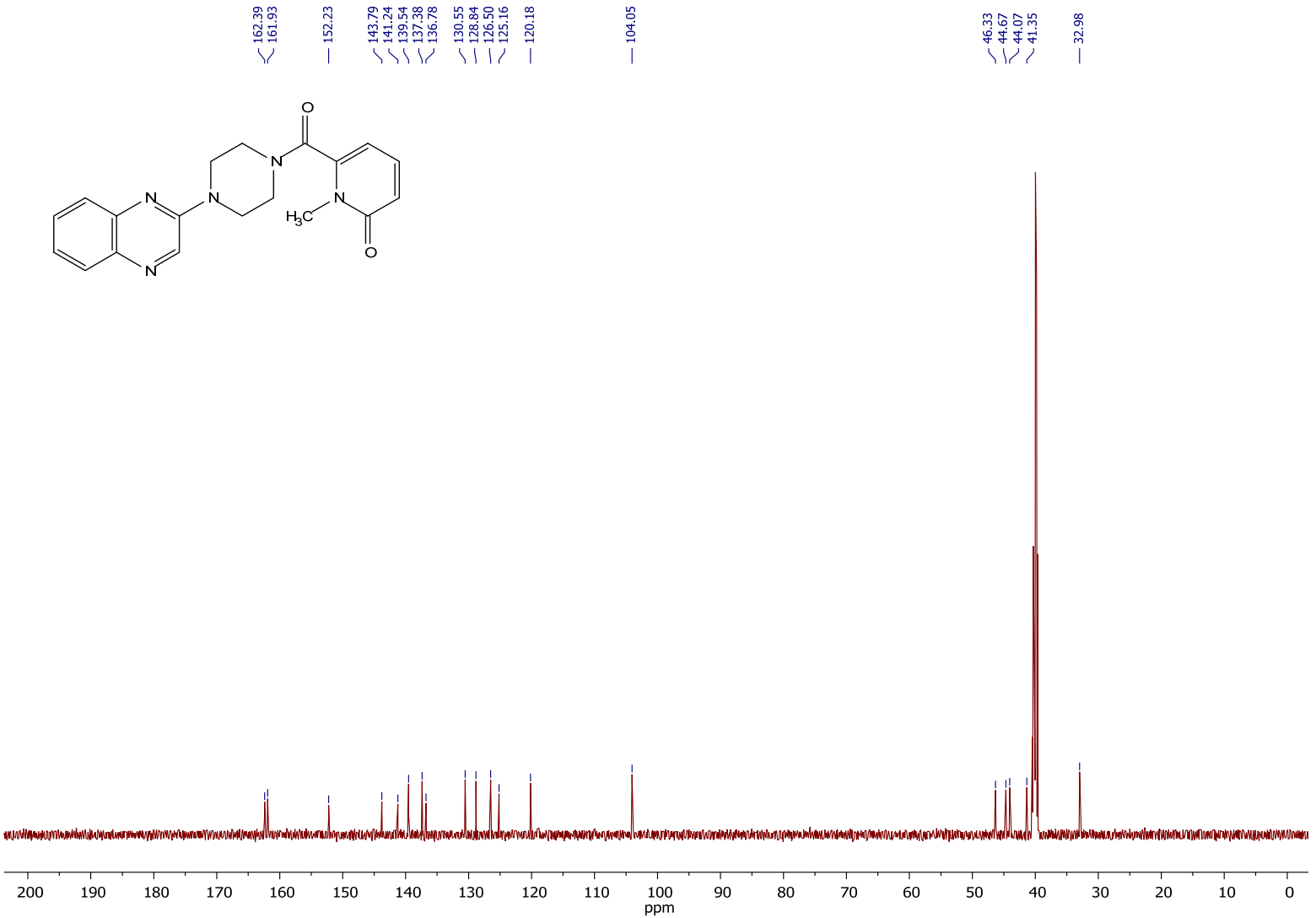
1-Methyl-5-(4-(quinoxalin-2-yl)piperazine-1-carbonyl)pyridin-2(1*H*)-one (**12**{*9*,*26*,*3*}), ^{1}H NMR (500 MHz, DMSO-d_6)



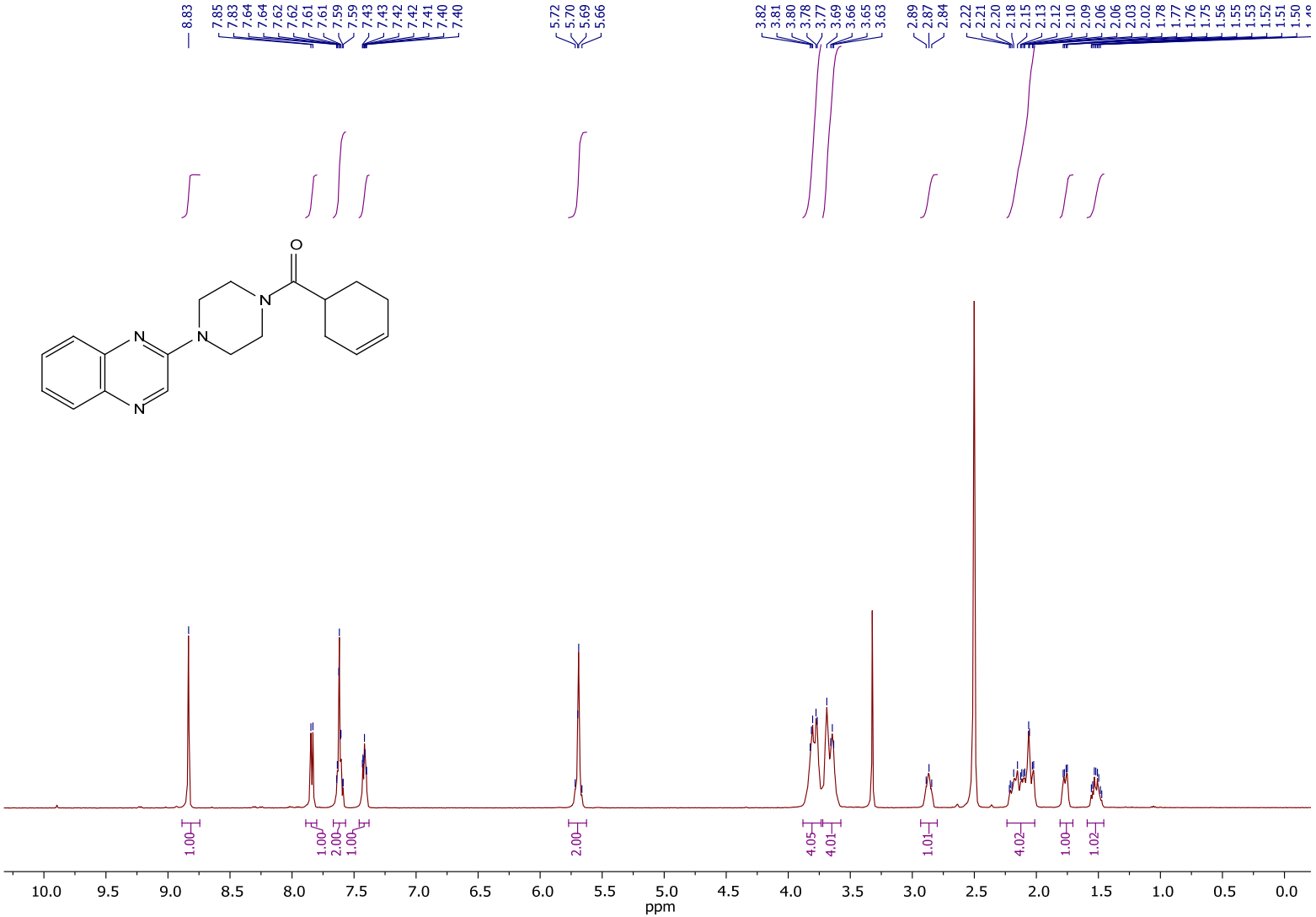
1-Methyl-5-(4-(quinoxalin-2-yl)piperazine-1-carbonyl)pyridin-2(1*H*)-one (**12**{*9*,*26*,*3*}), ^{13}C NMR (126 MHz, DMSO-d_6)



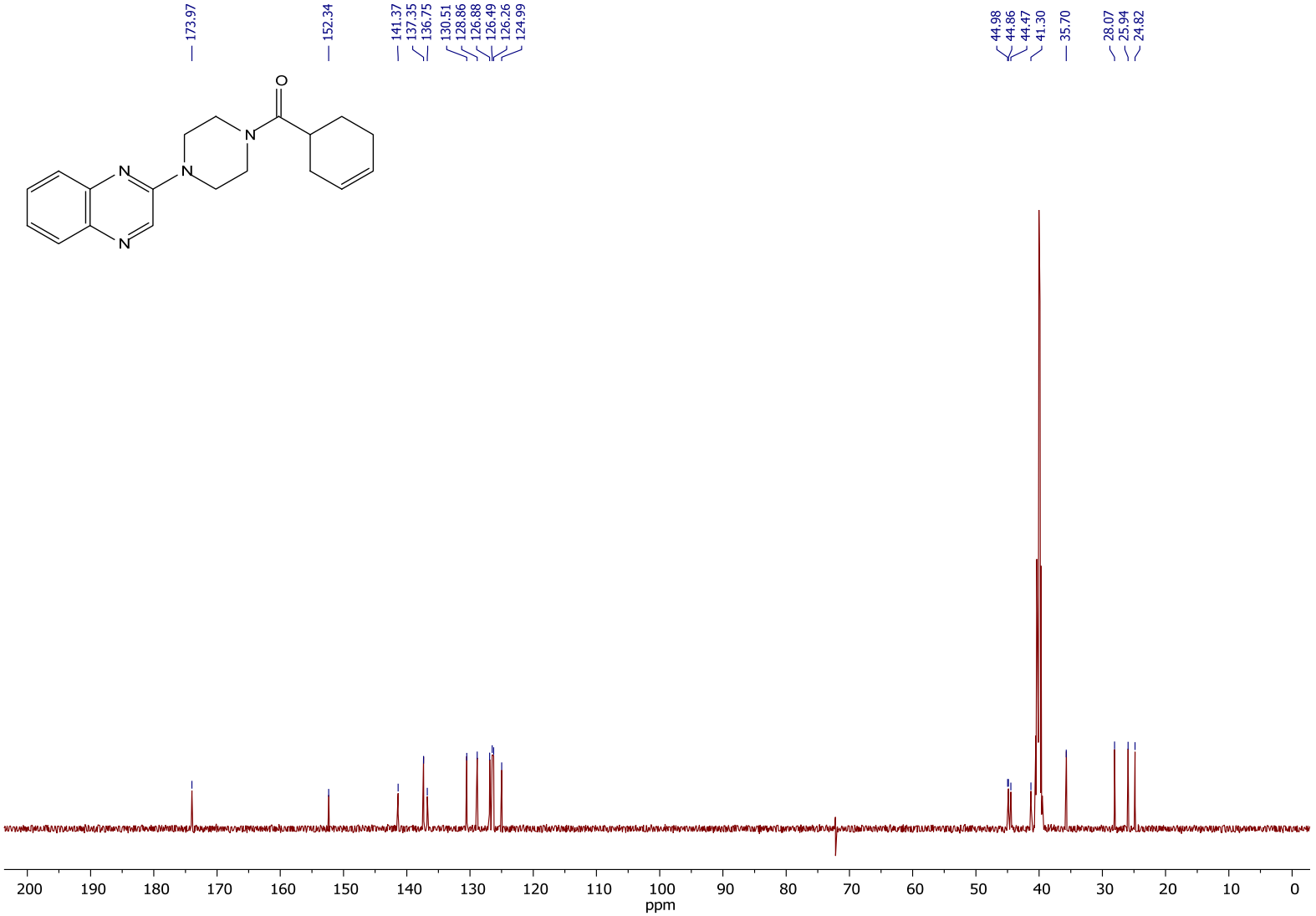
1-Methyl-6-(4-(quinoxalin-2-yl)piperazine-1-carbonyl)pyridin-2(1*H*)-one (**12**{*9*,*27*,*3*}), ^{1}H NMR (500 MHz, DMSO-d_6)



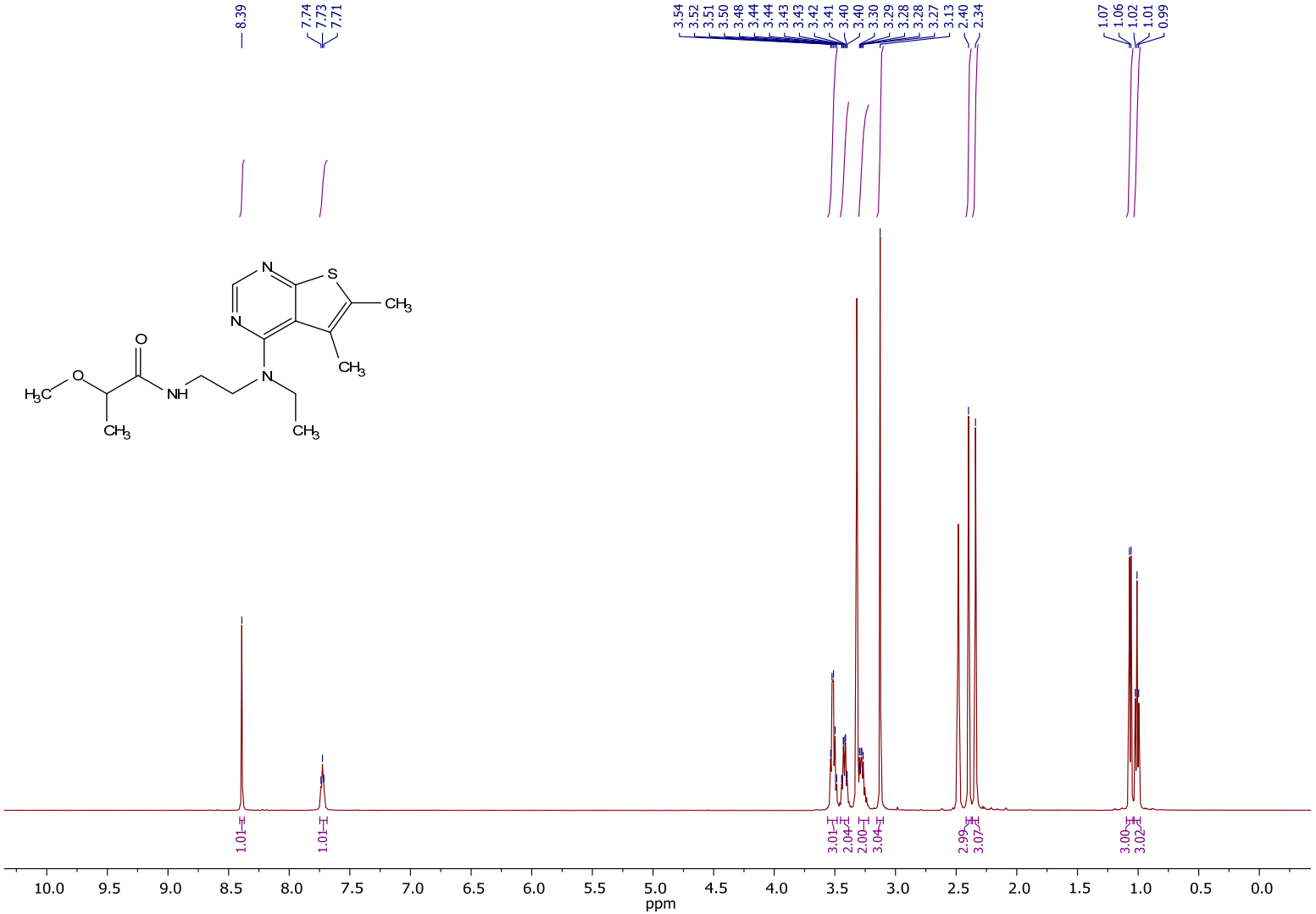
1-Methyl-6-(4-(quinoxalin-2-yl)piperazine-1-carbonyl)pyridin-2(1*H*)-one (**12**{*9*,*27*,*3*}), ^{13}C NMR (126 MHz, DMSO-d_6)



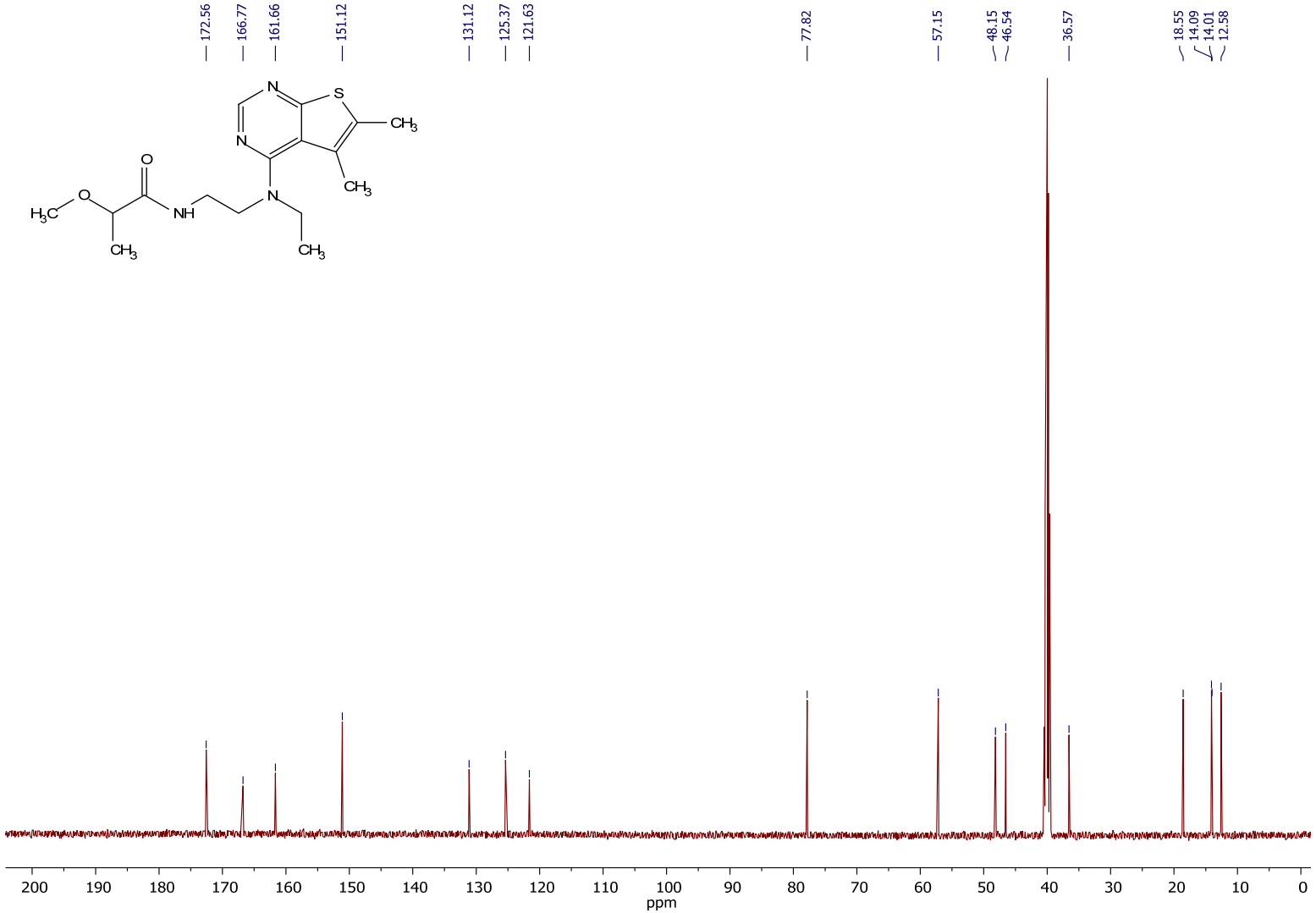
Cyclohex-3-en-1-yl(4-(quinoxalin-2-yl)piperazin-1-yl)methanone (**12**{*9*,*28*,*3*}), ^{1}H NMR (500 MHz, DMSO-d_6)



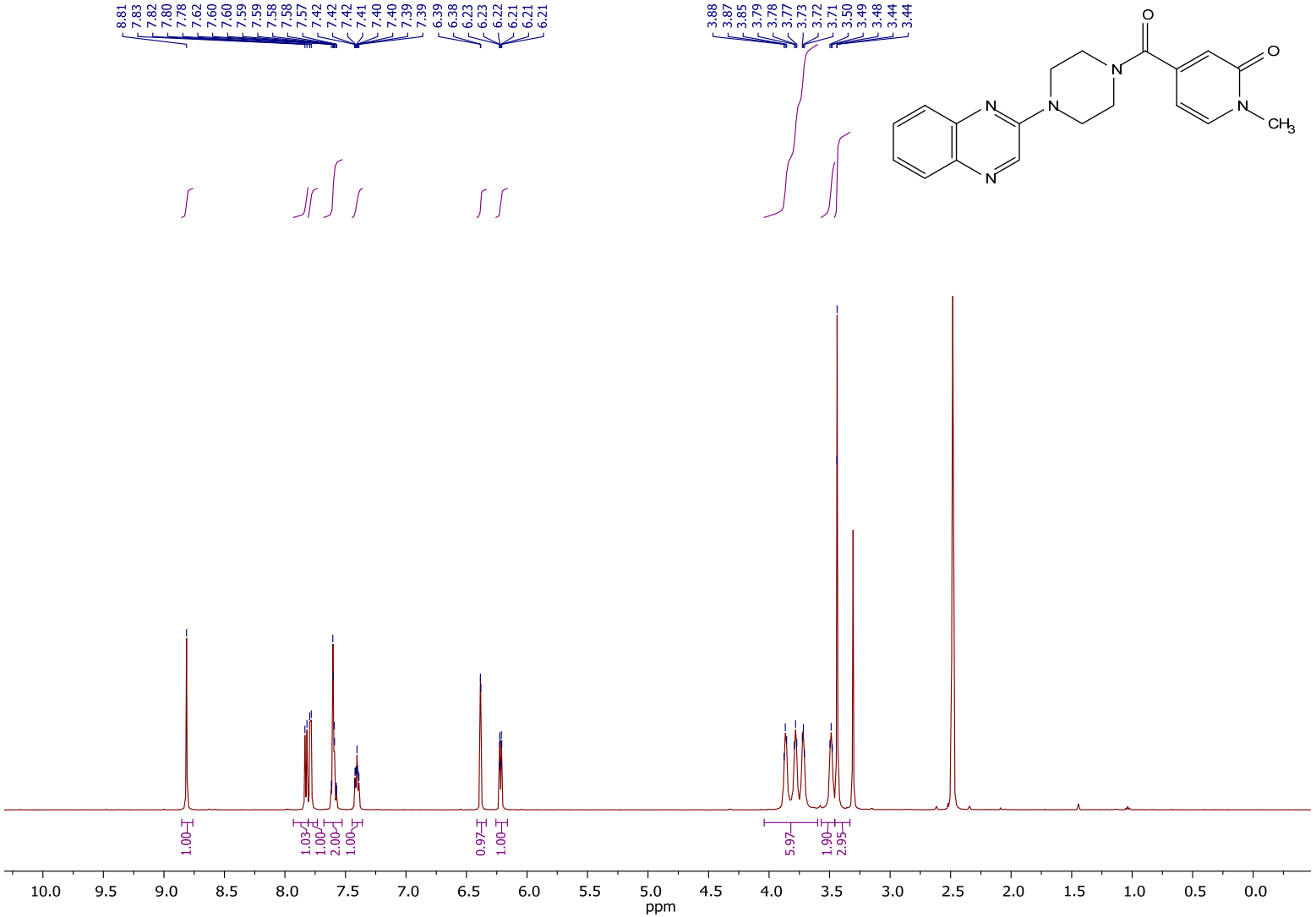
Cyclohex-3-en-1-yl(4-(quinoxalin-2-yl)piperazin-1-yl)methanone (**12**{*9*,*28*,*3*}), ^{13}C NMR (126 MHz, DMSO-d_6)



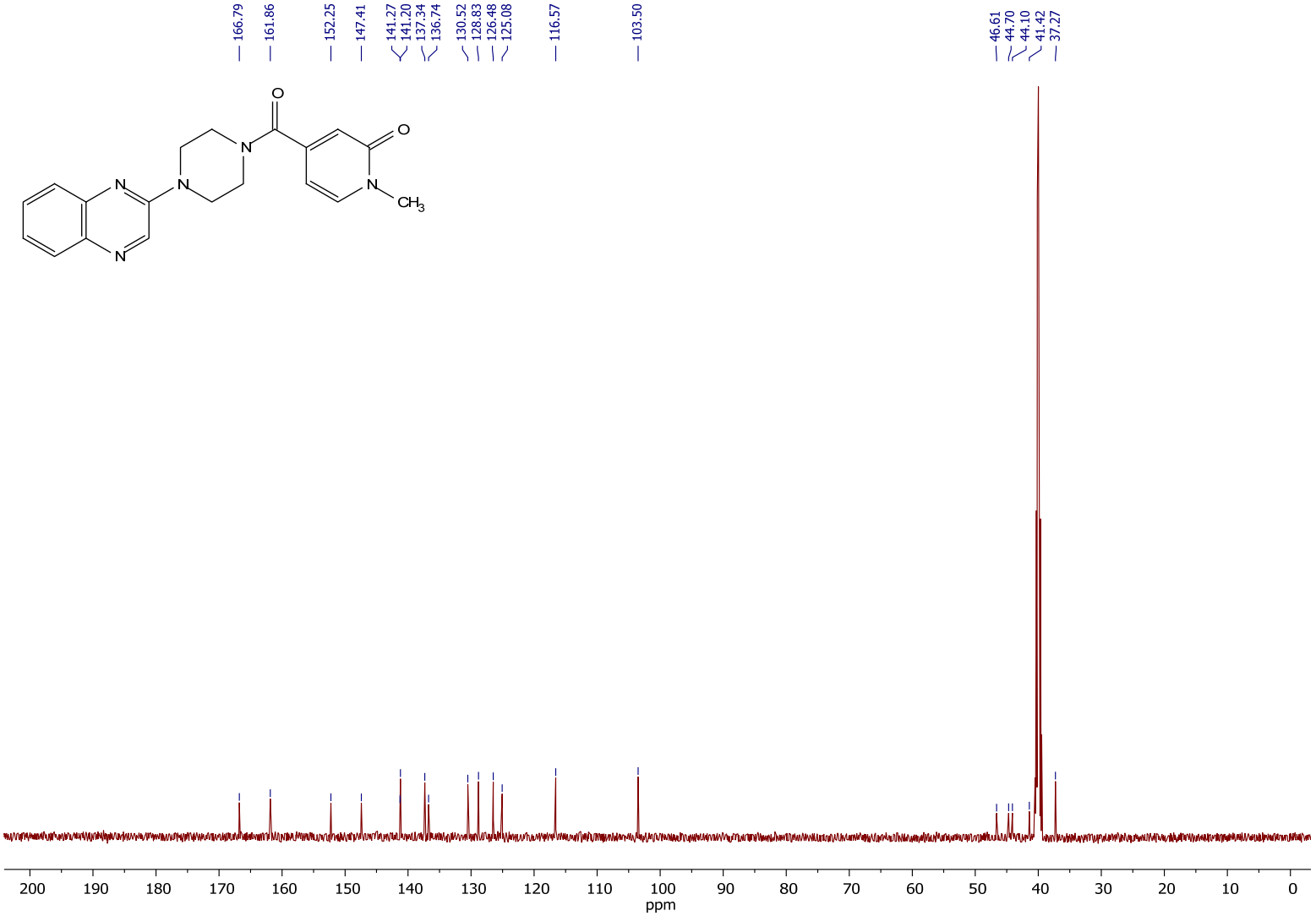
N-(2-((5,6-Dimethylthieno[2,3-*d*]pyrimidin-4-yl)(ethyl)amino)ethyl)-2-methoxypropanamide (**12**{*45*,*44*,*24*}), ^{1}H NMR (500 MHz, DMSO-d_6)



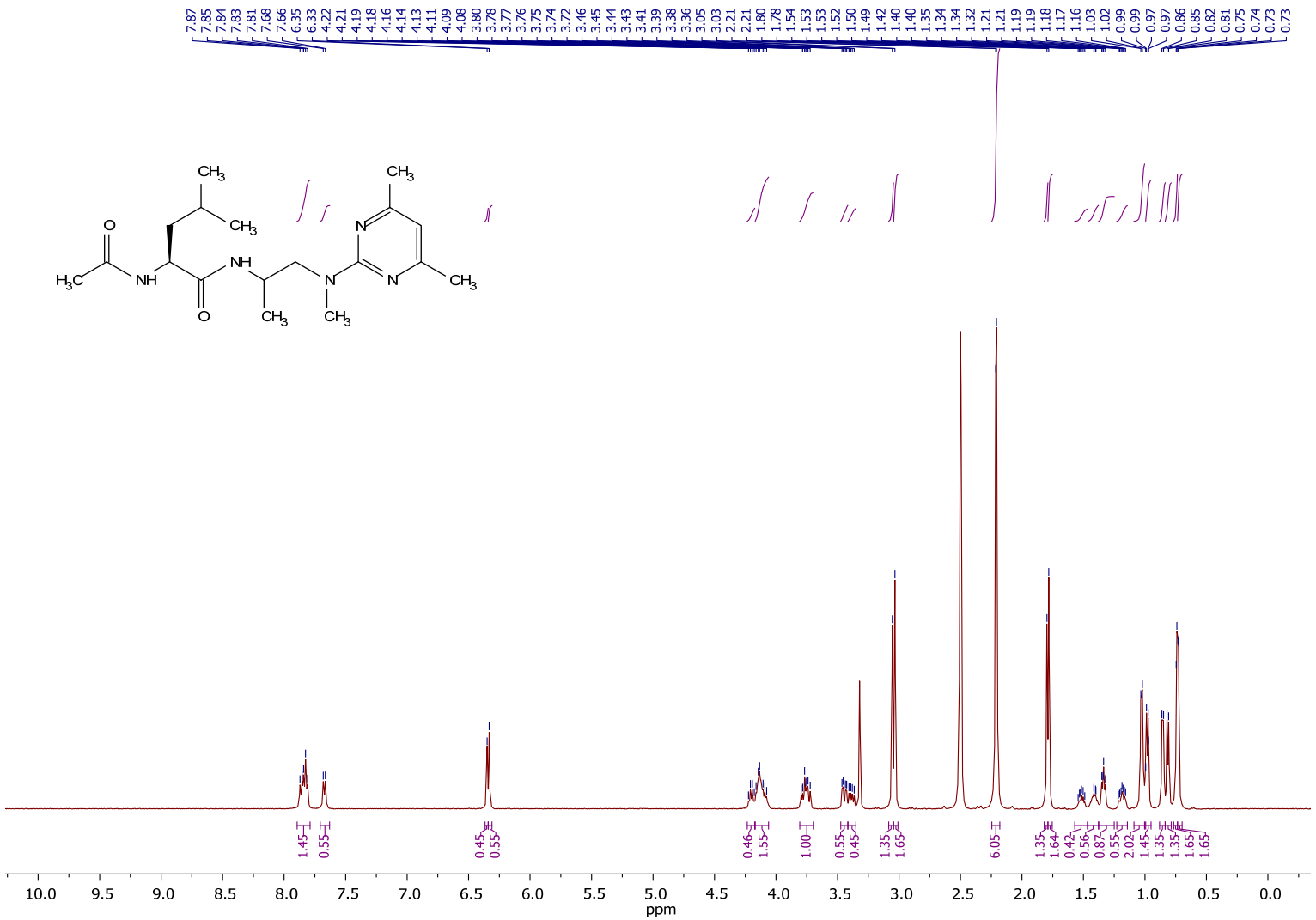
N-(2-((5,6-Dimethylthieno[2,3-*d*]pyrimidin-4-yl)(ethyl)amino)ethyl)-2-methoxypropanamide (**12**{*45*,*44*,*24*}), ^{13}C NMR (126 MHz, DMSO-d_6)



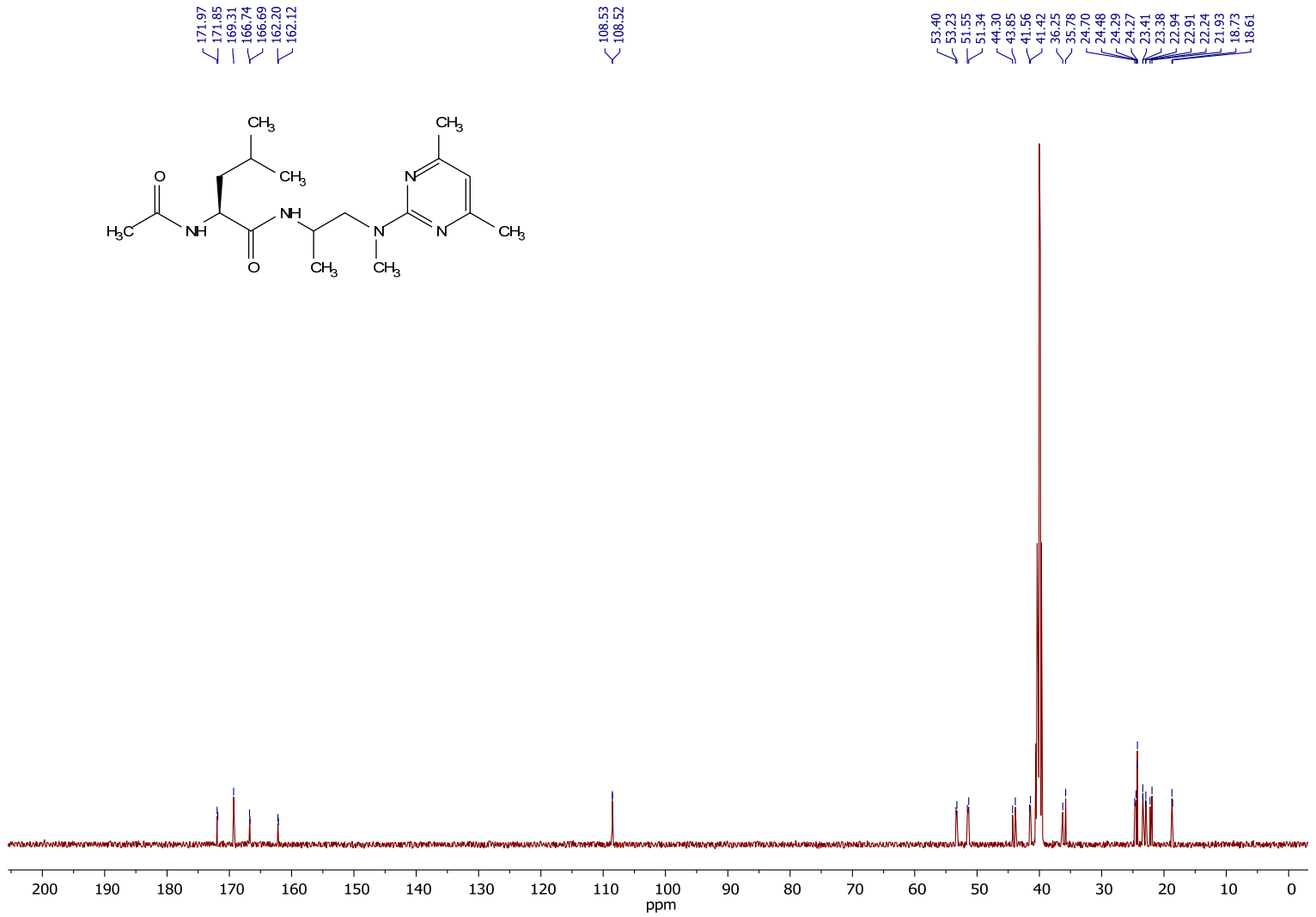
1-Methyl-4-(4-(quinoxalin-2-yl)piperazine-1-carbonyl)pyridin-2(1*H*)-one (**12**{*9*,*48*,*3*}), ^{1}H NMR (500 MHz, DMSO-d_6)



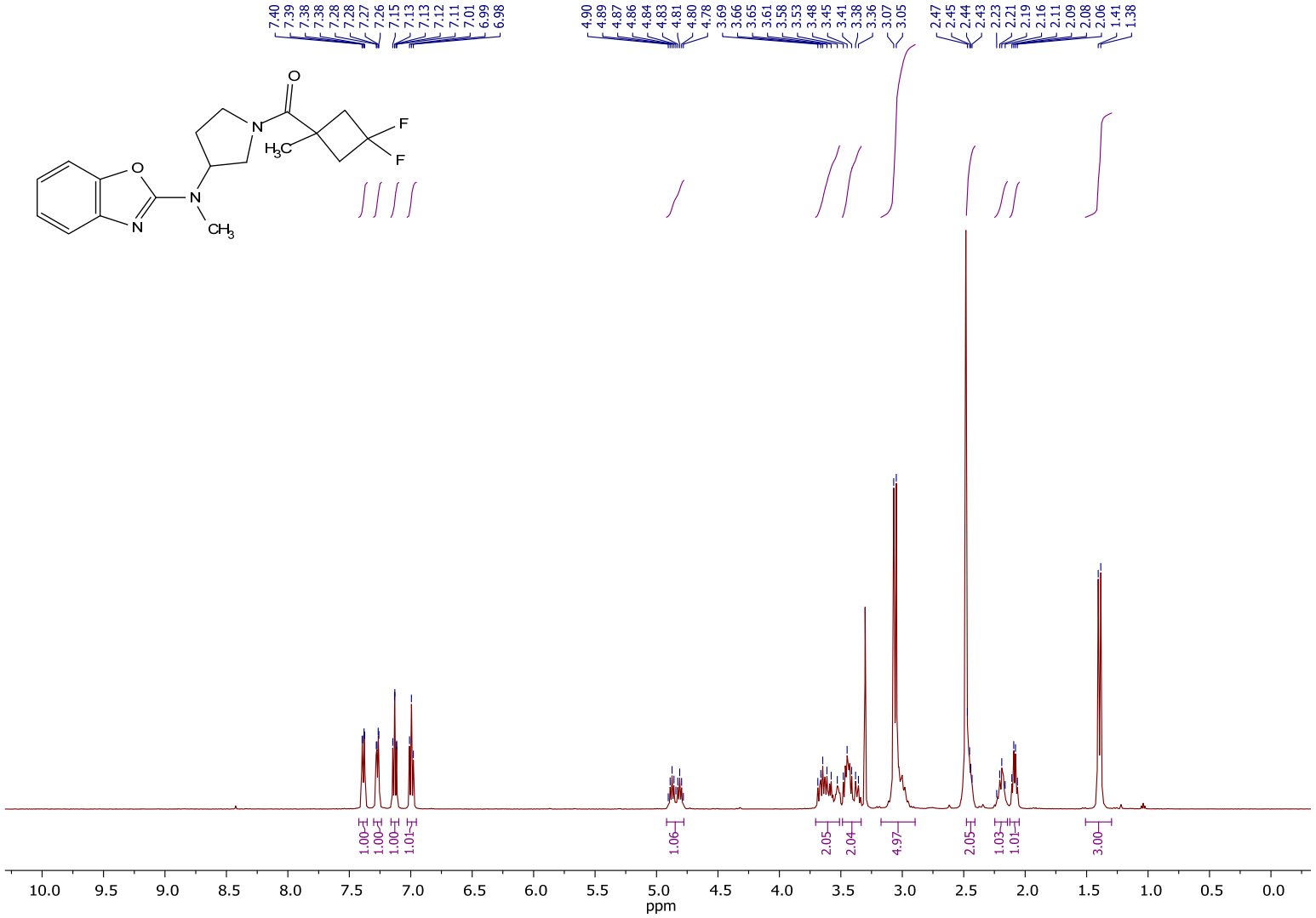
1-Methyl-4-(4-(quinoxalin-2-yl)piperazine-1-carbonyl)pyridin-2(1*H*)-one (**12**{*9*,*48*,*3*}), ^{13}C NMR (126 MHz, DMSO-d_6)



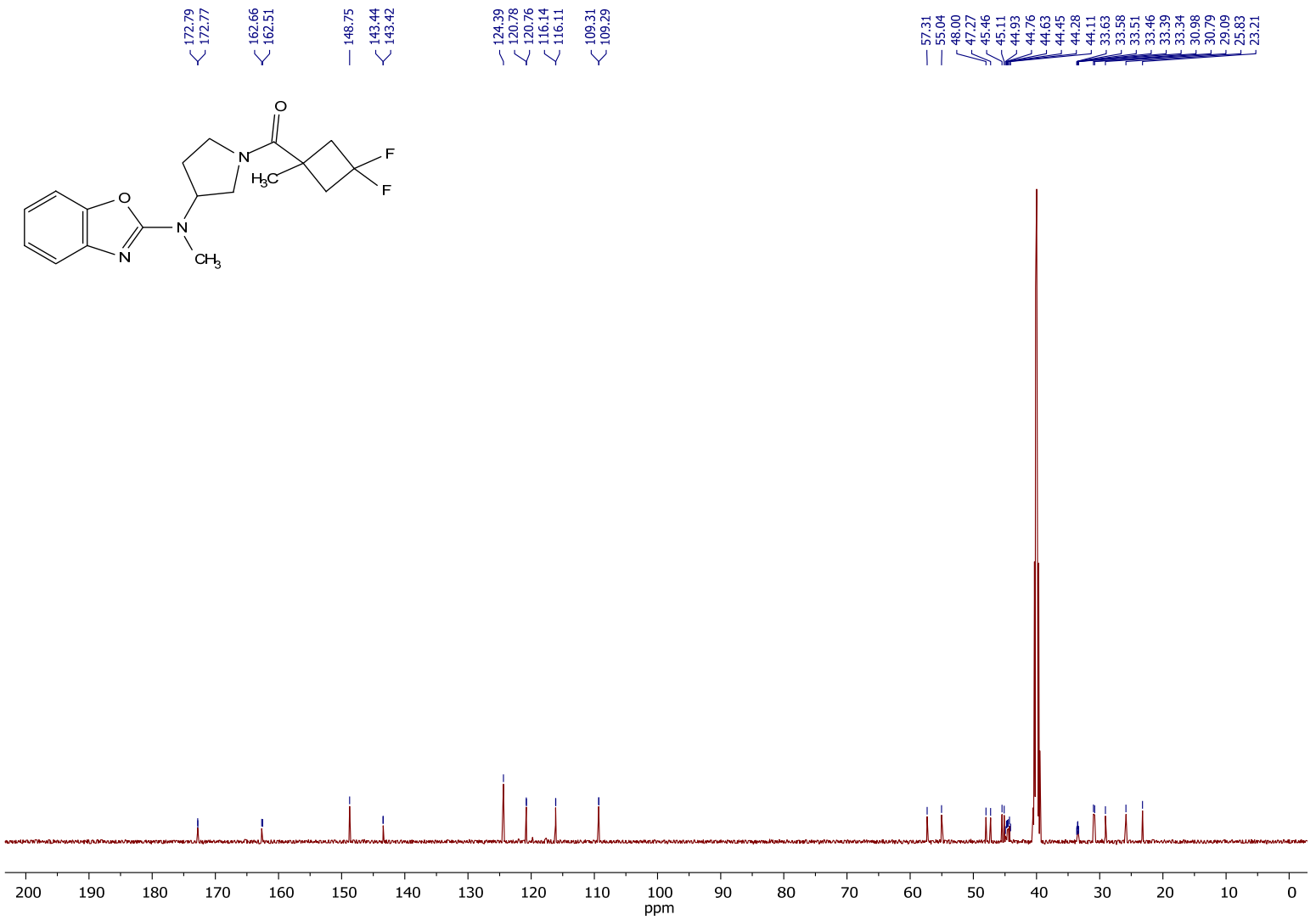
(2*S*)-2-Acetamido-*N*-(1-((4,6-dimethylpyrimidin-2-yl)(methyl)amino)propan-2-yl)-4-methylpentanamide (**12**{*68*,*82*,*32*}), ^{1}H NMR (500 MHz, DMSO-d_6)



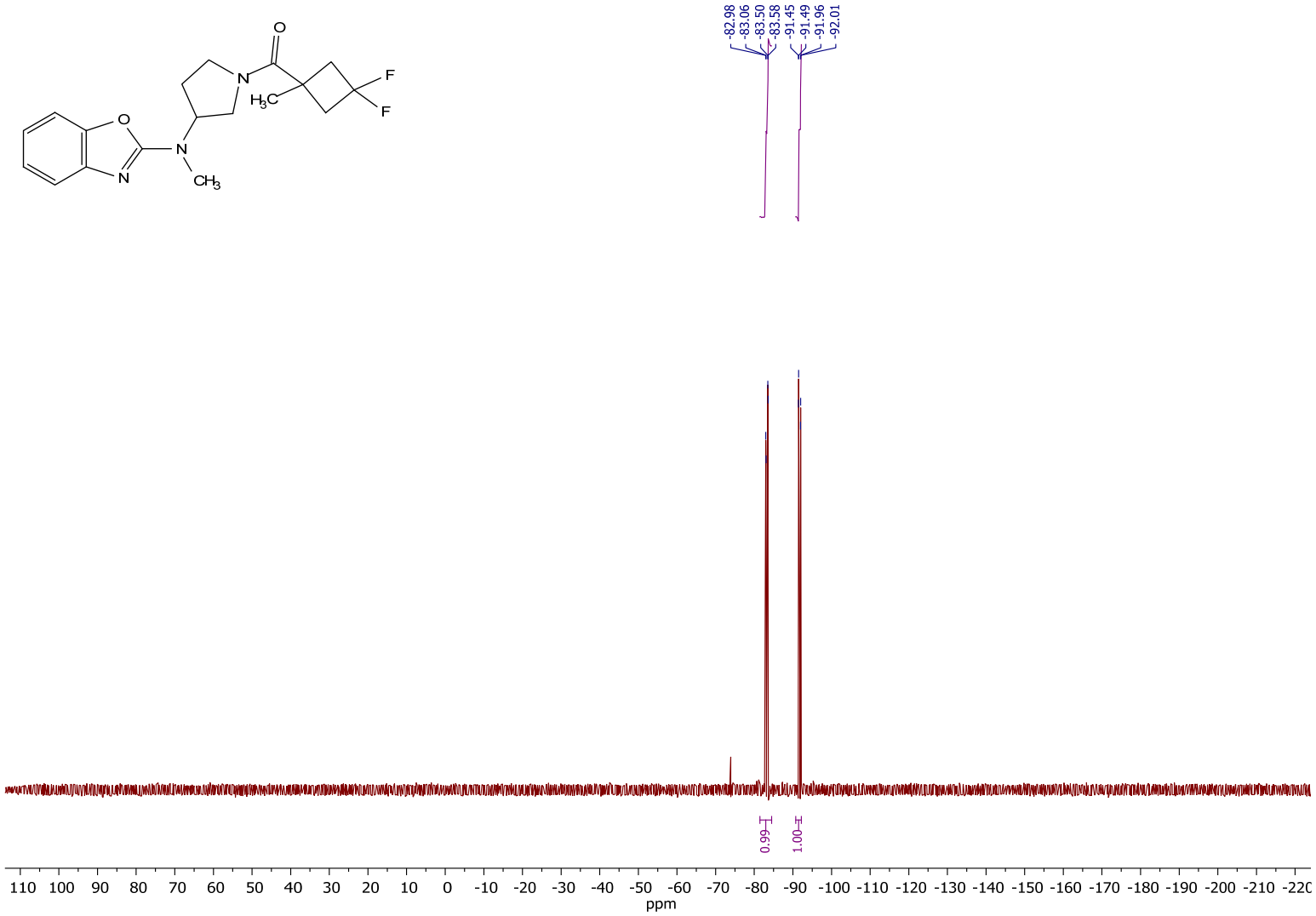
(2*S*)-2-Acetamido-*N*-(1-((4,6-dimethylpyrimidin-2-yl)(methyl)amino)propan-2-yl)-4-methylpentanamide (**12**{*68*,*82*,*32*}), ^{13}C NMR (126 MHz, DMSO-d_6)



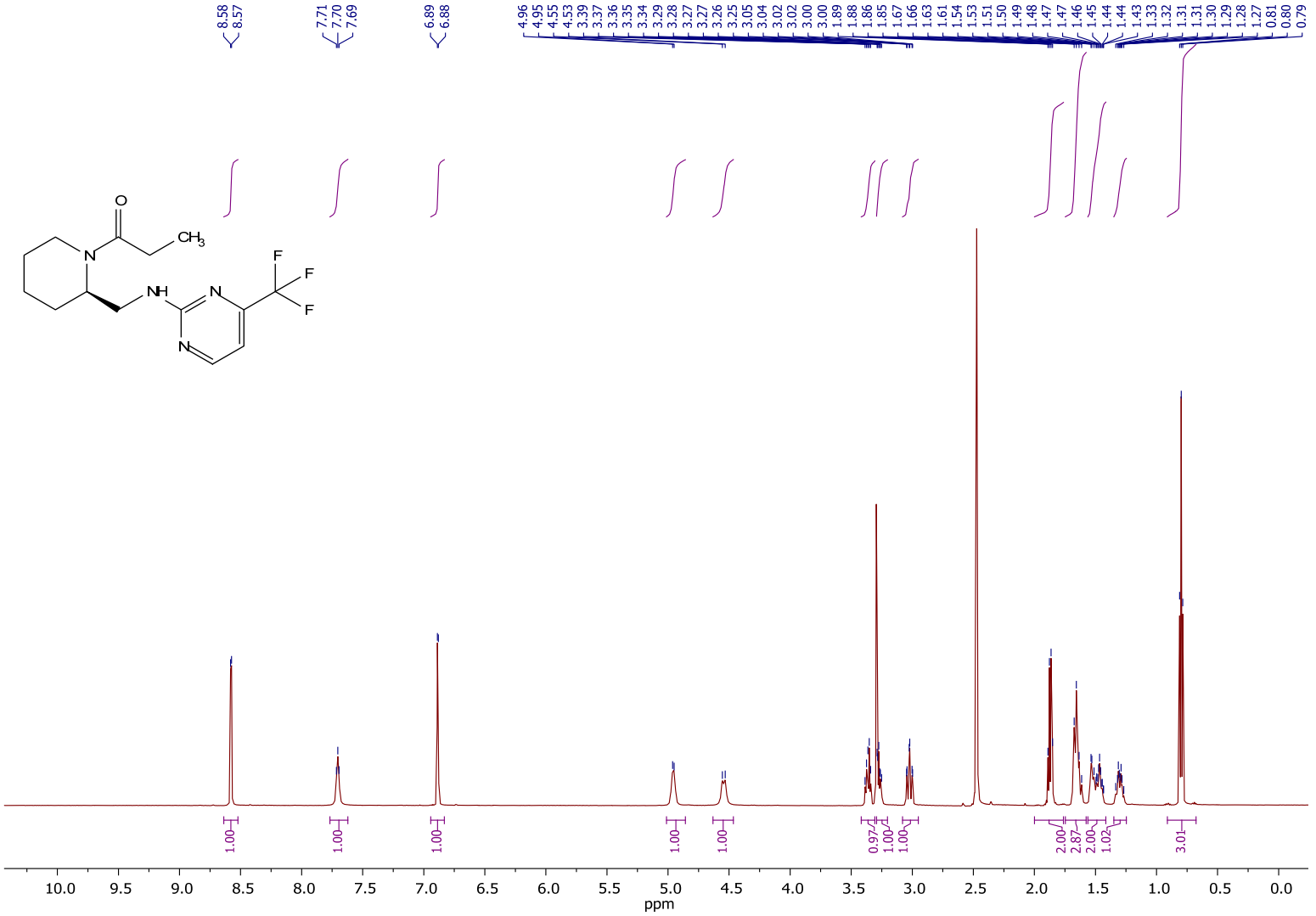
(3-(Benzo[*d*]oxazol-2-yl(methyl)amino)pyrrolidin-1-yl)(3,3-difluoro-1-methylcyclobutyl)methanone (**12**{*81*,*39*,*30*}), ^{1}H NMR (500 MHz, DMSO-d_6)



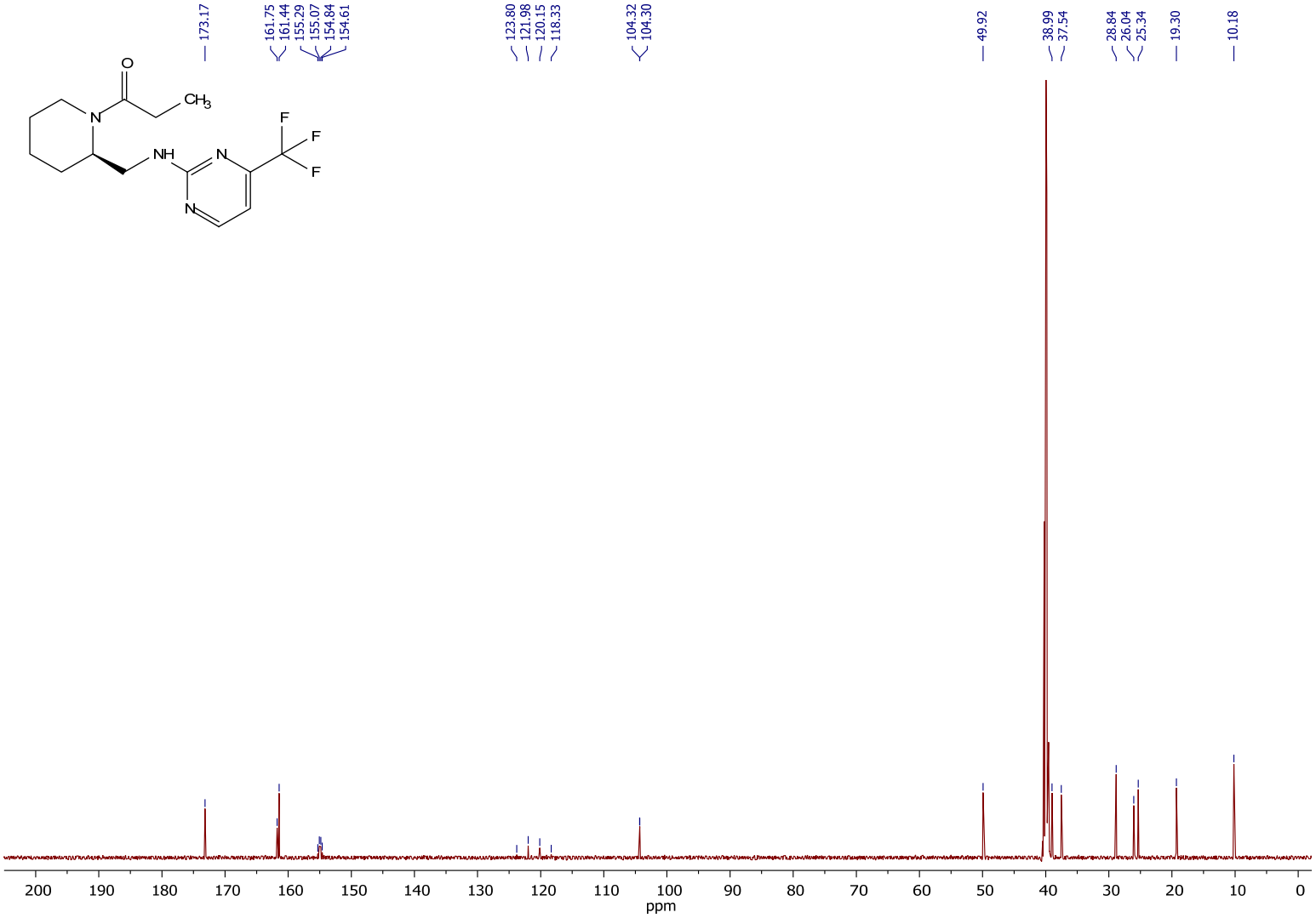
(3-(Benzo[*d*]oxazol-2-yl(methyl)amino)pyrrolidin-1-yl)(3,3-difluoro-1-methylcyclobutyl)methanone (**12**{*81*,*39*,*30*}), ^{13}C NMR (126 MHz, DMSO-d_6)



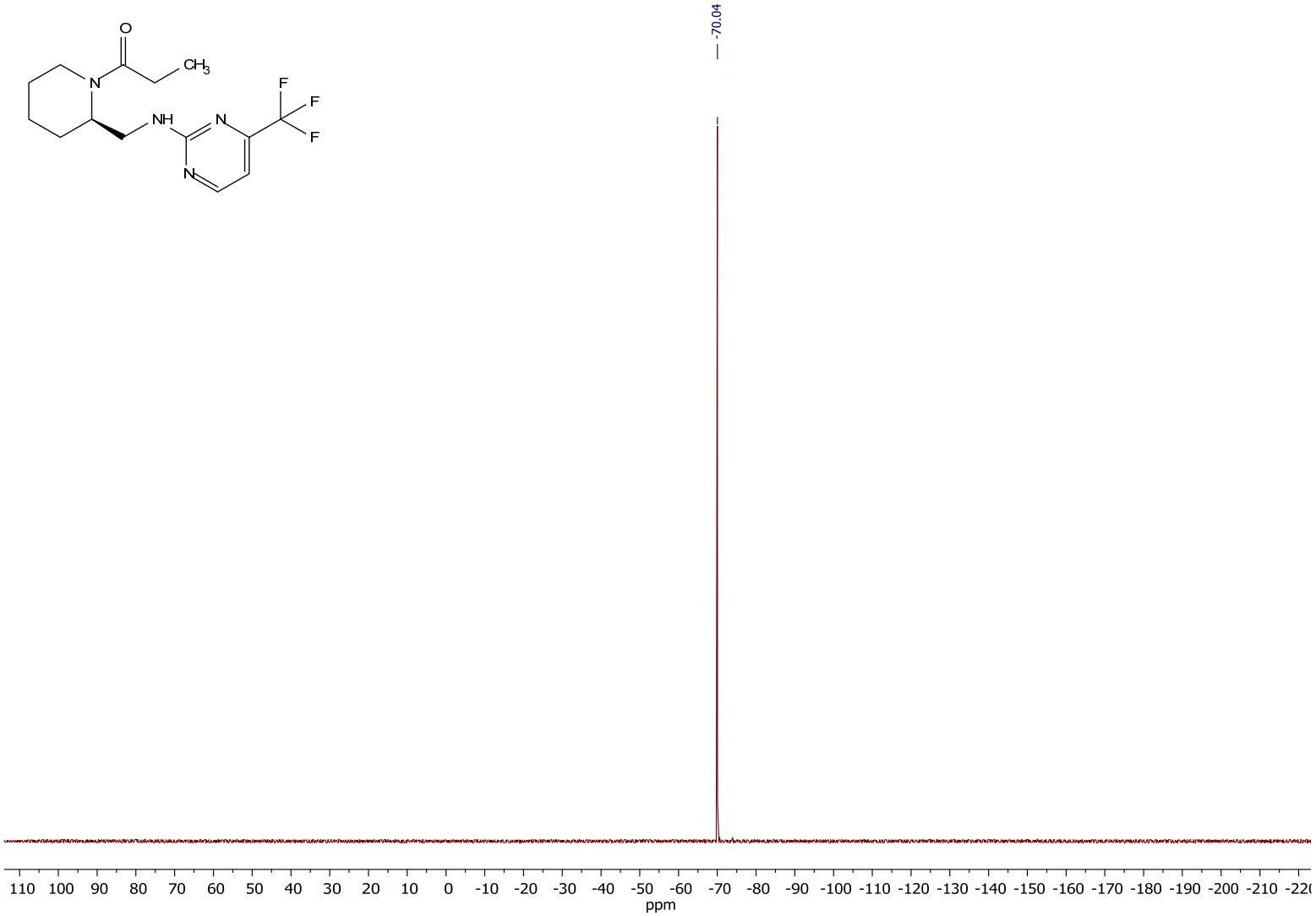
(3-(Benzo[*d*]oxazol-2-yl(methyl)amino)pyrrolidin-1-yl)(3,3-difluoro-1-methylcyclobutyl)methanone (**12**{*81*,*39*,*30*}), ^{19}F NMR (376 MHz, DMSO-d_6)



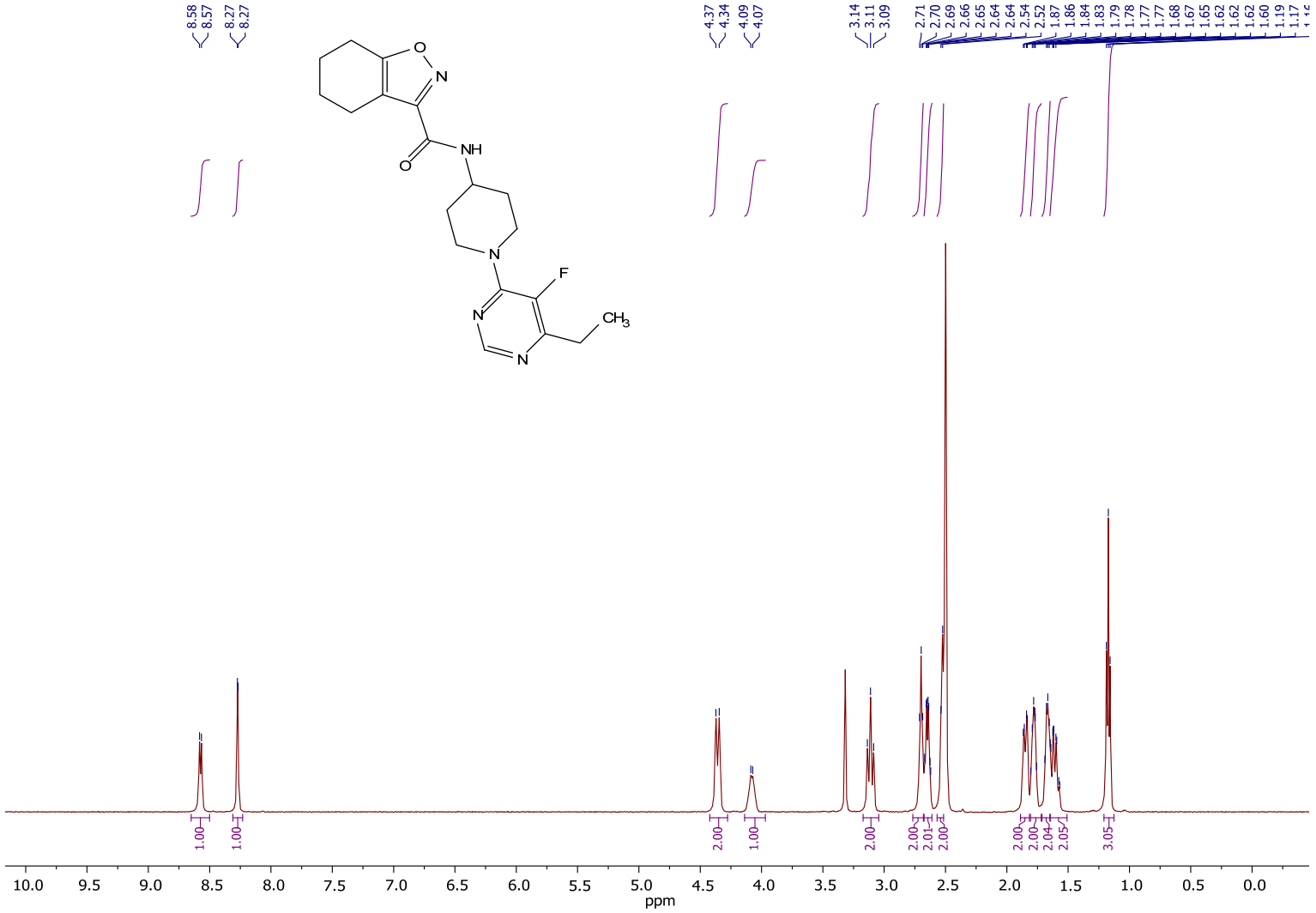
(*R*)-1-(2-(((4-(Trifluoromethyl)pyrimidin-2-yl)amino)methyl)piperidin-1-yl)propan-1-one (**12**{*84*,*40*,*34*}), ^{1}H NMR (600 MHz, DMSO-d_6)



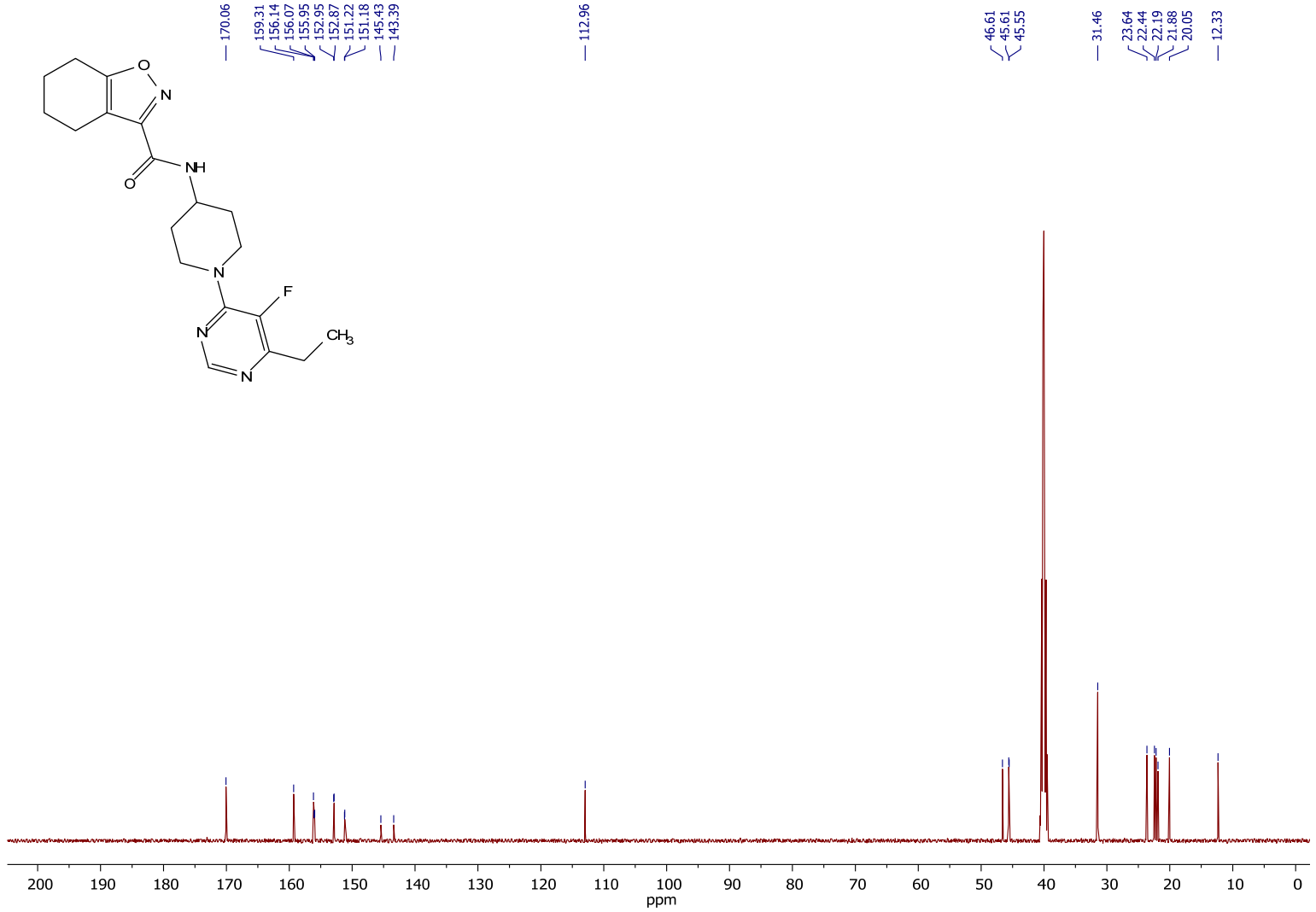
(*R*)-1-(2-(((4-(Trifluoromethyl)pyrimidin-2-yl)amino)methyl)piperidin-1-yl)propan-1-one (**12**{*84*,*40*,*34*}), ^{13}C NMR (151 MHz, DMSO-d_6)



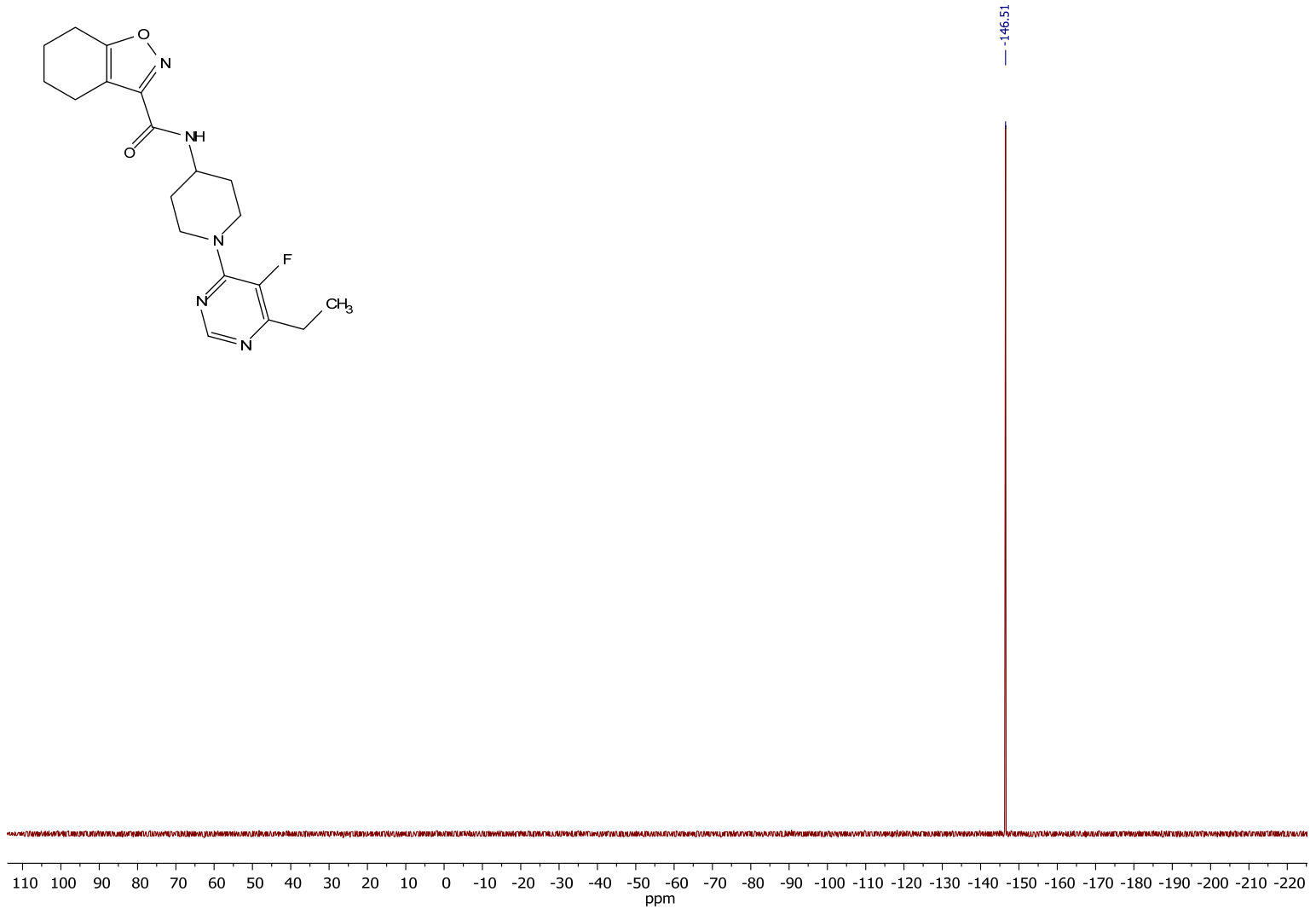
(*R*)-1-(2-(((4-(Trifluoromethyl)pyrimidin-2-yl)amino)methyl)piperidin-1-yl)propan-1-one (**12**{*84*,*40*,*34*}), ^{19}F NMR (376 MHz, DMSO-d_6)



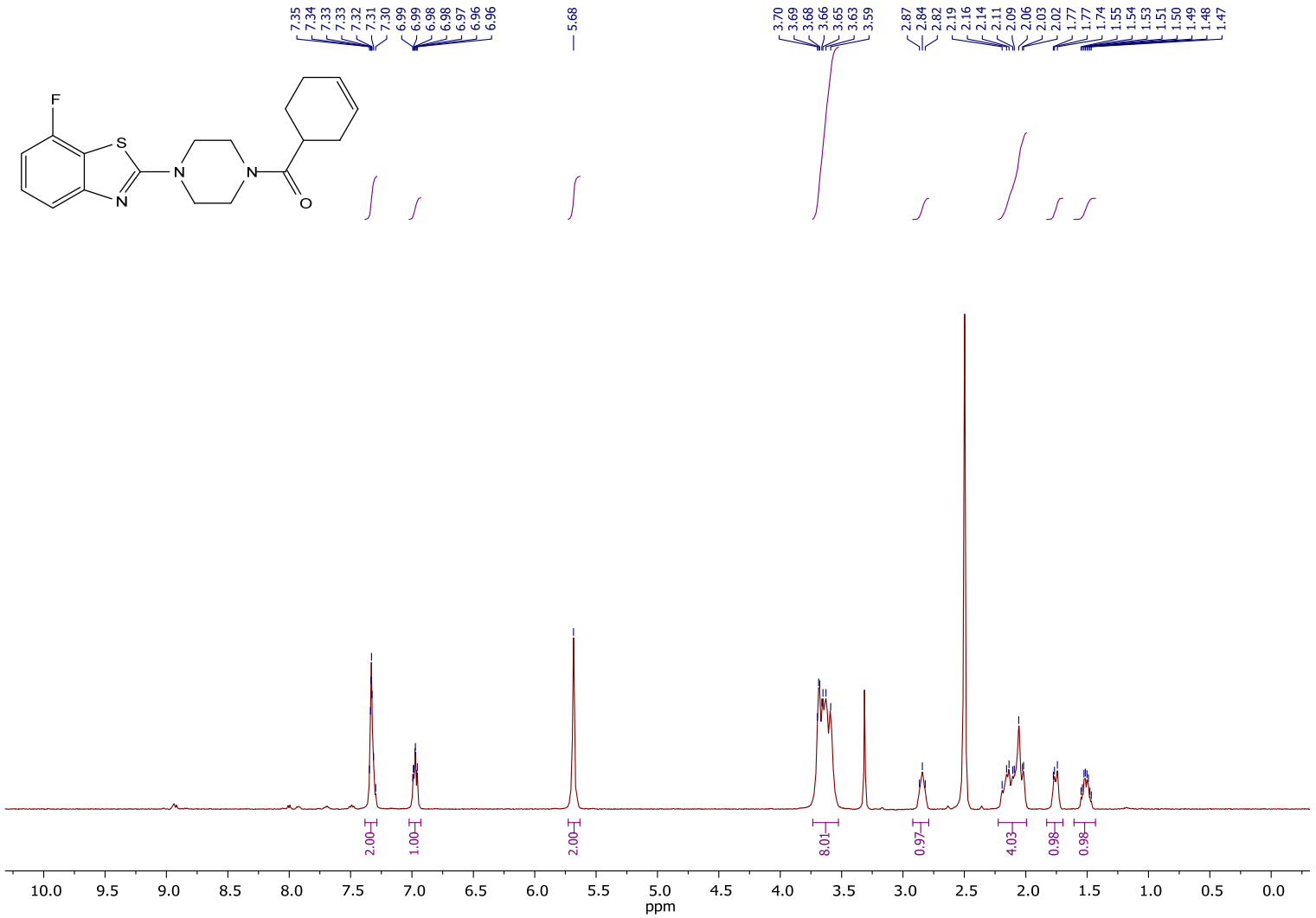
N-(1-(6-Ethyl-5-fluoropyrimidin-4-yl)piperidin-4-yl)-4,5,6,7-tetrahydrobenzo[*d*]isoxazole-3-carboxamide (**12**{*79*,*130*,*39*}), ^{1}H NMR (500 MHz, DMSO-d_6)



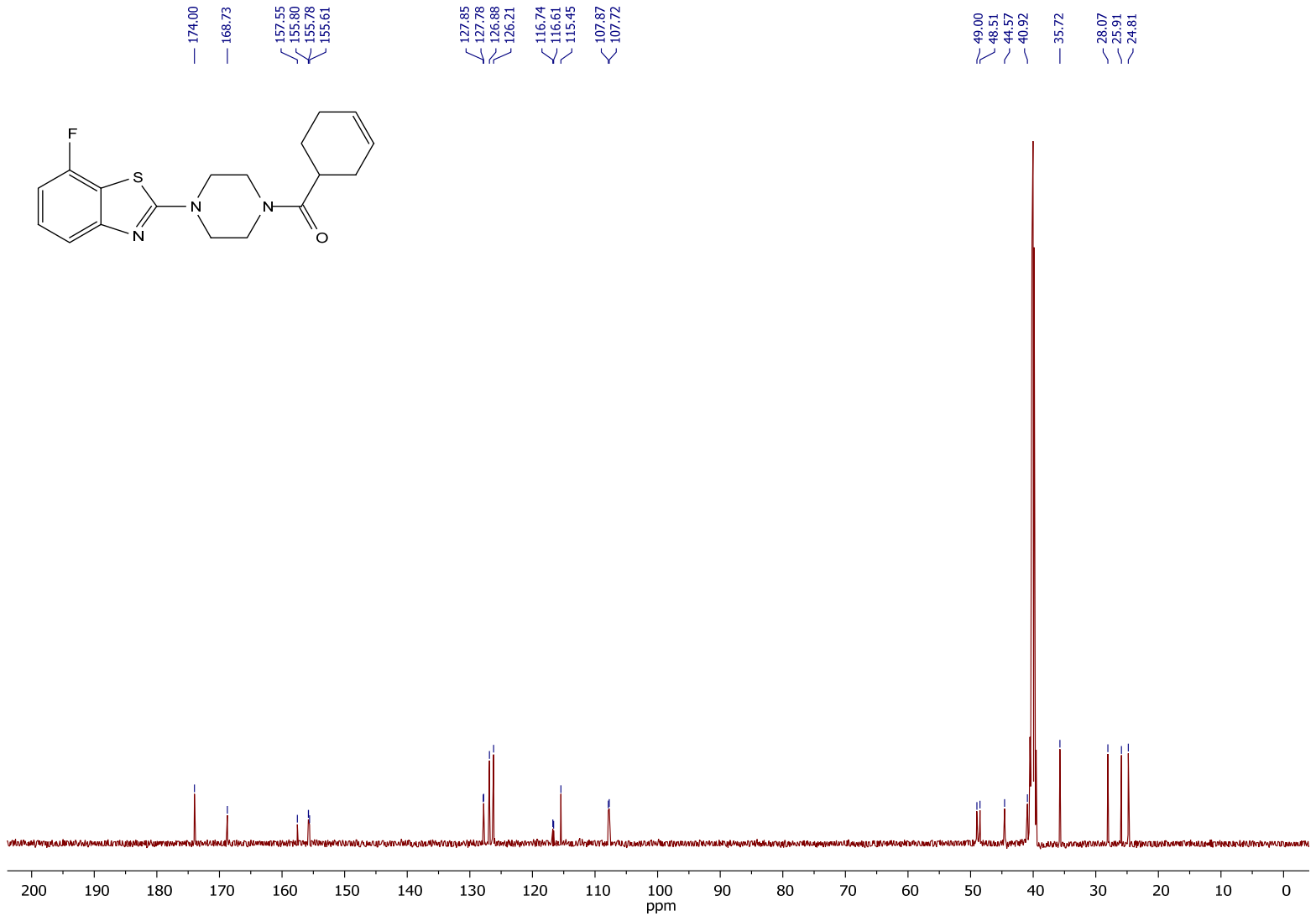
N-(1-(6-Ethyl-5-fluoropyrimidin-4-yl)piperidin-4-yl)-4,5,6,7-tetrahydrobenzo[*d*]isoxazole-3-carboxamide (**12**{*79*,*130*,*39*}), ^{13}C NMR (126 MHz, DMSO-d_6)



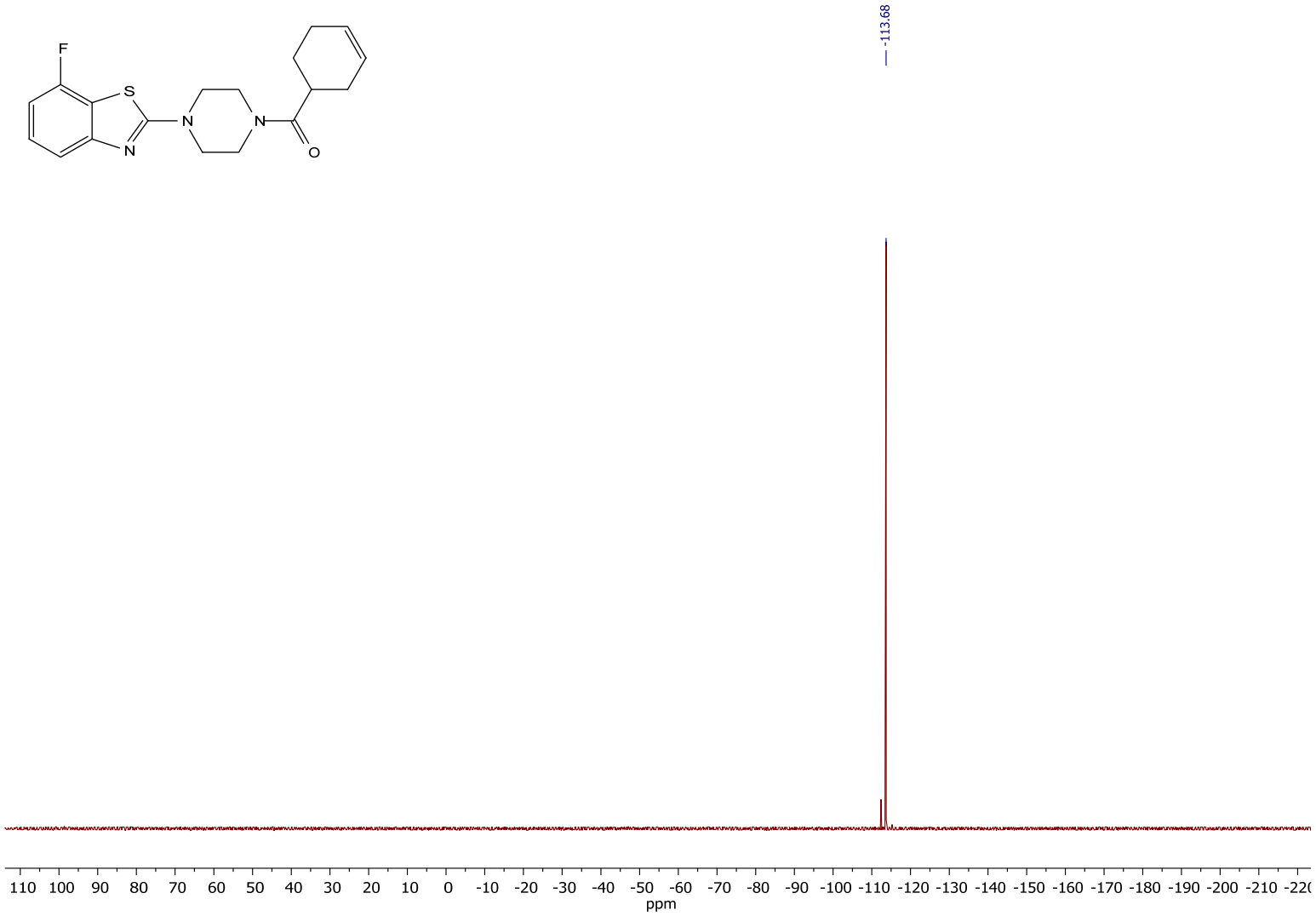
N-(1-(6-Ethyl-5-fluoropyrimidin-4-yl)piperidin-4-yl)-4,5,6,7-tetrahydrobenzo[*d*]isoxazole-3-carboxamide (**12**{*79*,*130*,*39*}), ^{19}F NMR (376 MHz, DMSO-d_6



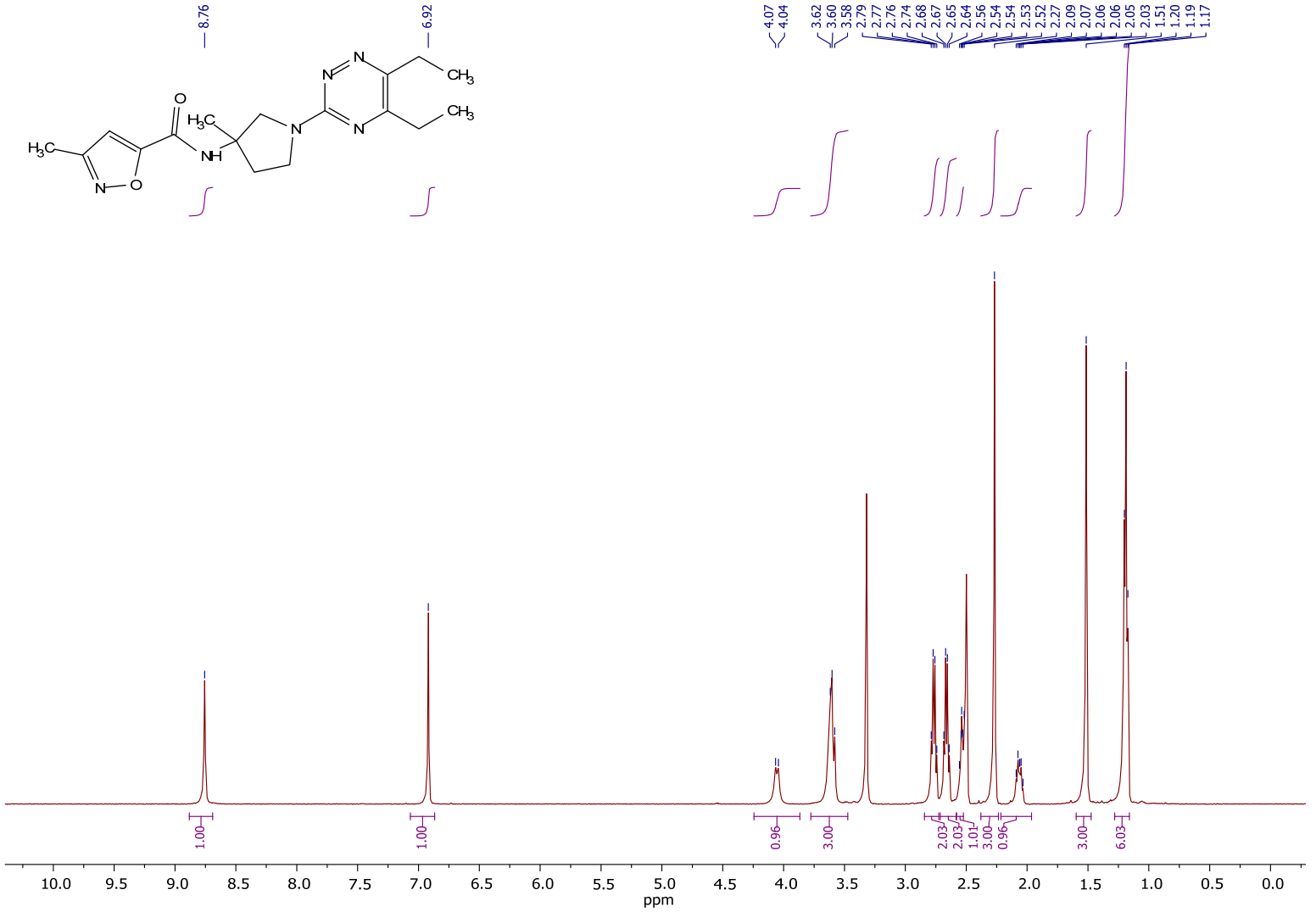
Cyclohex-3-en-1-yl(4-(7-fluorobenzo[*d*]thiazol-2-yl)piperazin-1-yl)methanone (**12**{*9*,*28*,*43*}), ^{1}H NMR (500 MHz, DMSO-d_6)



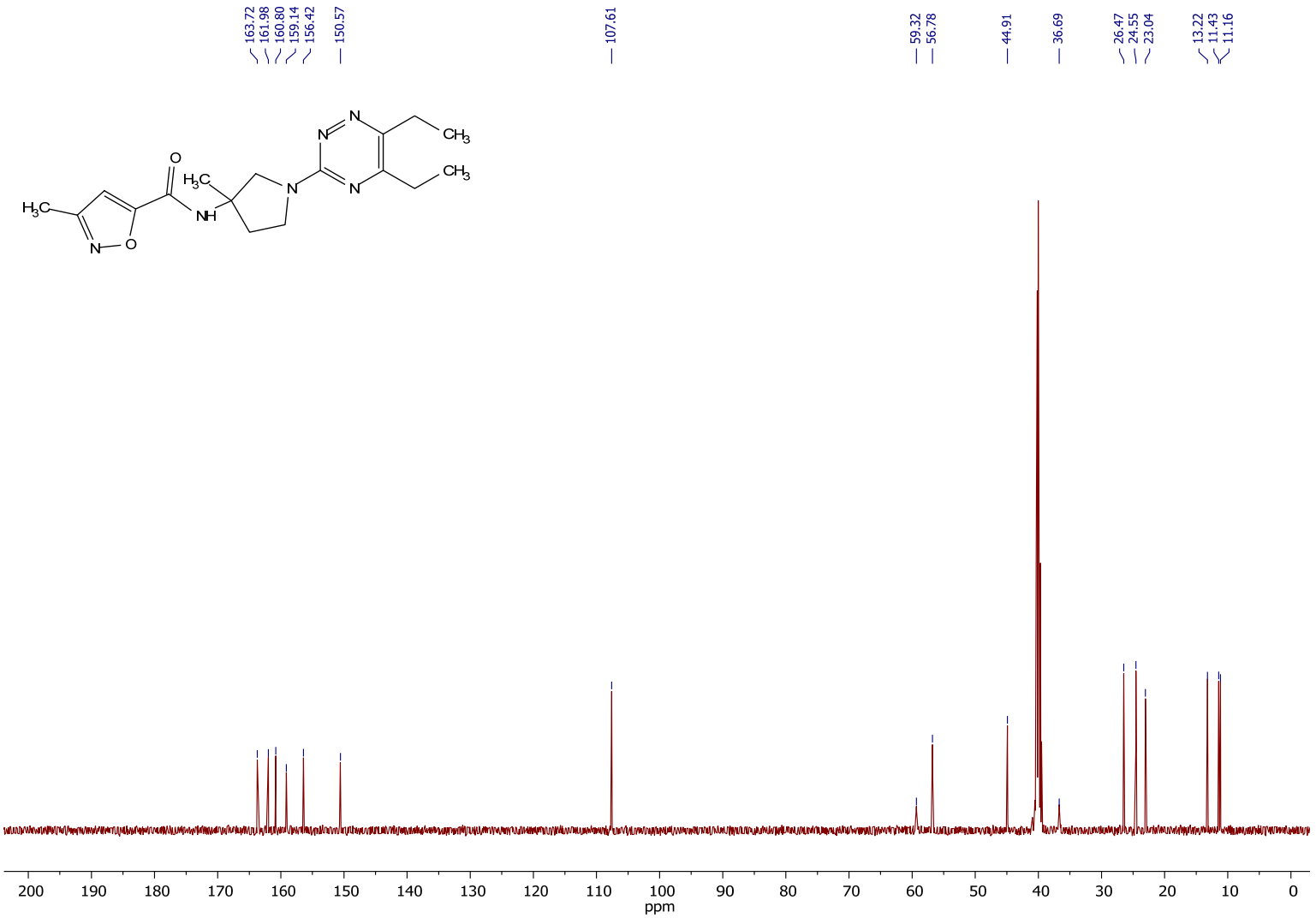
Cyclohex-3-en-1-yl(4-(7-fluorobenzo[*d*]thiazol-2-yl)piperazin-1-yl)methanone (**12**{*9*,*28*,*43*}), ^{13}C NMR (126 MHz, DMSO-d_6)



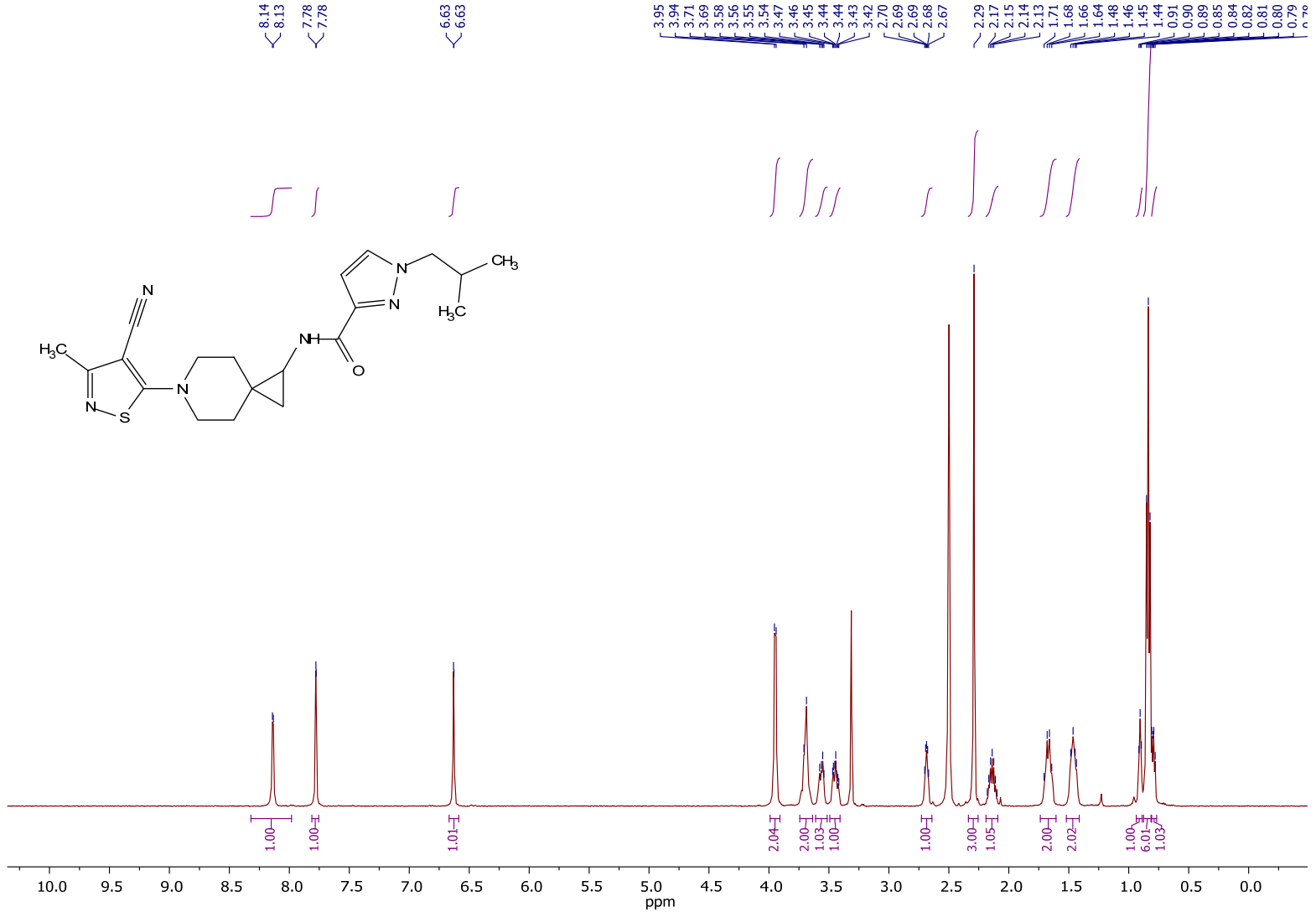
Cyclohex-3-en-1-yl(4-(7-fluorobenzo[*d*]thiazol-2-yl)piperazin-1-yl)methanone (**12**{*9*,*28*,*43*}), ^{19}F NMR (376 MHz, DMSO-d_6)



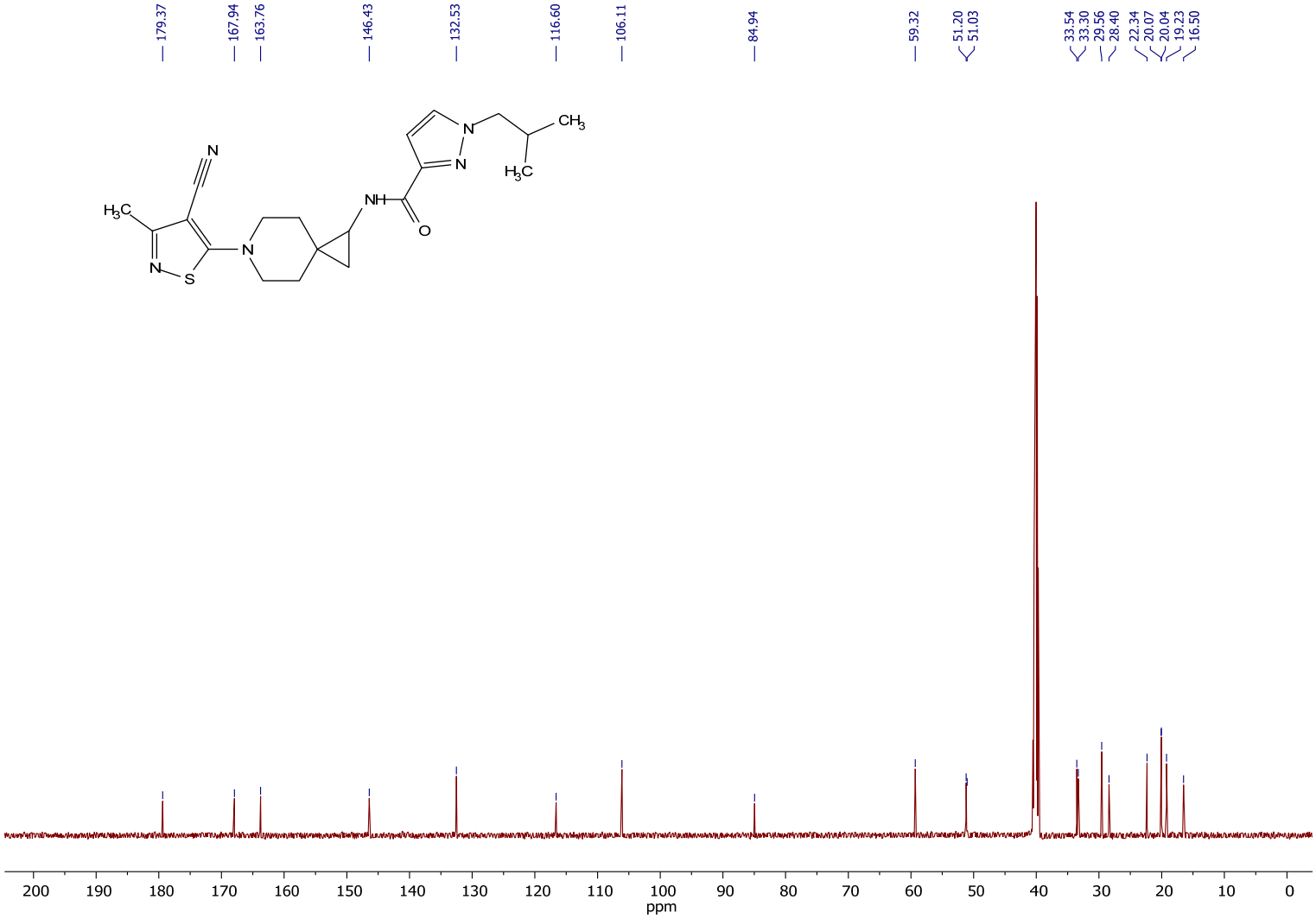
N-(1-(5,6-Diethyl-1,2,4-triazin-3-yl)-3-methylpyrrolidin-3-yl)-3-methylisoxazole-5-carboxamide **12**{*49*,*150*,*31*}), ^{1}H NMR (500 MHz, DMSO-d_6)



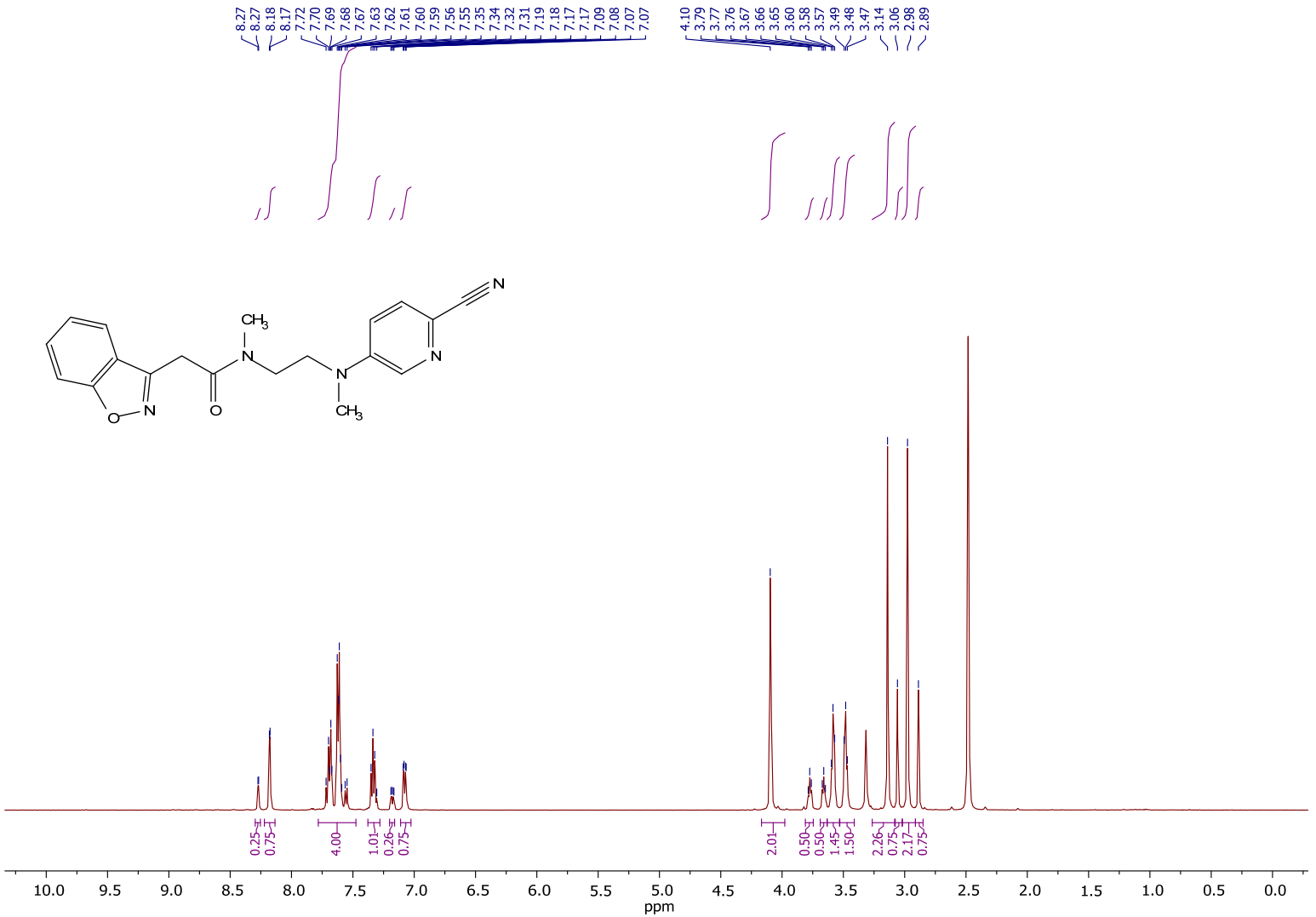
N-(1-(5,6-Diethyl-1,2,4-triazin-3-yl)-3-methylpyrrolidin-3-yl)-3-methylisoxazole-5-carboxamide (**12**{*49*,*150*,*31*}), ^{13}C NMR (126 MHz, DMSO-d_6)



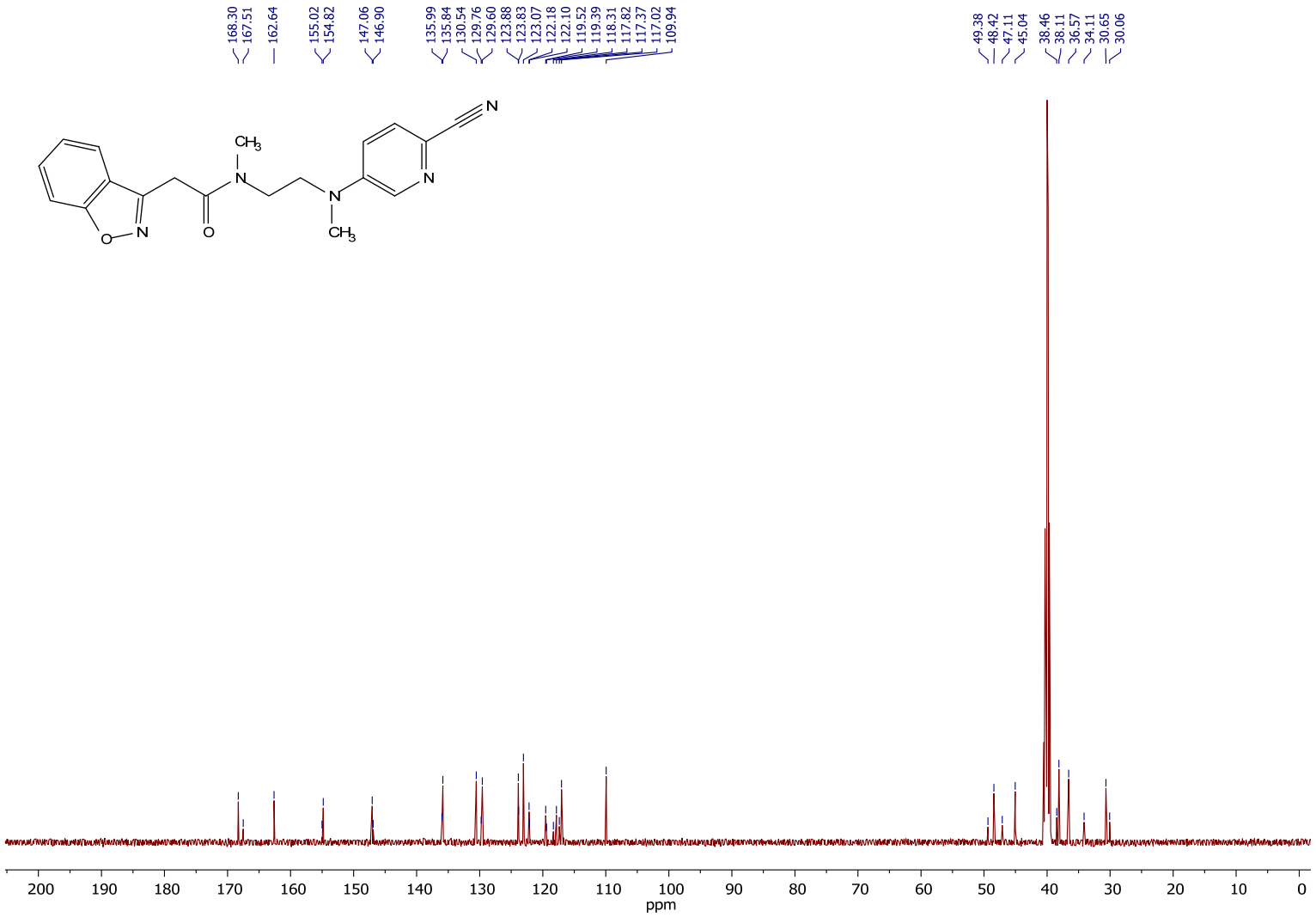
N-(6-(4-Cyano-3-methylisothiazol-5-yl)-6-azaspiro[2.5]octan-1-yl)-1-isobutyl-1*H*-pyrazole-3-carboxamide (**12**{*31*,*29*,*13*}), ^{1}H NMR (500 MHz, DMSO-d_6)



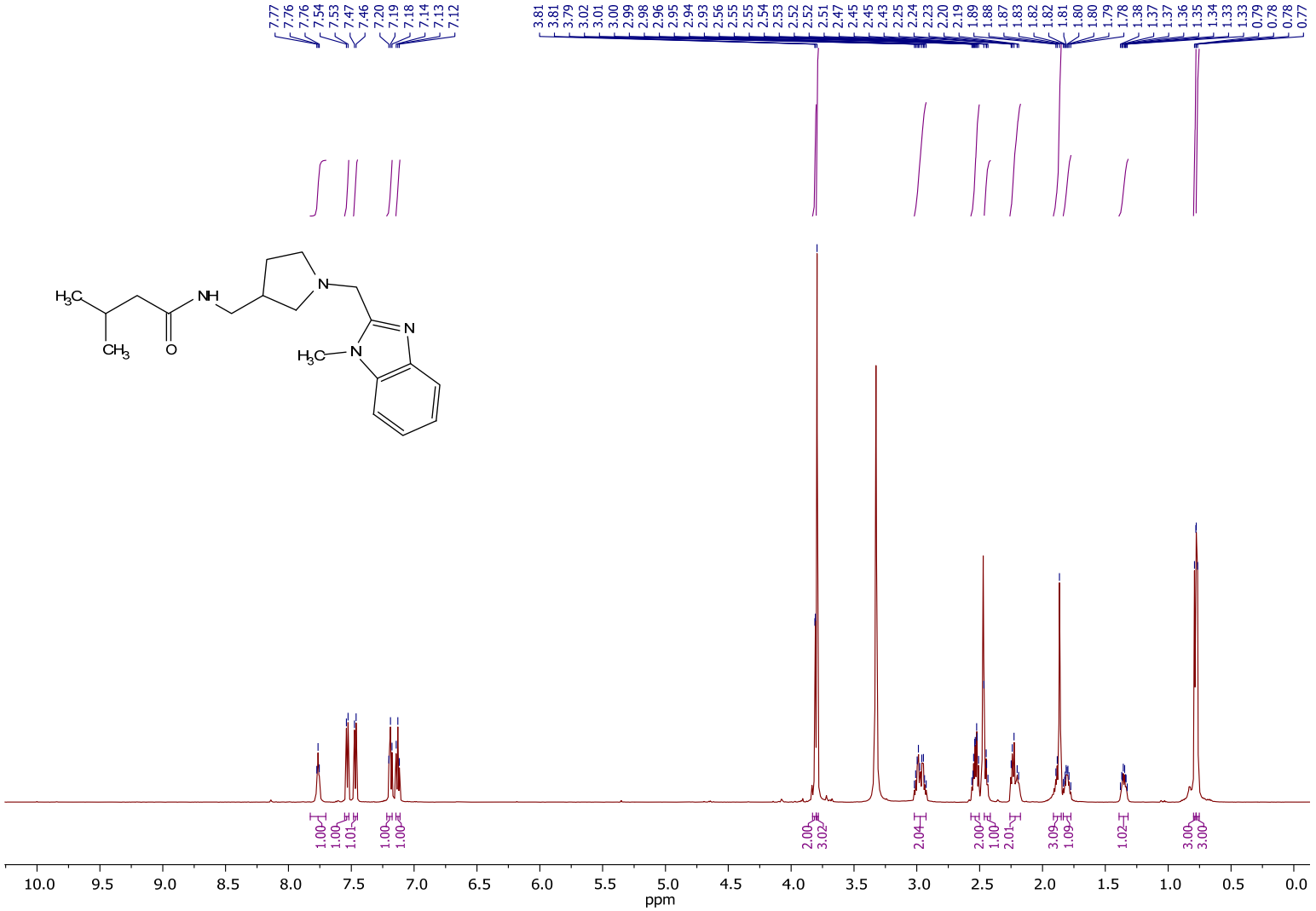
N-(6-(4-Cyano-3-methylisothiazol-5-yl)-6-azaspiro[2.5]octan-1-yl)-1-isobutyl-1*H*-pyrazole-3-carboxamide (**12**{*31*,*29*,*13*}), ^{13}C NMR (126 MHz, DMSO-d_6)



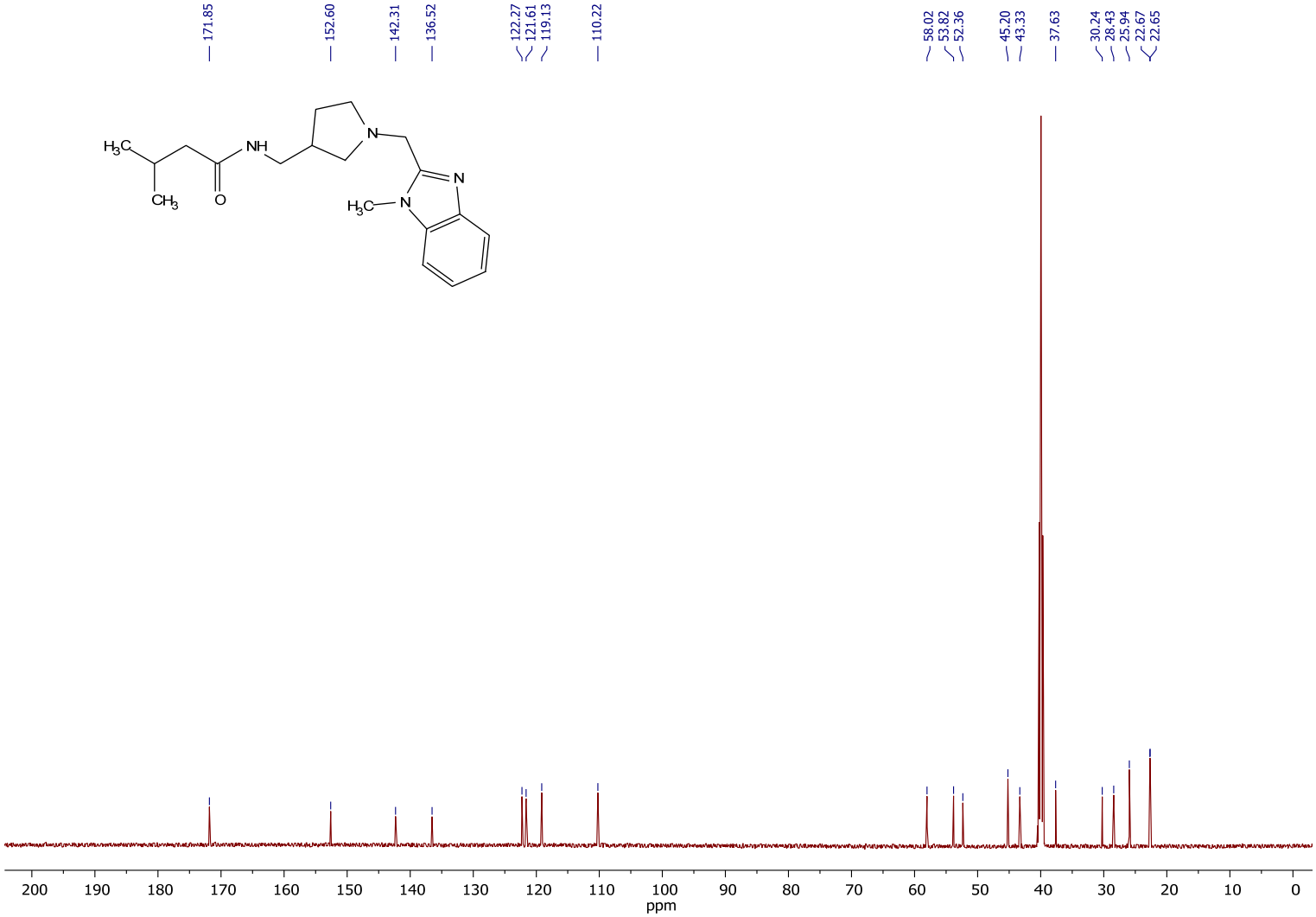
2-(Benzo[*d*]isoxazol-3-yl)-*N*-(2-((6-cyanopyridin-3-yl)(methyl)amino)ethyl)-*N*-methylacetamide (**12**{*2*,*23*,*11*}), ^{1}H NMR (500 MHz, DMSO-d_6)



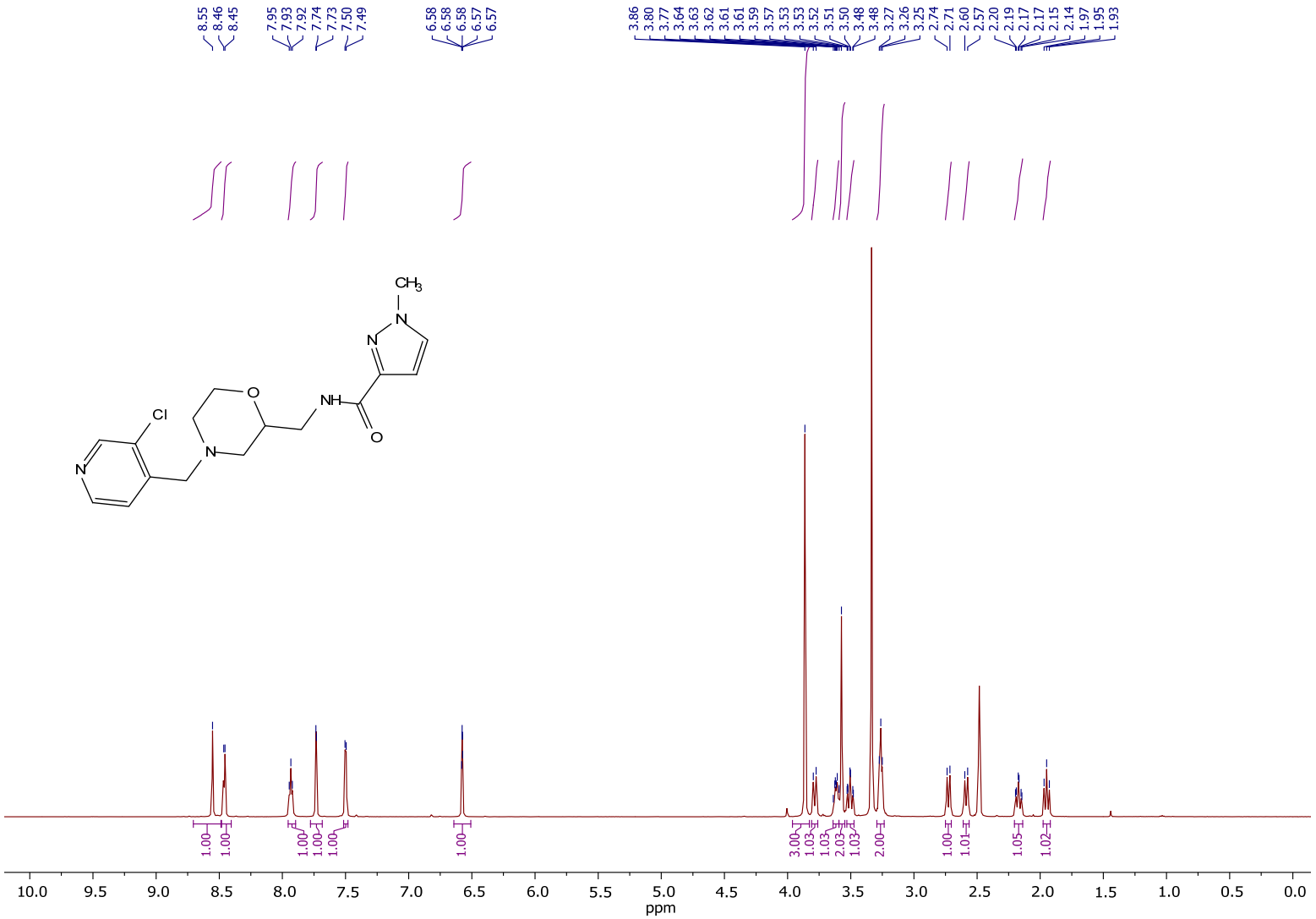
2-(Benzo[*d*]isoxazol-3-yl)-*N*-(2-((6-cyanopyridin-3-yl)(methyl)amino)ethyl)-*N*-methylacetamide (**12**{*2*,*23*,*11*}), ^{13}C NMR (126 MHz, DMSO-d_6)



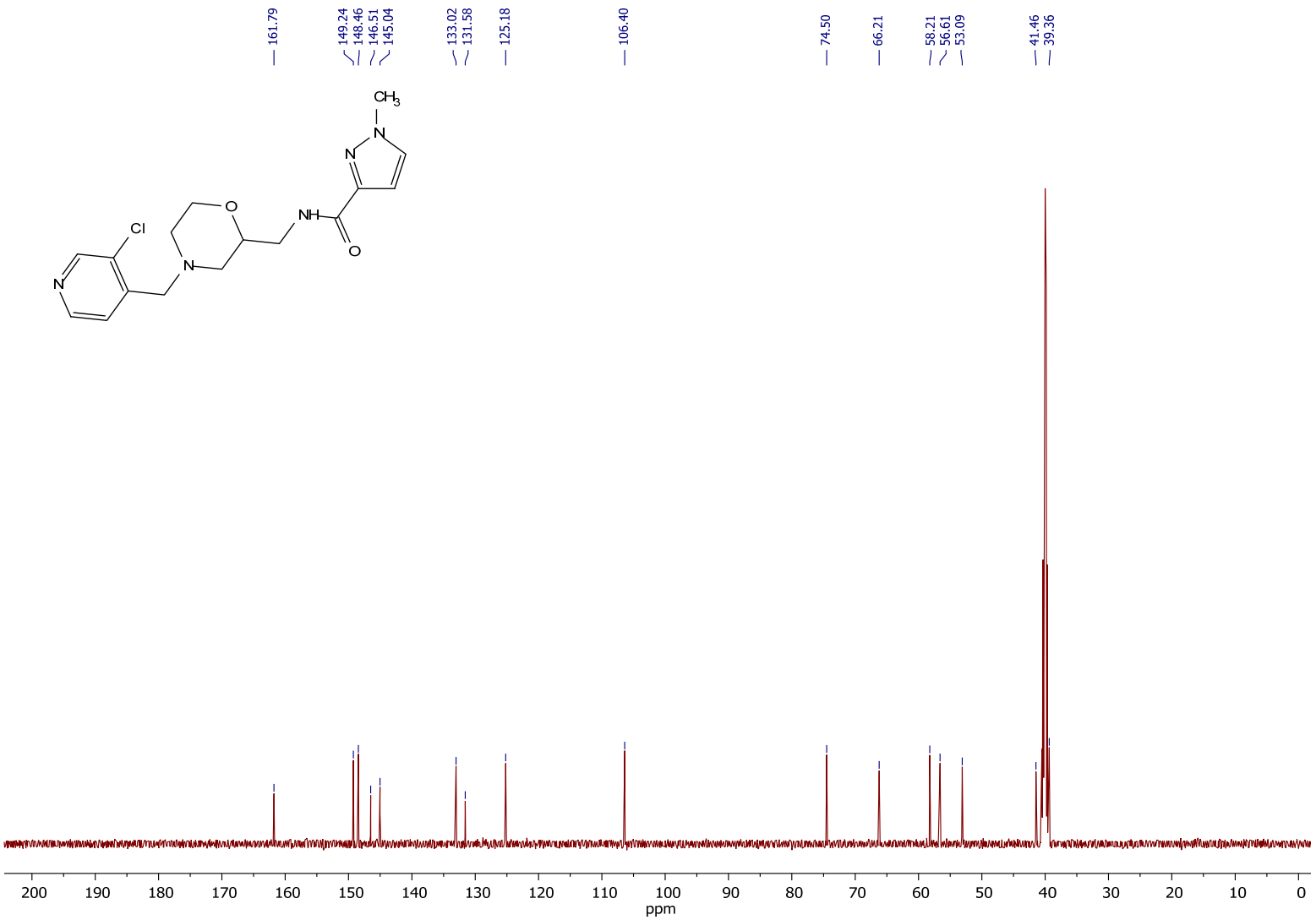
3-Methyl-*N*-((1-((1-methyl-1*H*-benzo[*d*]imidazol-2-yl)methyl)pyrrolidin-3-yl)methyl)butanamide (**13**{*85*,*113*,*14*}), ^{1}H NMR (600 MHz, DMSO-d_6)



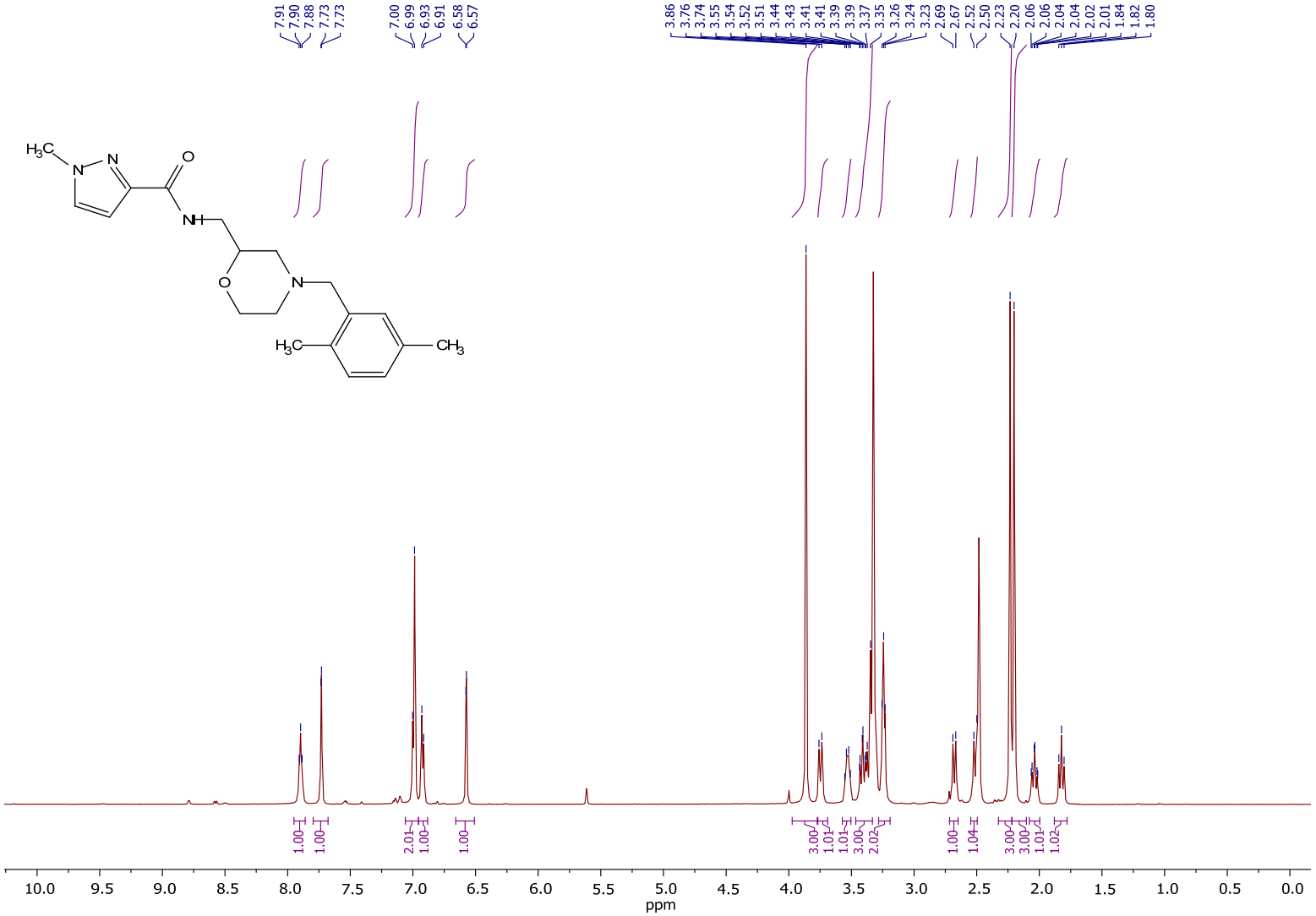
3-Methyl-*N*-((1-((1-methyl-1*H*-benzo[*d*]imidazol-2-yl)methyl)pyrrolidin-3-yl)methyl)butanamide (**13**{*85*,*113*,*14*}), ^{13}C NMR (151 MHz, DMSO-d_6)



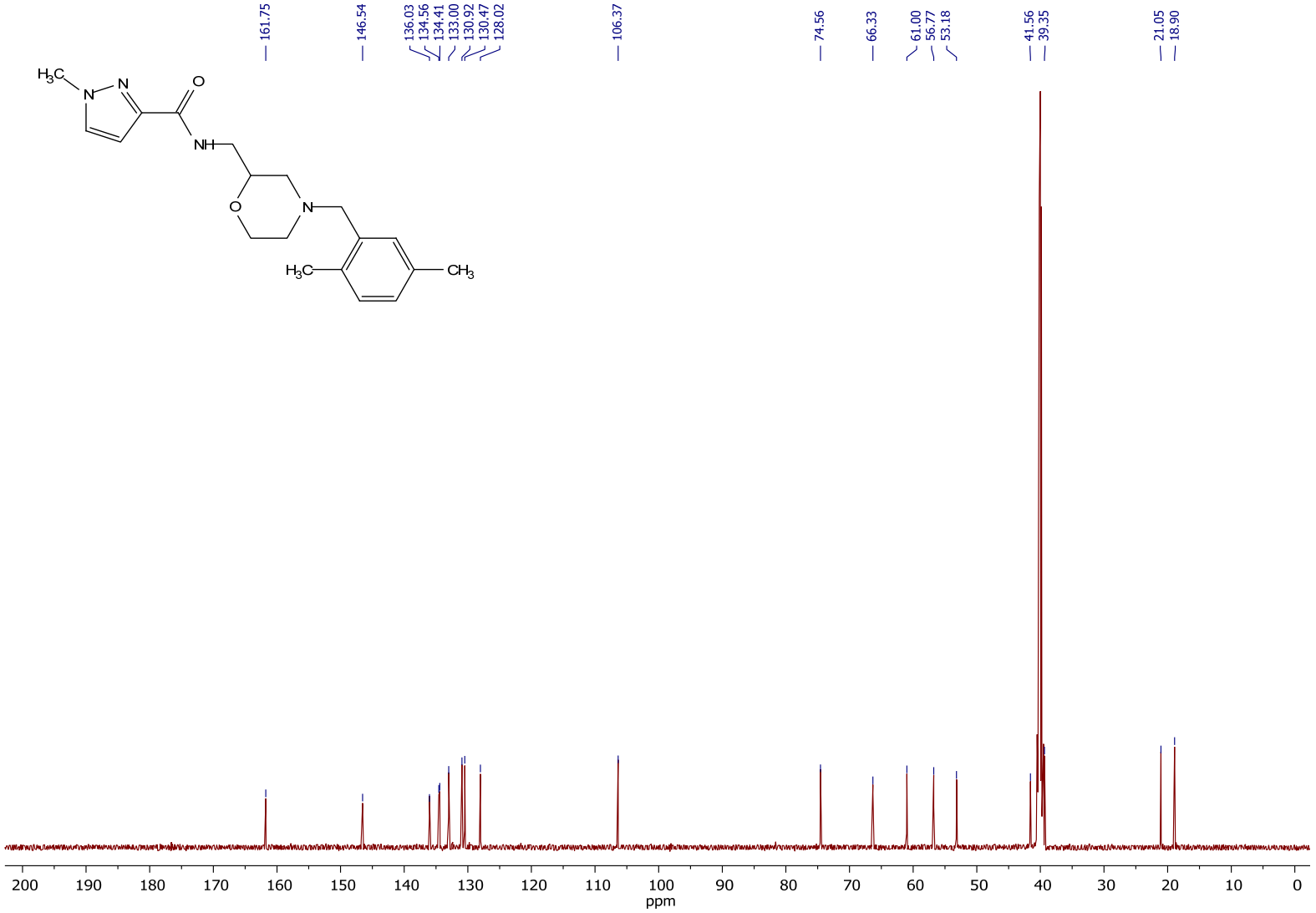
N-((4-((3-Chloropyridin-4-yl)methyl)morpholin-2-yl)methyl)-1-methyl-1*H*-pyrazole-3-carboxamide (**13**{*74*,*107*,*20*}), ^{1}H NMR (500 MHz, DMSO-d_6)



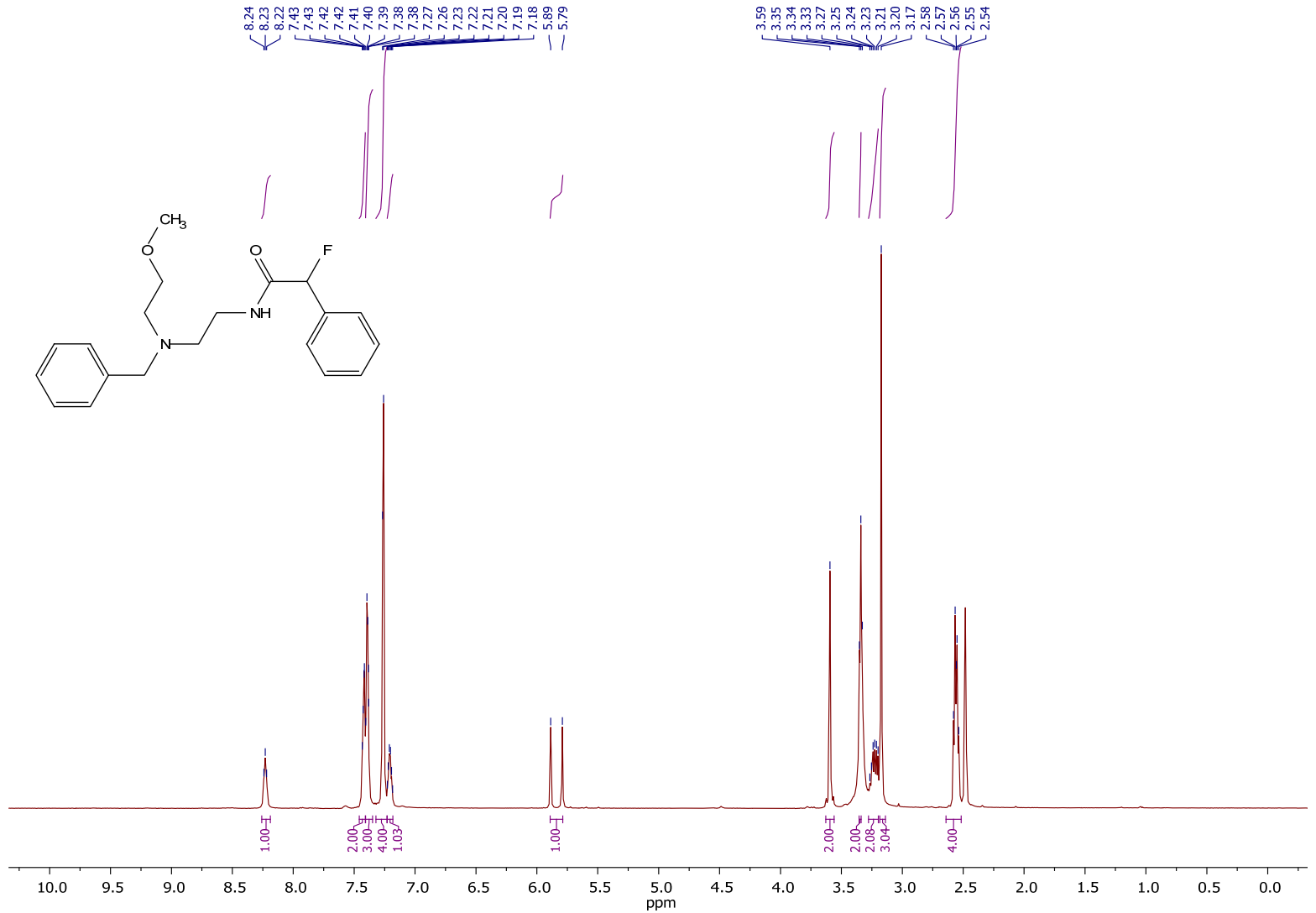
N-((4-((3-Chloropyridin-4-yl)methyl)morpholin-2-yl)methyl)-1-methyl-1*H*-pyrazole-3-carboxamide (**13**{*74*,*107*,*20*}), ^{13}C NMR (126 MHz, DMSO-d_6)



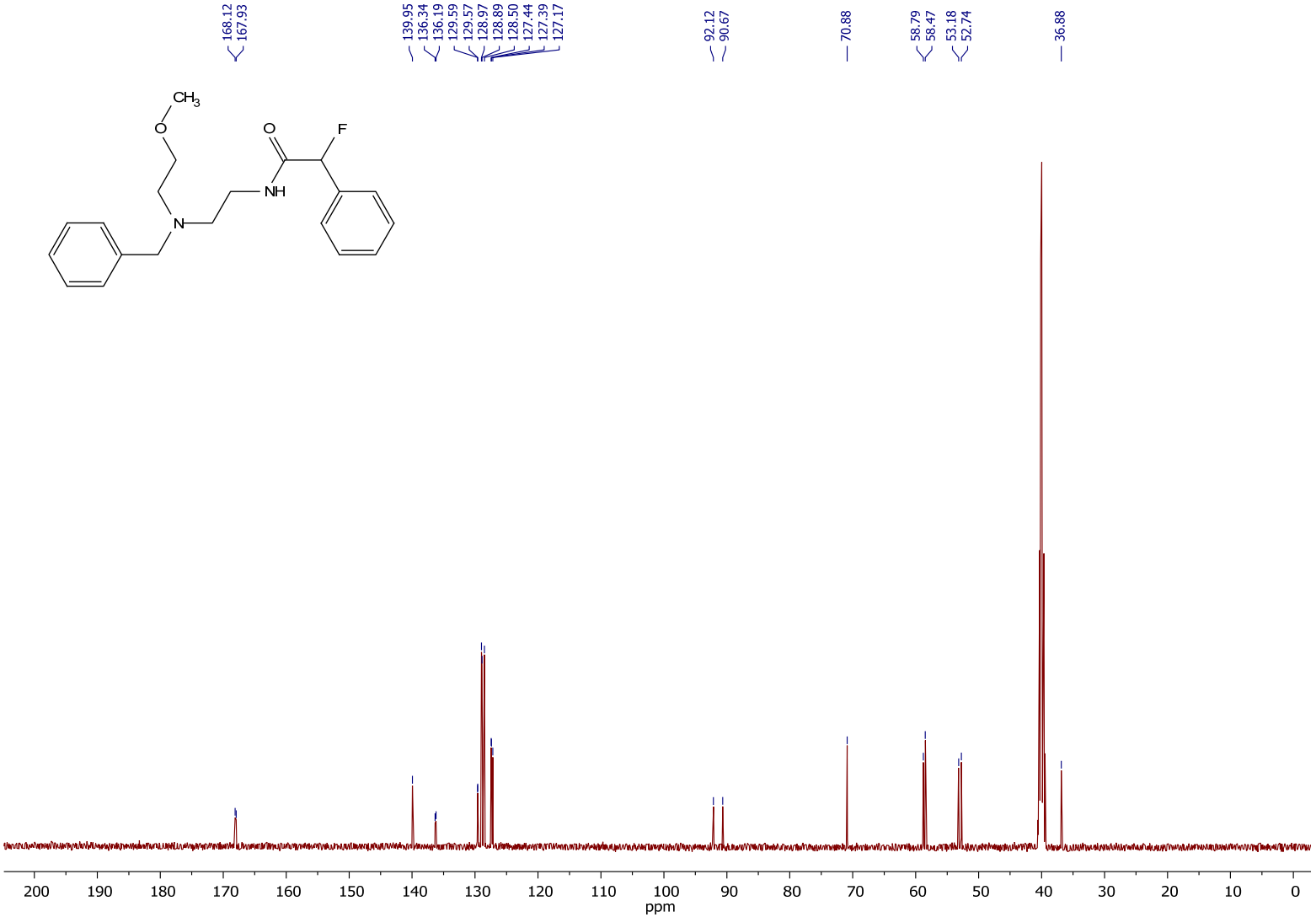
N-((4-(2,5-Dimethylbenzyl)morpholin-2-yl)methyl)-1-methyl-1*H*-pyrazole-3-carboxamide (**13**{*74*,*107*,*21*}), ^{1}H NMR (500 MHz, DMSO-d_6)



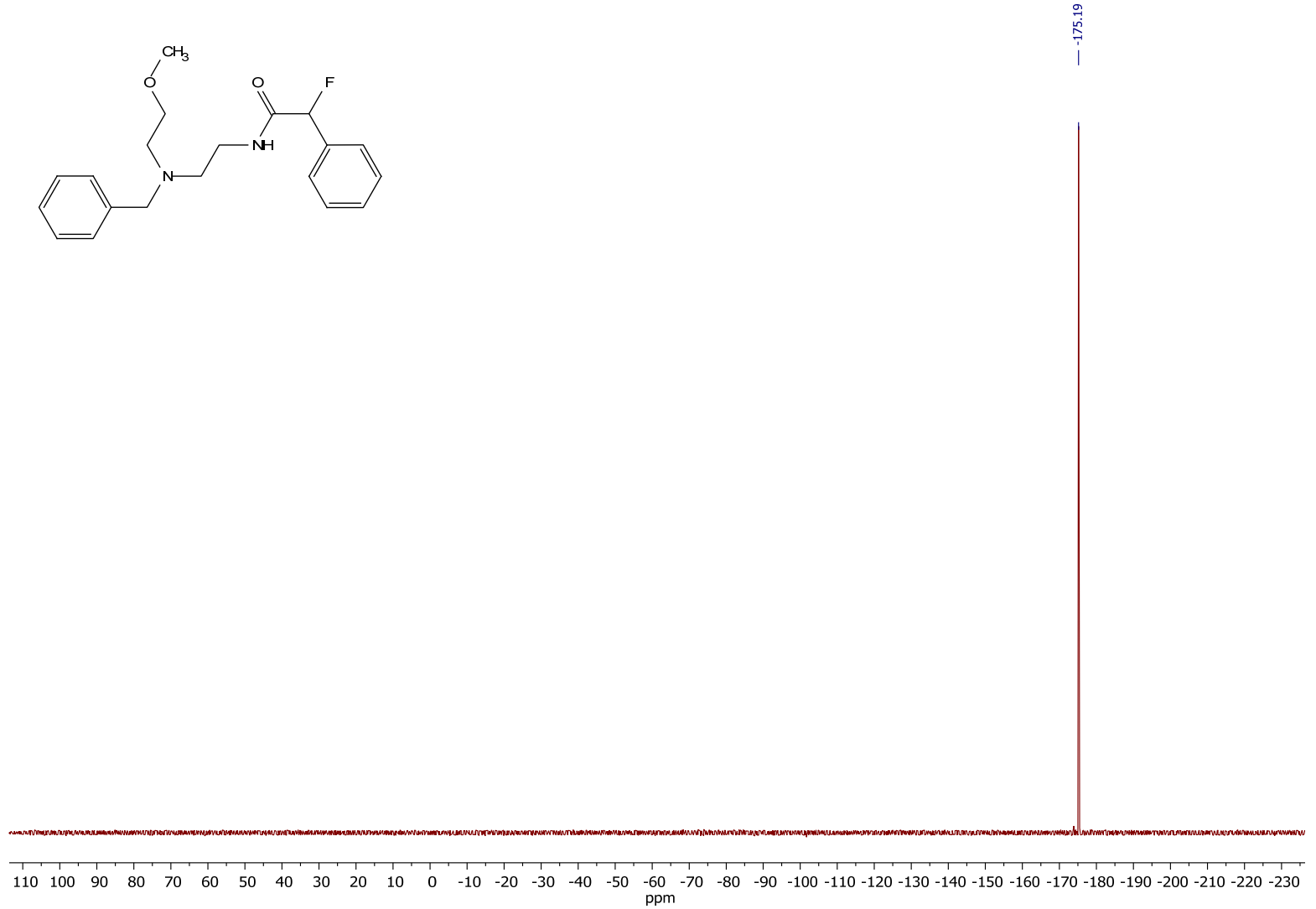
N-((4-(2,5-Dimethylbenzyl)morpholin-2-yl)methyl)-1-methyl-1*H*-pyrazole-3-carboxamide (**13**{*74*,*107*,*21*}), ^{13}C NMR (126 MHz, DMSO-d_6)



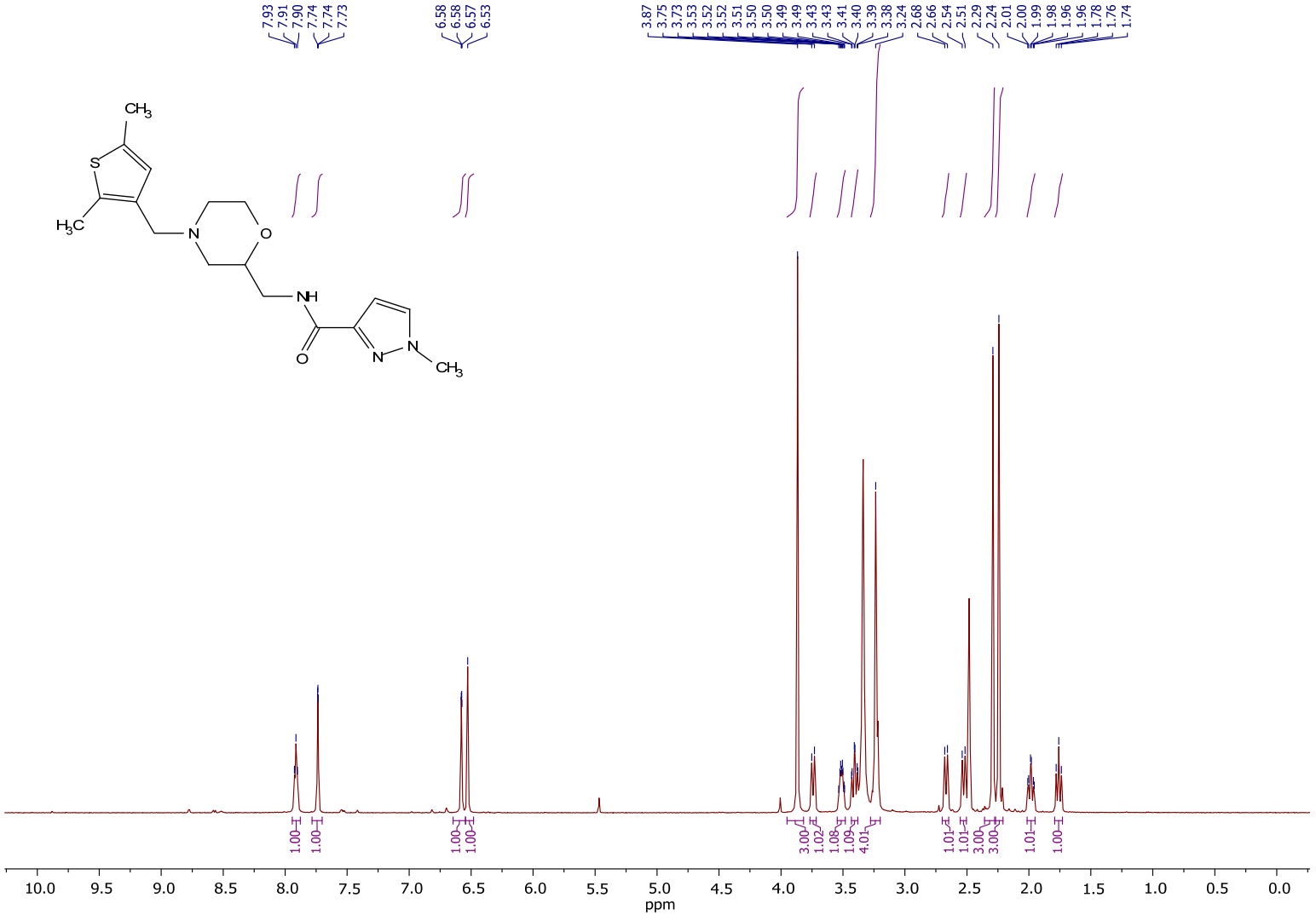
N-(2-(Benzyl(2-methoxyethyl)amino)ethyl)-2-fluoro-2-phenylacetamide (**13**{*107*,*152*,*23*}), ^{1}H NMR (500 MHz, DMSO-d_6



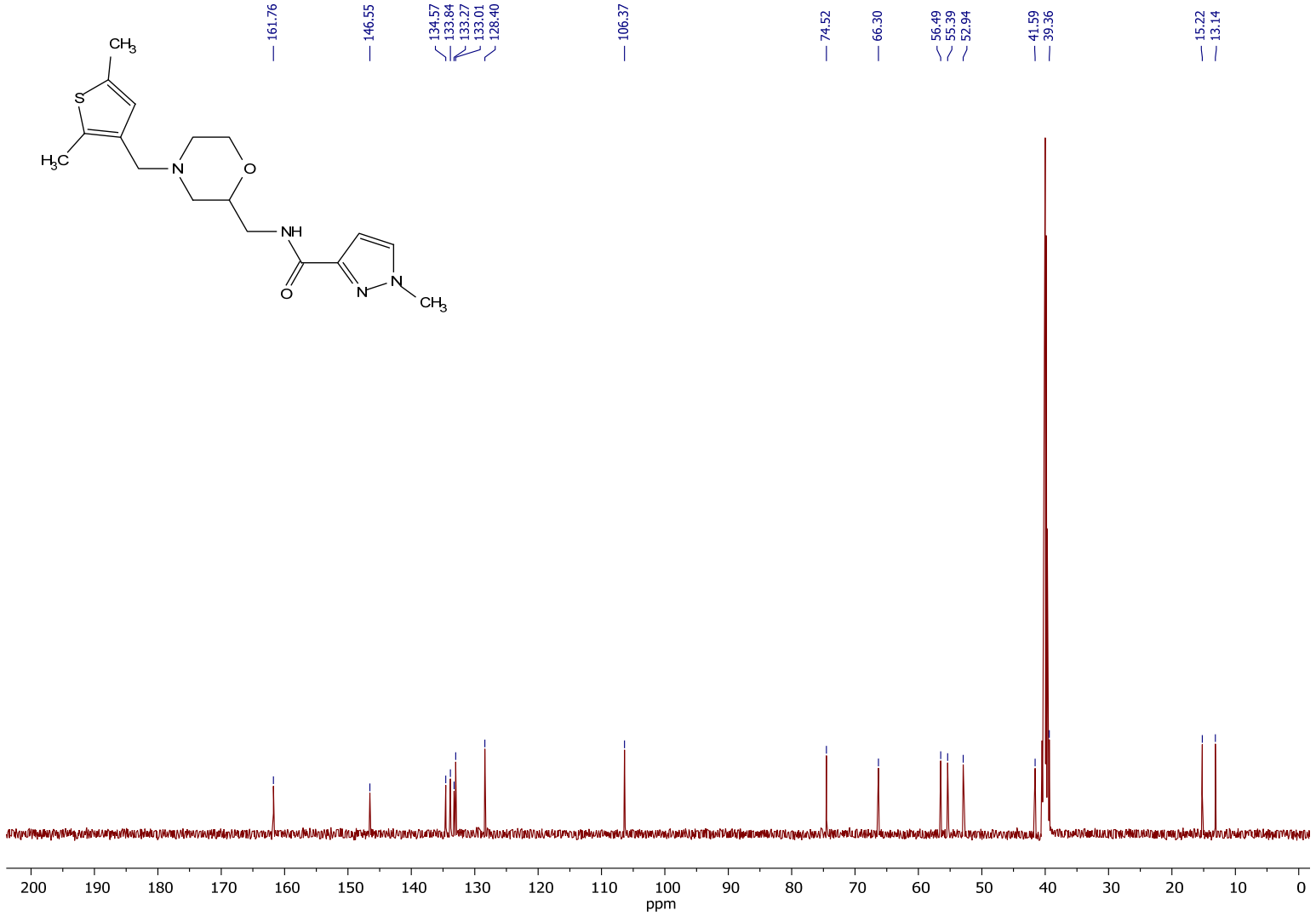
N-(2-(Benzyl(2-methoxyethyl)amino)ethyl)-2-fluoro-2-phenylacetamide (**13**{*107*,*152*,*23*}), ^{13}C NMR (126 MHz, DMSO-d_6)



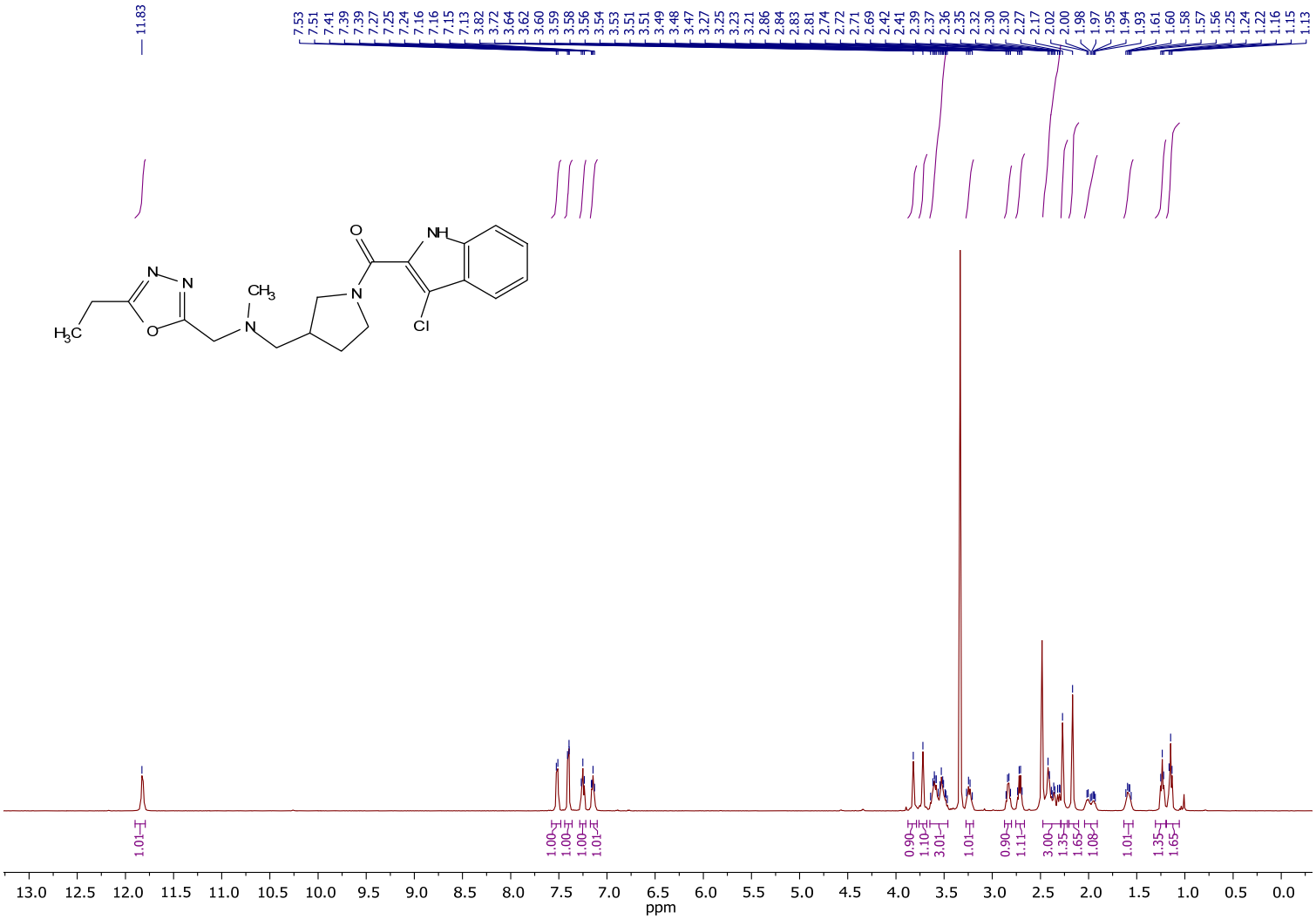
N-(2-(Benzyl(2-methoxyethyl)amino)ethyl)-2-fluoro-2-phenylacetamide (**13**{*107*,*152*,*23*}), ^{19}F NMR (376 MHz, DMSO-d_6)



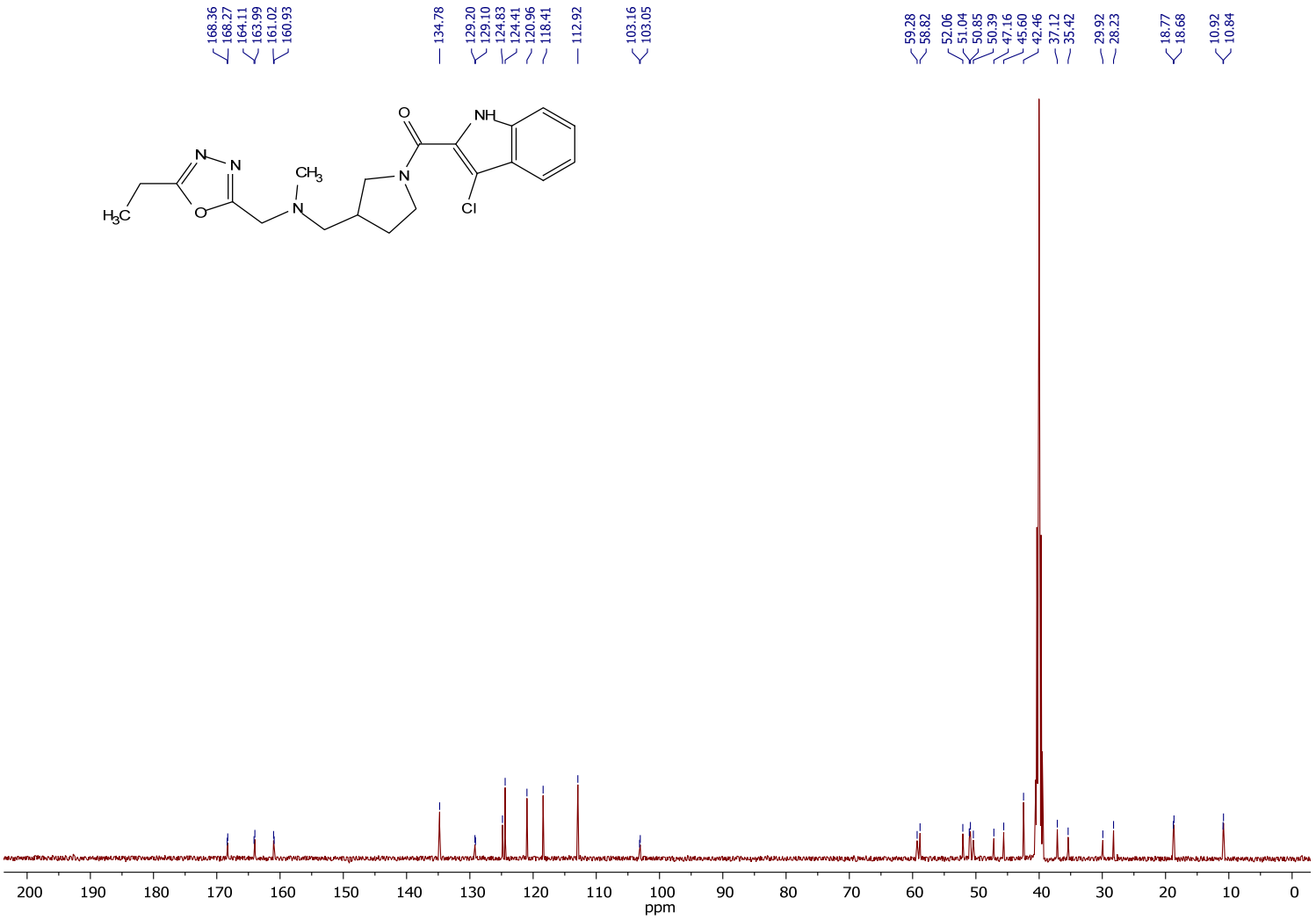
N-((4-((2,5-Dimethylthiophen-3-yl)methyl)morpholin-2-yl)methyl)-1-methyl-1*H*-pyrazole-3-carboxamide (**13**{*74*,*107*,*27*}), ^{1}H NMR (500 MHz, DMSO-d_6)



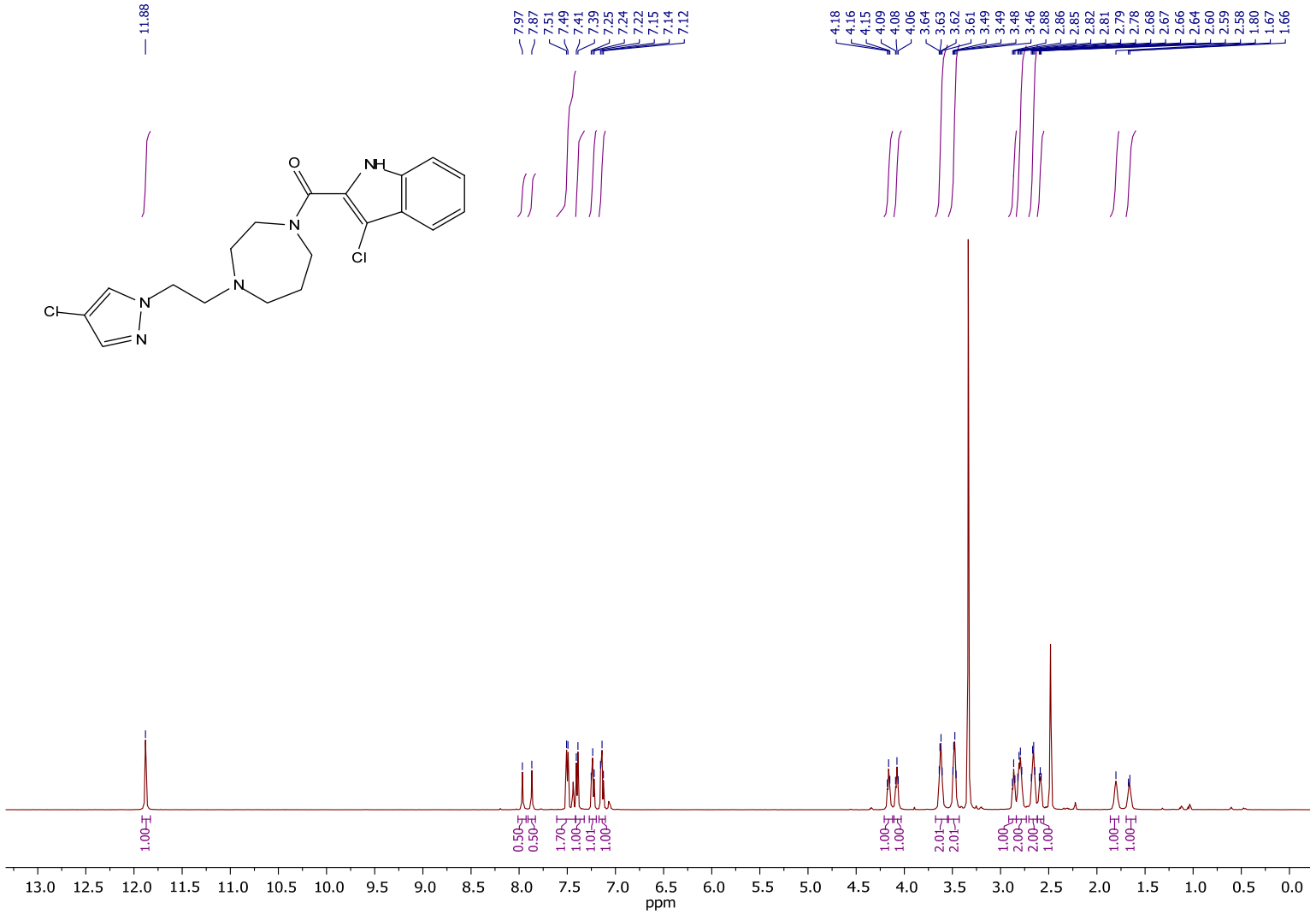
N-((4-((2,5-Dimethylthiophen-3-yl)methyl)morpholin-2-yl)methyl)-1-methyl-1*H*-pyrazole-3-carboxamide (**13**{*74*,*107*,*27*}), ^{13}C NMR (126 MHz, DMSO-d_6)



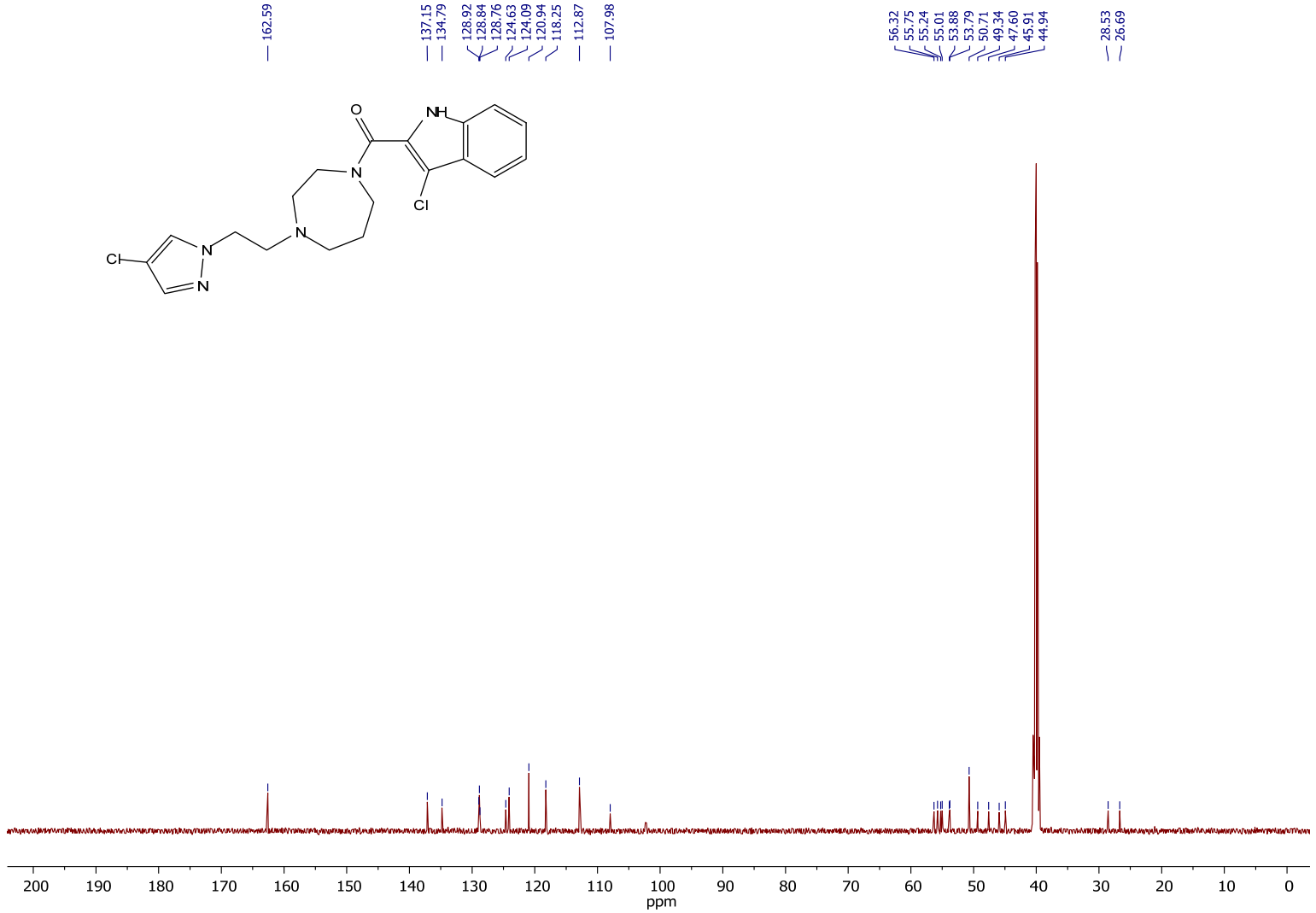
(3-Chloro-1*H*-indol-2-yl)(3-((((5-ethyl-1,3,4-oxadiazol-2-yl)methyl)(methyl)amino)methyl)pyrrolidin-1-yl)methanone (**13**{*44*,*129*,*33*}), ^{1}H NMR (500 MHz, DMSO-d_6)



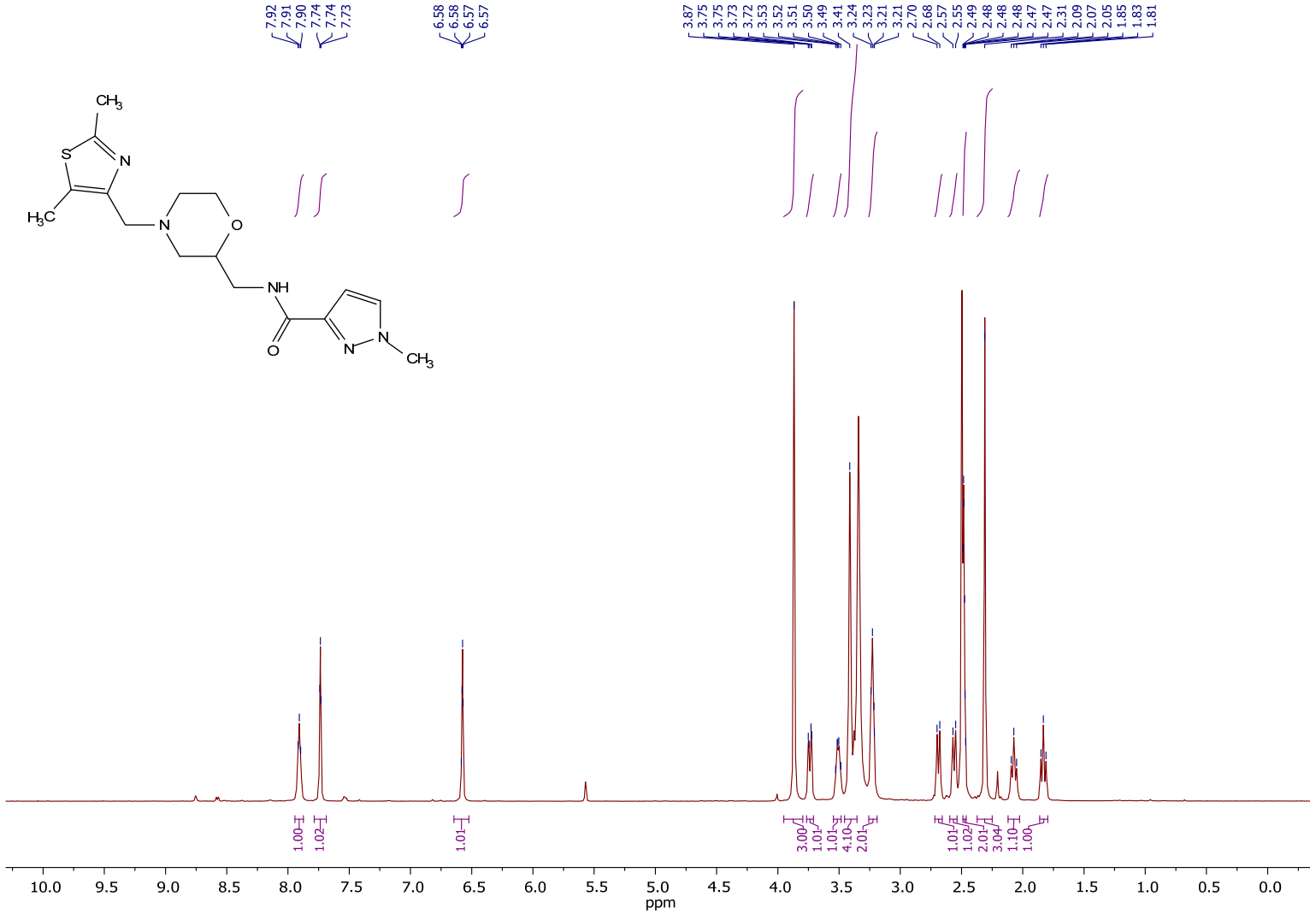
(3-Chloro-1*H*-indol-2-yl)(3-((((5-ethyl-1,3,4-oxadiazol-2-yl)methyl)(methyl)amino)methyl)pyrrolidin-1-yl)methanone (**13**{*44*,*129*,*33*}), ^{13}C NMR (126 MHz, DMSO-d_6)



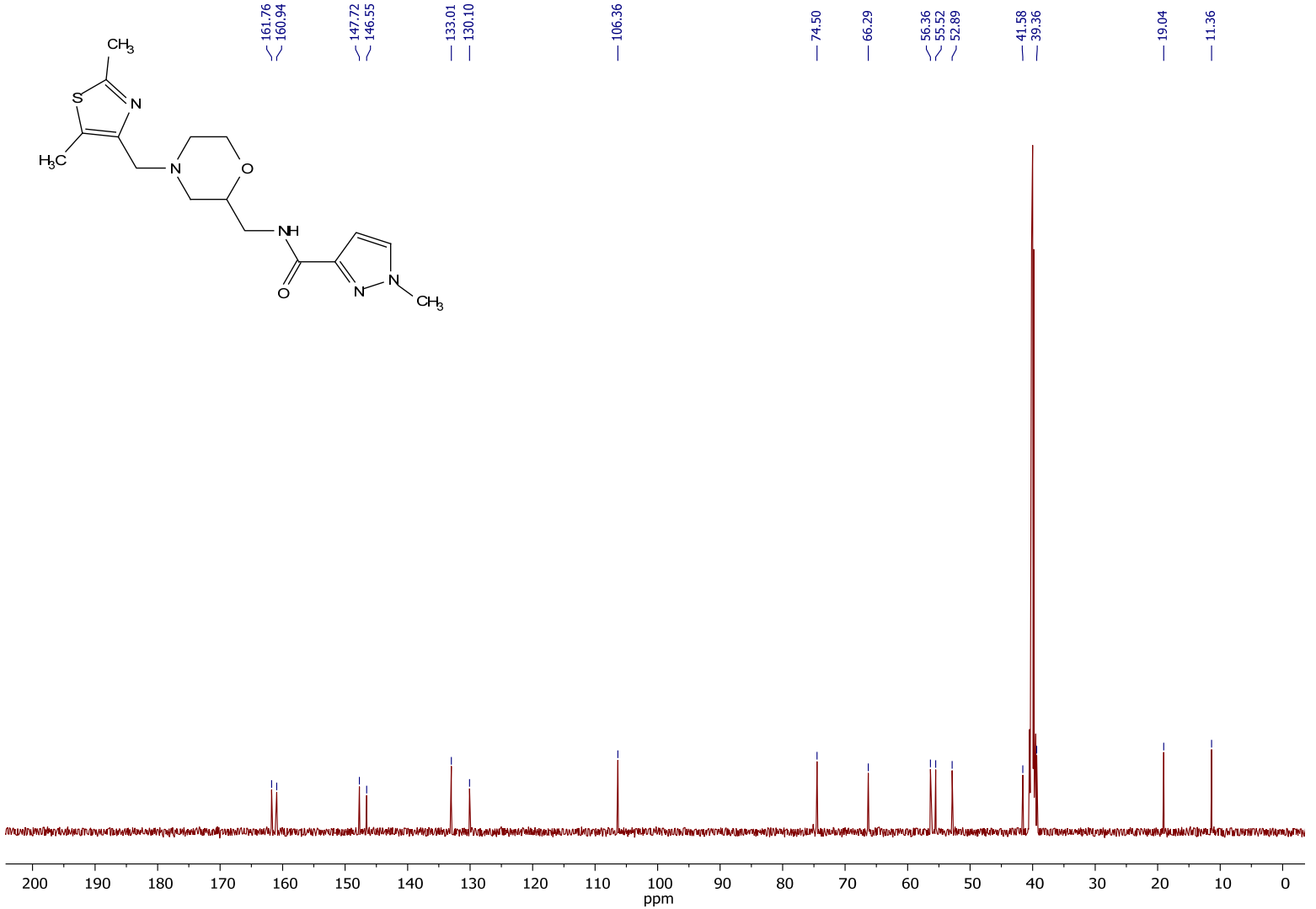
(3-Chloro-1*H*-indol-2-yl)(4-(2-(4-chloro-1*H*-pyrazol-1-yl)ethyl)-1,4-diazepan-1-yl)methanone (**13**{*23*,*129*,*34*}), ^{1}H NMR (500 MHz, DMSO-d_6)



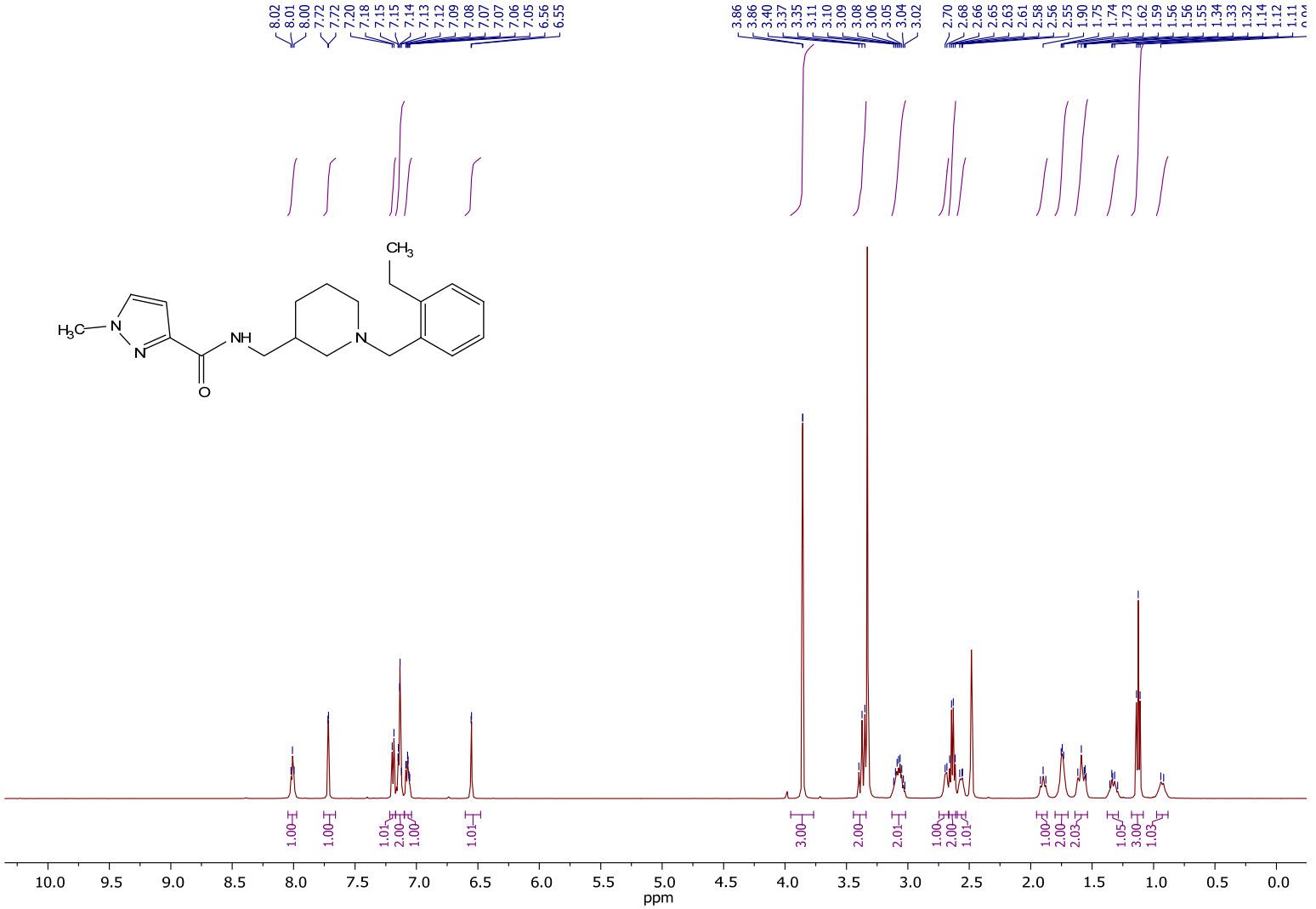
(3-Chloro-1*H*-indol-2-yl)(4-(2-(4-chloro-1*H*-pyrazol-1-yl)ethyl)-1,4-diazepan-1-yl)methanone (**13**{*23*,*129*,*34*}), ^{13}C NMR (126 MHz, DMSO-d_6)



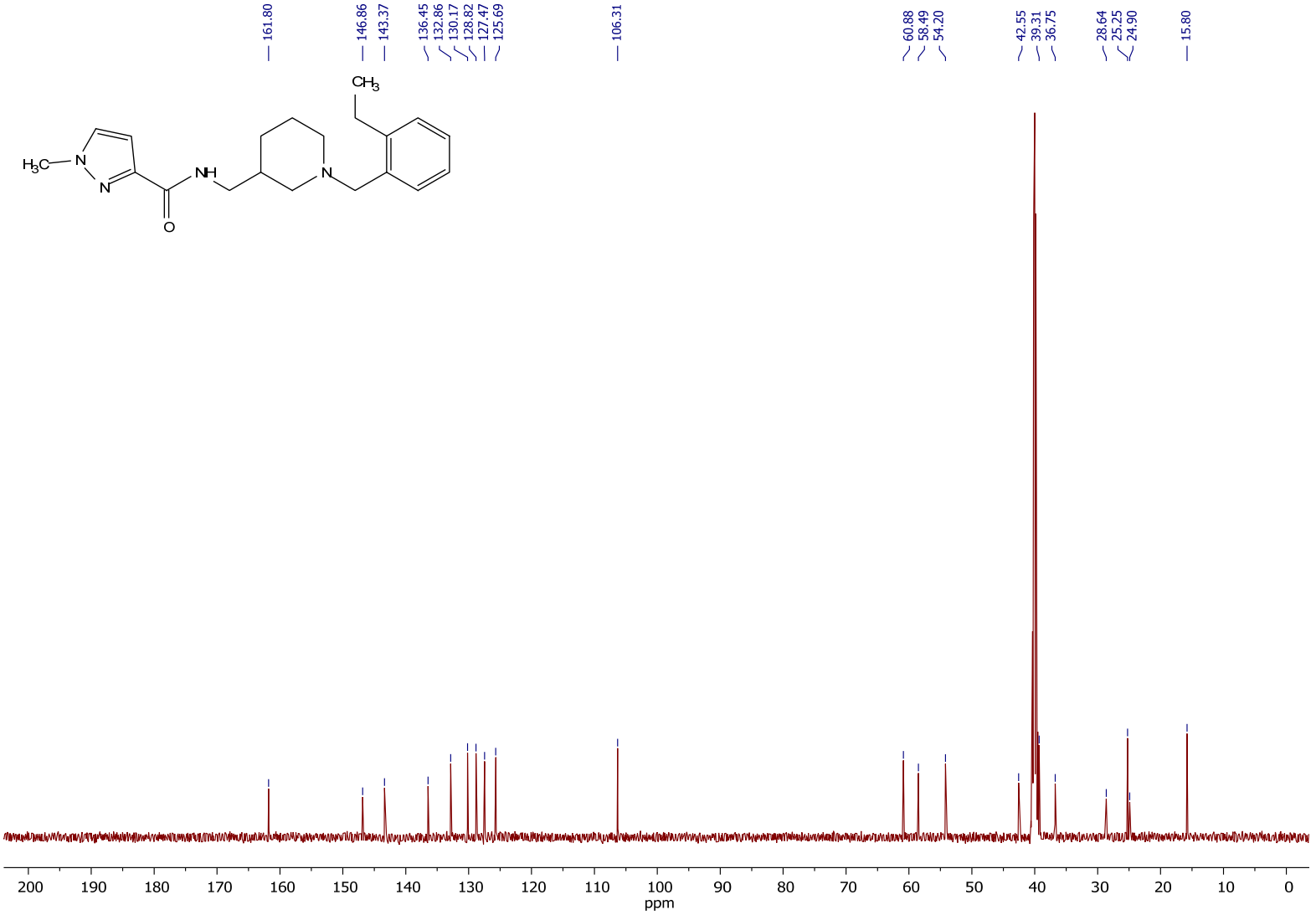
N-((4-((2,5-Dimethylthiazol-4-yl)methyl)morpholin-2-yl)methyl)-1-methyl-1*H*-pyrazole-3-carboxamide (**13**{*74*,*107*,*35*}), ^{1}H NMR (500 MHz, DMSO-d_6)



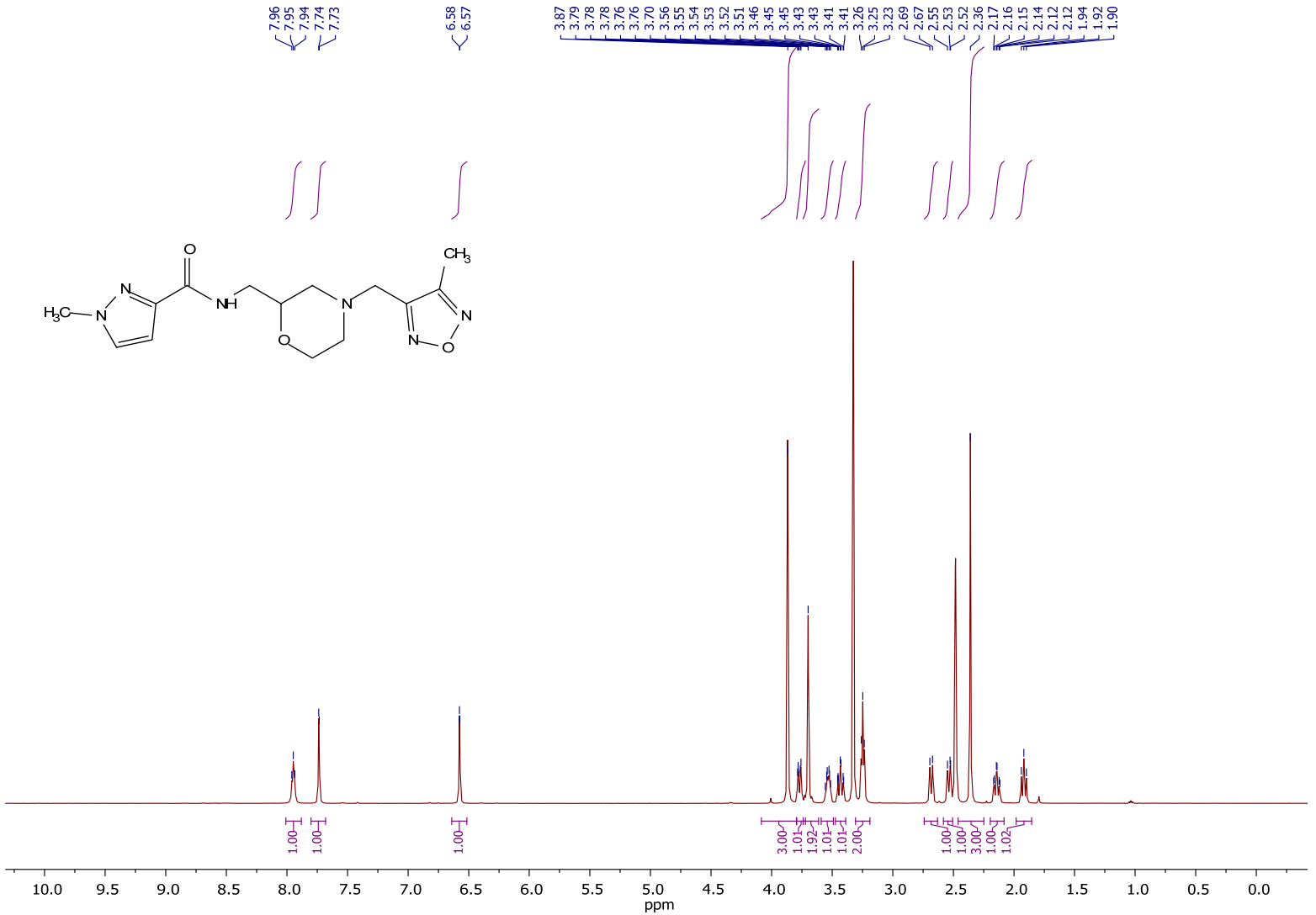
N-((4-((2,5-Dimethylthiazol-4-yl)methyl)morpholin-2-yl)methyl)-1-methyl-1*H*-pyrazole-3-carboxamide (**13**{*74*,*107*,*35*}), ^{13}C NMR (126 MHz, DMSO-d_6)



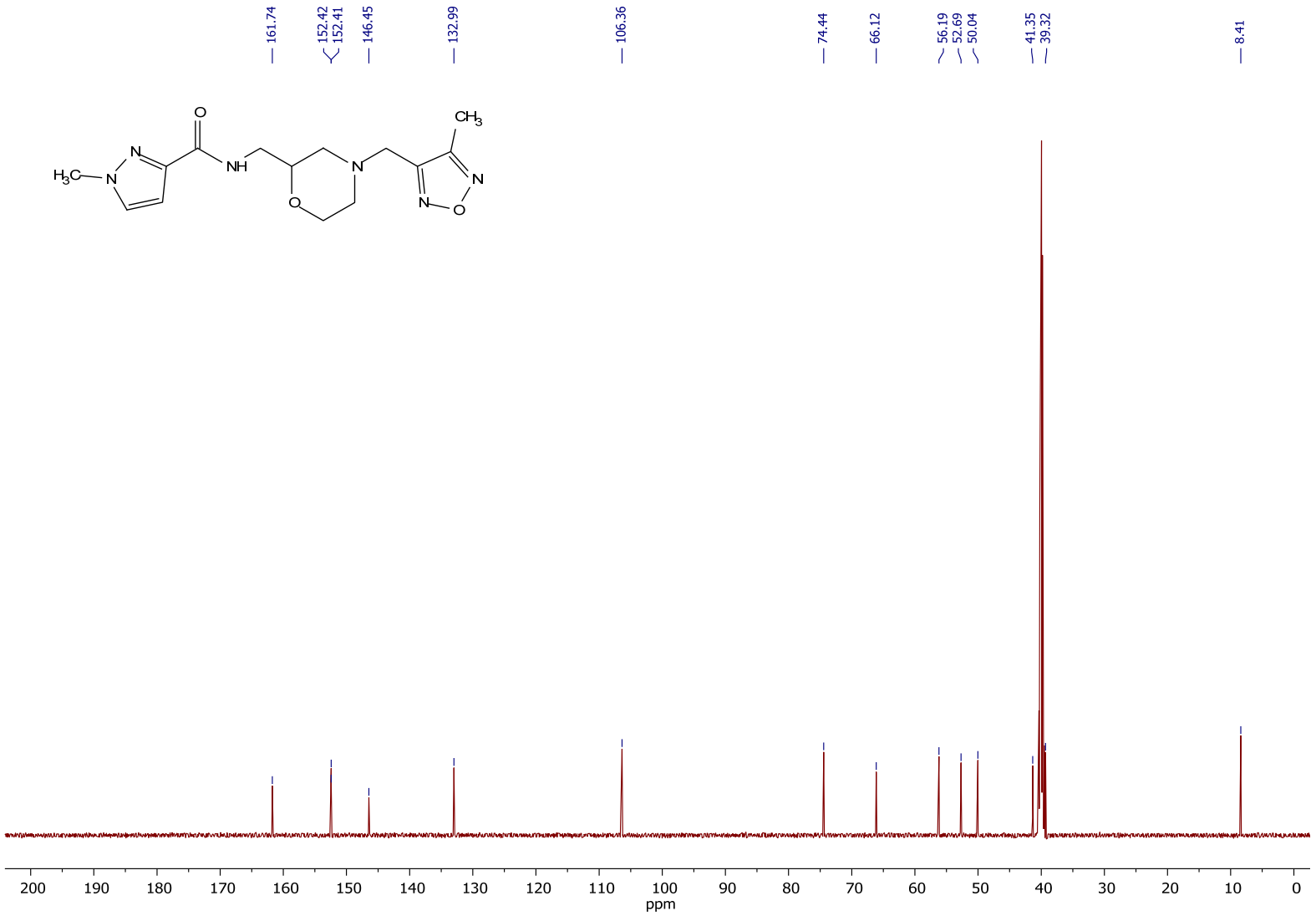
N-((1-(2-Ethylbenzyl)piperidin-3-yl)methyl)-1-methyl-1*H*-pyrazole-3-carboxamide (**13**{*102*,*107*,*29*}), ^{1}H NMR (500 MHz, DMSO-d_6)



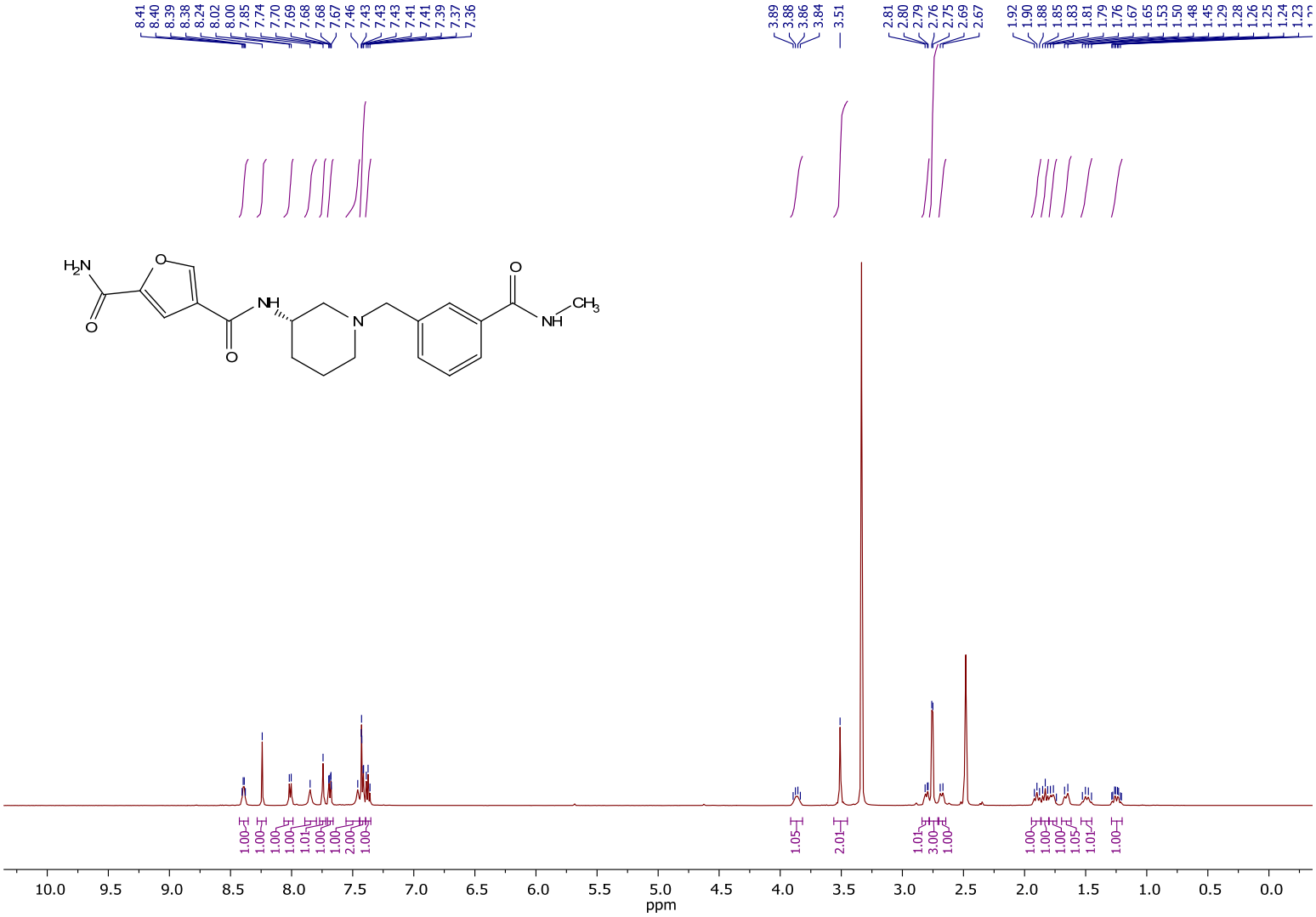
N-((1-(2-Ethylbenzyl)piperidin-3-yl)methyl)-1-methyl-1*H*-pyrazole-3-carboxamide (**13**{*102*,*107*,*29*}), ^{13}C NMR (126 MHz, DMSO-d_6)



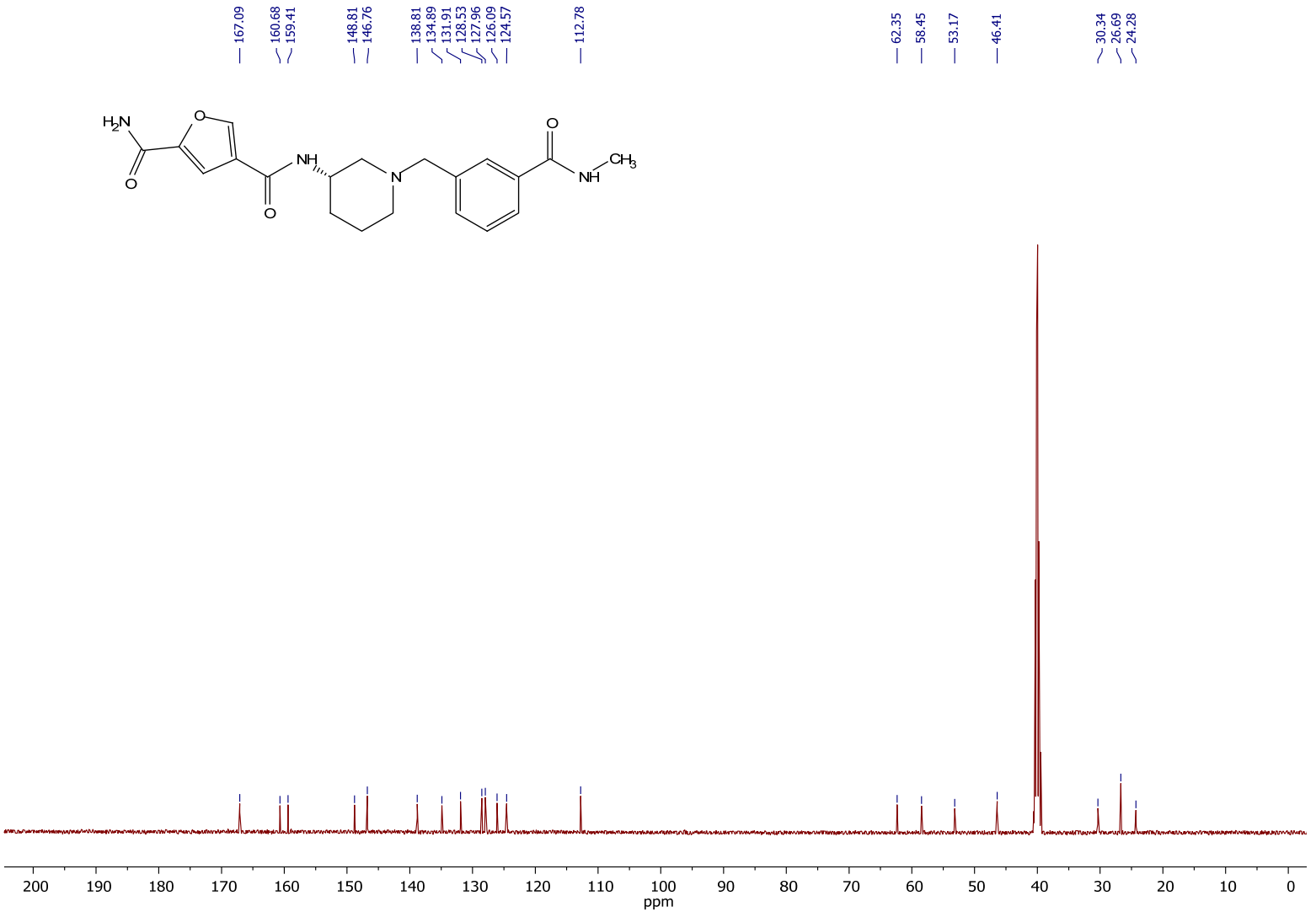
1-Methyl-*N*-((4-((4-methyl-1,2,5-oxadiazol-3-yl)methyl)morpholin-2-yl)methyl)-1*H*-pyrazole-3-carboxamide (**13**{*74*,*107*,*38*}), ^{1}H NMR (500 MHz, DMSO-d_6)



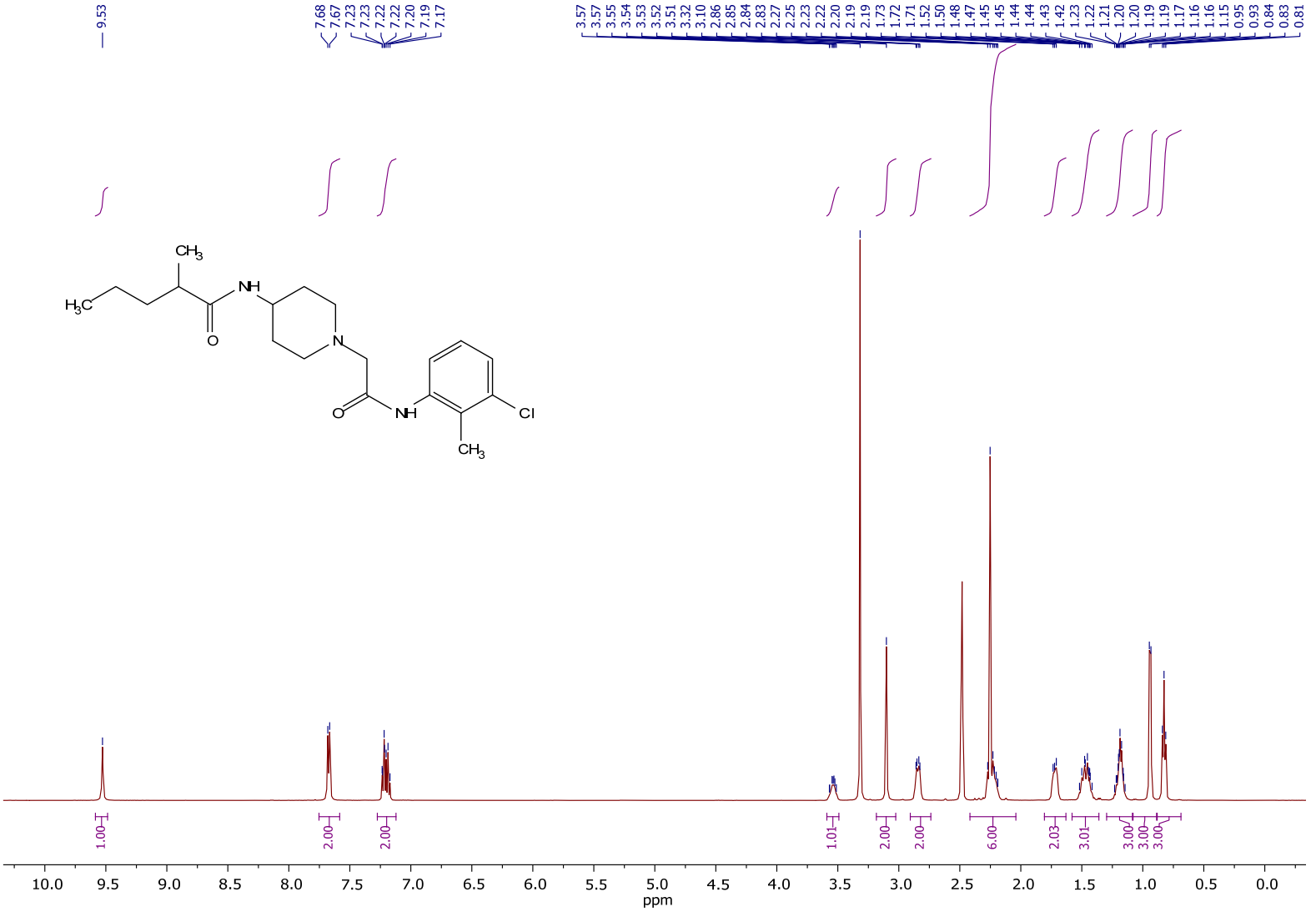
1-Methyl-*N*-((4-((4-methyl-1,2,5-oxadiazol-3-yl)methyl)morpholin-2-yl)methyl)-1*H*-pyrazole-3-carboxamide (**13**{*74*,*107*,*38*}), ^{13}C NMR (151 MHz, DMSO-d_6)



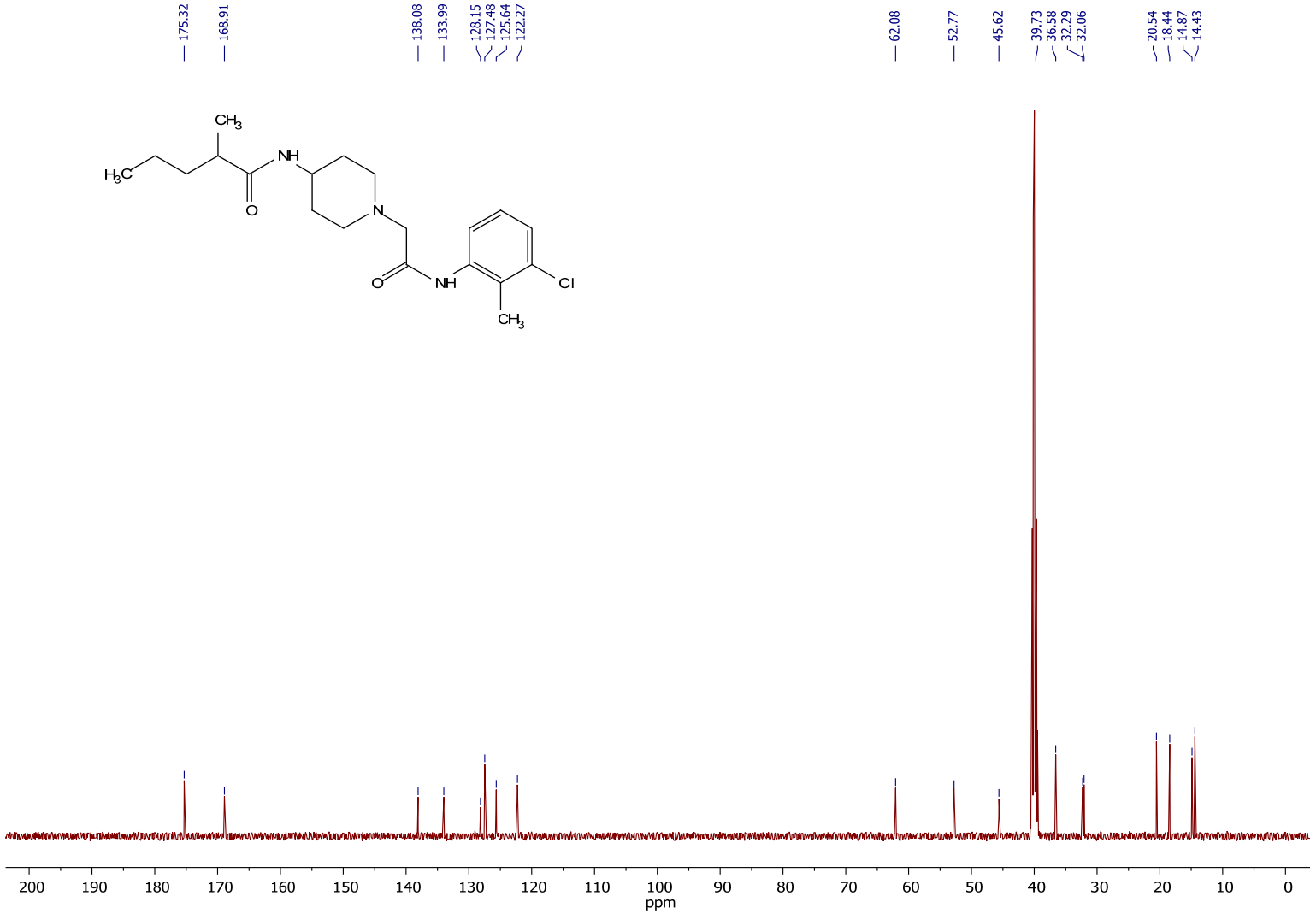
(*S*)-N^4-(1-(3-(Methylcarbamoyl)benzyl)piperidin-3-yl)furan-2,4-dicarboxamide (**13**{*139*,*243*,*50*}), ^{1}H NMR (500 MHz, DMSO-d_6)



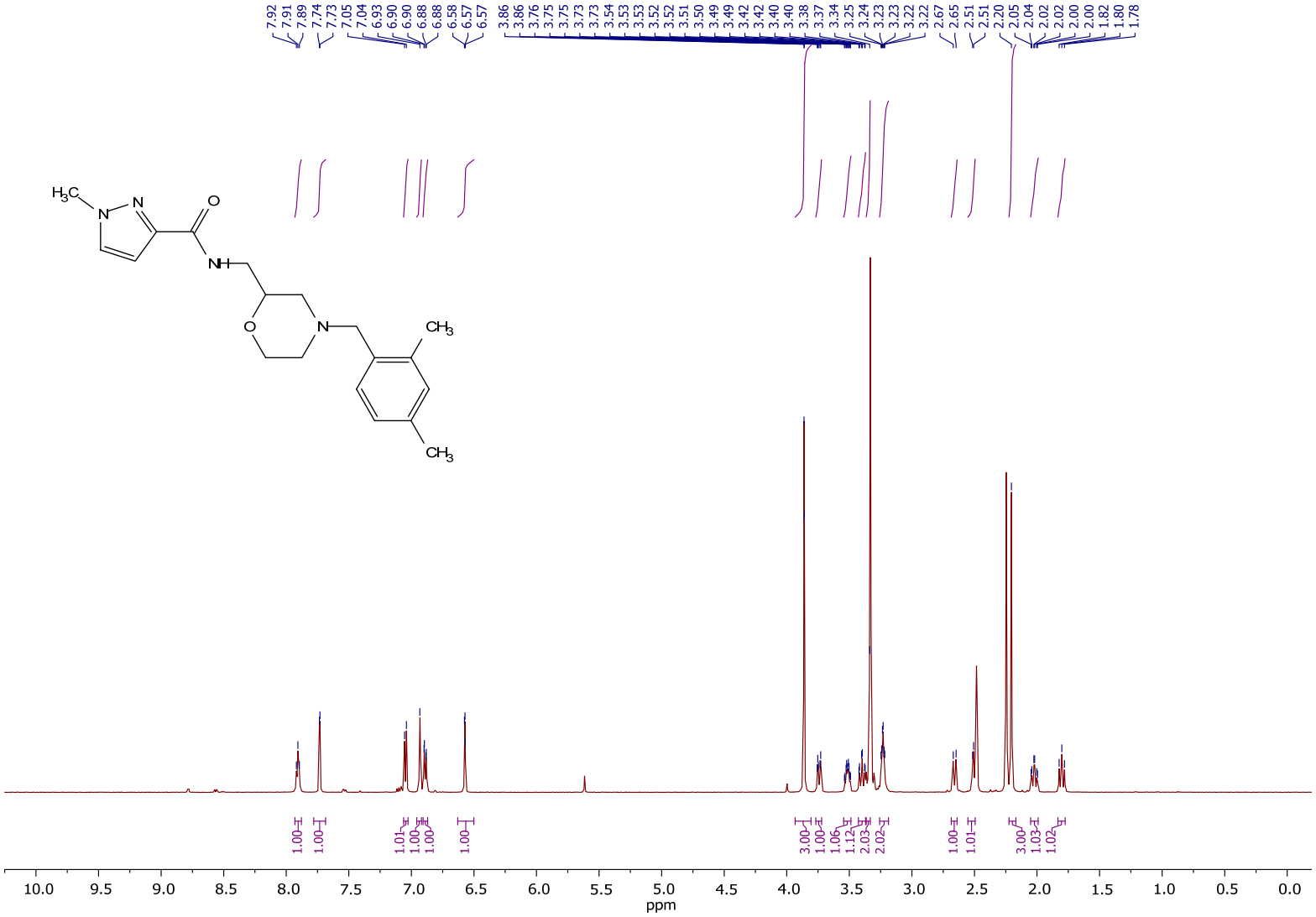
(*S*)-*N*^{4}-(1-(3-(Methylcarbamoyl)benzyl)piperidin-3-yl)furan-2,4-dicarboxamide (**13**{*139*,*243*,*50*}), ^{13}C NMR (126 MHz, DMSO-d_6)



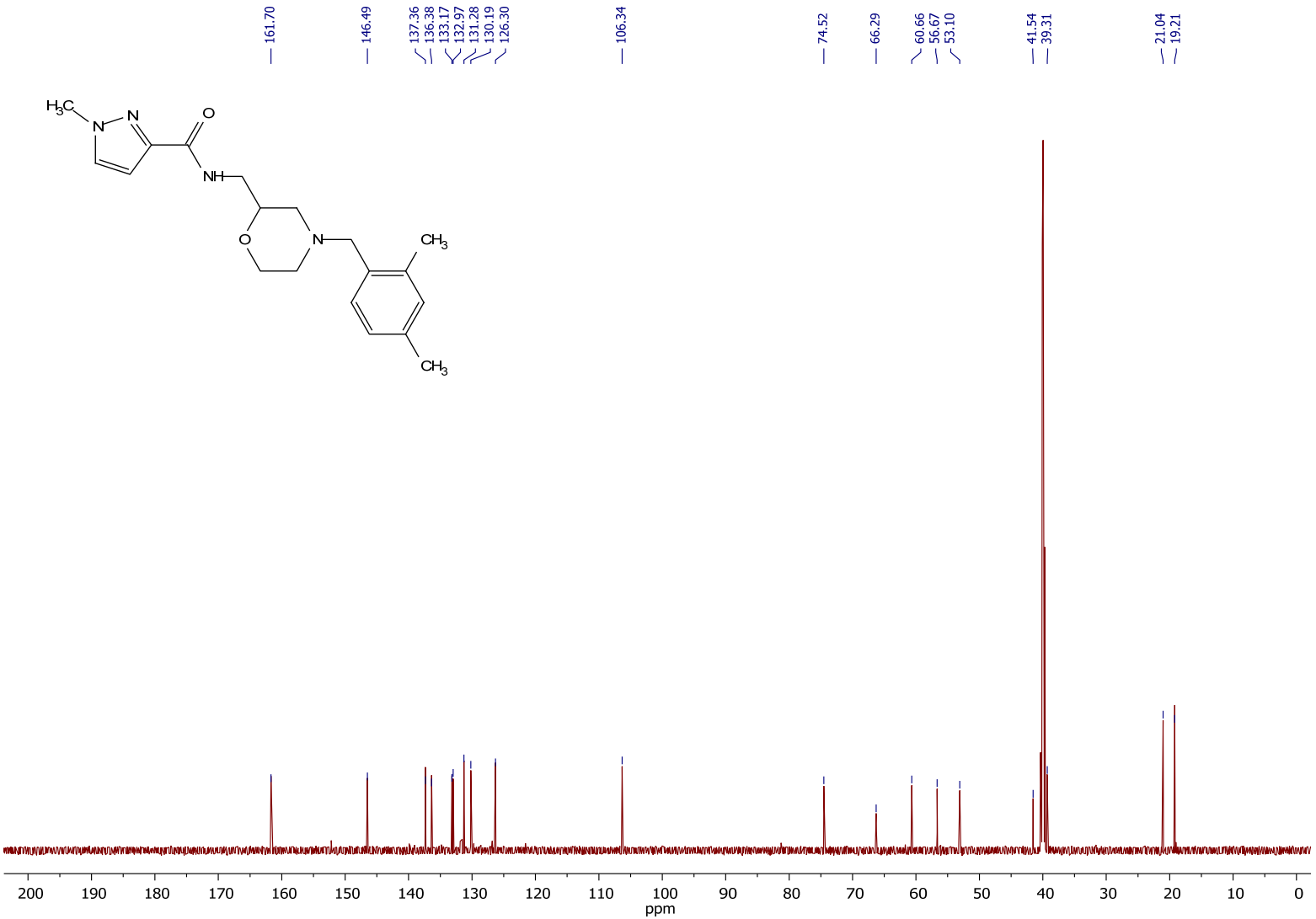
N-(1-(2-((3-Chloro-2-methylphenyl)amino)-2-oxoethyl)piperidin-4-yl)-2-methylpentanamide (**13**{*79*,*95*,*11*}), ^{1}H NMR (500 MHz, DMSO-d_6)



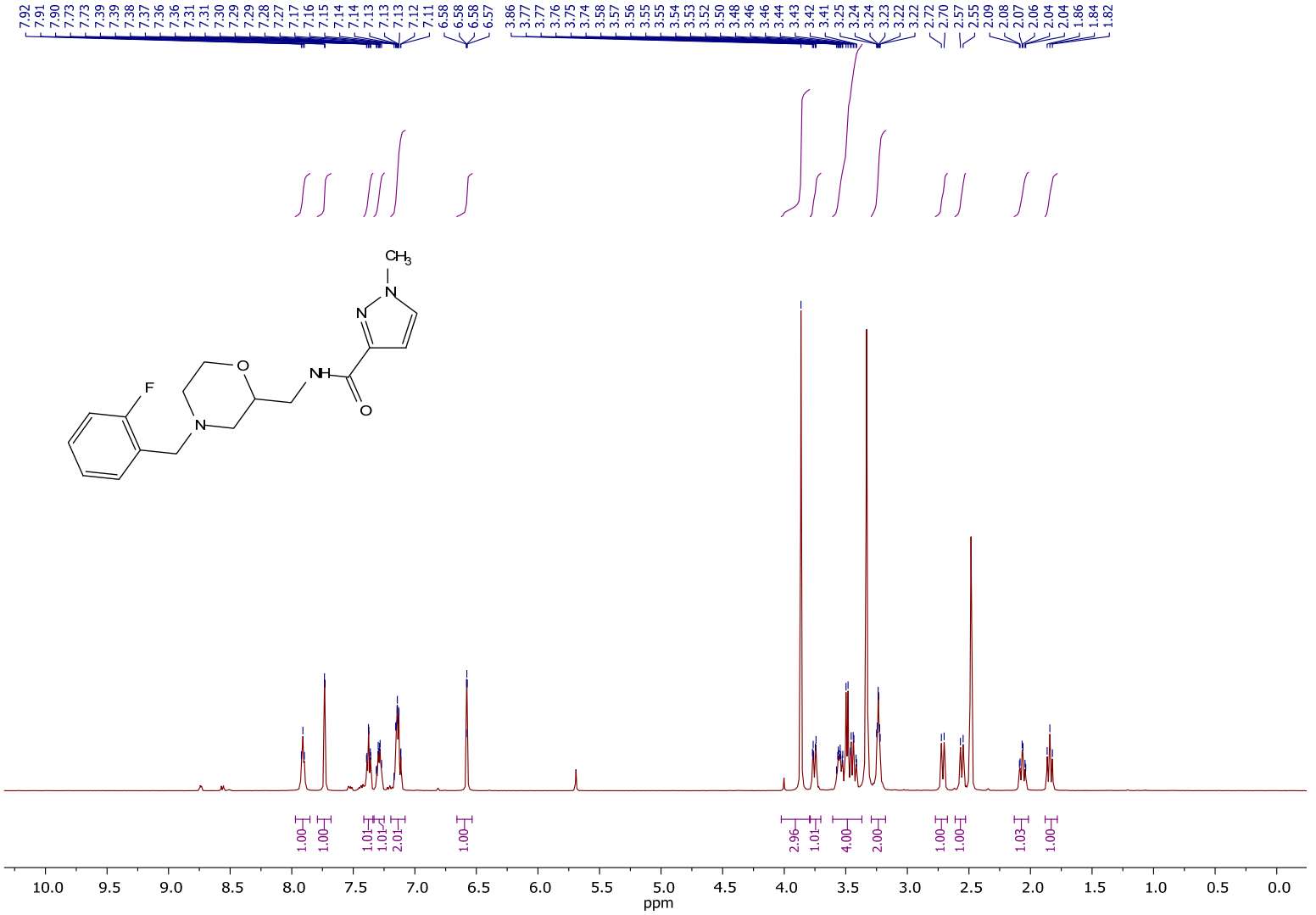
N-(1-(2-((3-Chloro-2-methylphenyl)amino)-2-oxoethyl)piperidin-4-yl)-2-methylpentanamide (**13**{*79*,*95*,*11*}), ^{13}C NMR (126 MHz, DMSO-d_6)



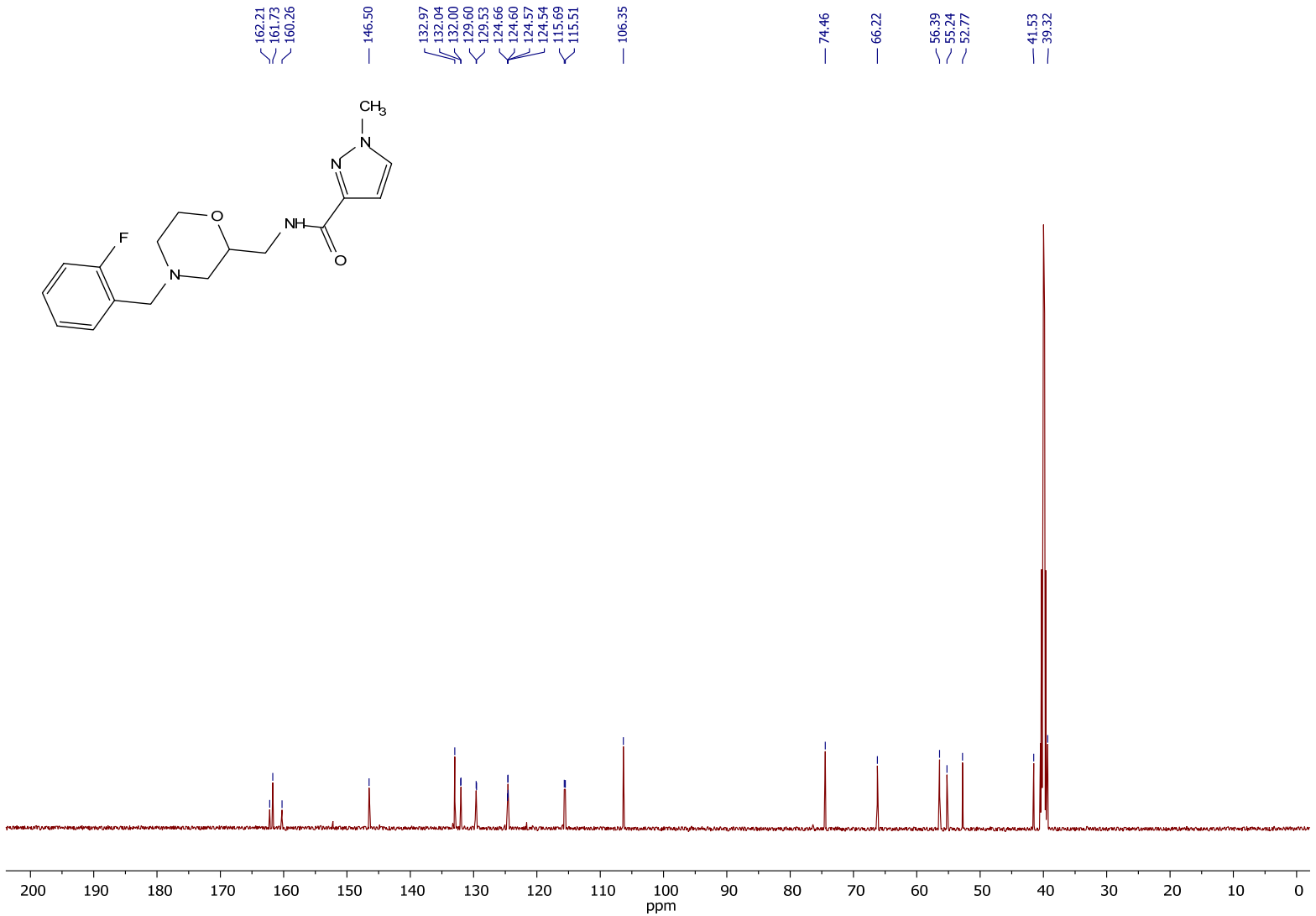
N-((4-(2,4-Dimethylbenzyl)morpholin-2-yl)methyl)-1-methyl-1*H*-pyrazole-3-carboxamide (**13**{*74*,*107*,*12*}), ^{1}H NMR (500 MHz, DMSO-d_6)



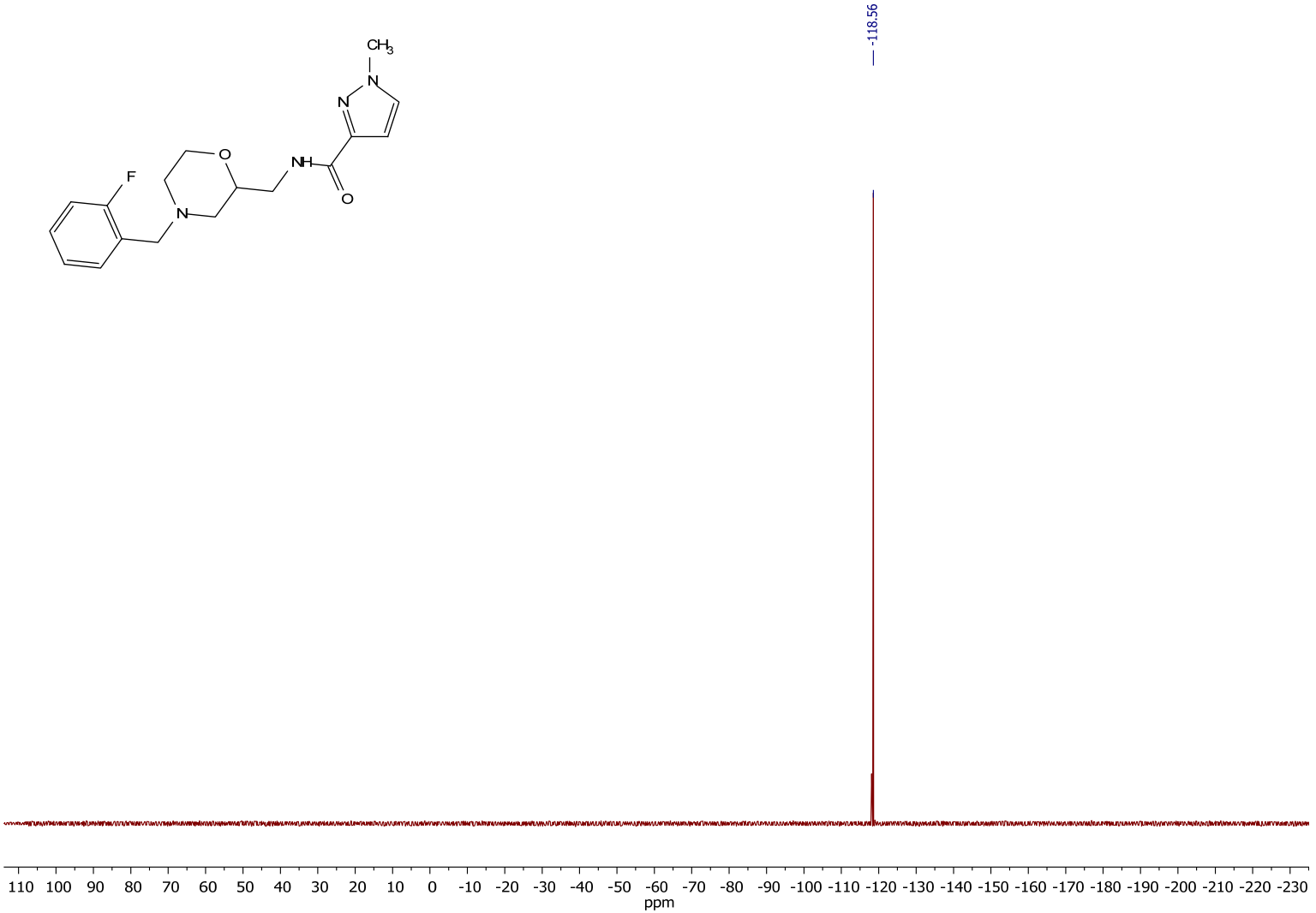
N-((4-(2,4-Dimethylbenzyl)morpholin-2-yl)methyl)-1-methyl-1*H*-pyrazole-3-carboxamide (**13**{*74*,*107*,*12*}), ^{13}C NMR (151 MHz, DMSO-d_6)



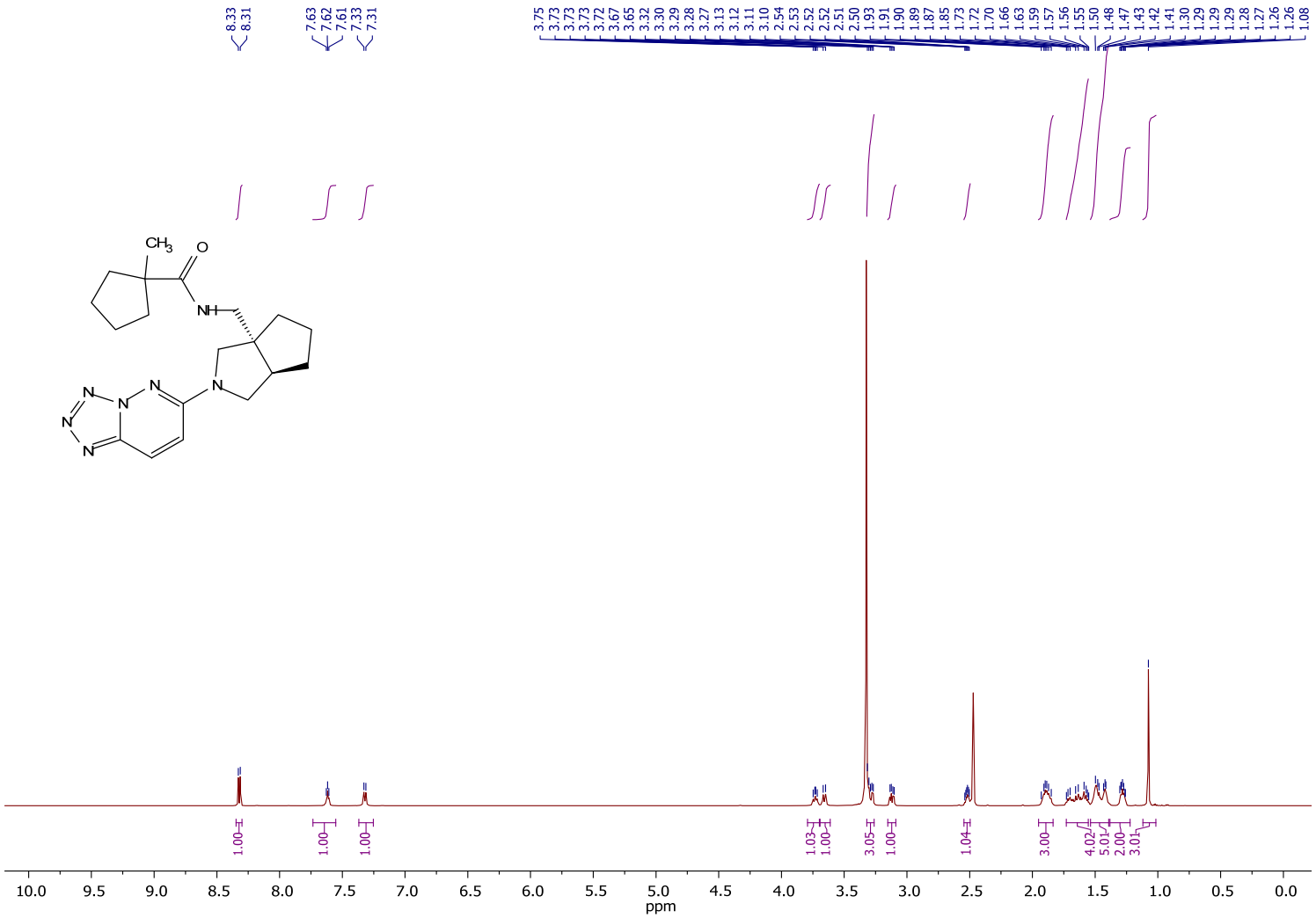
N-((4-(2-Fluorobenzyl)morpholin-2-yl)methyl)-1-methyl-1*H*-pyrazole-3-carboxamide (**13**{*74*,*107*,*25*}), ^{1}H NMR (500 MHz, DMSO-d_6)



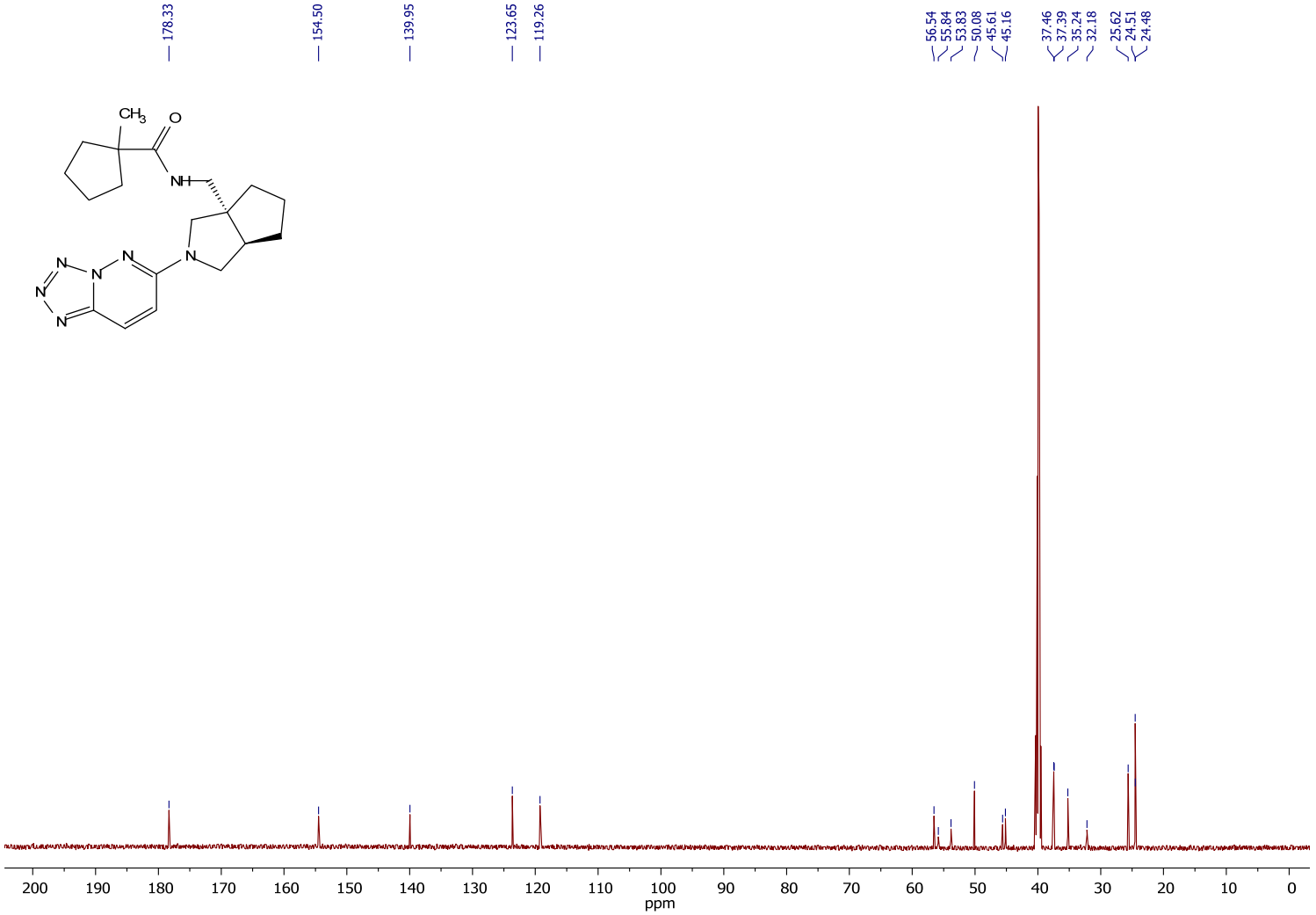
N-((4-(2-Fluorobenzyl)morpholin-2-yl)methyl)-1-methyl-1*H*-pyrazole-3-carboxamide (**13**{*74*,*107*,*25*}), ^{13}C NMR (126 MHz, DMSO-d_6)



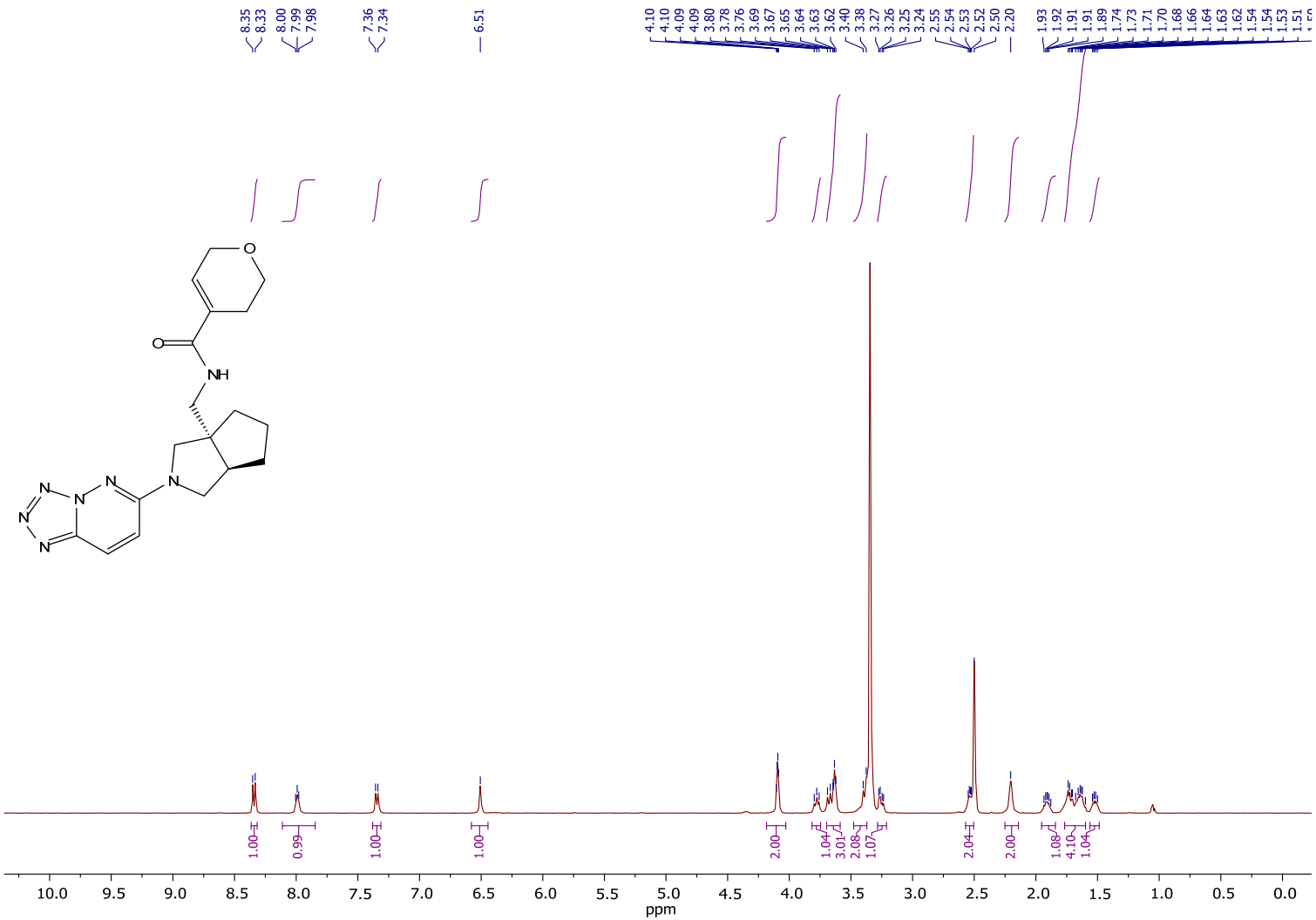
N-((4-(2-Fluorobenzyl)morpholin-2-yl)methyl)-1-methyl-1*H*-pyrazole-3-carboxamide (**13**{*74*,*107*,*25*}), ^{19}F NMR (376 MHz, DMSO-d_6)



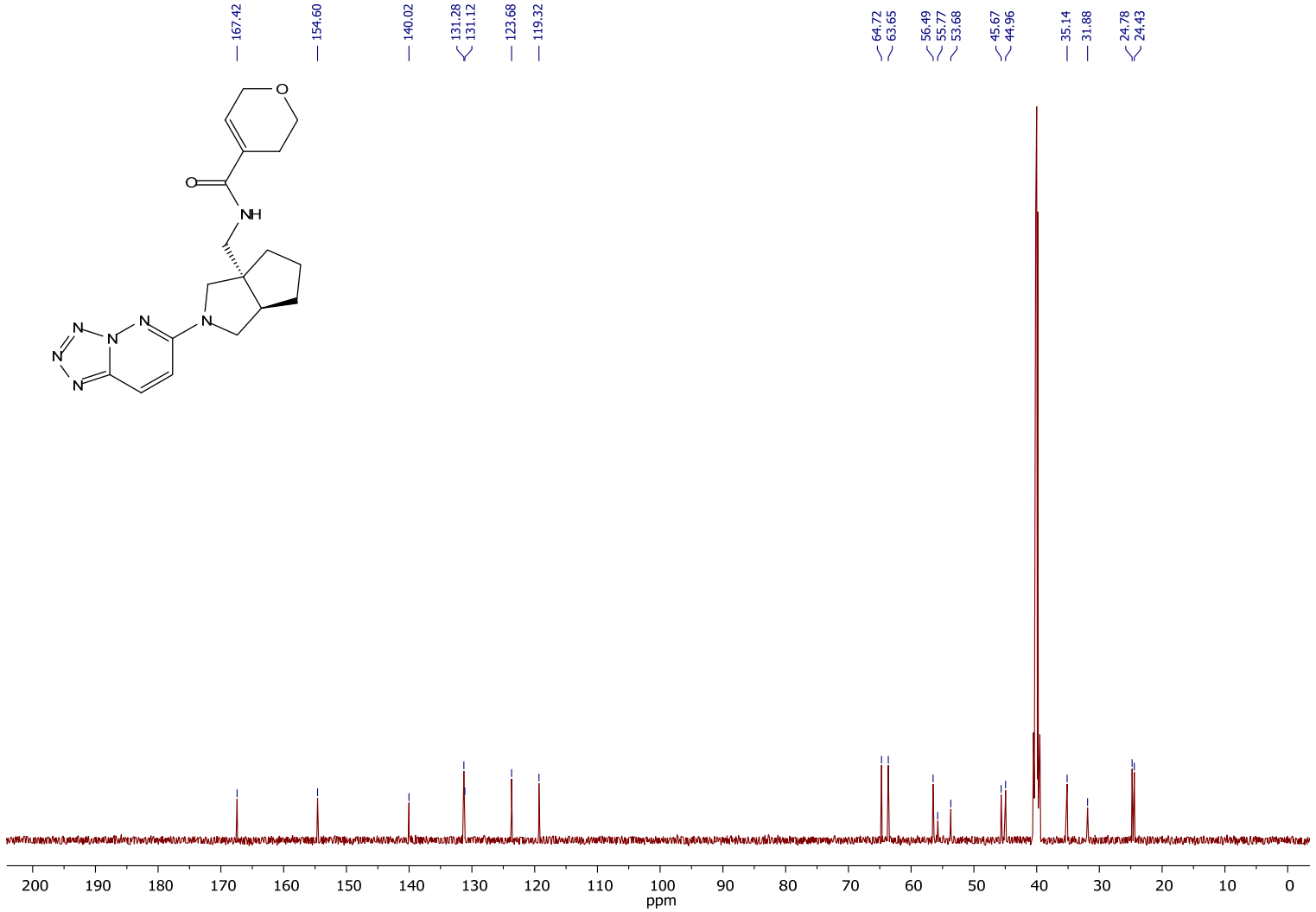
rac-1-Methyl-*N*-(((3*aR*,6*aS*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)hexahydrocyclopenta[*c*]pyrrol-3*a*(1*H*)-yl)methyl)cyclopentane-1-carboxamide (**14**{*19*,*35*,*360*}), ^{1}H NMR (600 MHz, DMSO-d_6)



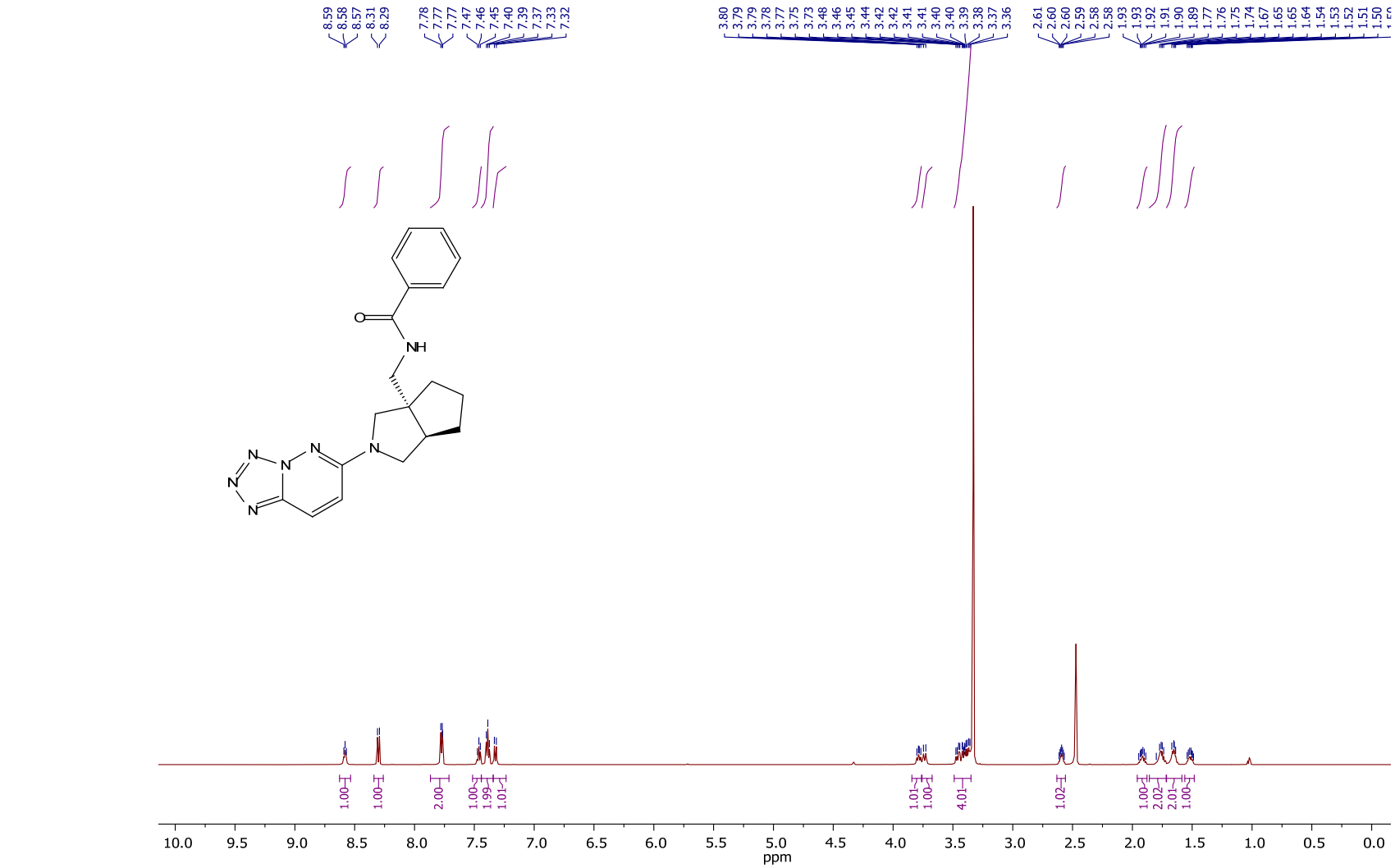
rac-1-Methyl-*N*-(((3*aR*,6*aS*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)hexahydrocyclopenta[*c*]pyrrol-3*a*(1*H*)-yl)methyl)cyclopentane-1-carboxamide (**14**{*19*,*35*,*360*}), ^{13}C NMR (151 MHz, DMSO-d_6)



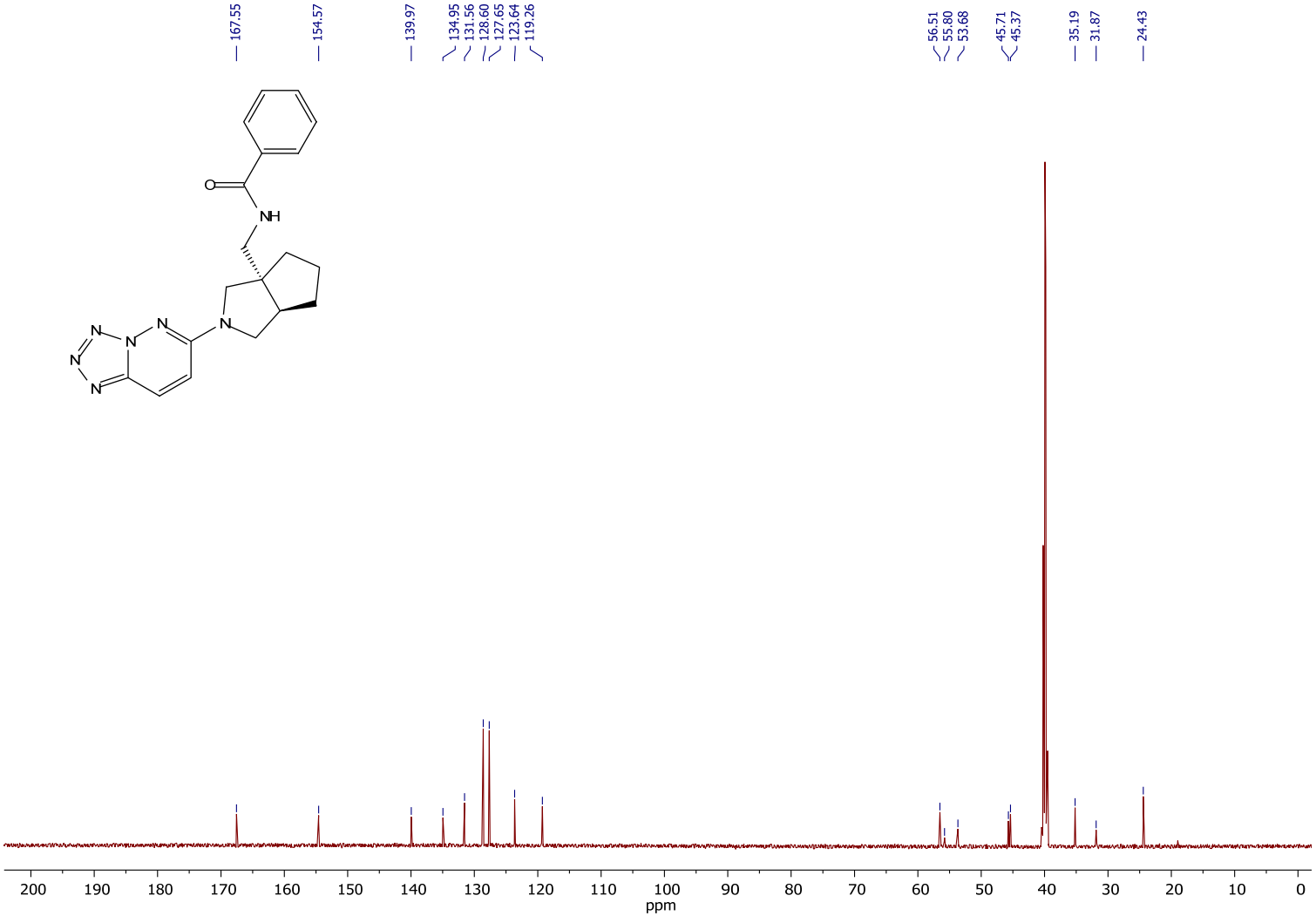
rac-*N*-(((3a*R*,6a*S*)-2-(Tetrazolo[1,5-*b*]pyridazin-6-yl)hexahydrocyclopenta[*c*]pyrrol-3a(1*H*)-yl)methyl)-3,6-dihydro-2*H*-pyran-4-carboxamide (**14**{*19*,*35*,*361*}), ^{1}H NMR (500 MHz, DMSO-d_6)



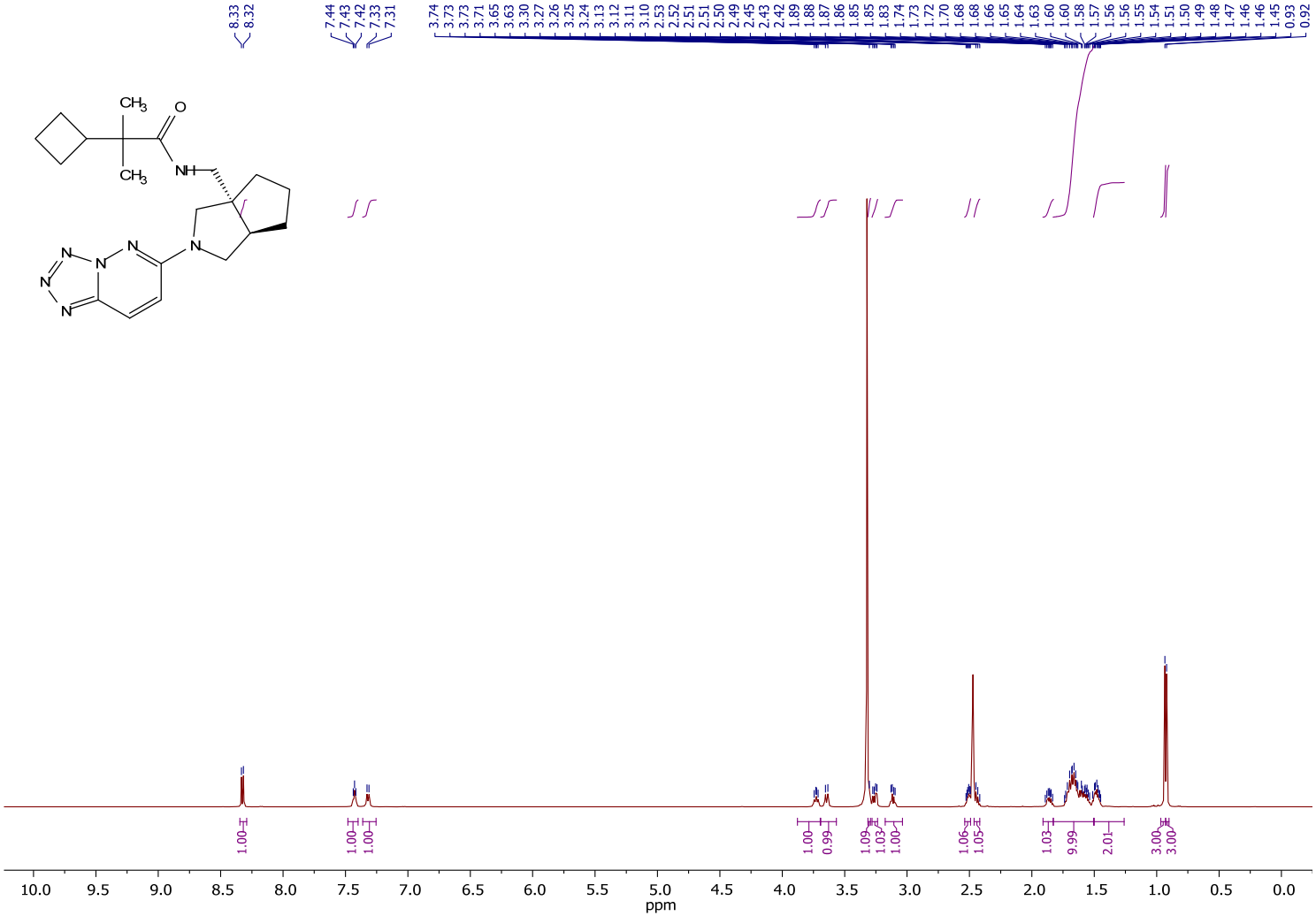
rac-*N*-(((3a*R*,6a*S*)-2-(Tetrazolo[1,5-*b*]pyridazin-6-yl)hexahydrocyclopenta[*c*]pyrrol-3a(1*H*)-yl)methyl)-3,6-dihydro-2*H*-pyran-4-carboxamide (**14**{*19*,*35*,*361*}), ^{13}C NMR (126 MHz, DMSO-d_6)



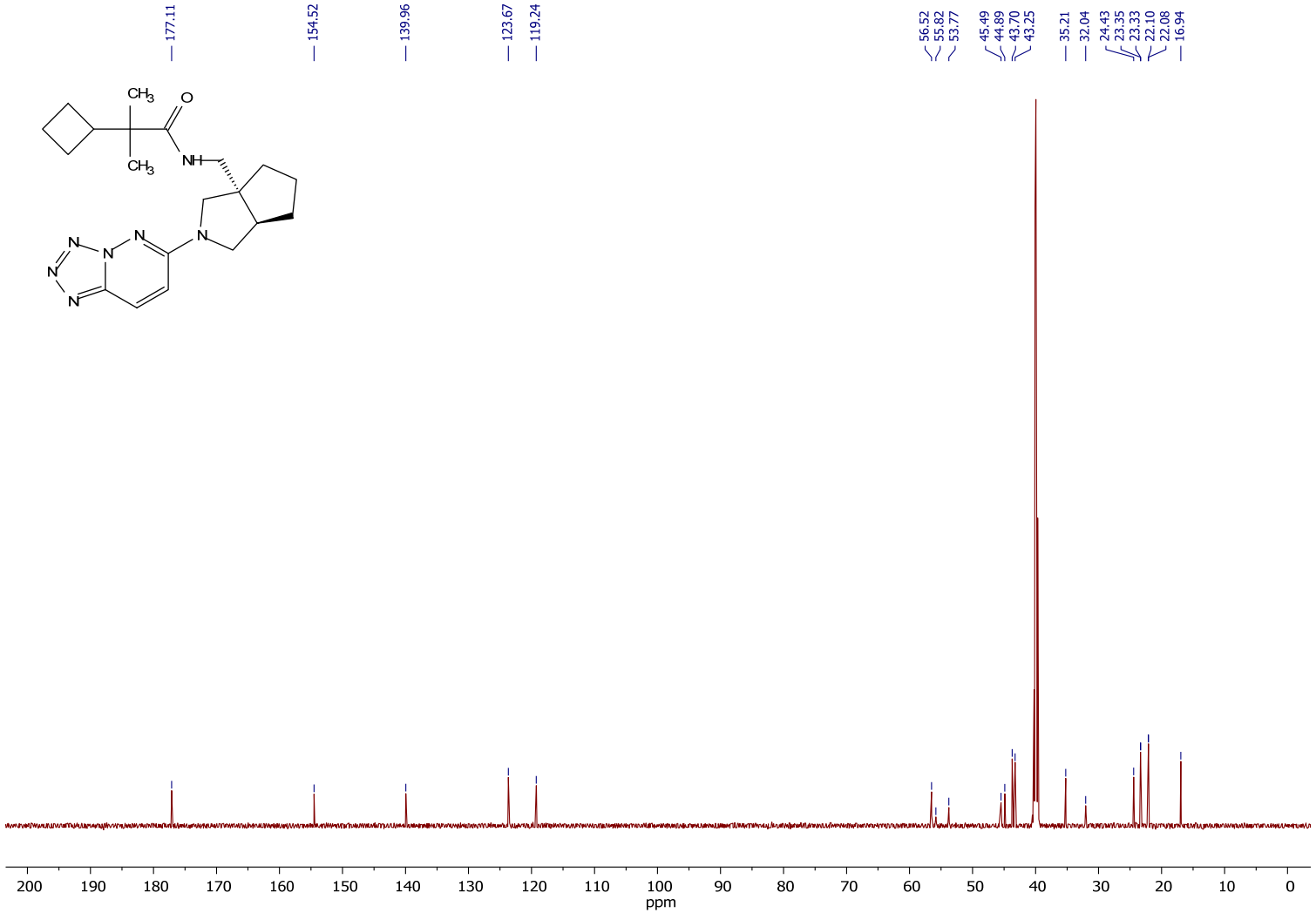
rac-*N*-(((3a*R*,6a*S*)-2-(Tetrazolo[1,5-*b*]pyridazin-6-yl)hexahydrocyclopenta[*c*]pyrrol-3a(1*H*)-yl)methyl)benzamide (**14**{*19*,*35*,*367*}), ^{1}H NMR (600 MHz, DMSO-d_6)



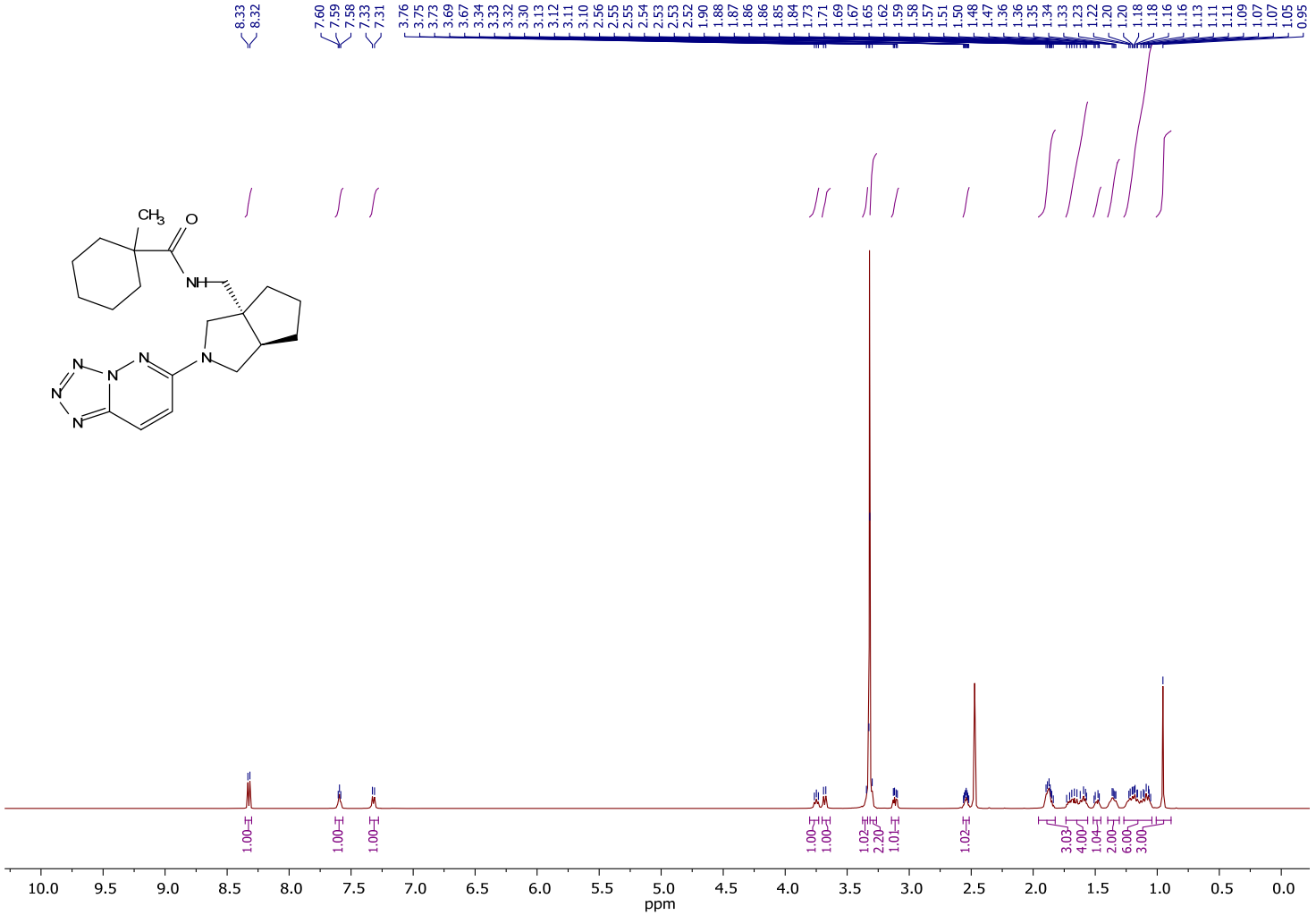
rac-*N*-(((3a*R*,6a*S*)-2-(Tetrazolo[1,5-*b*]pyridazin-6-yl)hexahydrocyclopenta[*c*]pyrrol-3a(1*H*)-yl)methyl)benzamide (**14**{*19*,*35*,*367*}), ^{13}C NMR (151 MHz, DMSO-d_6)



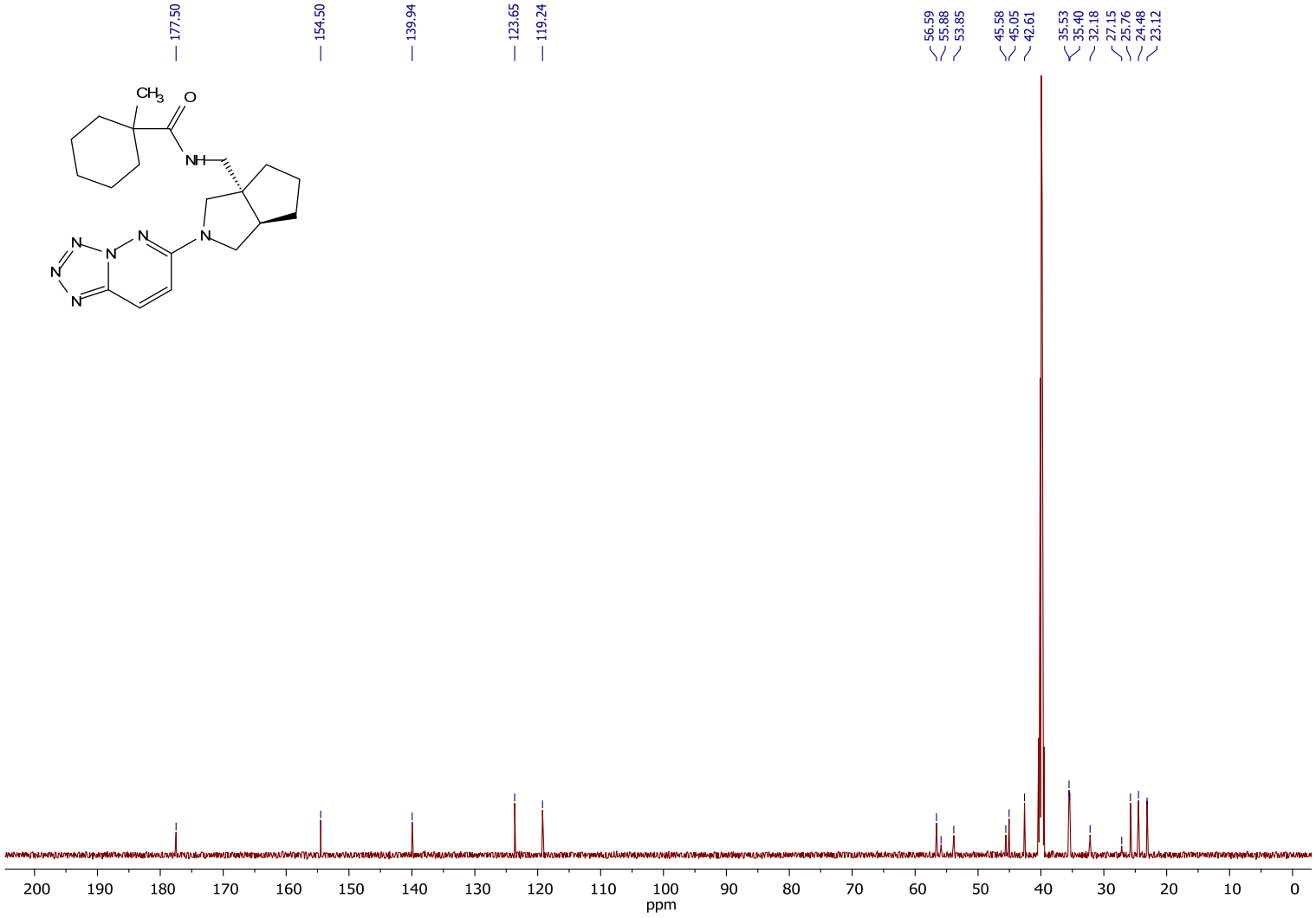
rac-2-Cyclobutyl-2-methyl-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)hexahydrocyclopenta[*c*]pyrrol-3a(1*H*)-yl)methyl)propanamide (**14**{*19*,*35*,*369*}), ^{1}H NMR (600 MHz, DMSO-d_6)



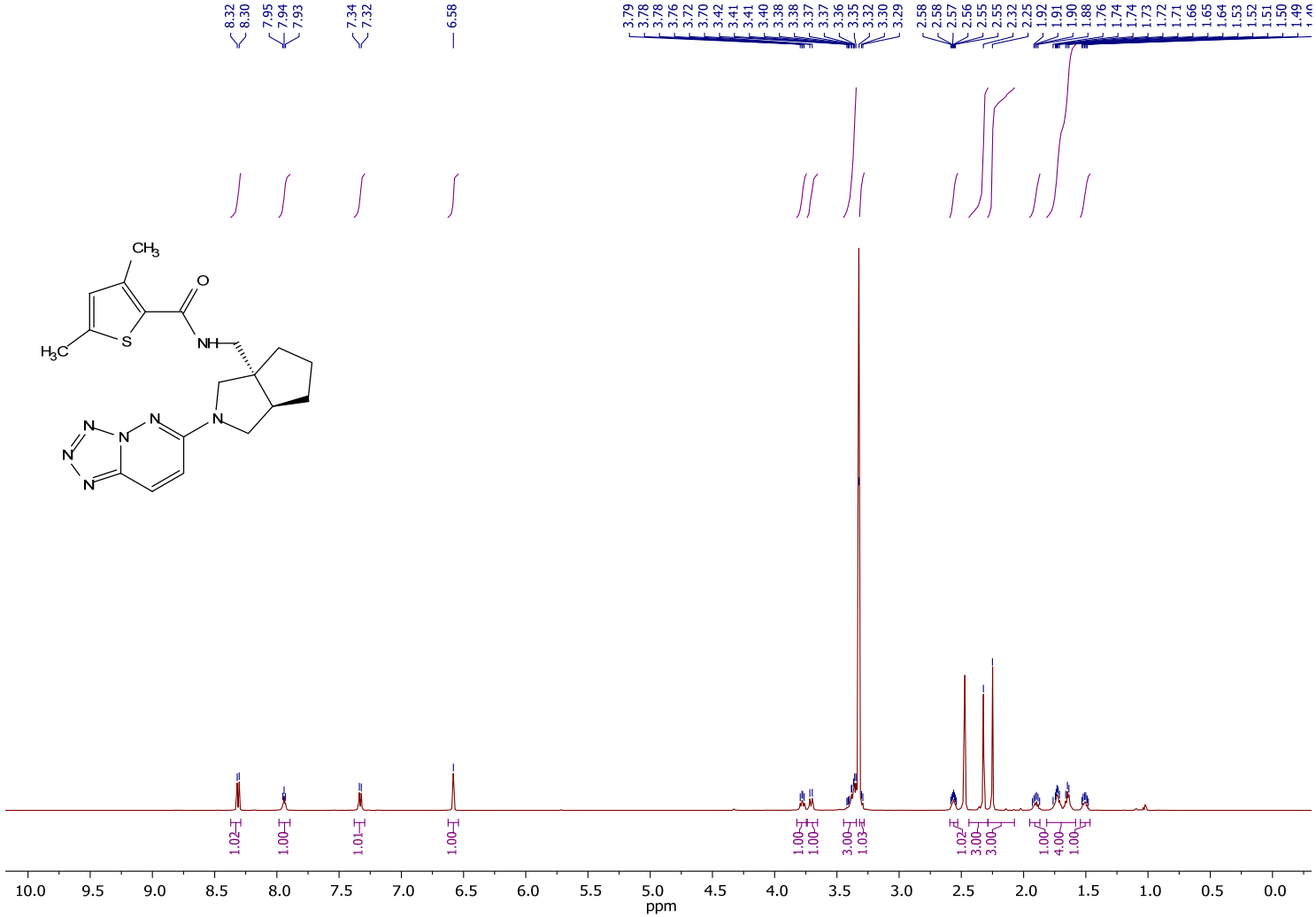
rac-2-Cyclobutyl-2-methyl-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)hexahydrocyclopenta[*c*]pyrrol-3a(1*H*)-yl)methyl)propanamide (**14**{*19*,*35*,*369*}), ^{13}C NMR (151 MHz, DMSO-d_6)



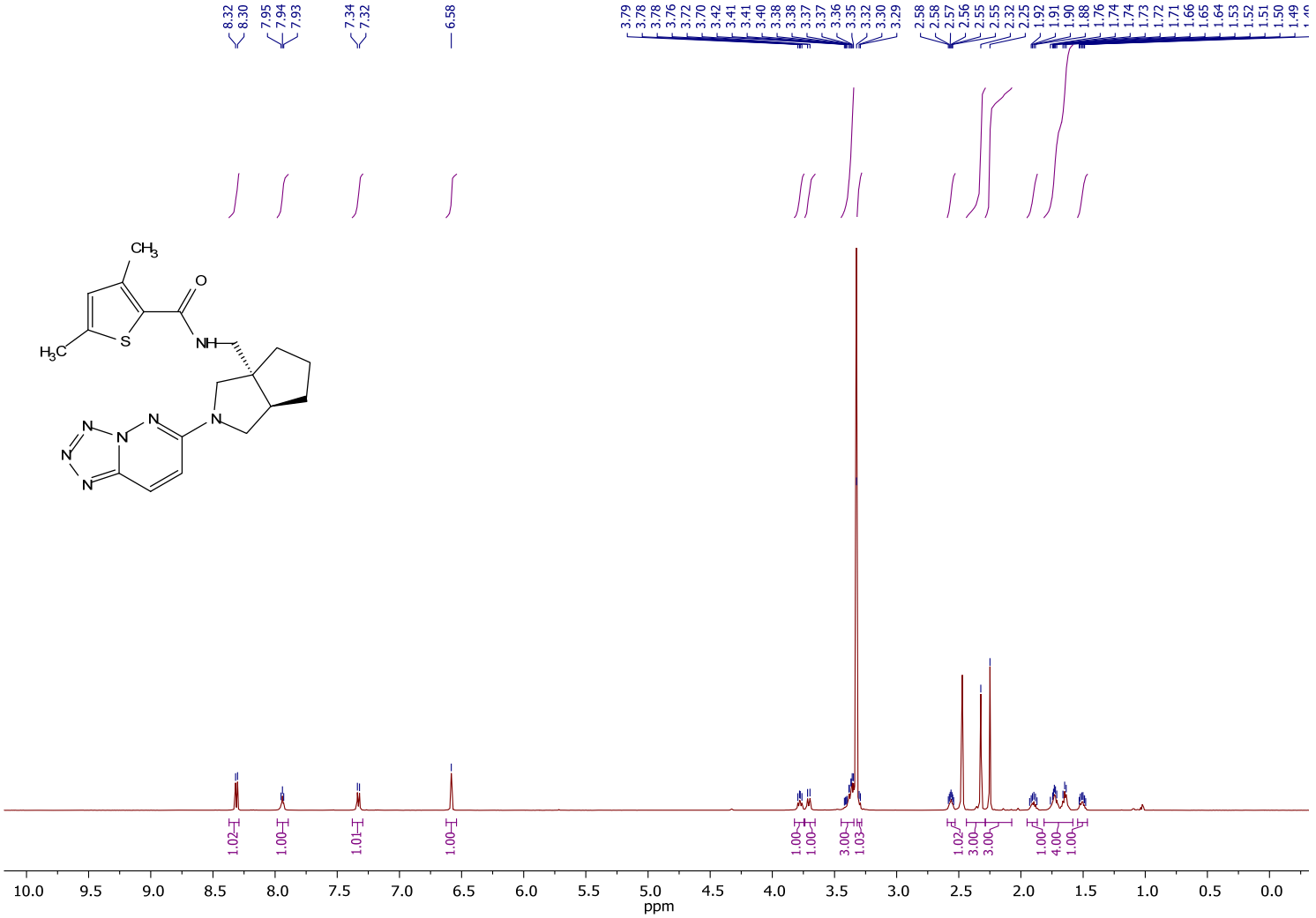
rac-1-Methyl-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)hexahydrocyclopenta[*c*]pyrrol-3a(1*H*)-yl)methyl)cyclohexane-1-carboxamide (**14**{*19*,*35*,*373*}), ^{1}H NMR (600 MHz, DMSO-d_6)



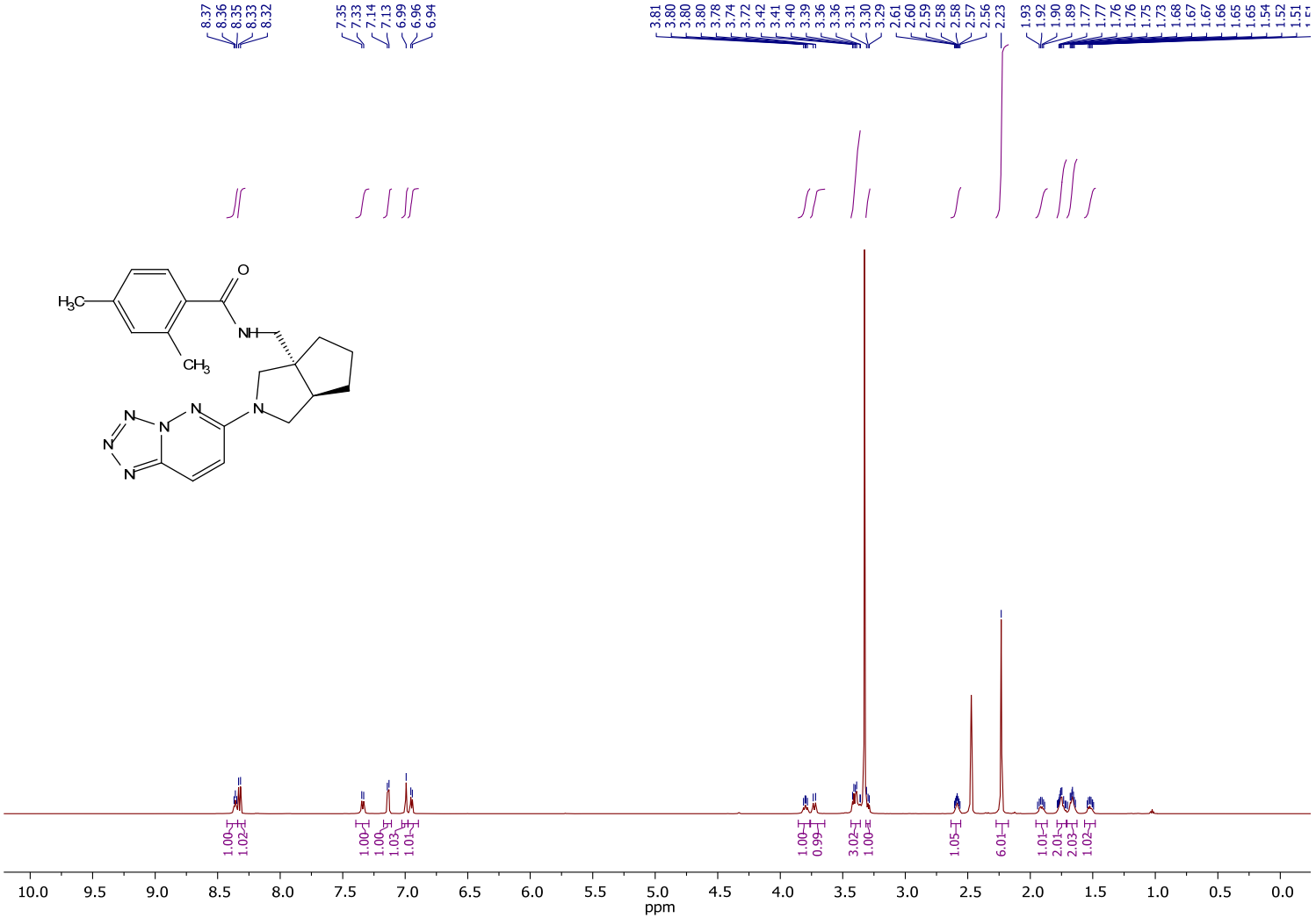
rac-1-Methyl-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)hexahydrocyclopenta[*c*]pyrrol-3a(1*H*)-yl)methyl)cyclohexane-1-carboxamide (**14**{*19*,*35*,*373*}), ^{13}C NMR (151 MHz, DMSO-d_6)



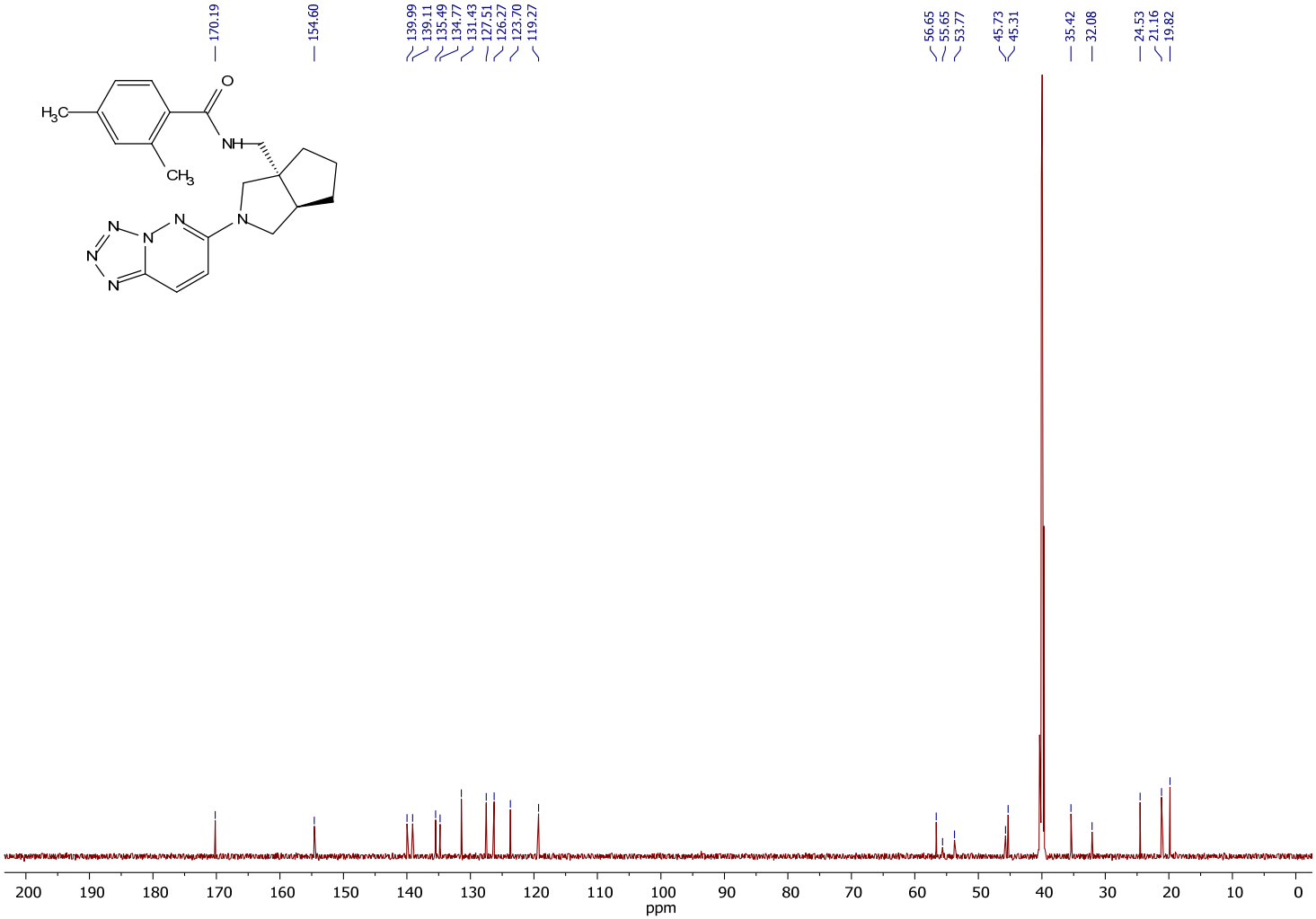
rac-3,5-Dimethyl-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)thiophene-2-carboxamide (**14**{*19*,*35*,*375*}), ^{1}H NMR (600 MHz, DMSO-d_6)



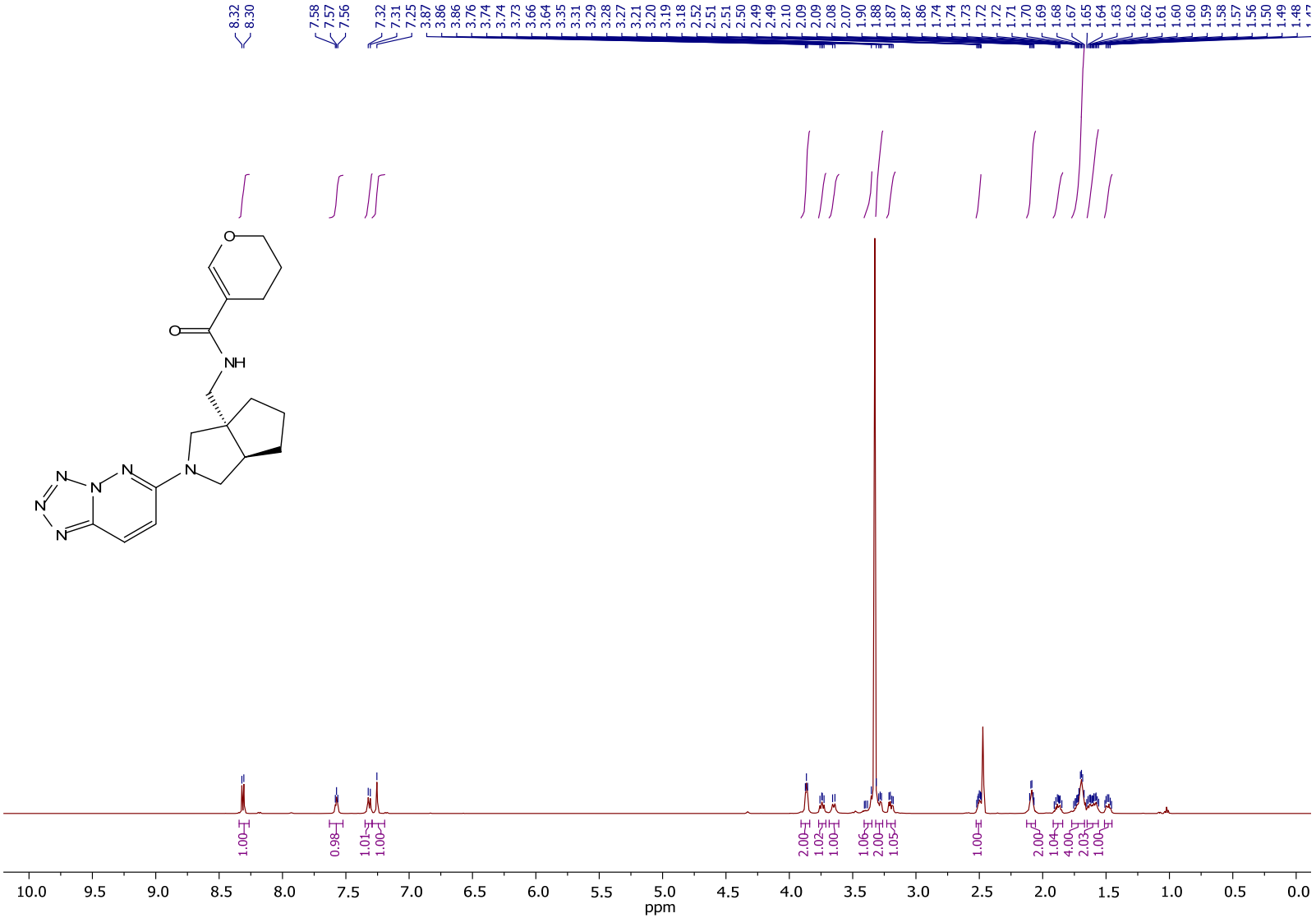
rac-3,5-Dimethyl-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)thiophene-2-carboxamide (**14**{*19*,*35*,*375*}), ^{13}C NMR (151 MHz, DMSO-d_6)



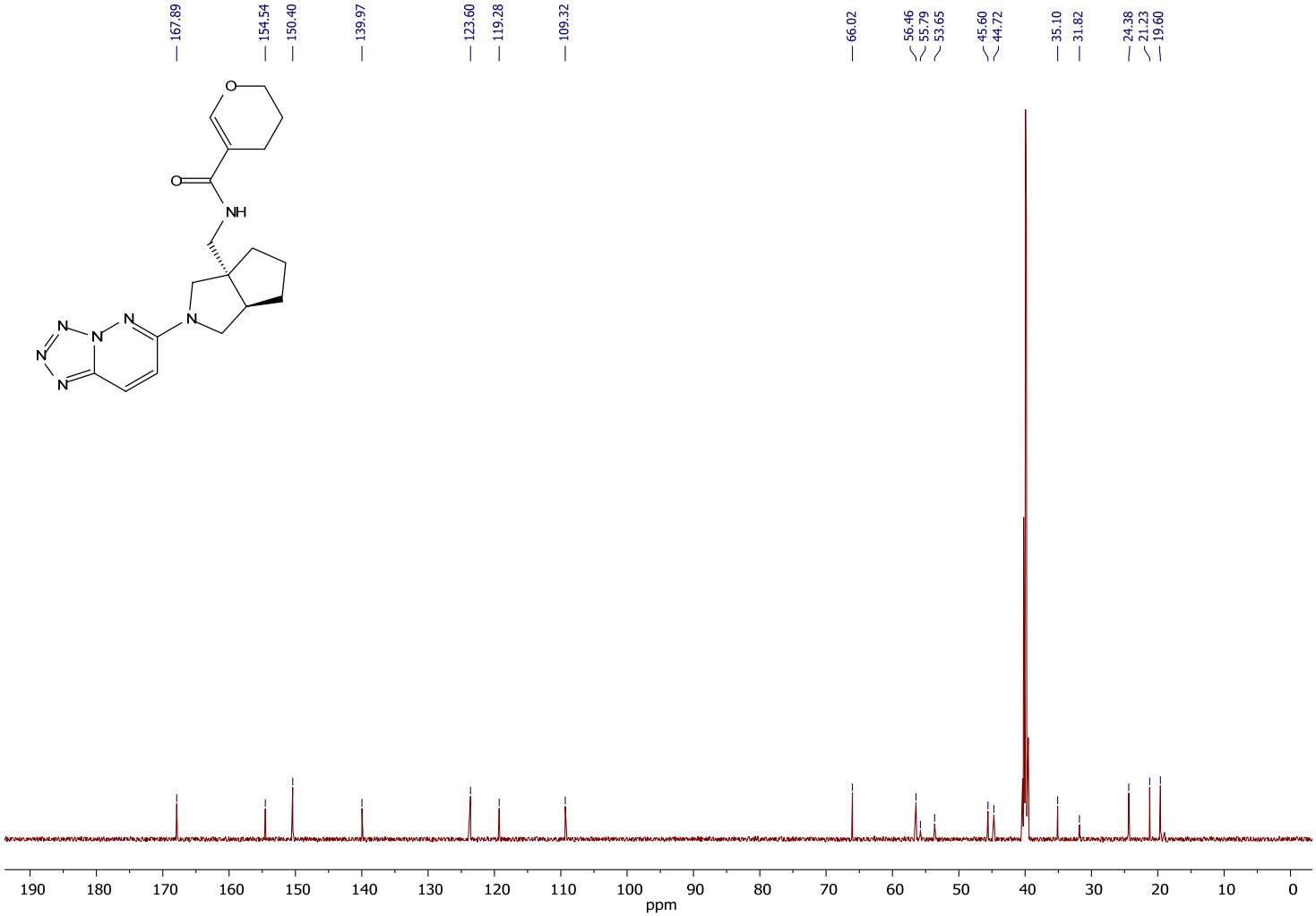
rac-2,4-Dimethyl-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)benzamide (**14**{*19*,*35*,*377*}), ^{1}H NMR (600 MHz, DMSO-d_6)



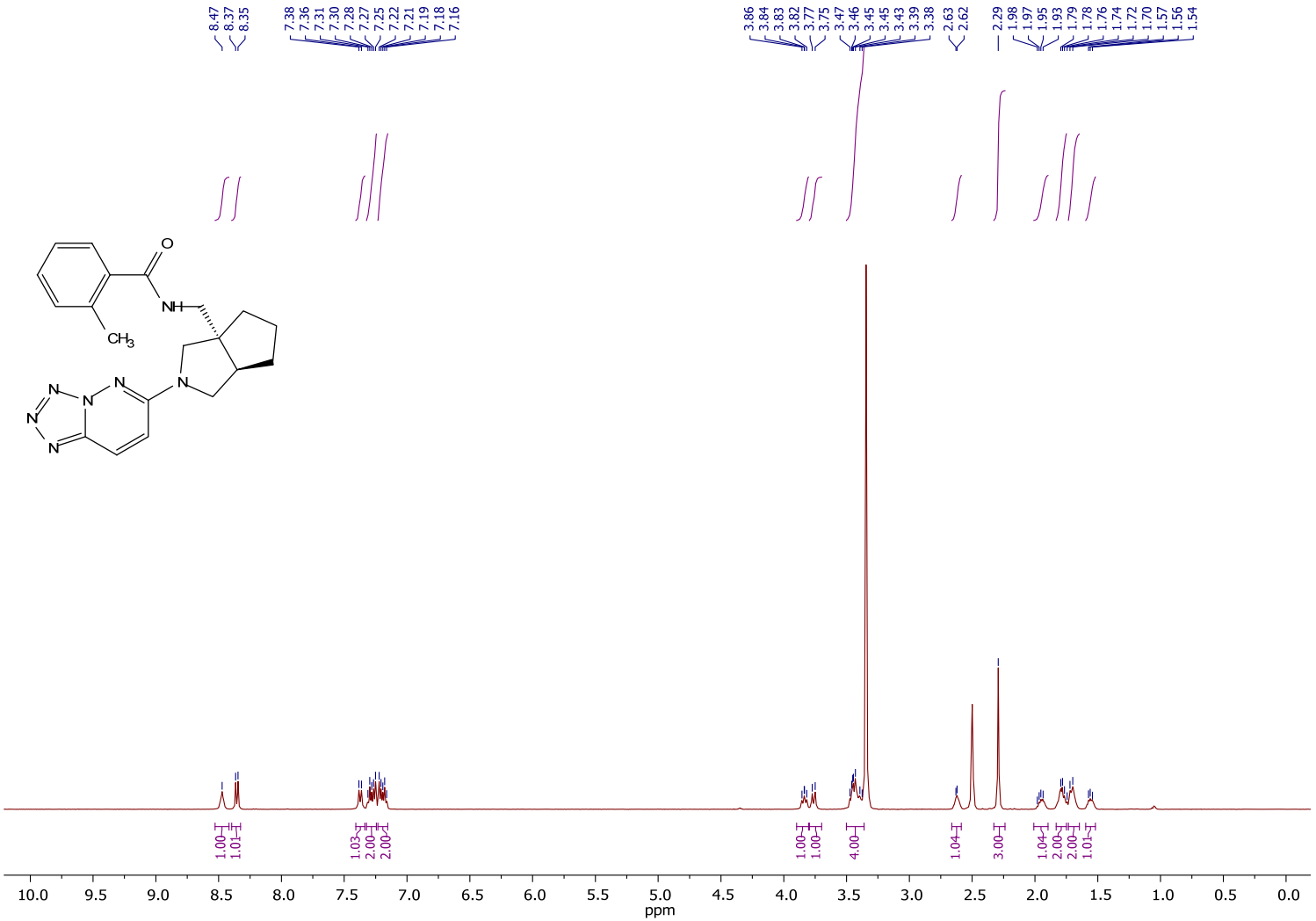
rac-2,4-Dimethyl-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)benzamide (**14**{*19*,*35*,*377*}), ^{13}C NMR (151 MHz, DMSO-d_6)



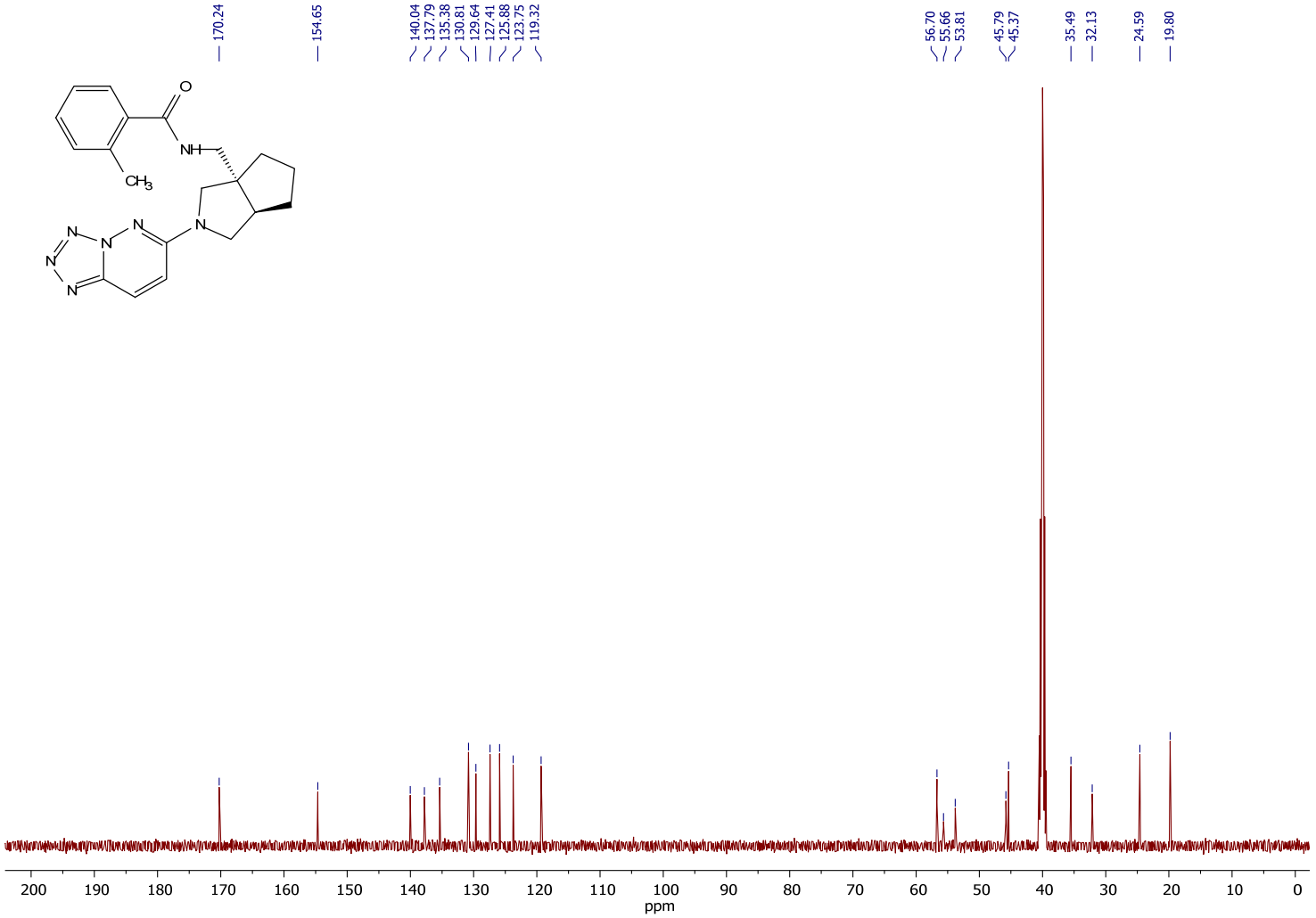
N-(((3a*S*,6a*R*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)-3,4-dihydro-2*H*-pyran-5-carboxamide (**14**{*19*,*35*,*378*}), ^{1}H NMR (600 MHz, DMSO-d_6)



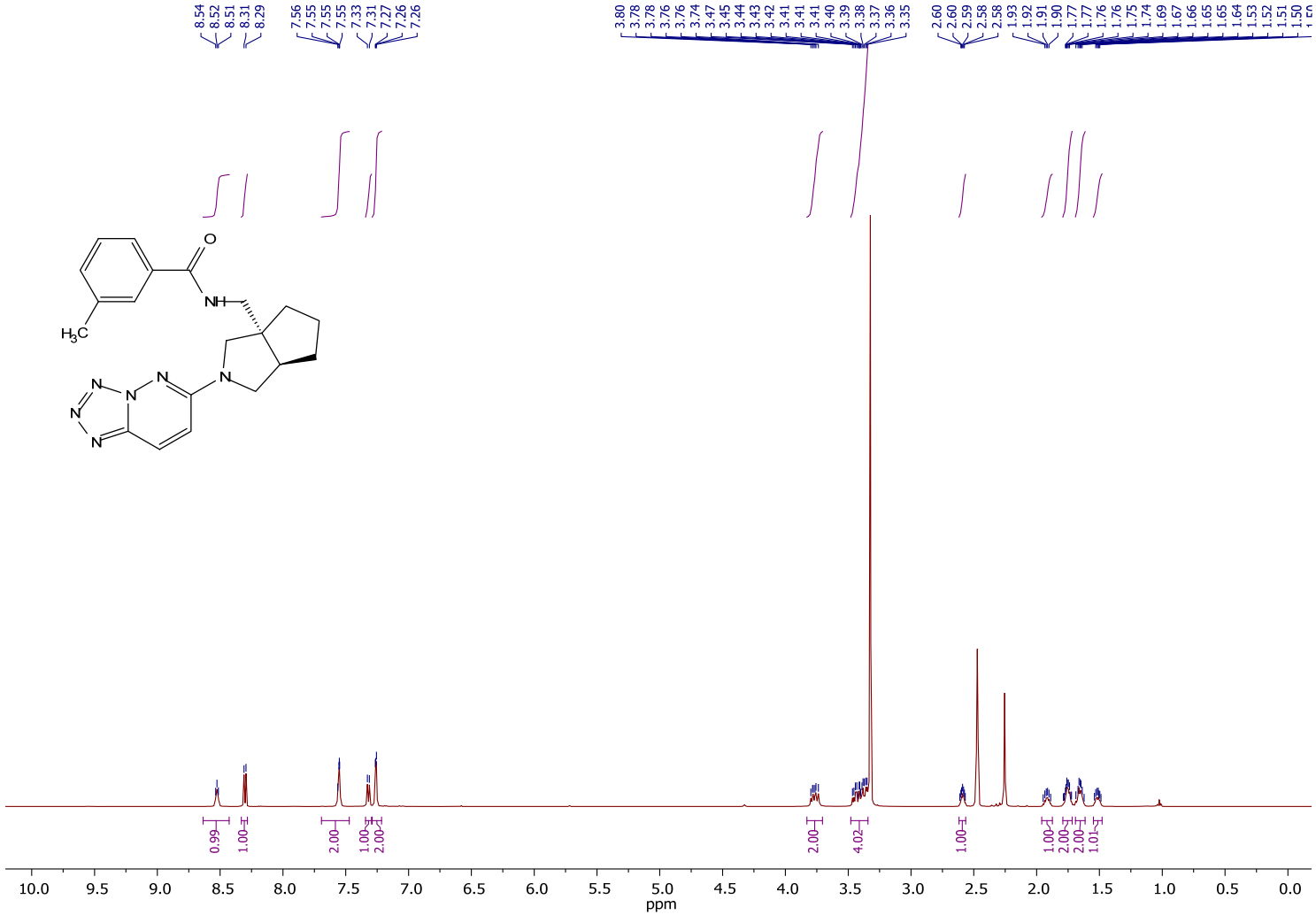
N-(((3a*S*,6a*R*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)-3,4-dihydro-2*H*-pyran-5-carboxamide (**14**{*19*,*35*,*378*}), ^{13}C NMR (151 MHz, DMSO-d_6)



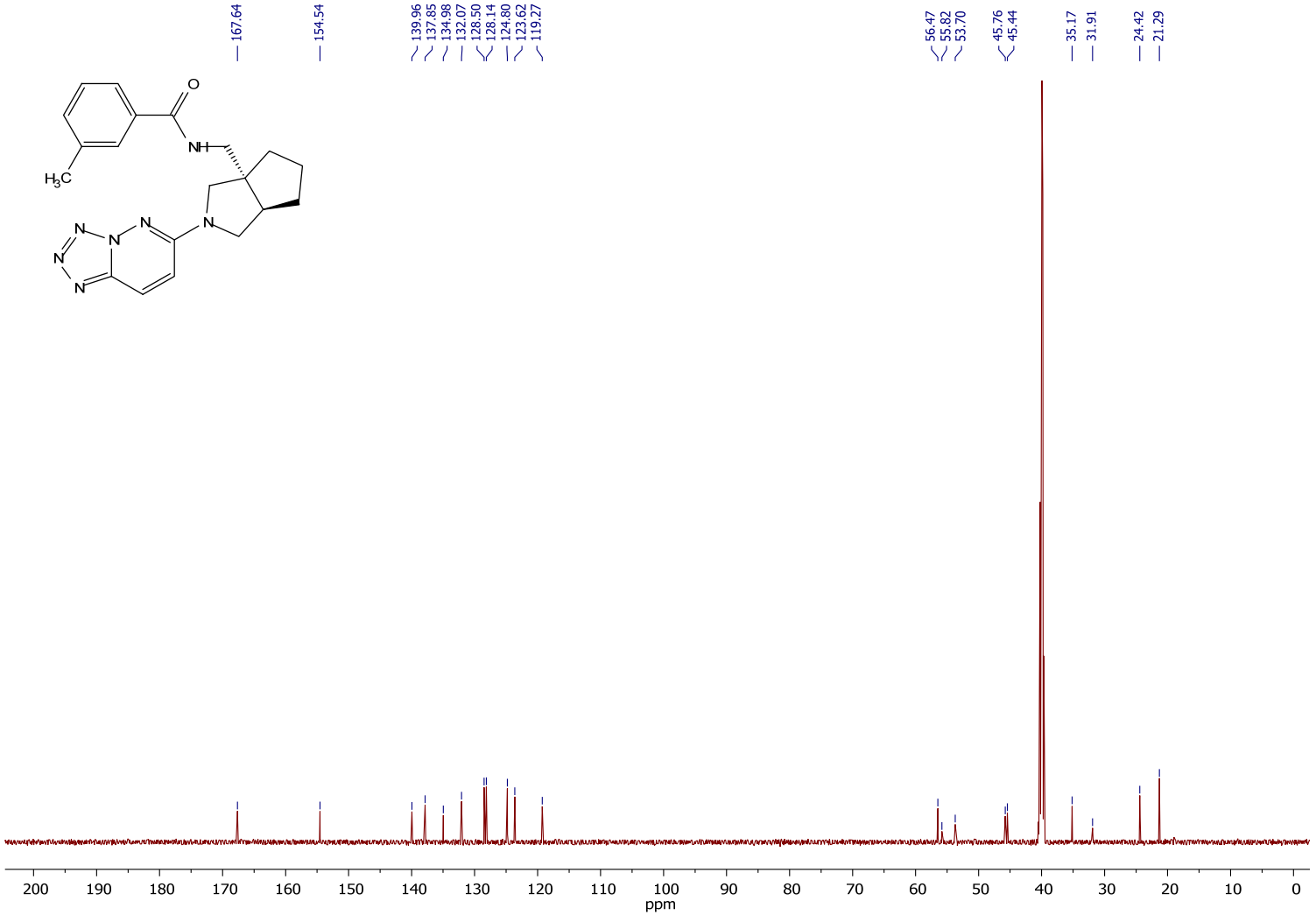
rac-2-Methyl-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)benzamide (**14**{*19*,*35*,*384*}), ^{1}H NMR (500 MHz, DMSO-d_6)



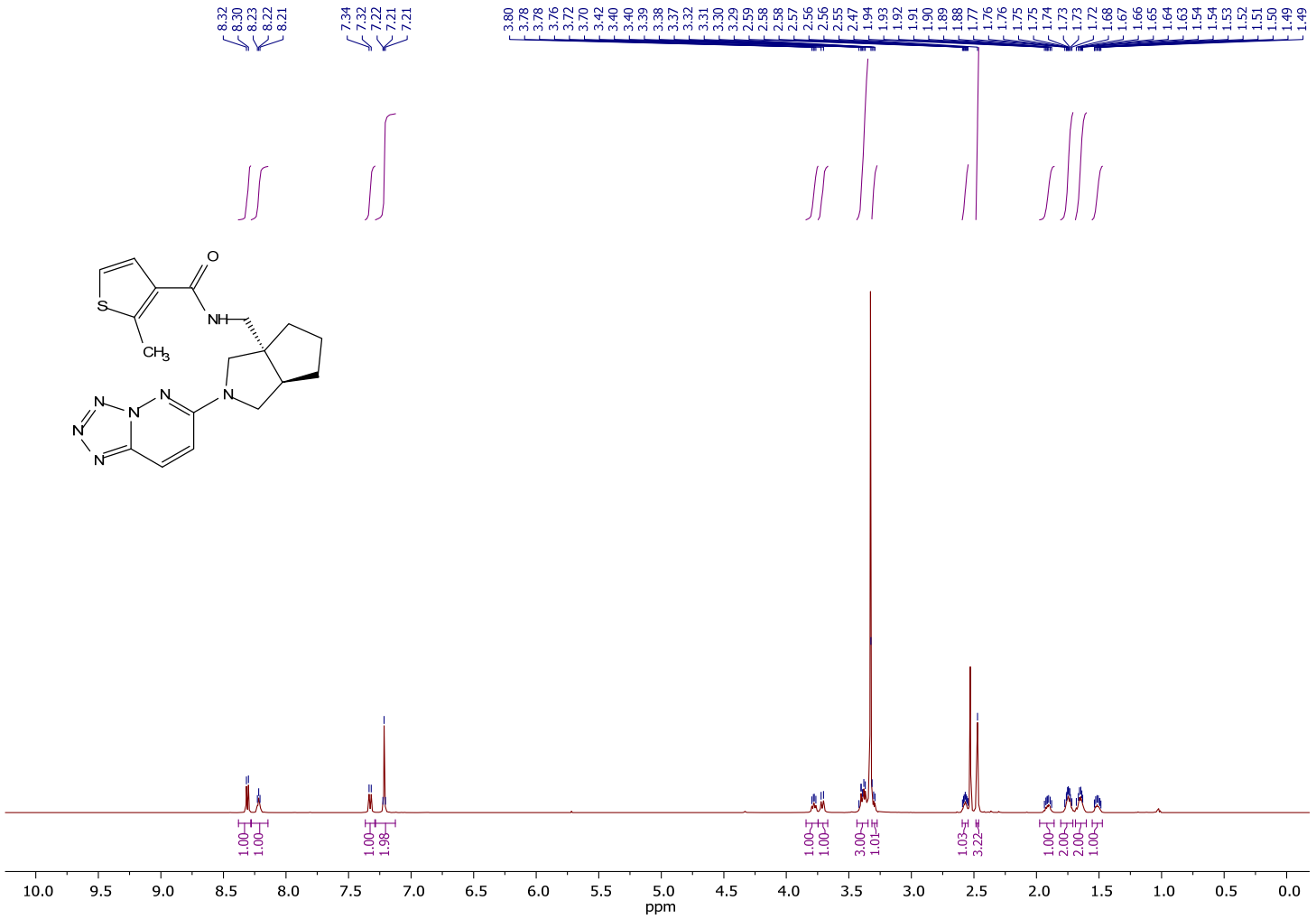
rac-2-Methyl-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)benzamide (**14**{*19*,*35*,*384*}), ^{13}C NMR (126 MHz, DMSO-d_6



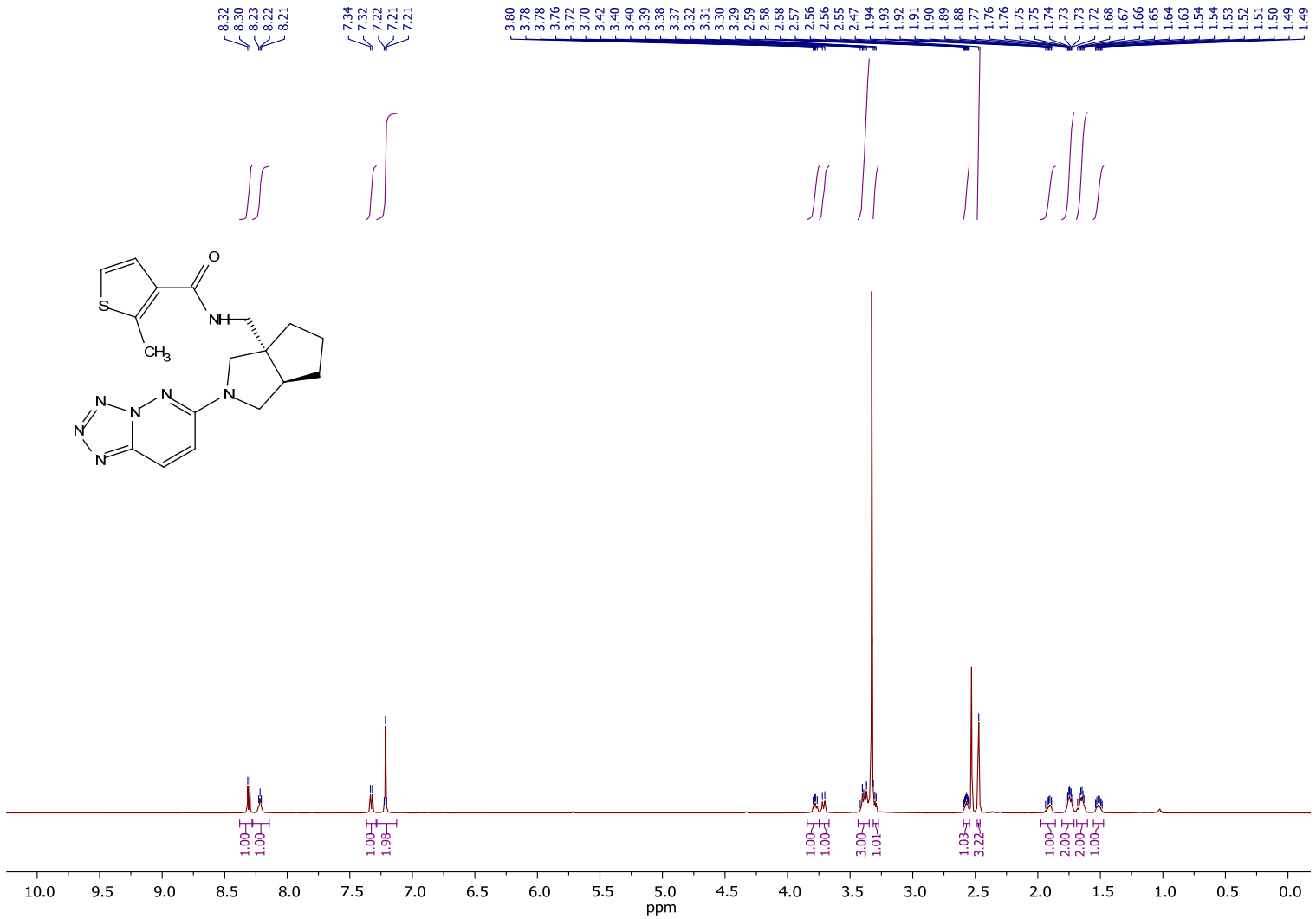
rac-3-Methyl-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)benzamide (**14**{*19*,*35*,*171*}), ^{1}H NMR (600 MHz, DMSO-d_6)



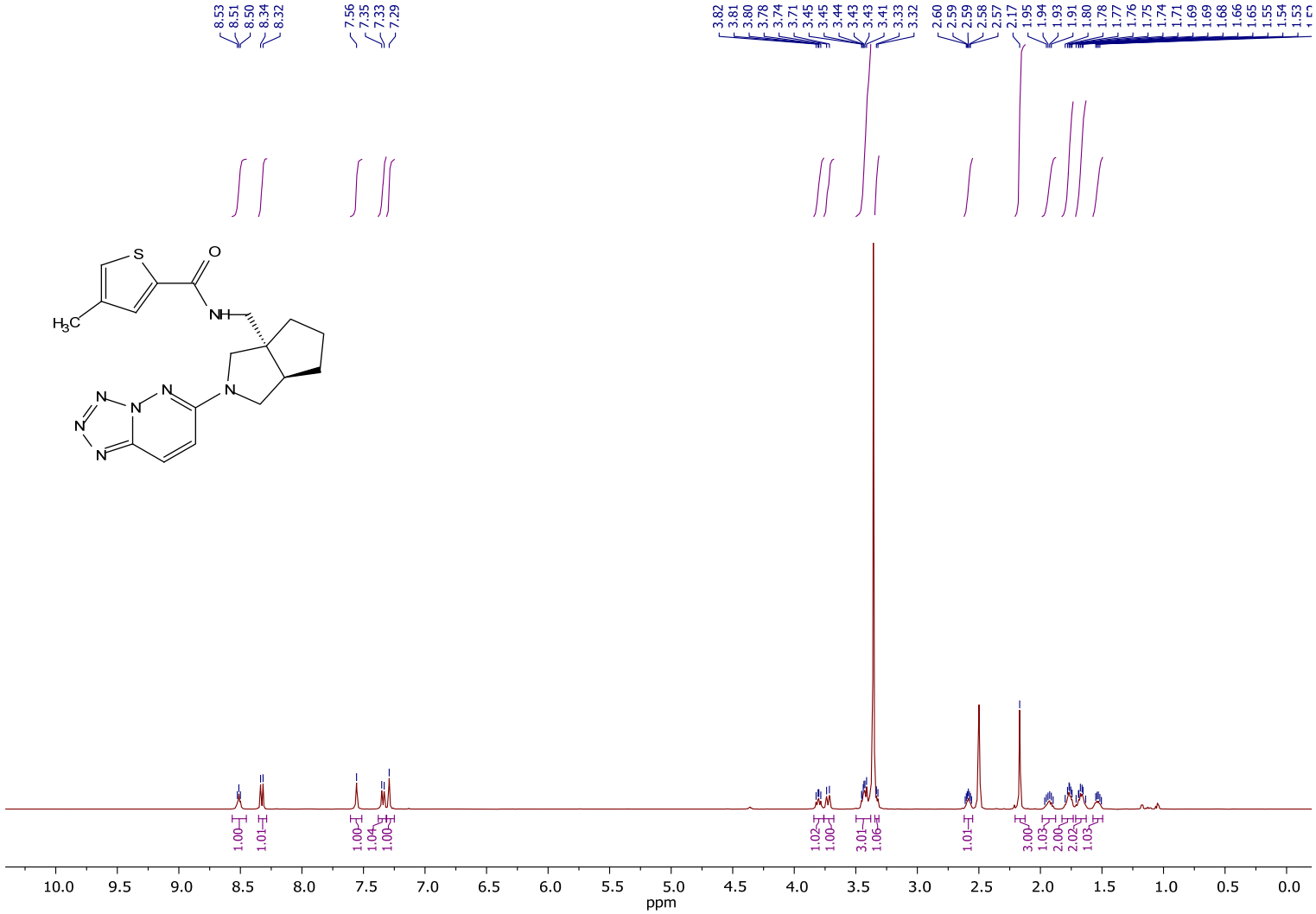
rac-3-Methyl-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)benzamide (**14**{*19*,*35*,*171*}), ^{13}C NMR (151 MHz, DMSO-d_6)



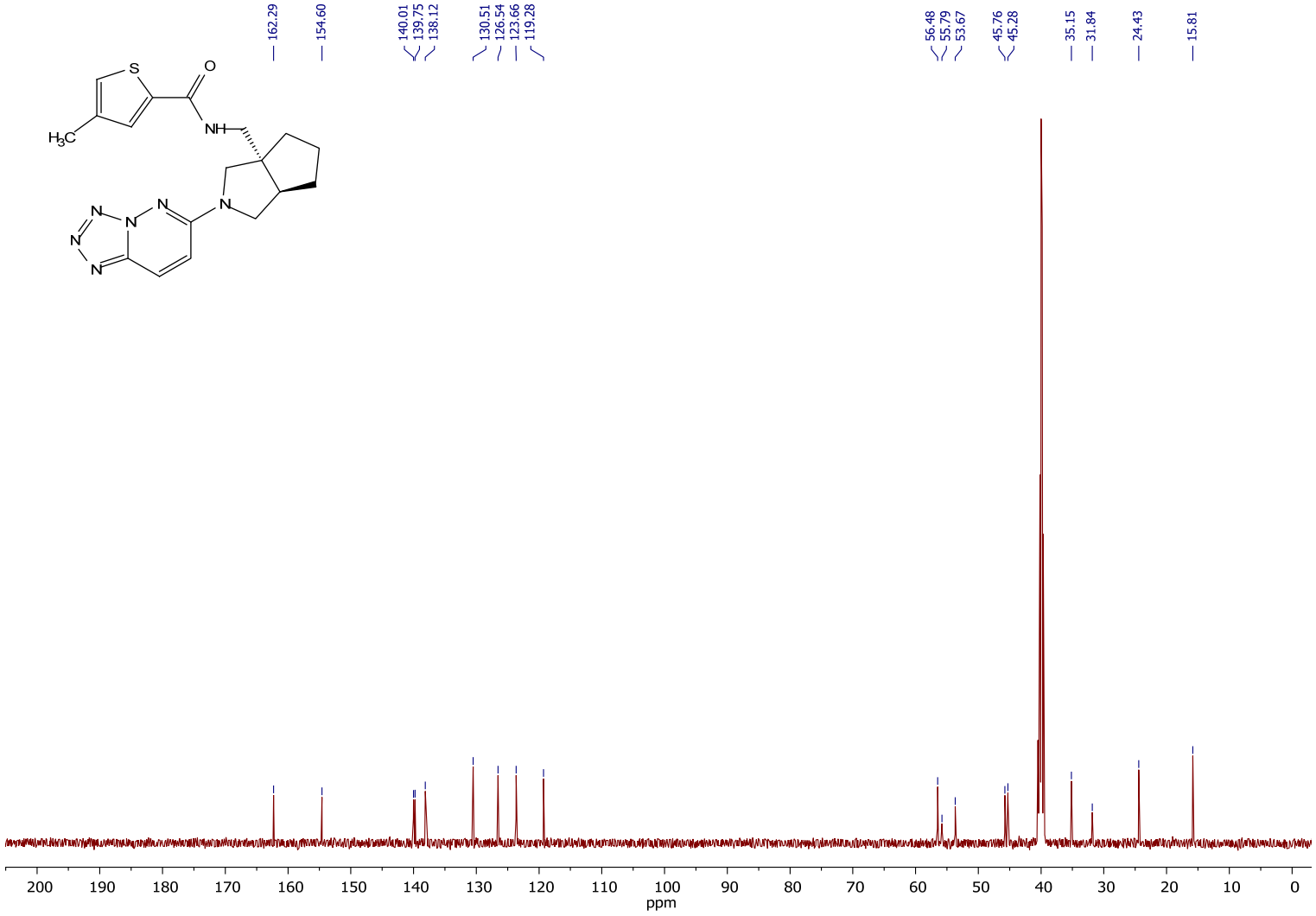
rac-2-Methyl-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)thiophene-3-carboxamide **14**{*19*,*35*,*390*}, ^{1}H NMR (600 MHz, DMSO-d_6)



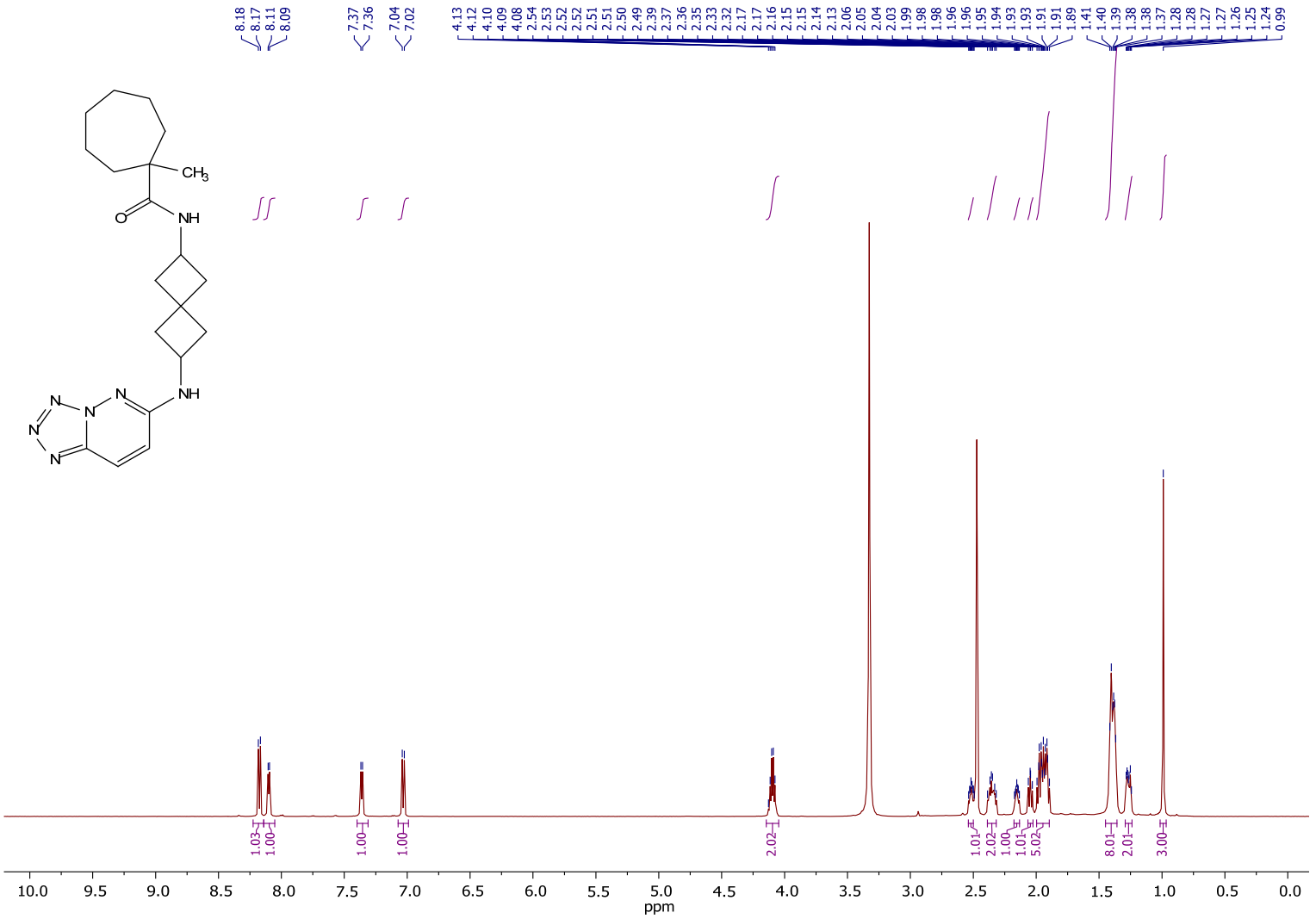
rac-2-Methyl-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)thiophene-3-carboxamide **14**{*19,35,390*}, ^{13}C NMR (151 MHz, DMSO-d_6)



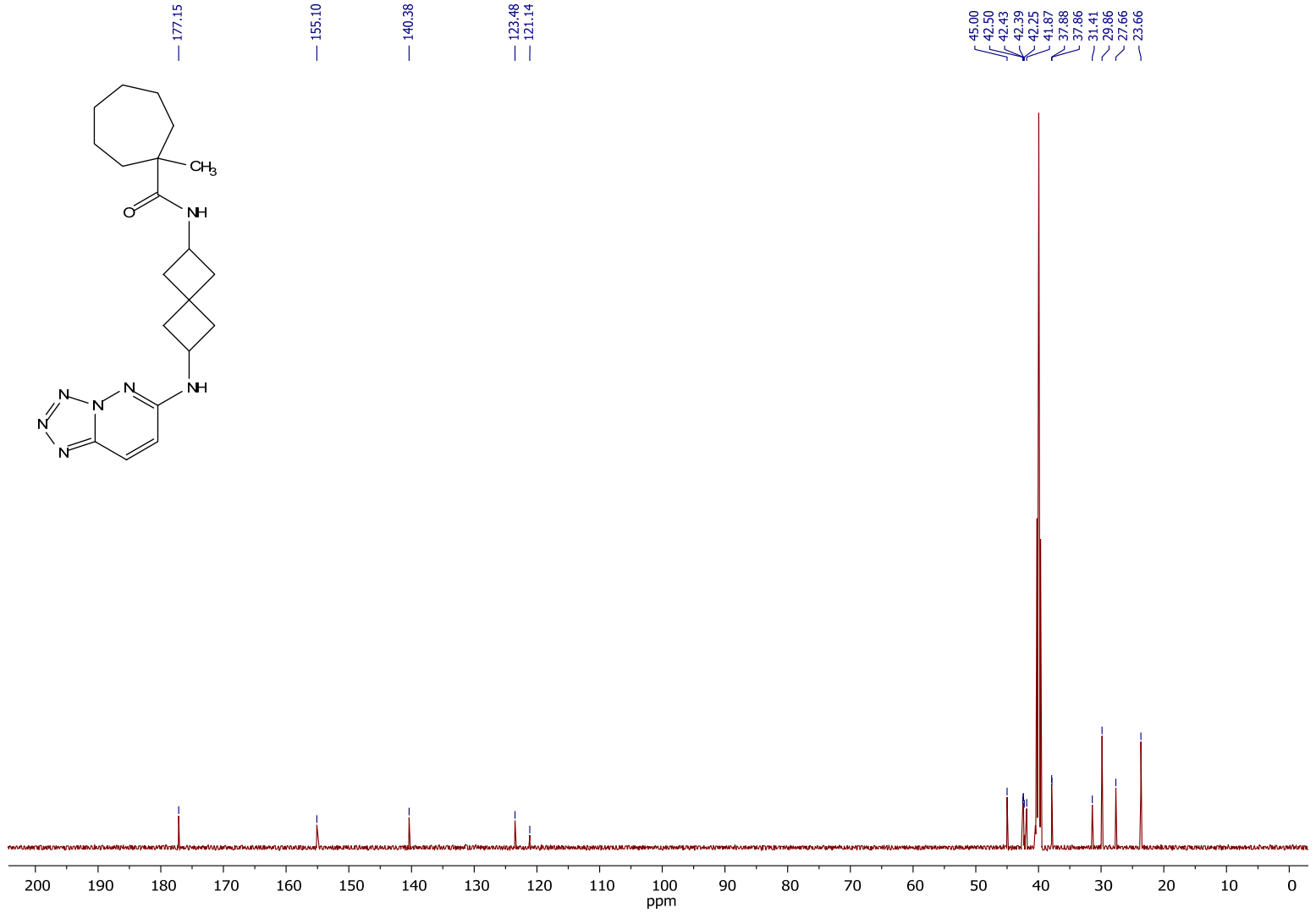
rac-4-Methyl-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)thiophene-2-carboxamide (**14**{*19*,*35*,*394*}), ^{1}H NMR (500 MHz, DMSO-d_6)



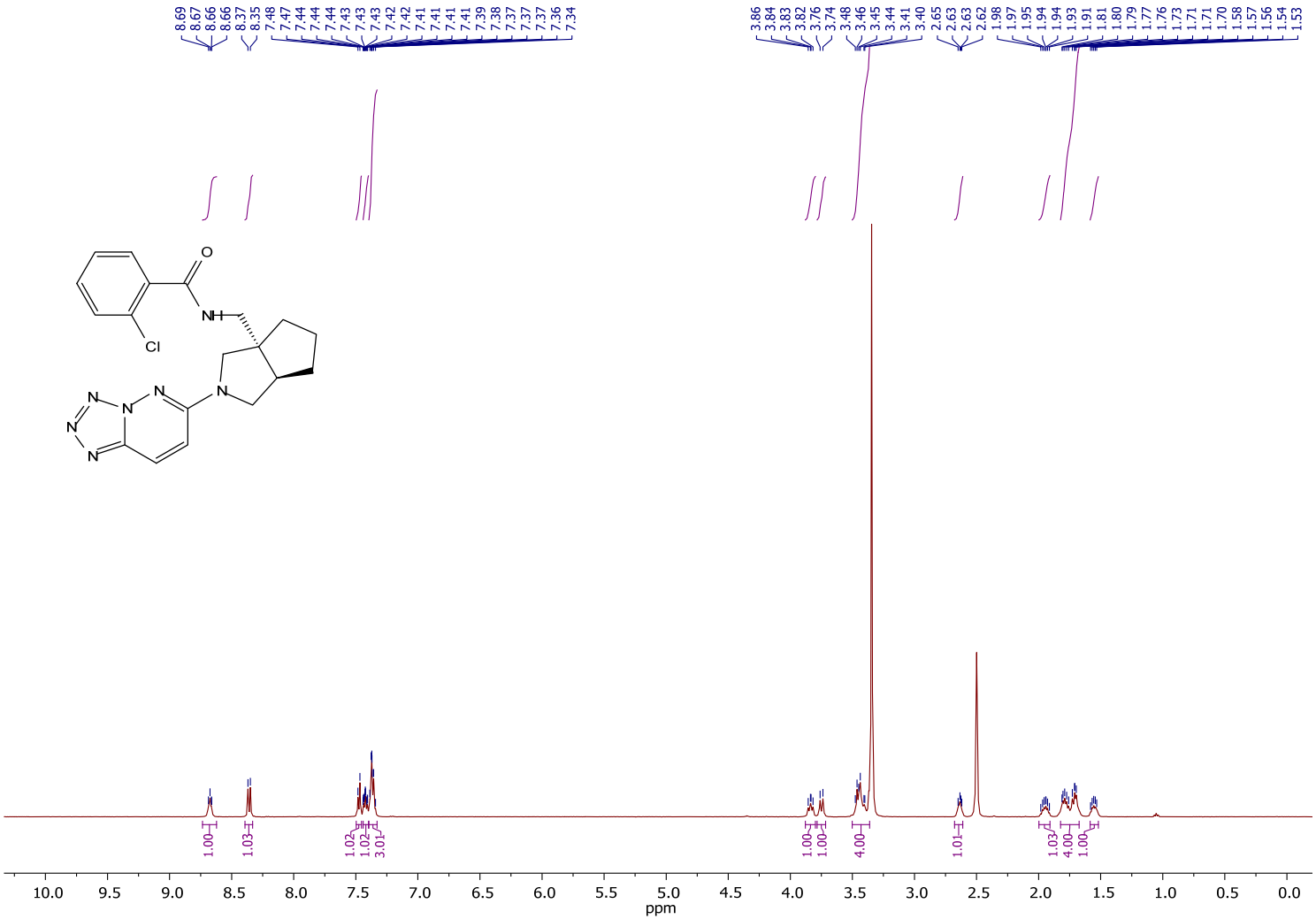
rac-4-Methyl-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)thiophene-2-carboxamide (**14**{*19*,*35*,*394*}), ^{13}C NMR (126 MHz, DMSO-d_6)



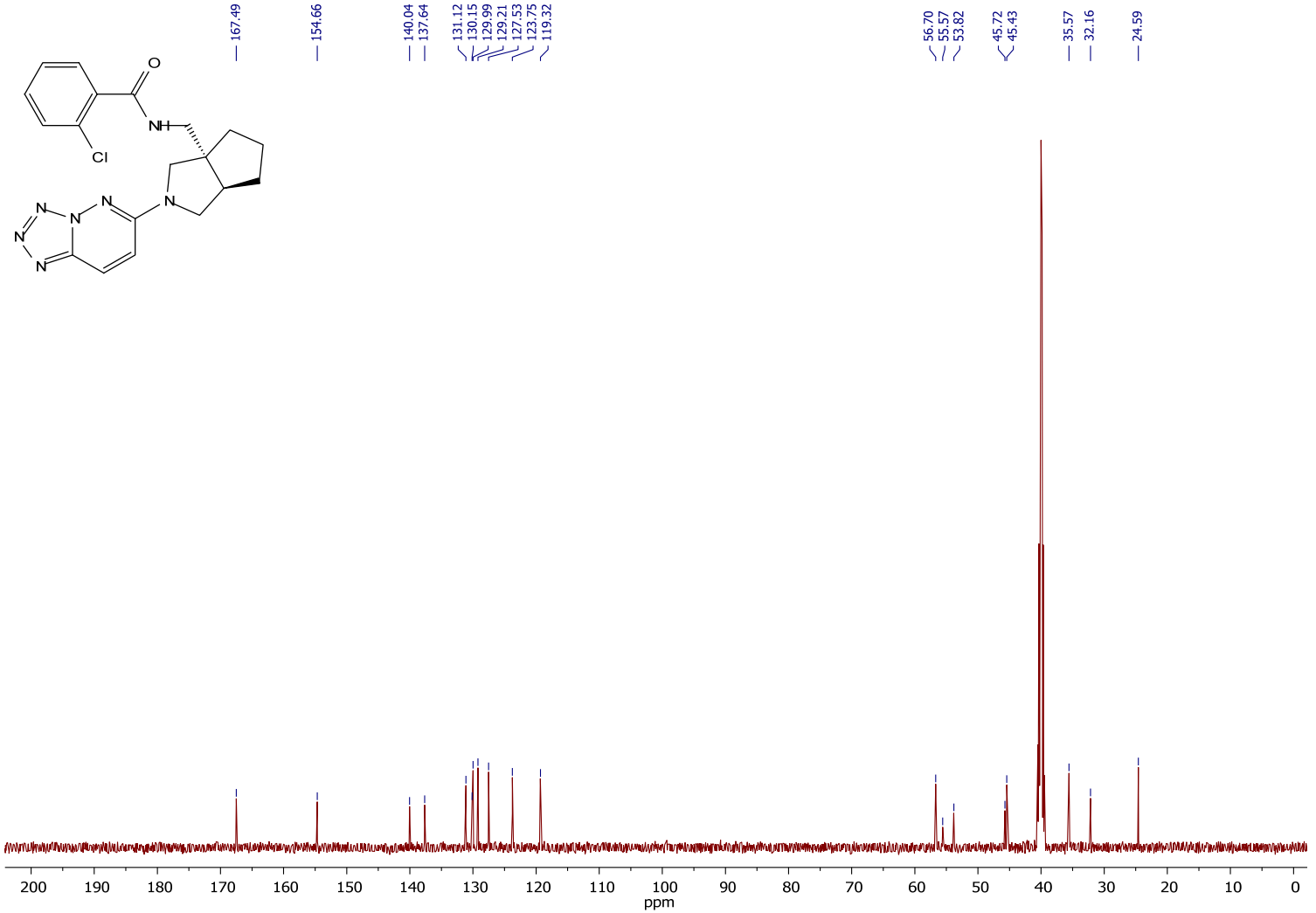
1-Methyl-*N*-(6-(tetrazolo[1,5-*b*]pyridazin-6-ylamino)spiro[3.3]heptan-2-yl)cycloheptanecarboxamide (**14**{*114*,*35*,*399*}), ^{1}H NMR (600 MHz, DMSO-d_6)



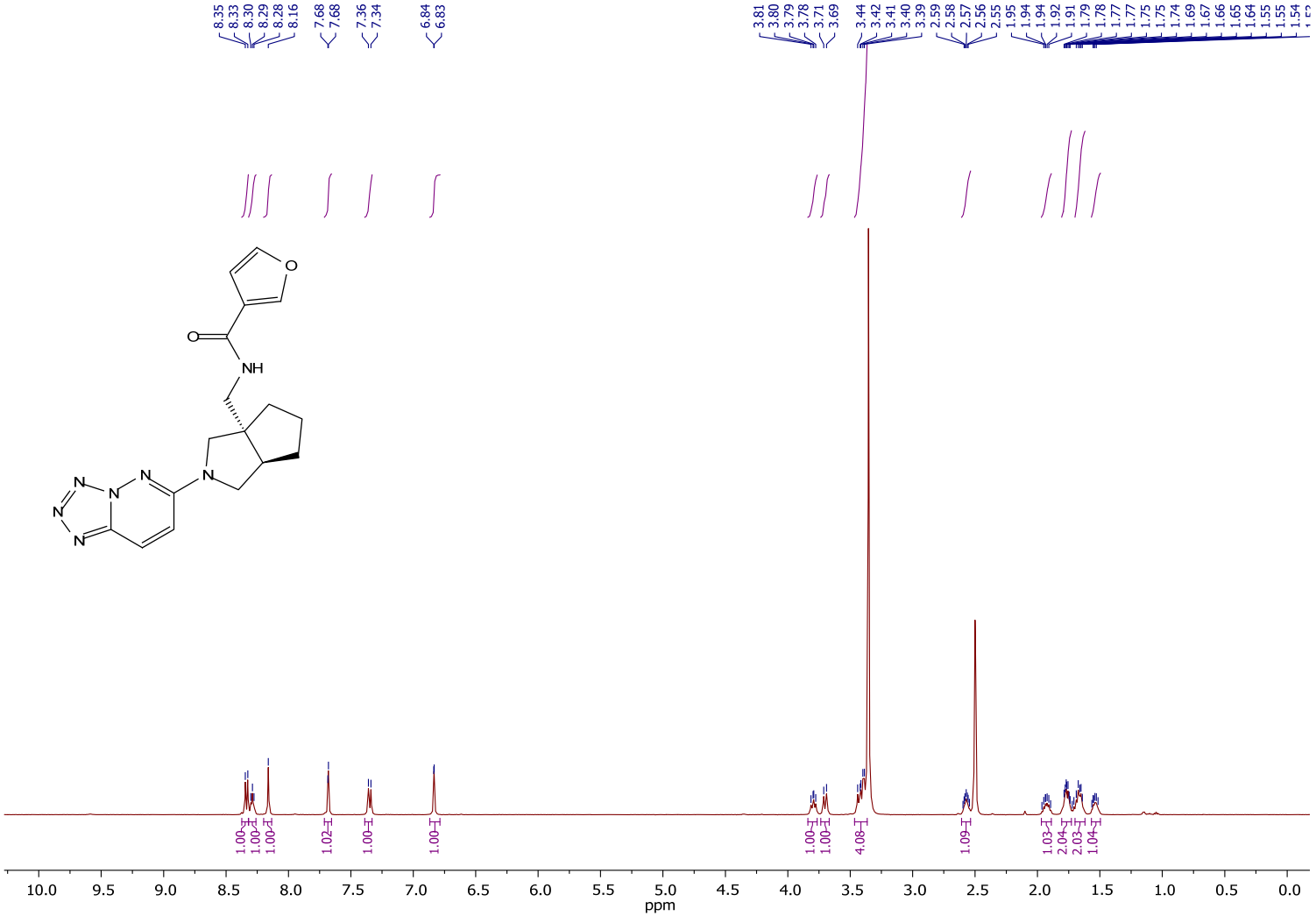
1-Methyl-*N*-(6-(tetrazolo[1,5-*b*]pyridazin-6-ylamino)spiro[3.3]heptan-2-yl)cycloheptanecarboxamide (**14**{*114*,*35*,*399*}), ^{13}C NMR (151 MHz, DMSO-d_6)



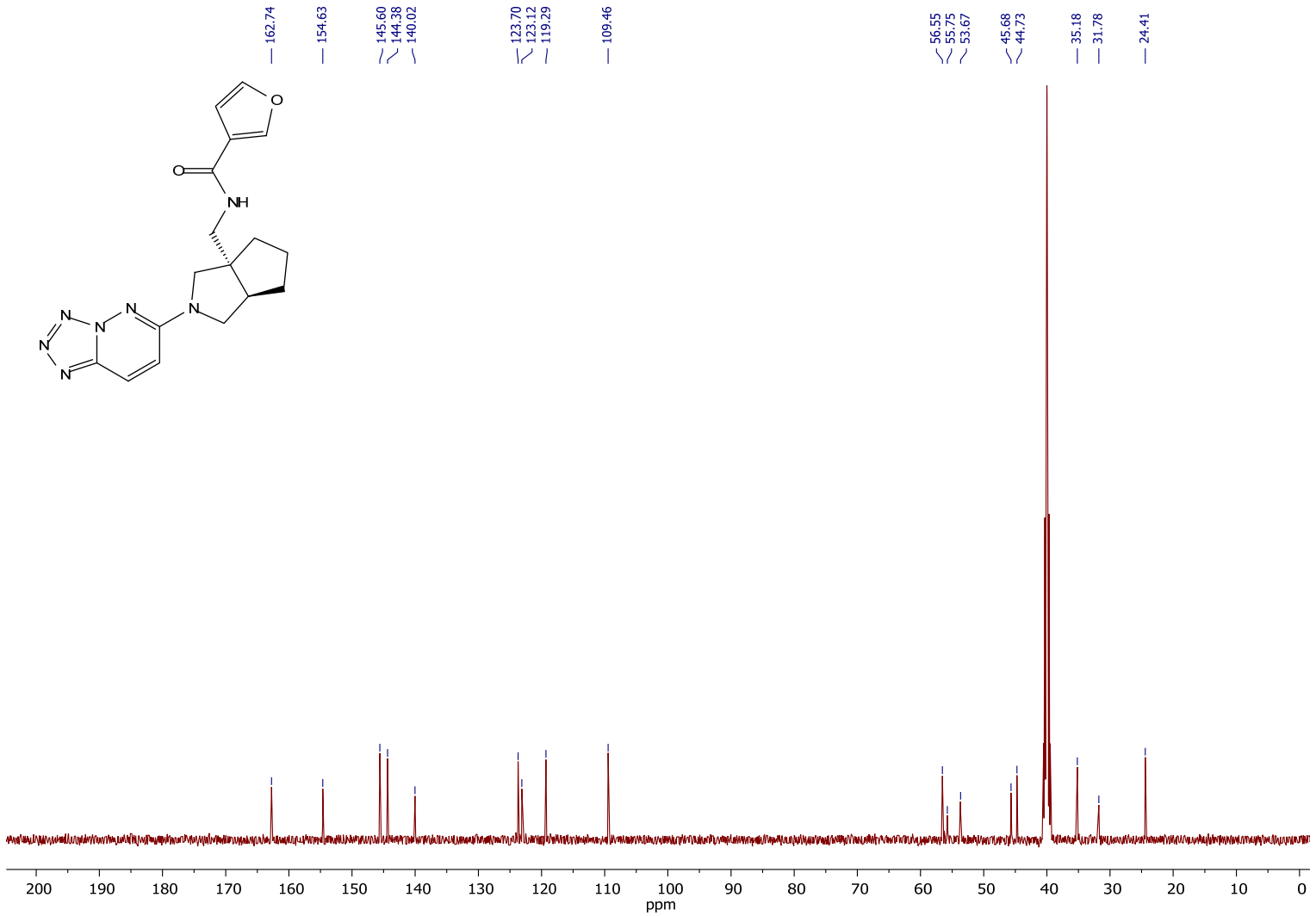
rac-2-Chloro-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)benzamide (**14**{*19*,*35*,*408*}), ^{1}H NMR (500 MHz, DMSO-d_6)



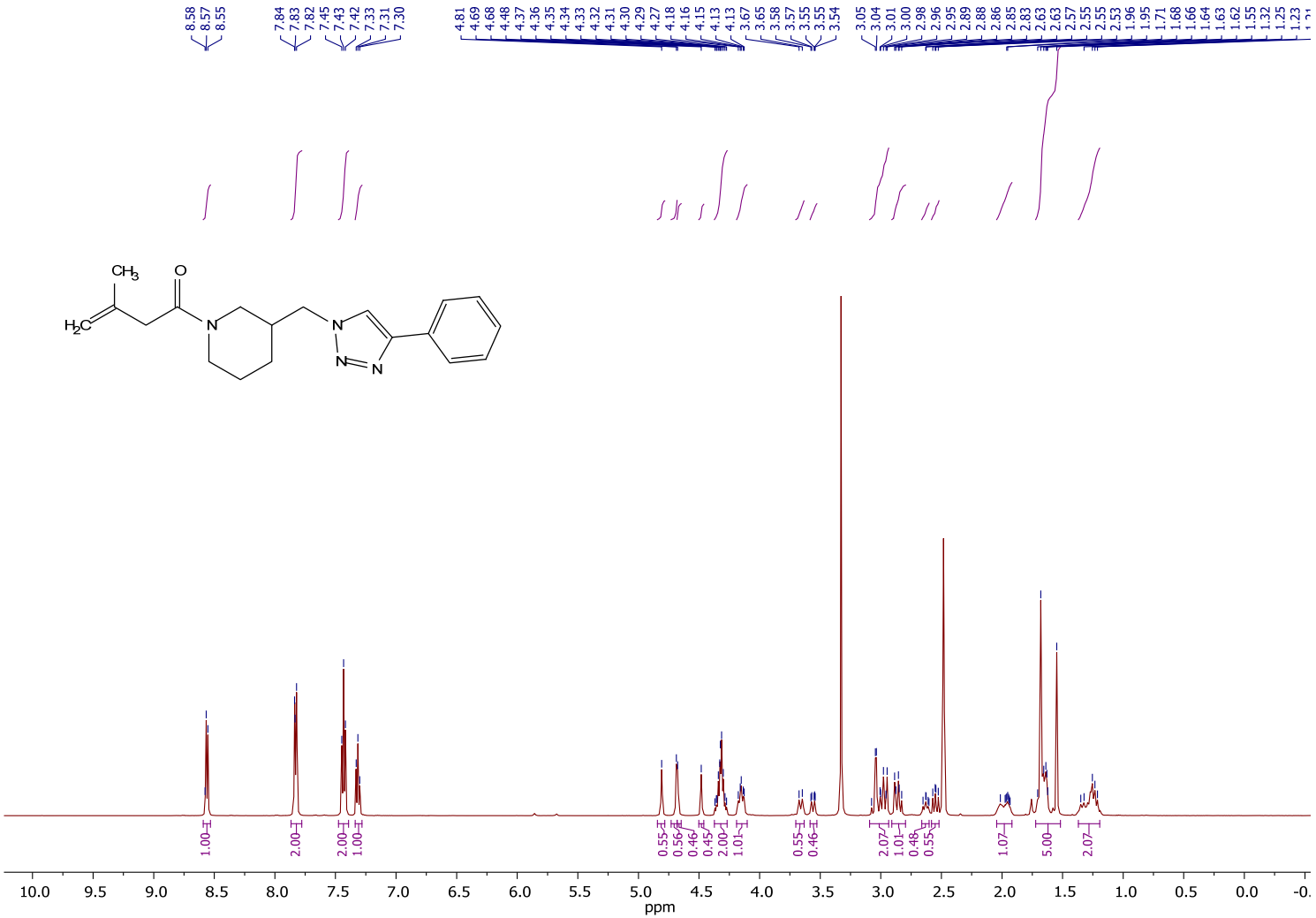
rac-2-Chloro-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)benzamide (**14**{*19*,*35*,*408*}), ^{13}C NMR (126 MHz, DMSO-d_6)



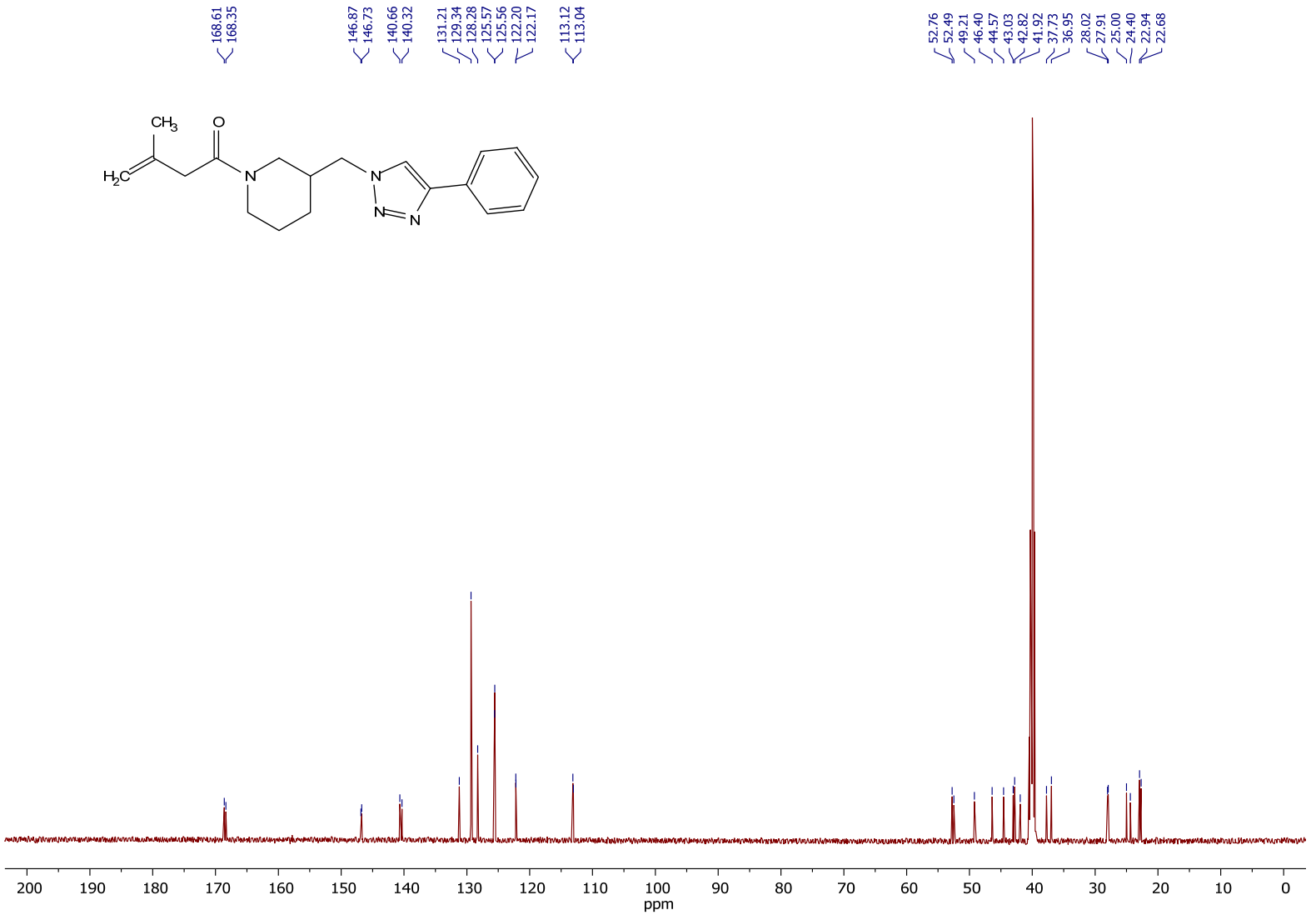
rac-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)furan-3-carboxamide (**14**{*19*,*35*,*32*}), ^{1}H NMR (500 MHz, DMSO-d_6)



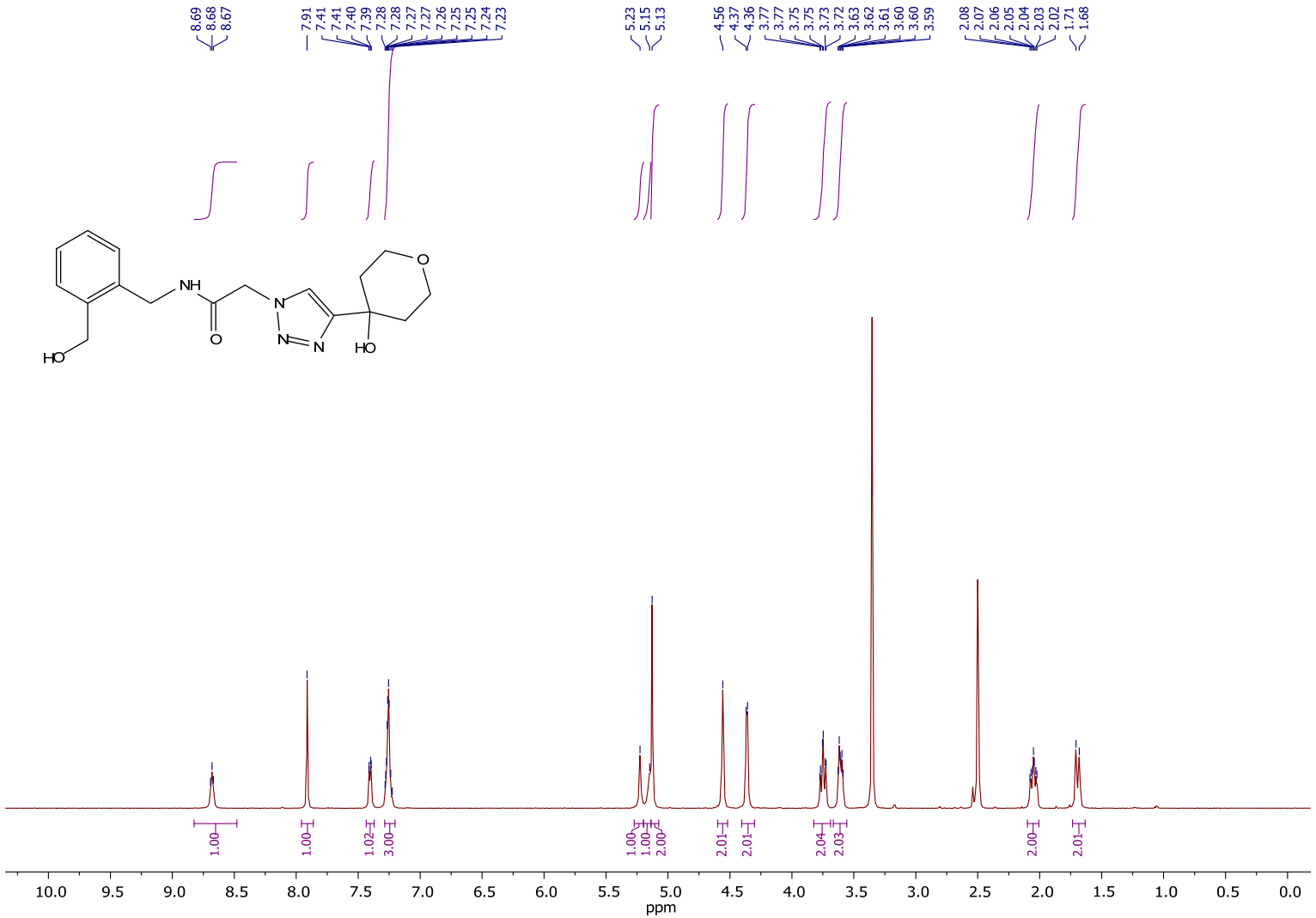
rac-*N*-(((3a*R*,6a*S*)-2-(tetrazolo[1,5-*b*]pyridazin-6-yl)octahydrocyclopenta[*c*]pyrrol-3a-yl)methyl)furan-3-carboxamide (**14**{*19*,*35*,*32*}), ^{13}C NMR (126 MHz, DMSO-d_6)



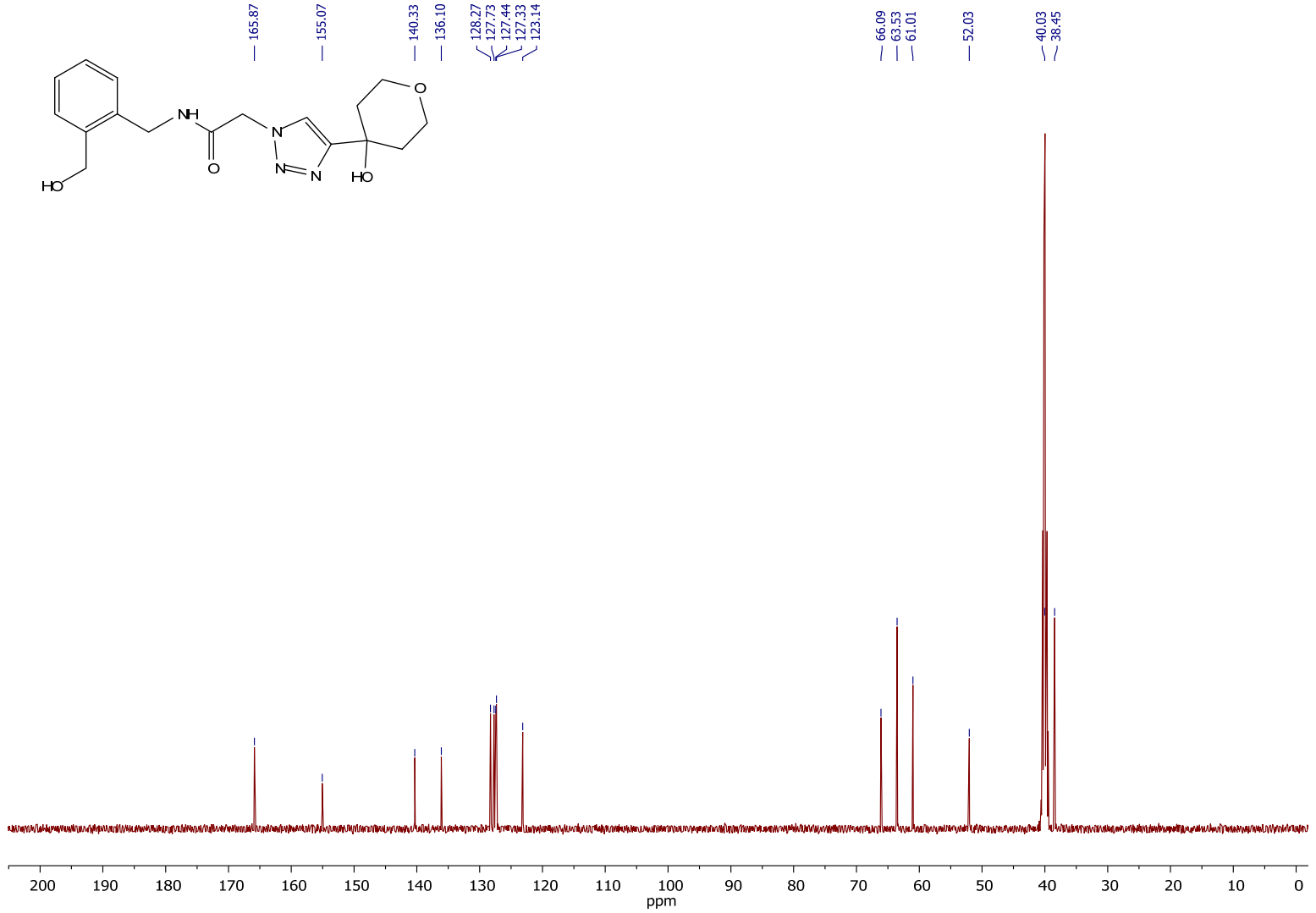
3-Methyl-1-(3-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)piperidin-1-yl)but-3-en-1-one (**15**{*5*,*7*,*7*}), ^{1}H NMR (500 MHz, DMSO-d_6)



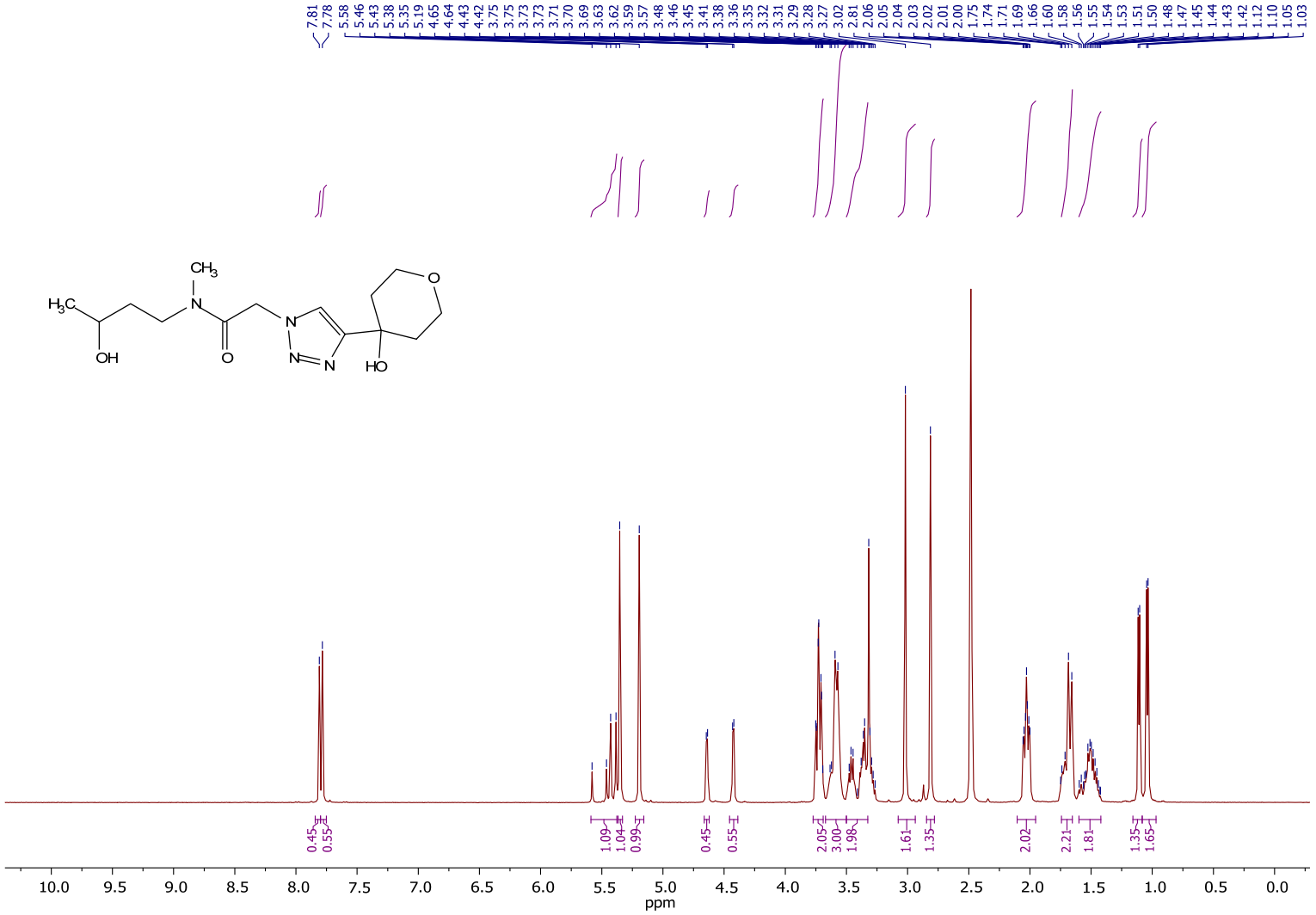
3-Methyl-1-(3-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)piperidin-1-yl)but-3-en-1-one (**15**{*5*,*7*,*7*}), ^{13}C NMR (126 MHz, DMSO-d_6)



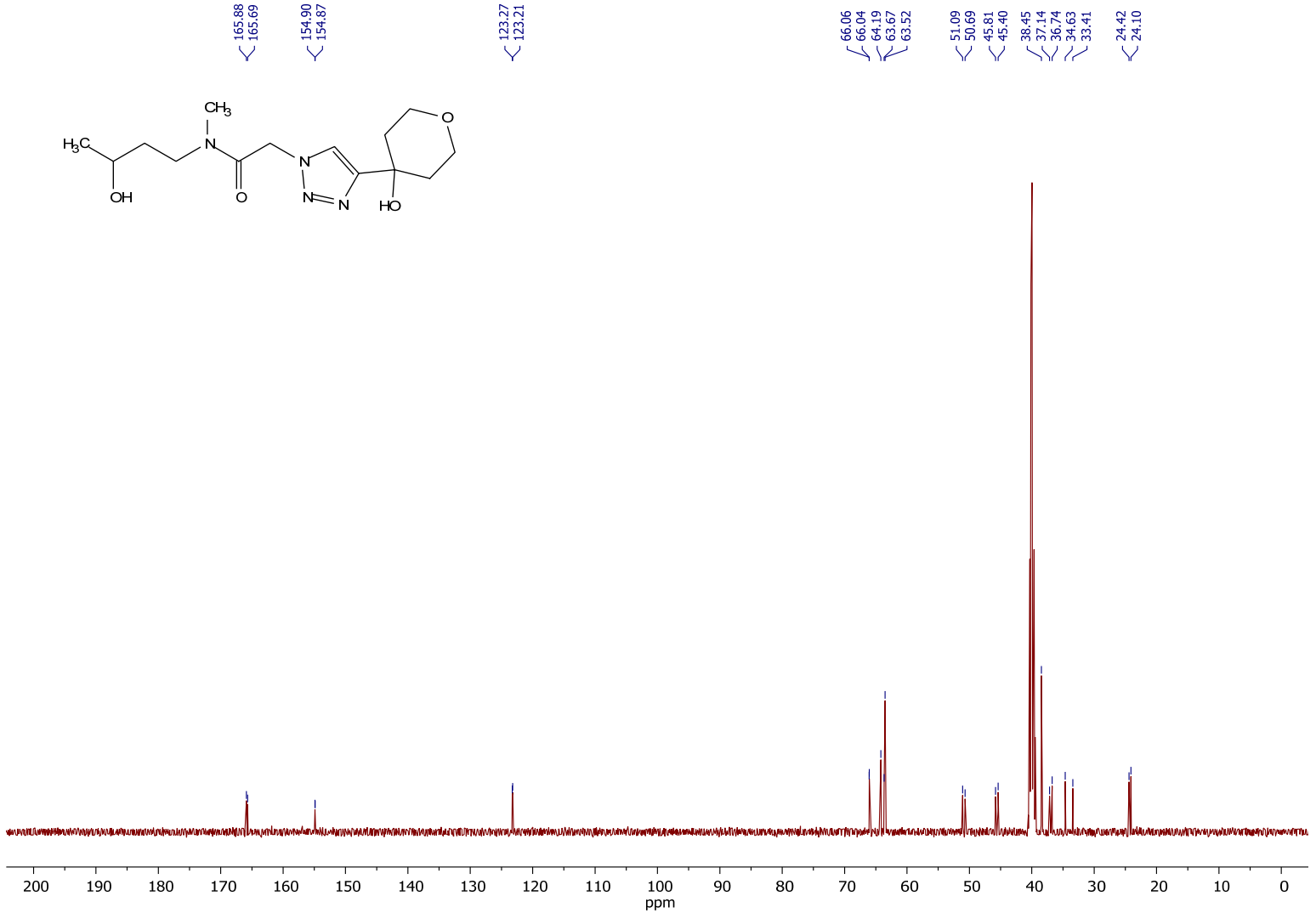
N-(3-Hydroxybutyl)-2-(4-(4-hydroxytetrahydro-2*H*-pyran-4-yl)-1*H*-1,2,3-triazol-1-yl)-*N*-methylacetamide (**15**{*3*,*20*,*38*}), ^{1}H NMR (500 MHz, DMSO-d_6)



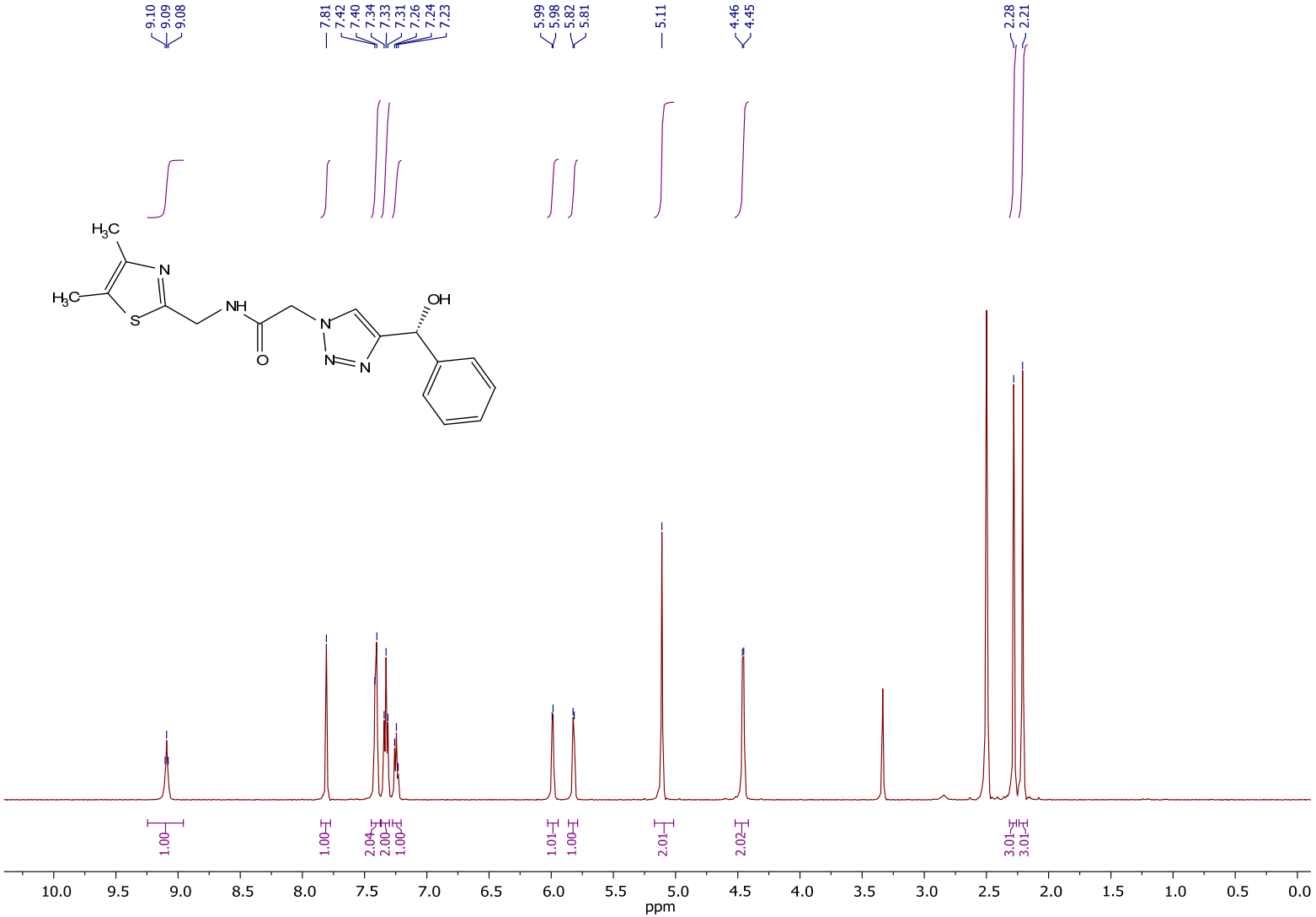
N-(3-Hydroxybutyl)-2-(4-(4-hydroxytetrahydro-2*H*-pyran-4-yl)-1*H*-1,2,3-triazol-1-yl)-*N*-methylacetamide (**15**{*3*,*20*,*38*}), ^{13}C NMR (126 MHz, DMSO-d_6)



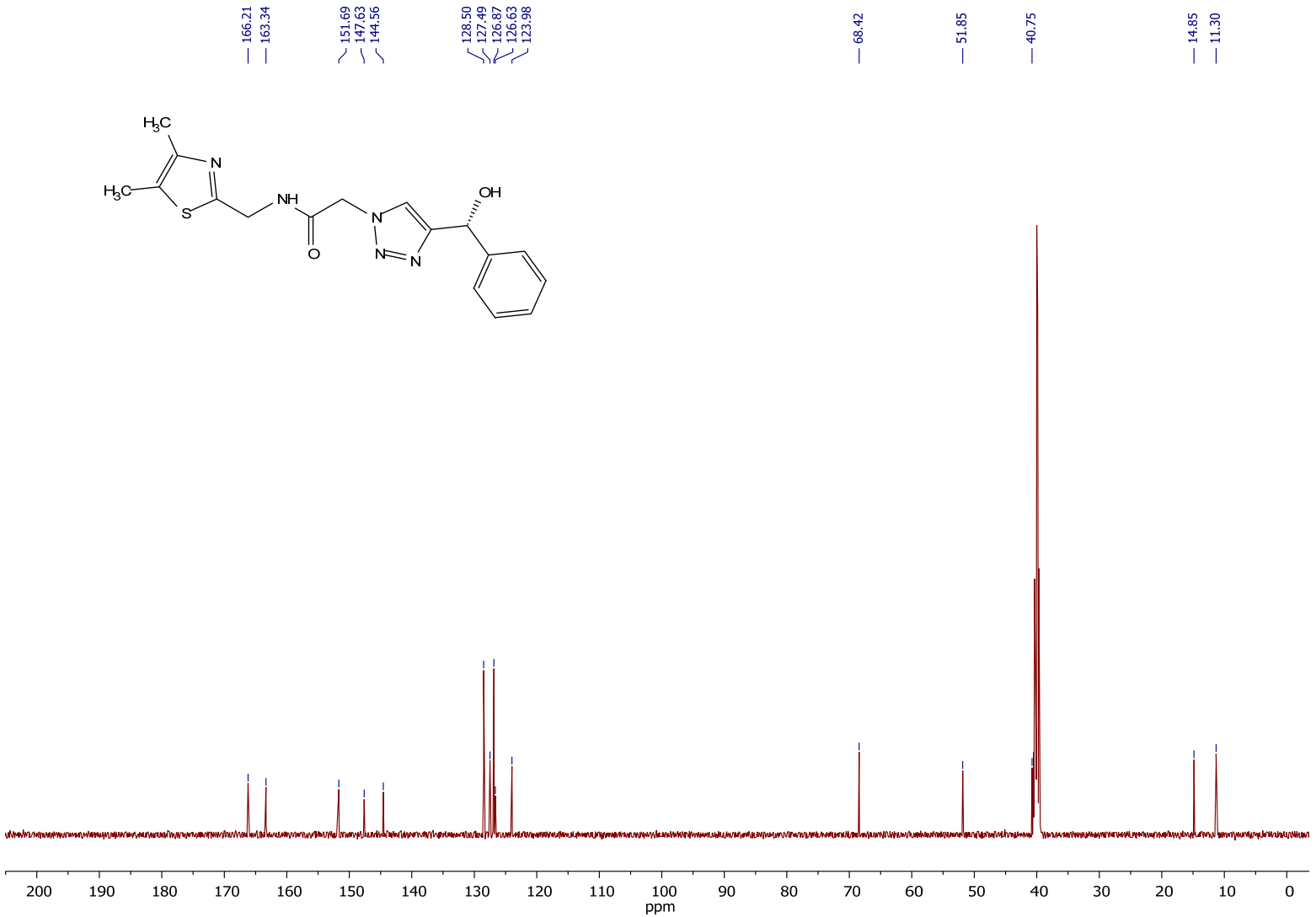
N-(3-Hydroxybutyl)-2-(4-(4-hydroxytetrahydro-2*H*-pyran-4-yl)-1*H*-1,2,3-triazol-1-yl)-*N*-methylacetamide (**15**{*3*,*20*,*38*}), ^{1}H NMR (500 MHz, DMSO-d_6)



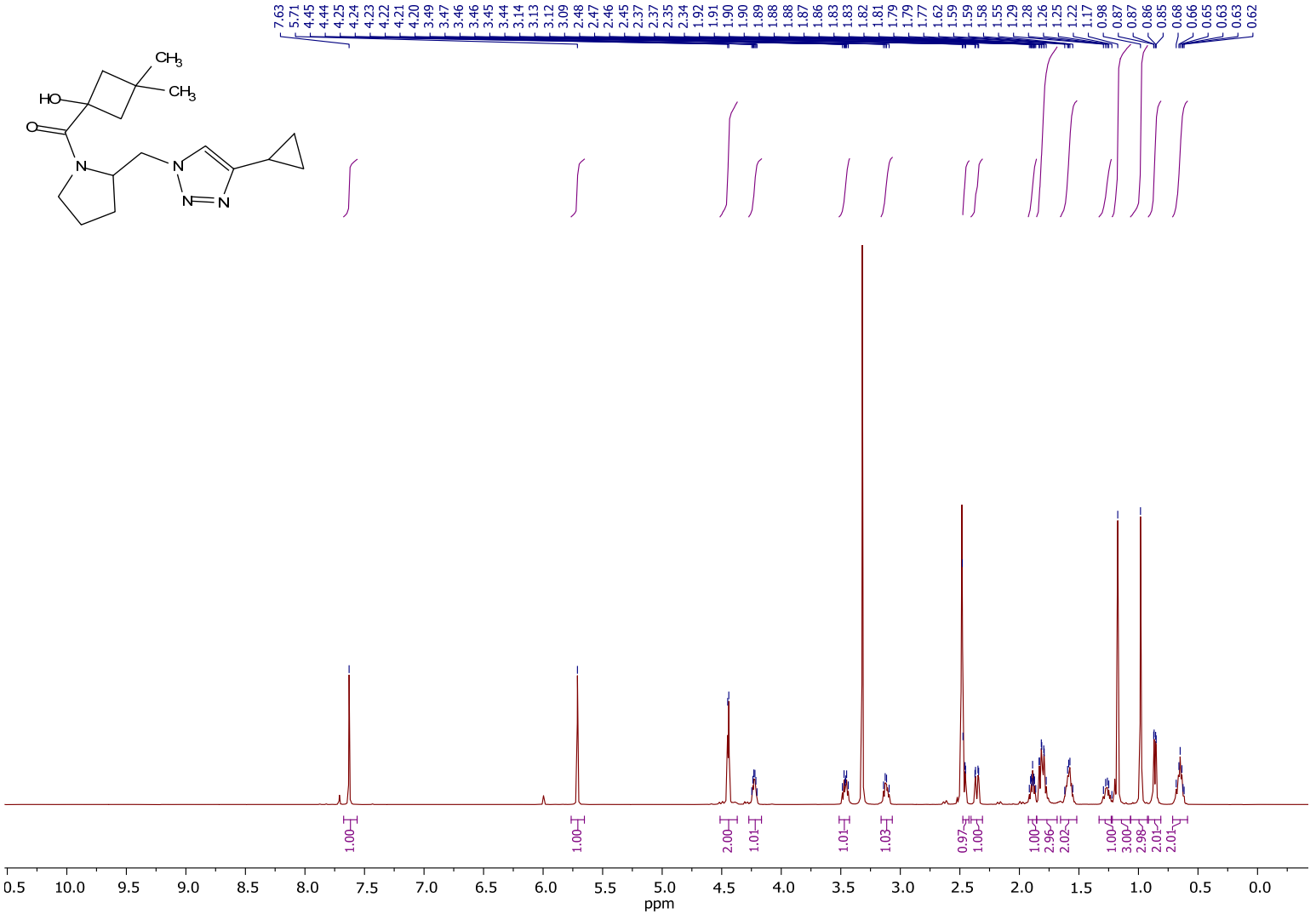
N-(3-Hydroxybutyl)-2-(4-(4-hydroxytetrahydro-2*H*-pyran-4-yl)-1*H*-1,2,3-triazol-1-yl)-*N*-methylacetamide (**15**{*3*,*20*,*38*}), ^{13}C NMR (126 MHz, DMSO-d_6)



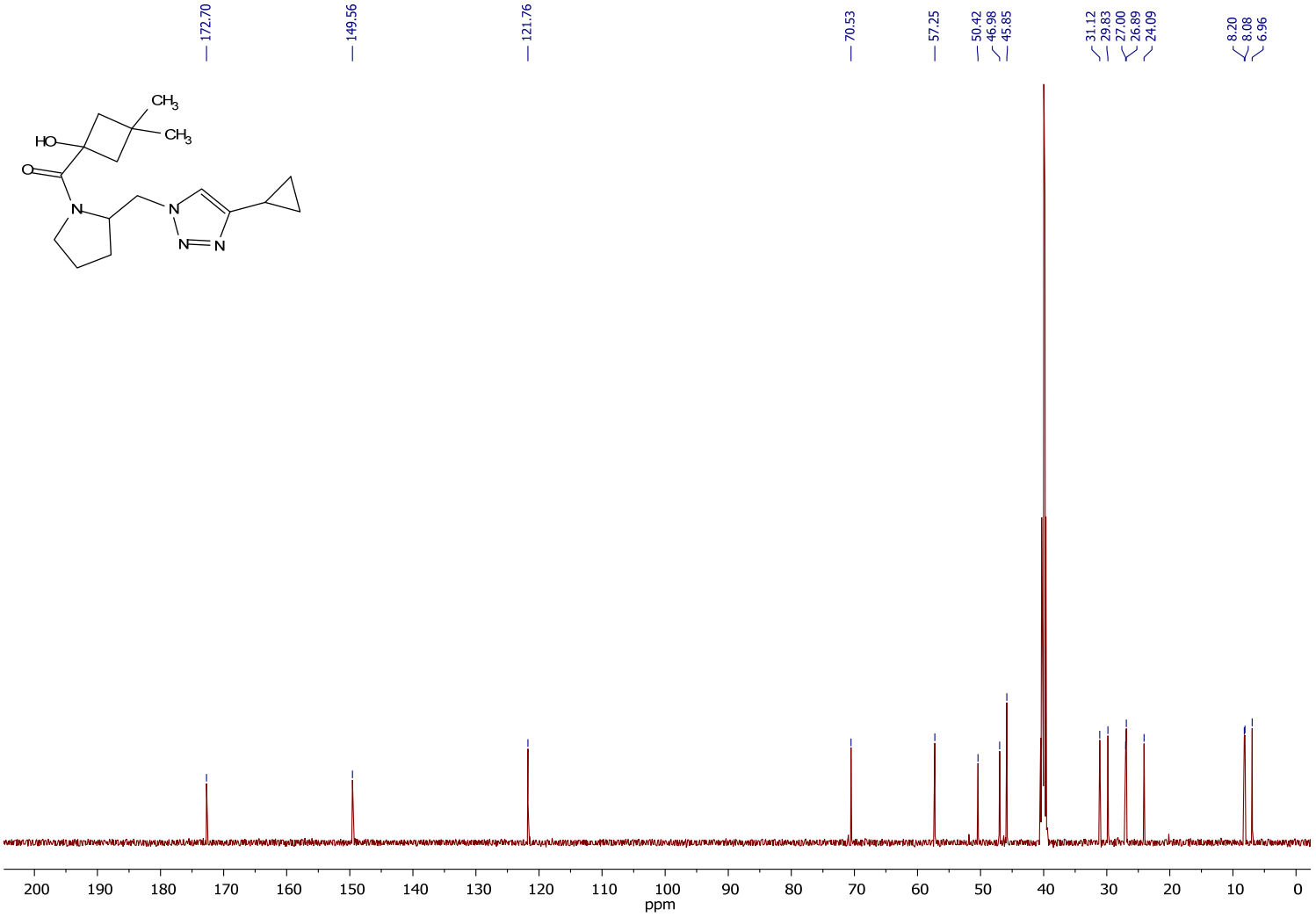
N-((4,5-Dimethylthiazol-2-yl)methyl)-2-(4-(hydroxy(phenyl)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (**15**{*3*,*21*,*37*}), ^{1}H NMR (500 MHz, DMSO-d_6)



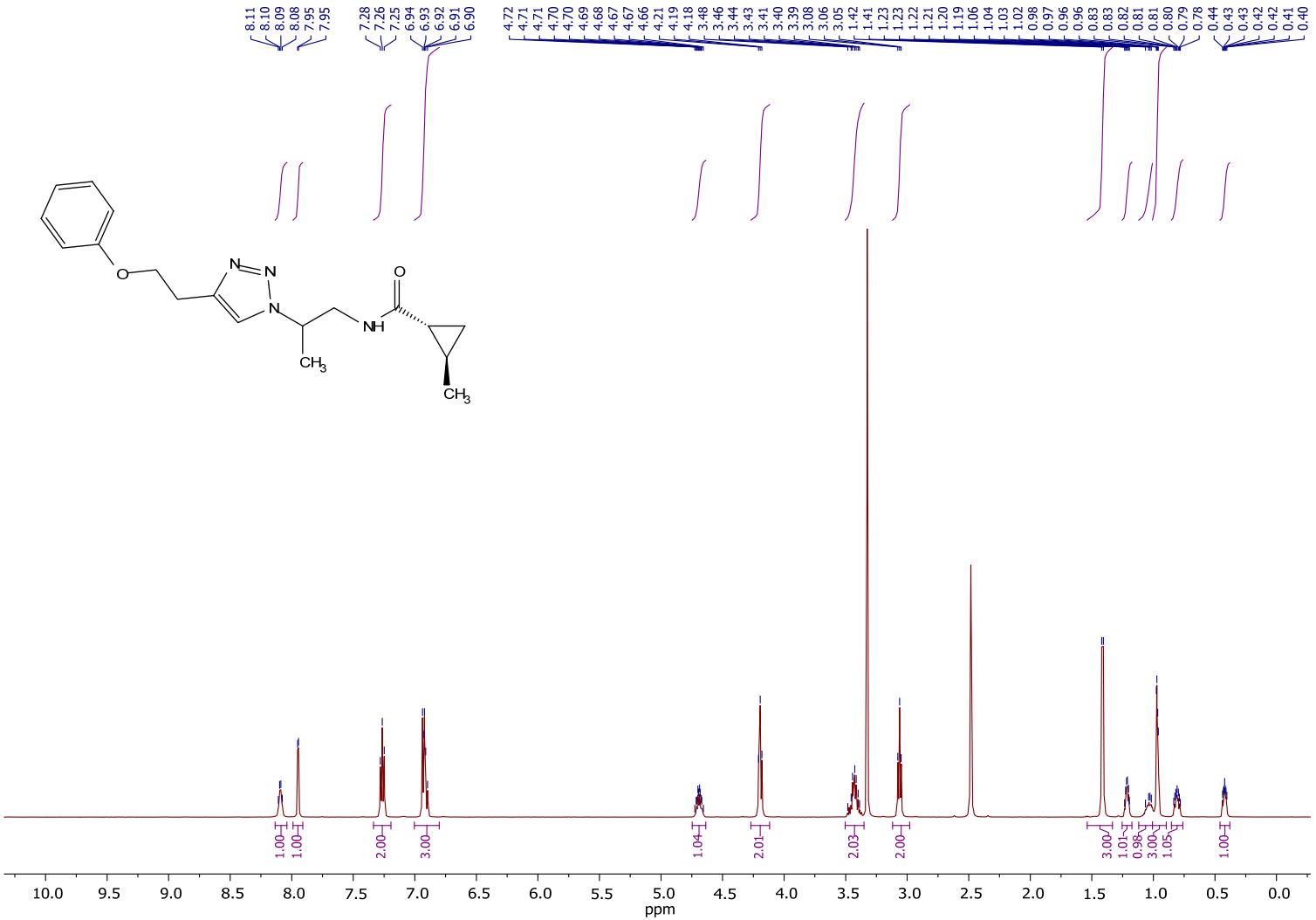
(*N*-((4,5-Dimethylthiazol-2-yl)methyl)-2-(4-(hydroxy(phenyl)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (**15**{*3*,*21*,*37*}), ^{13}C NMR (126 MHz, DMSO-d_6)



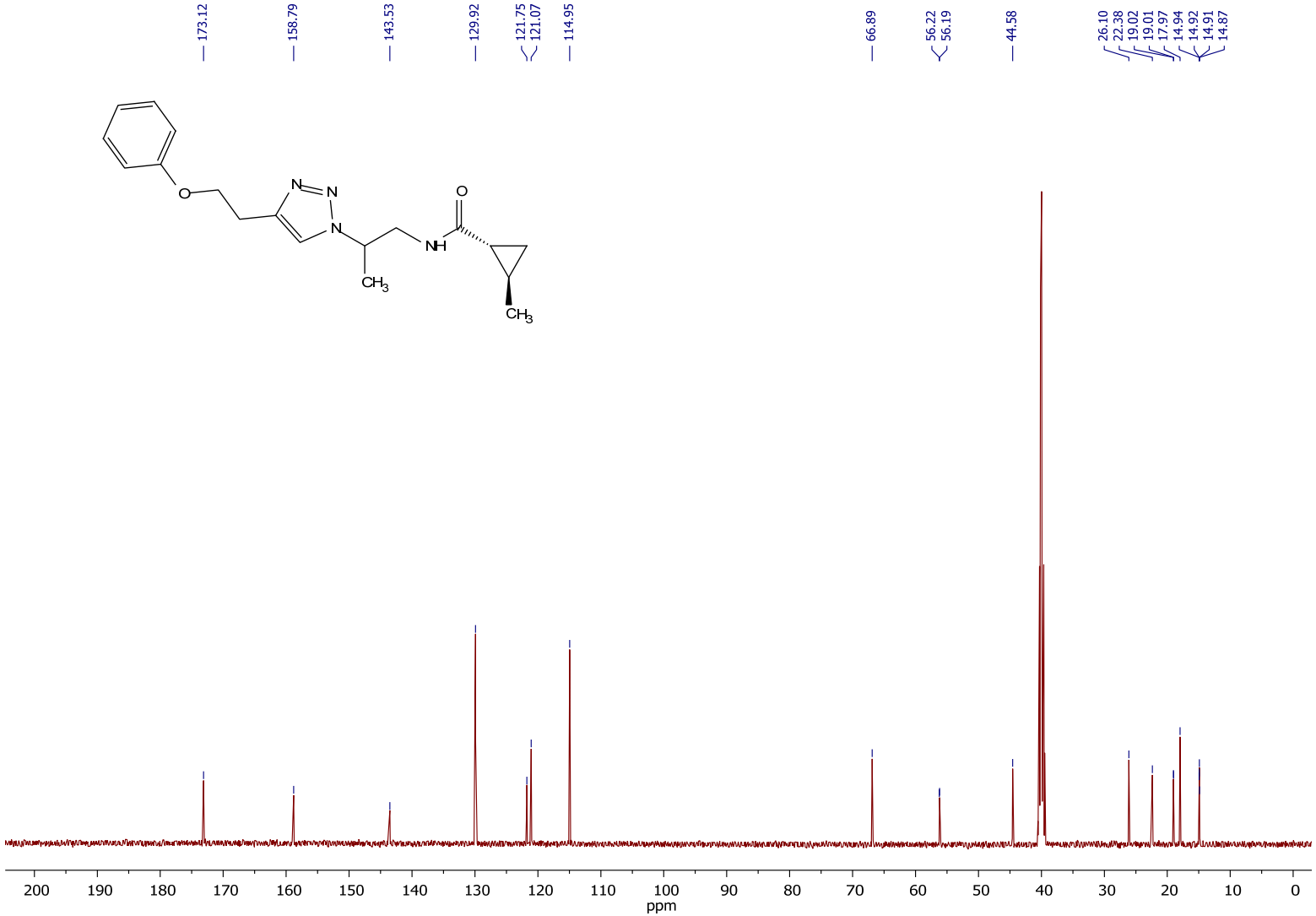
(2-((4-Cyclopropyl-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidin-1-yl)(1-hydroxy-3,3-dimethylcyclobutyl)methanone (**15**{*1*,*6*,*6*}), ^{1}H NMR (500 MHz, DMSO-d_6)



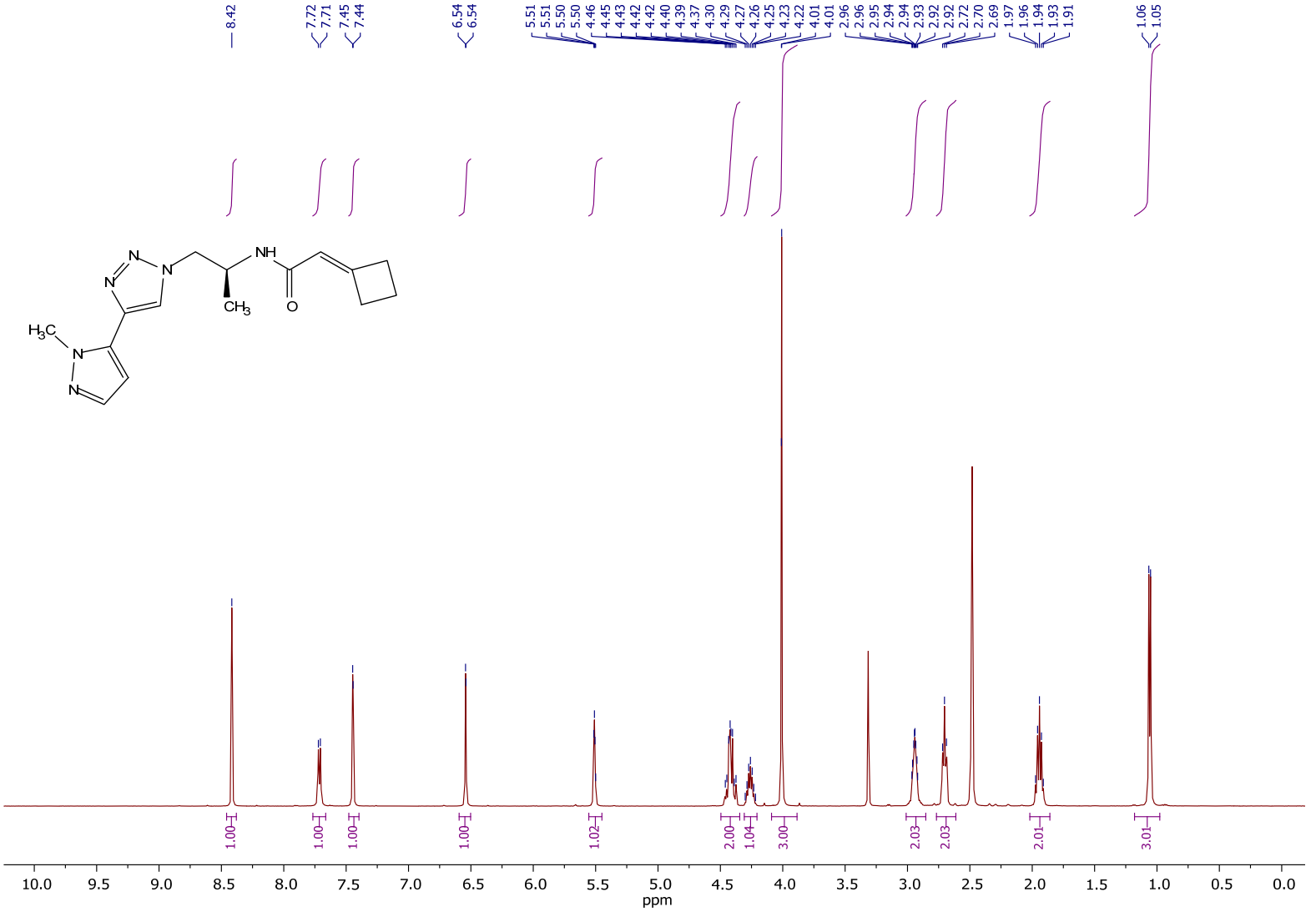
(2-((4-Cyclopropyl-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidin-1-yl)(1-hydroxy-3,3-dimethylcyclobutyl)methanone (**15**{*1*,*6*,*6*}), ^{13}C NMR (126 MHz, DMSO-d_6)



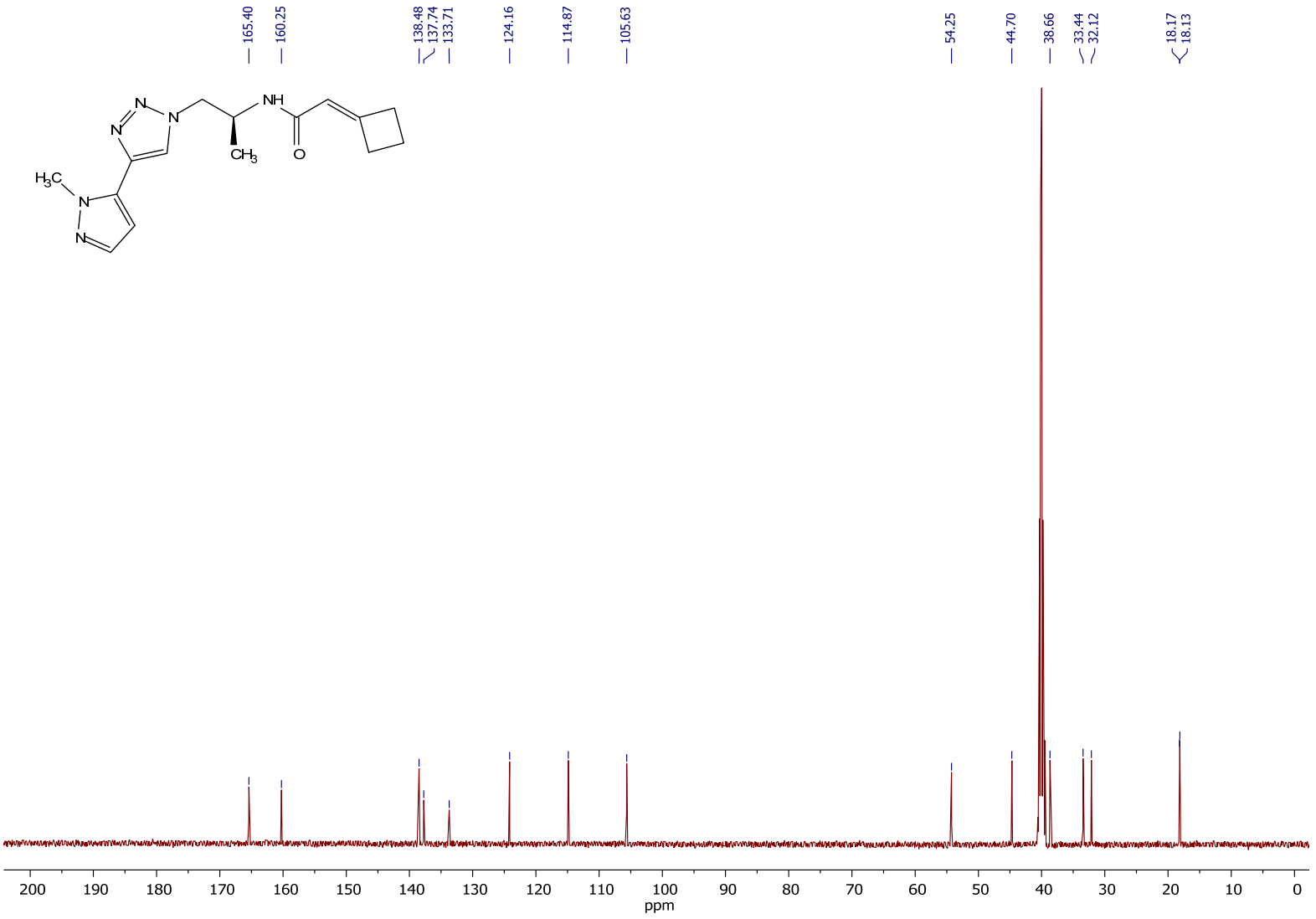
rac-(1*R*,2*R*)-2-Methyl-*N*-(2-(4-(2-phenoxyethyl)-1*H*-1,2,3-triazol-1-yl)propyl)cyclopropanecarboxamide (**15**{*4*,*4*,*4*}), ^{1}H NMR (500 MHz, DMSO-d_6)



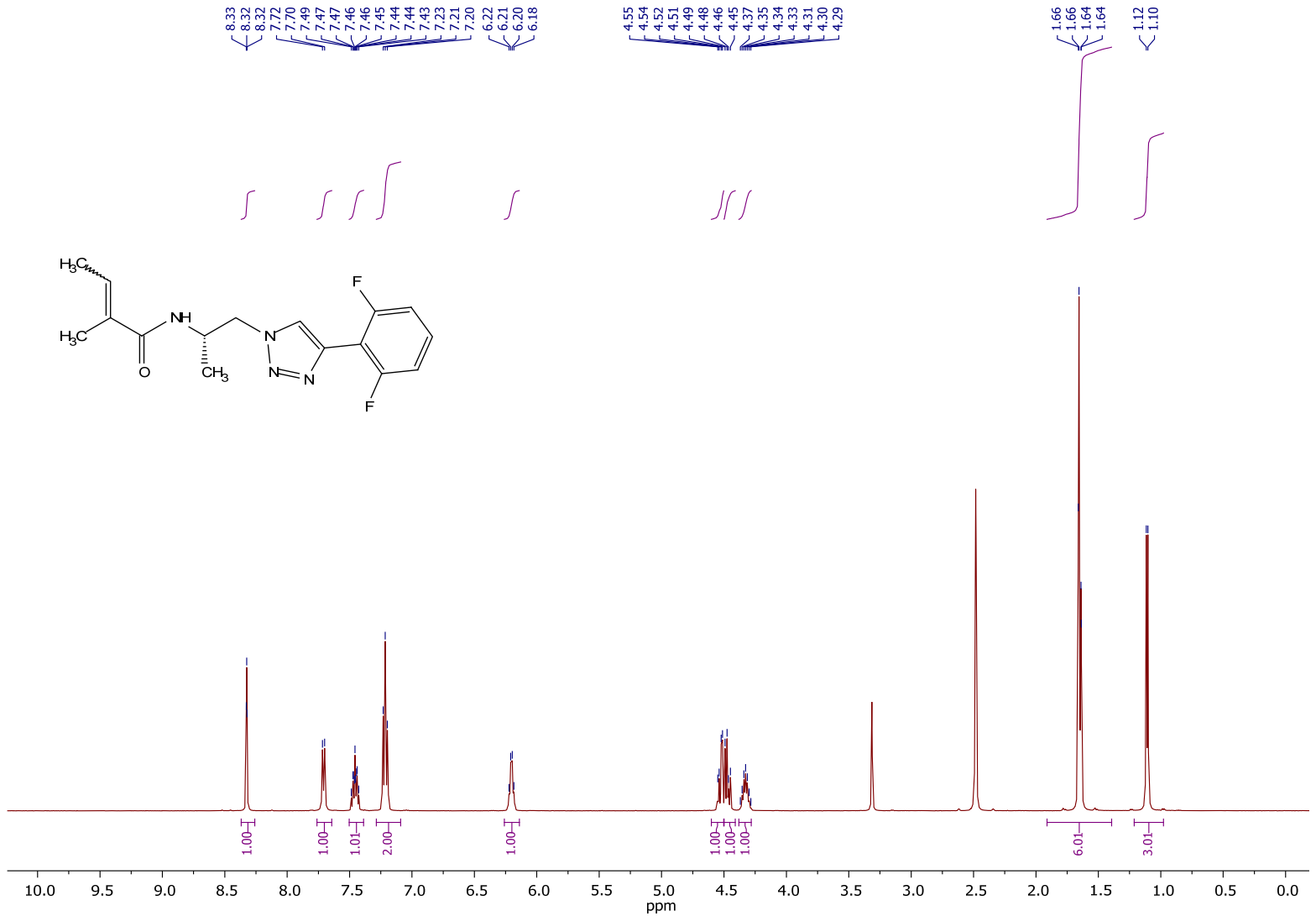
rac-(1*R*,2*R*)-2-Methyl-*N*-(2-(4-(2-phenoxyethyl)-1*H*-1,2,3-triazol-1-yl)propyl)cyclopropanecarboxamide (**15**{*4*,*4*,*4*}), ^{13}C NMR (126 MHz, DMSO-d_6)



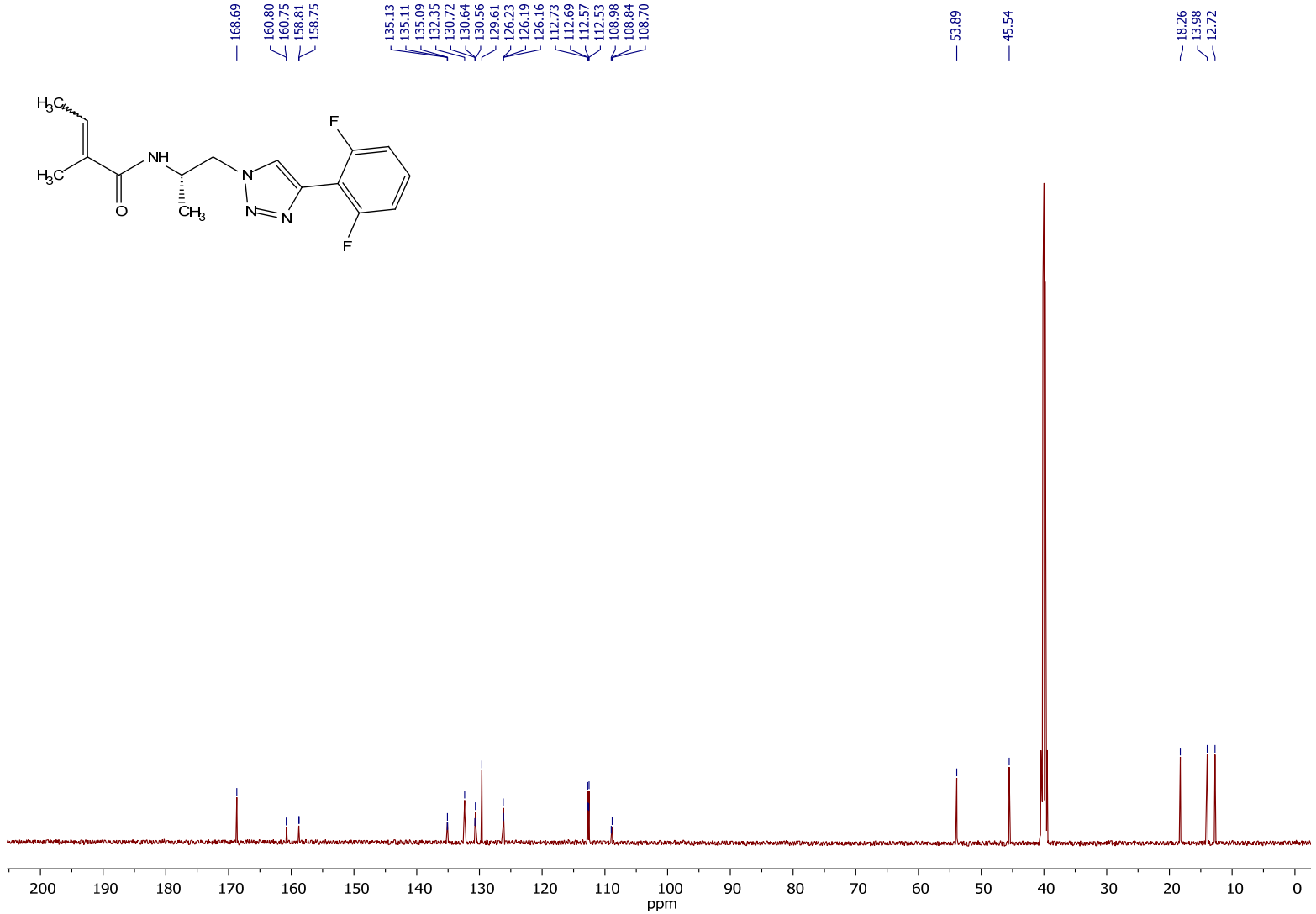
(*S*)-2-Cyclobutylidene-*N*-(1-(4-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)acetamide **15**{*6*,*11*,*11*}, ^{1}H NMR (500 MHz, DMSO-d_6)



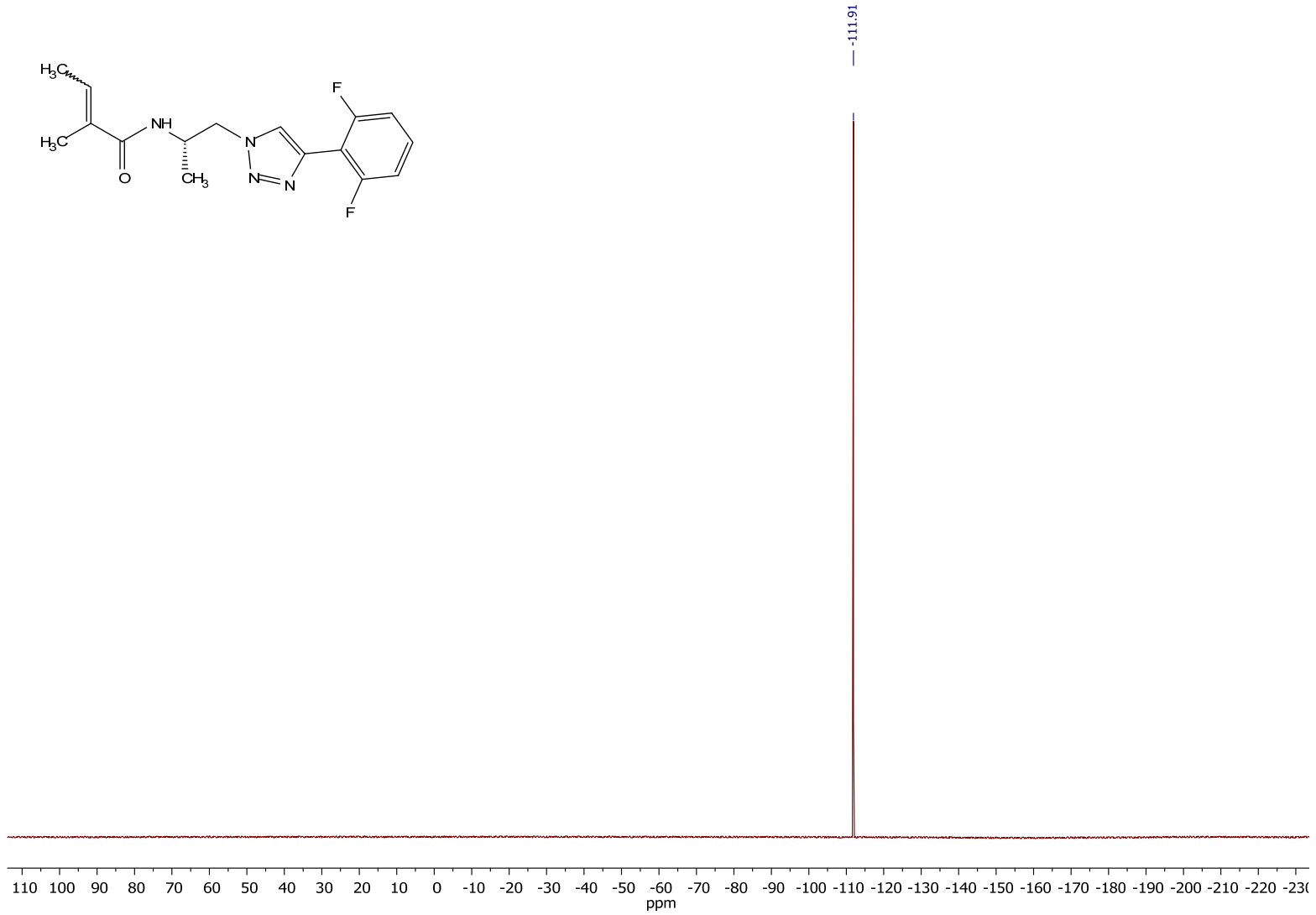
(*S*)-2-Cyclobutylidene-*N*-(1-(4-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)acetamide **15**{*6*,*11*,*11*}, ^{13}C NMR (126 MHz, DMSO-d_6)



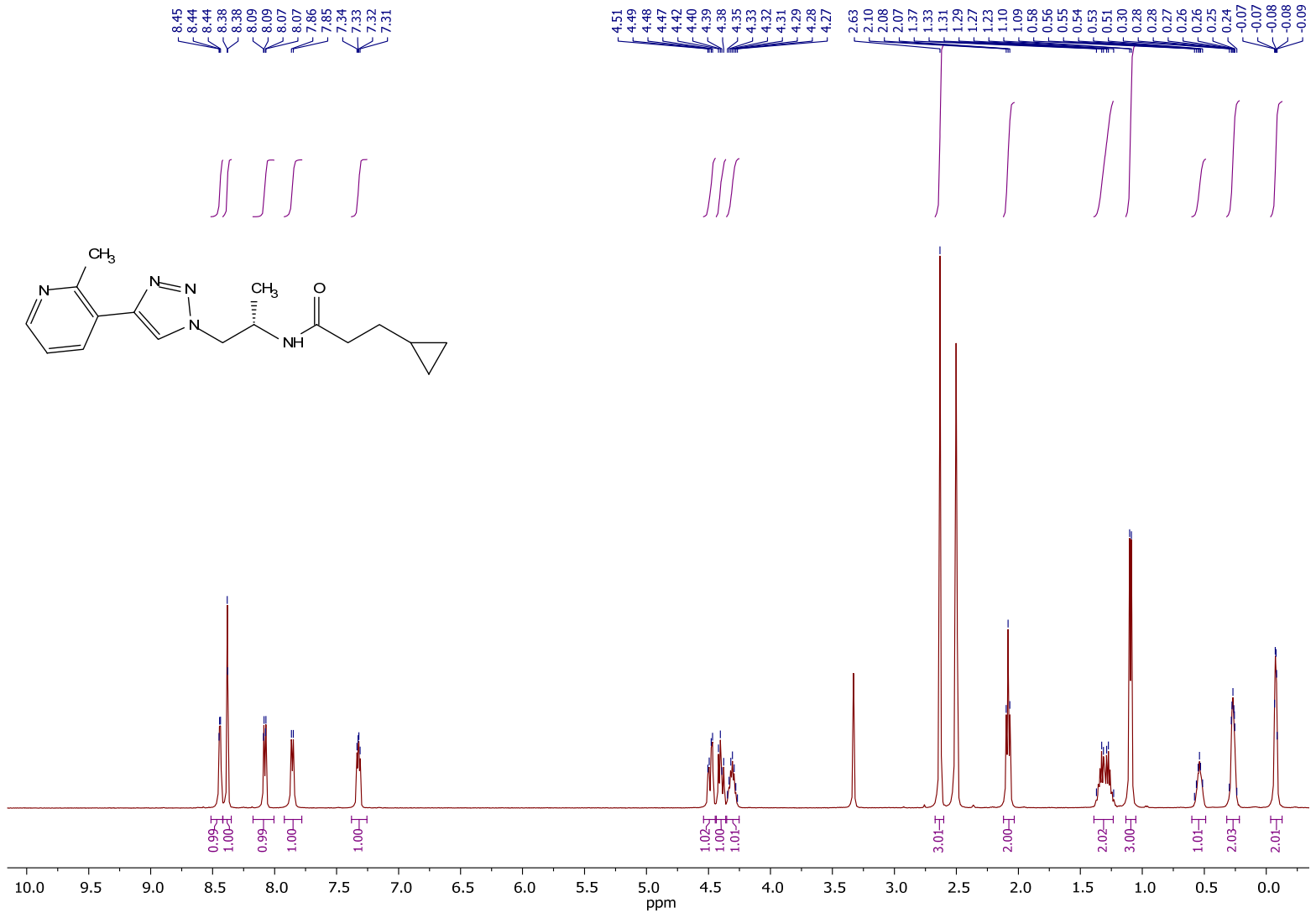
(*S*)-*N*-(1-(4-(2,6-Difluorophenyl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)-2-methylbut-2-enamide (**15**{*6*,*1*,*8*}), ^{1}H NMR (500 MHz, DMSO-d_6)



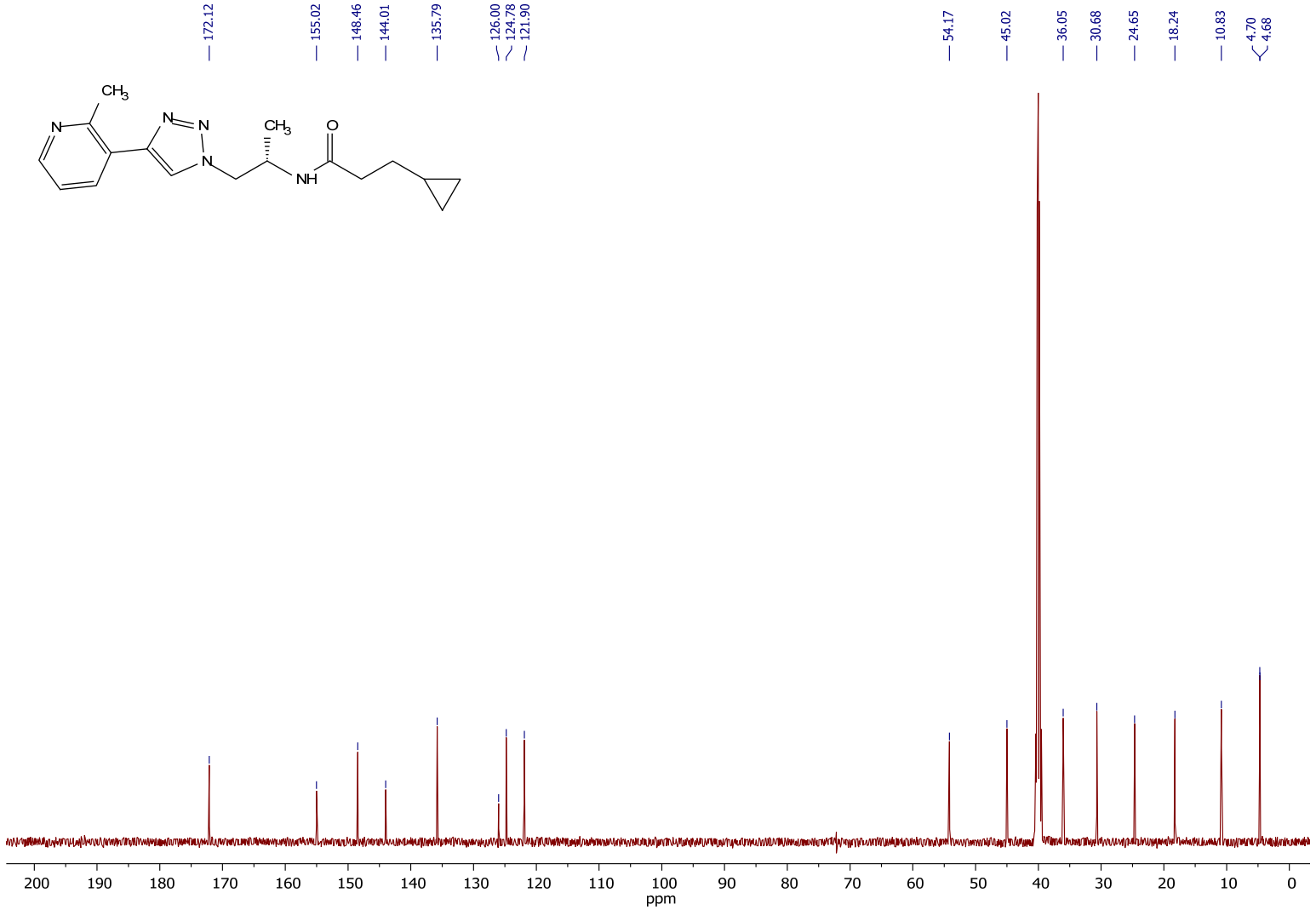
(*S*)-*N*-(1-(4-(2,6-Difluorophenyl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)-2-methylbut-2-enamide (**15**{*6*,*1*,*8*}), ^{13}C NMR (126 MHz, DMSO-d_6)



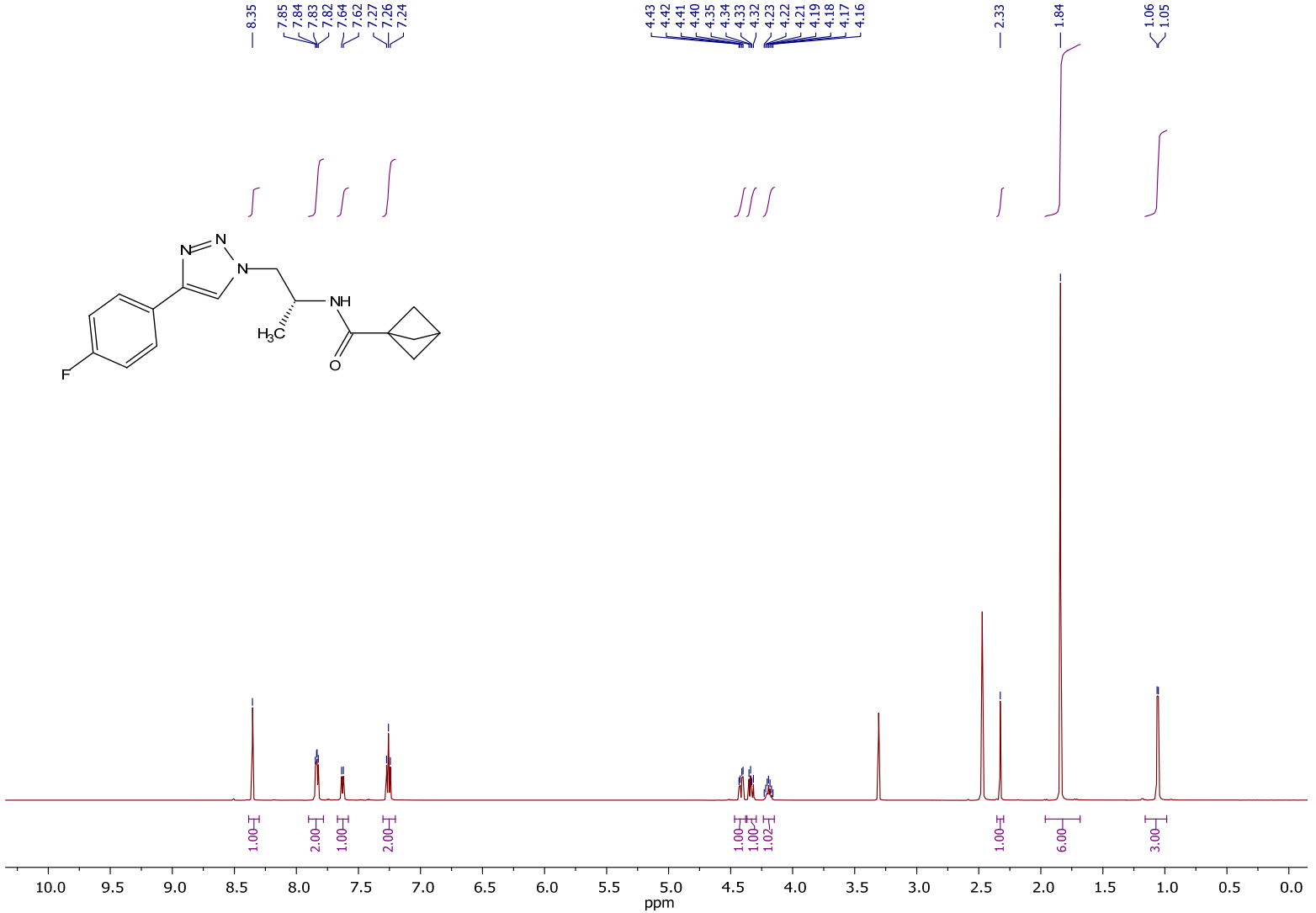
(*S*)-*N*-(1-(4-(2,6-Difluorophenyl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)-2-methylbut-2-enamide (**15**{*6*,*1*,*8*}), ^{19}F NMR (376 MHz, DMSO-d_6)



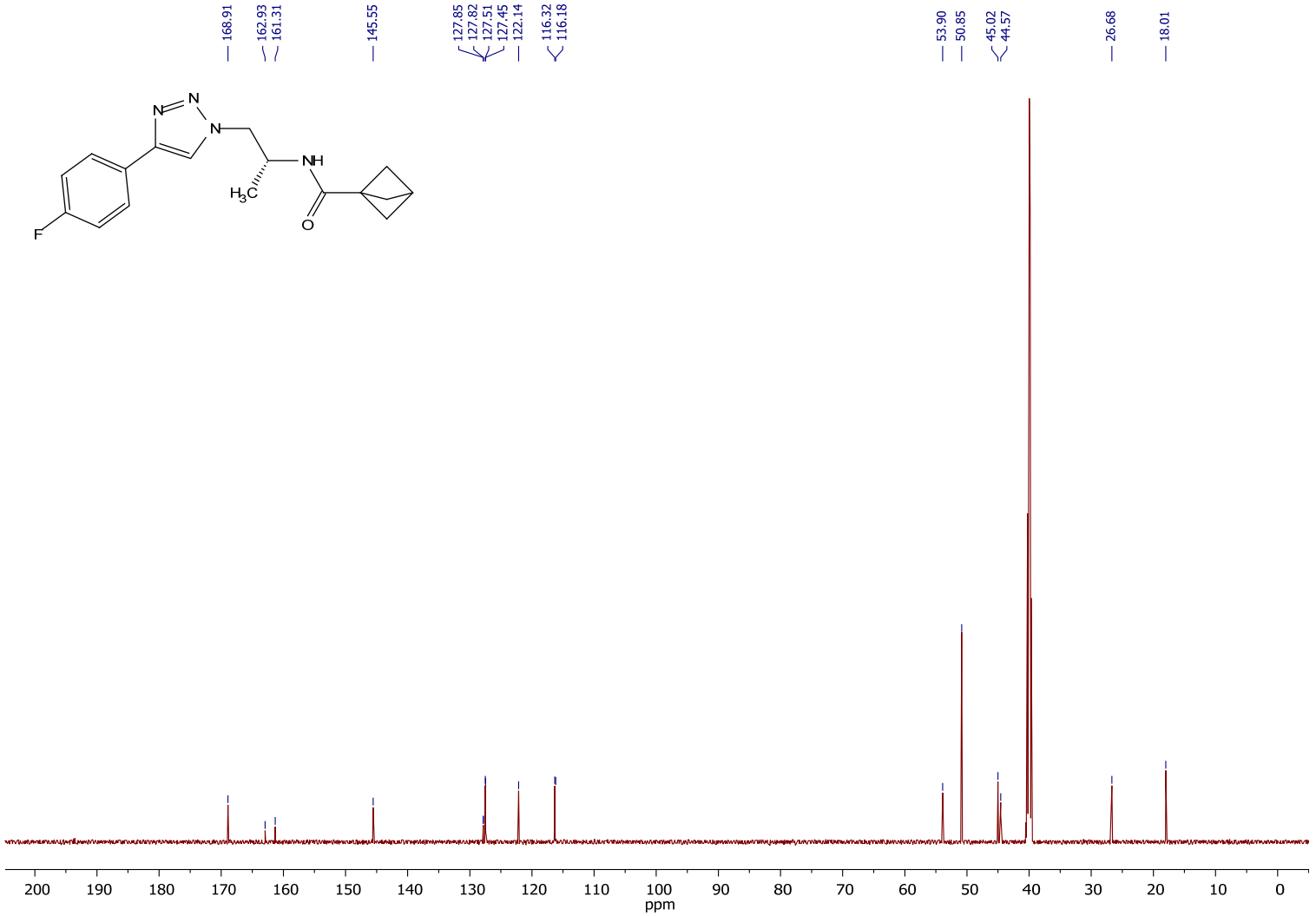
(*S*)-3-Cyclopropyl-*N*-(1-(4-(2-methylpyridin-3-yl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)propanamide (**15**{*6*,*27*,*27*}), ^{1}H NMR (500 MHz, DMSO-d_6)



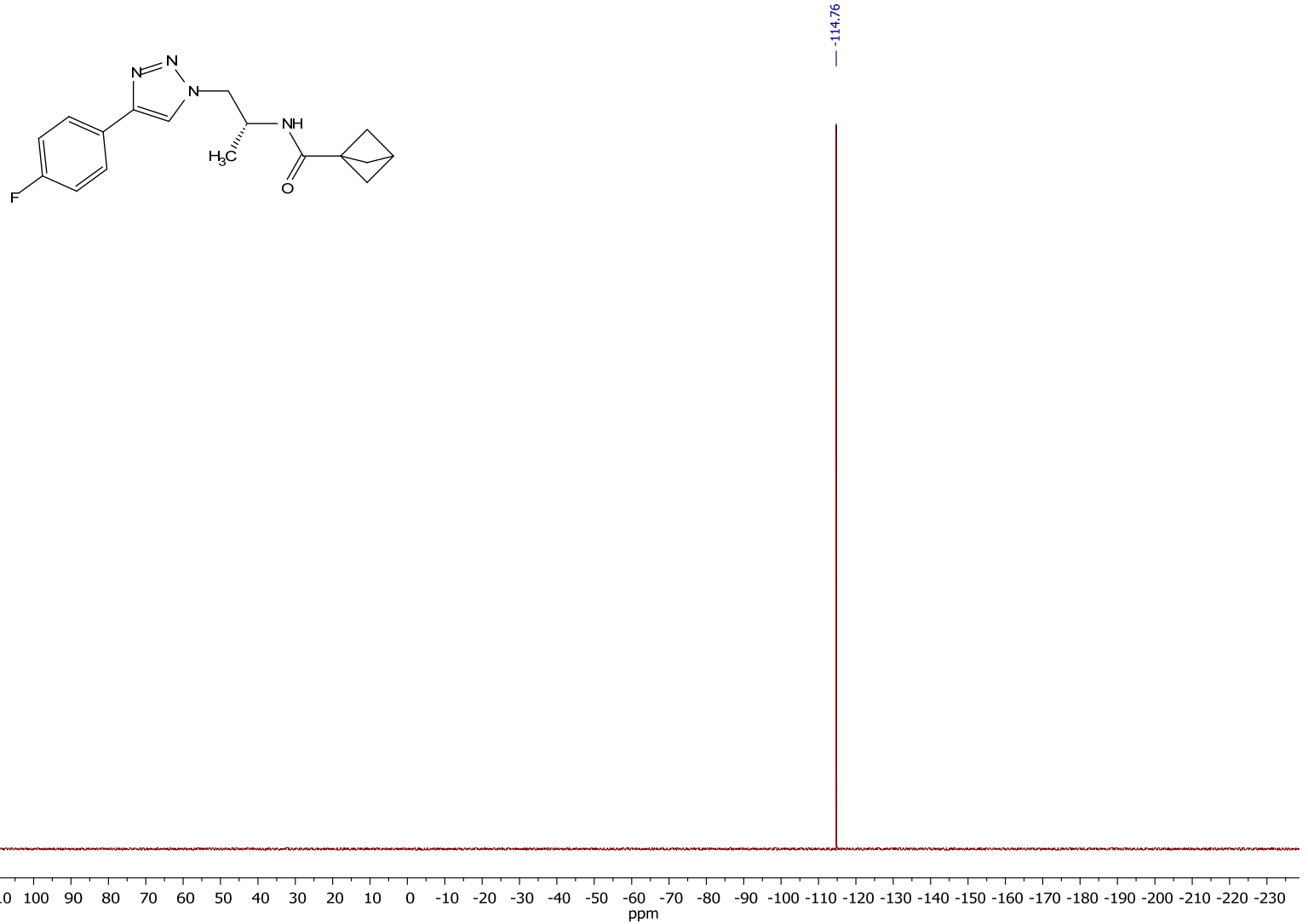
(*S*)-3-Cyclopropyl-*N*-(1-(4-(2-methylpyridin-3-yl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)propanamide (**15**{*6*,*27*,*27*}), ^{13}C NMR (126 MHz, DMSO-d_6)



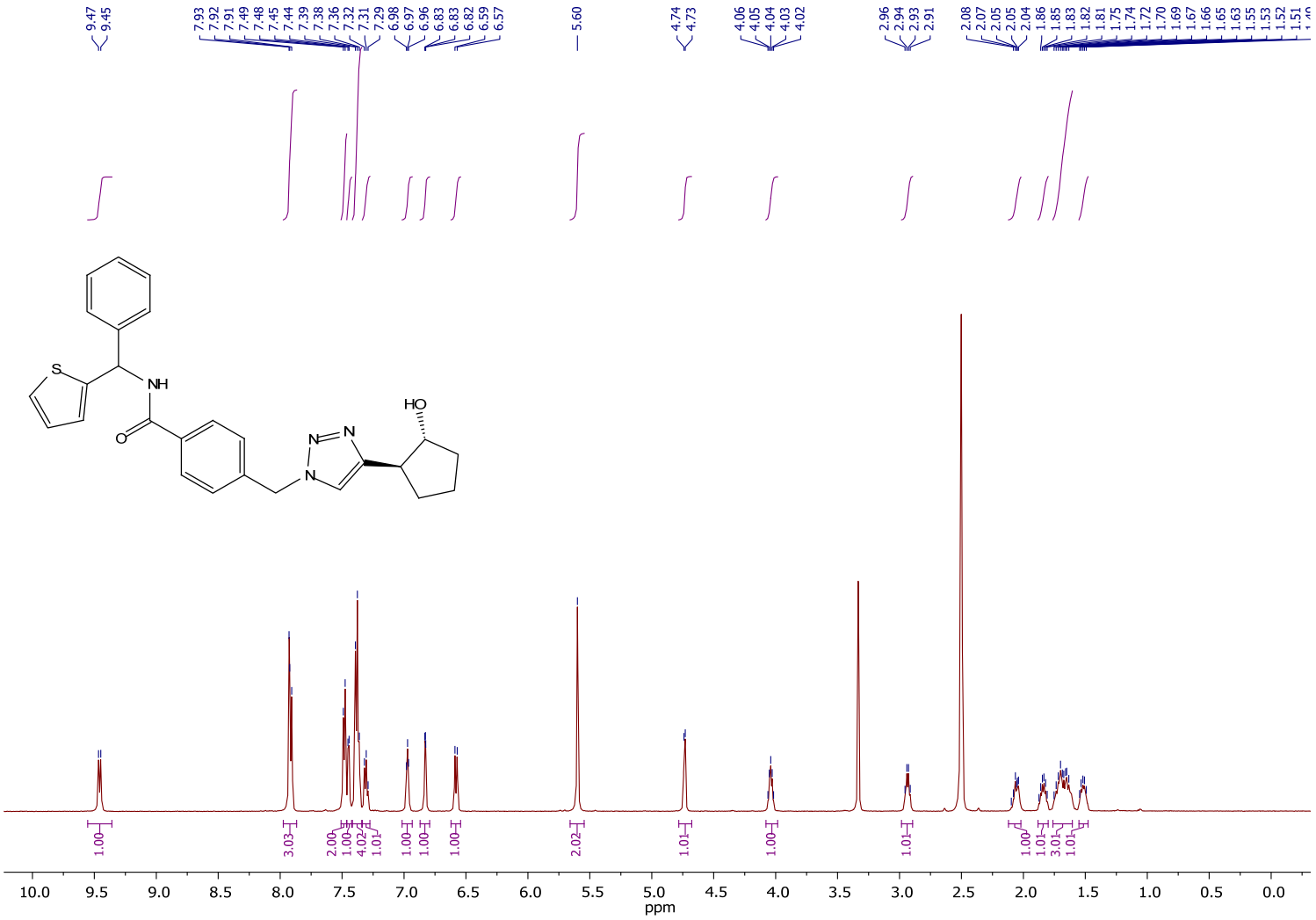
(*R*)-*N*-(1-(4-(4-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)bicyclo[1.1.1]pentane-1-carboxamide (**15**{*2*,*2*,*2*}), ^{1}H NMR (600 MHz, DMSO-d_6)



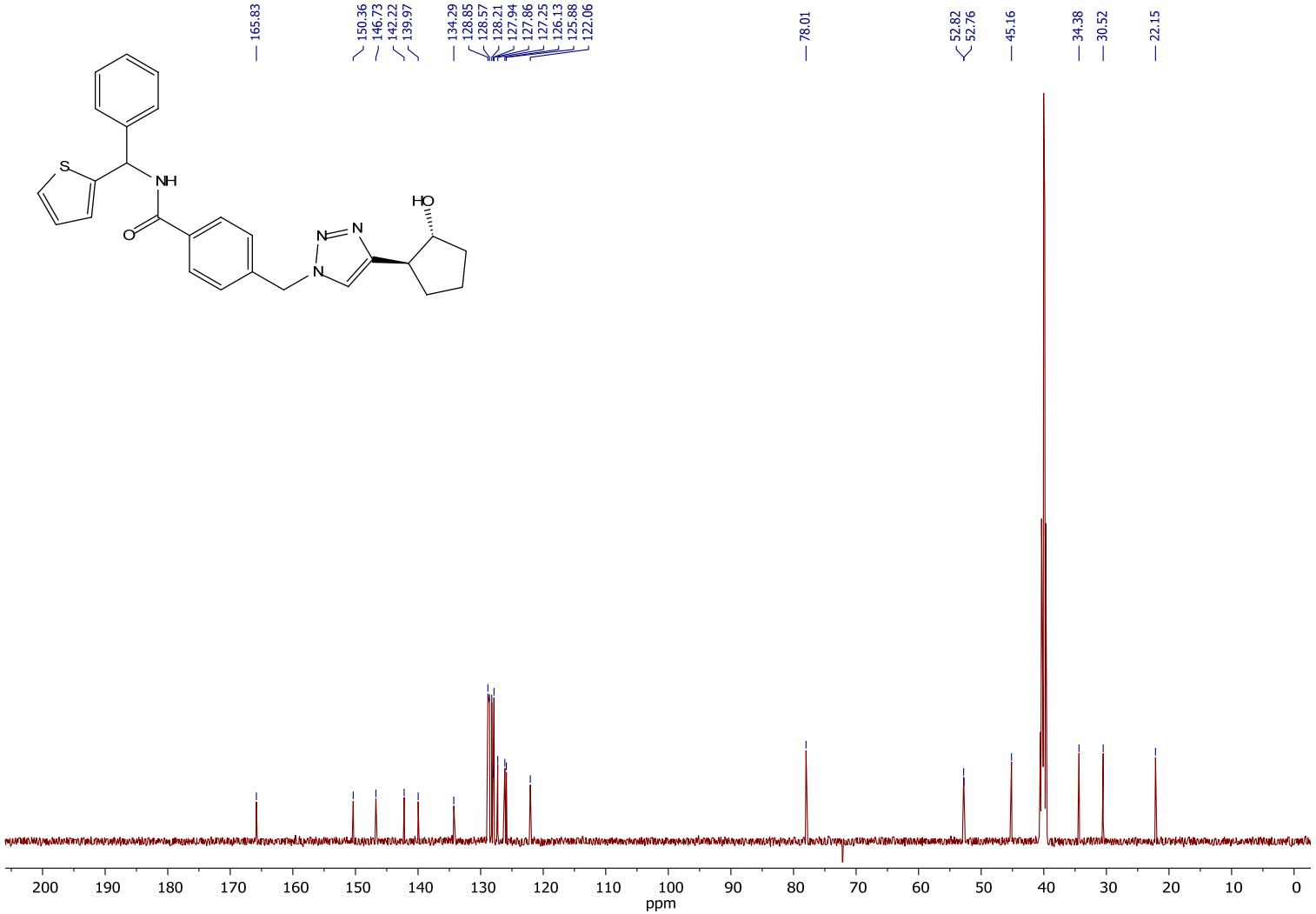
(*R*)-*N*-(1-(4-(4-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)bicyclo[1.1.1]pentane-1-carboxamide (**15**{*2*,*2*,*2*}), ^{13}C NMR (151 MHz, DMSO-d_6)



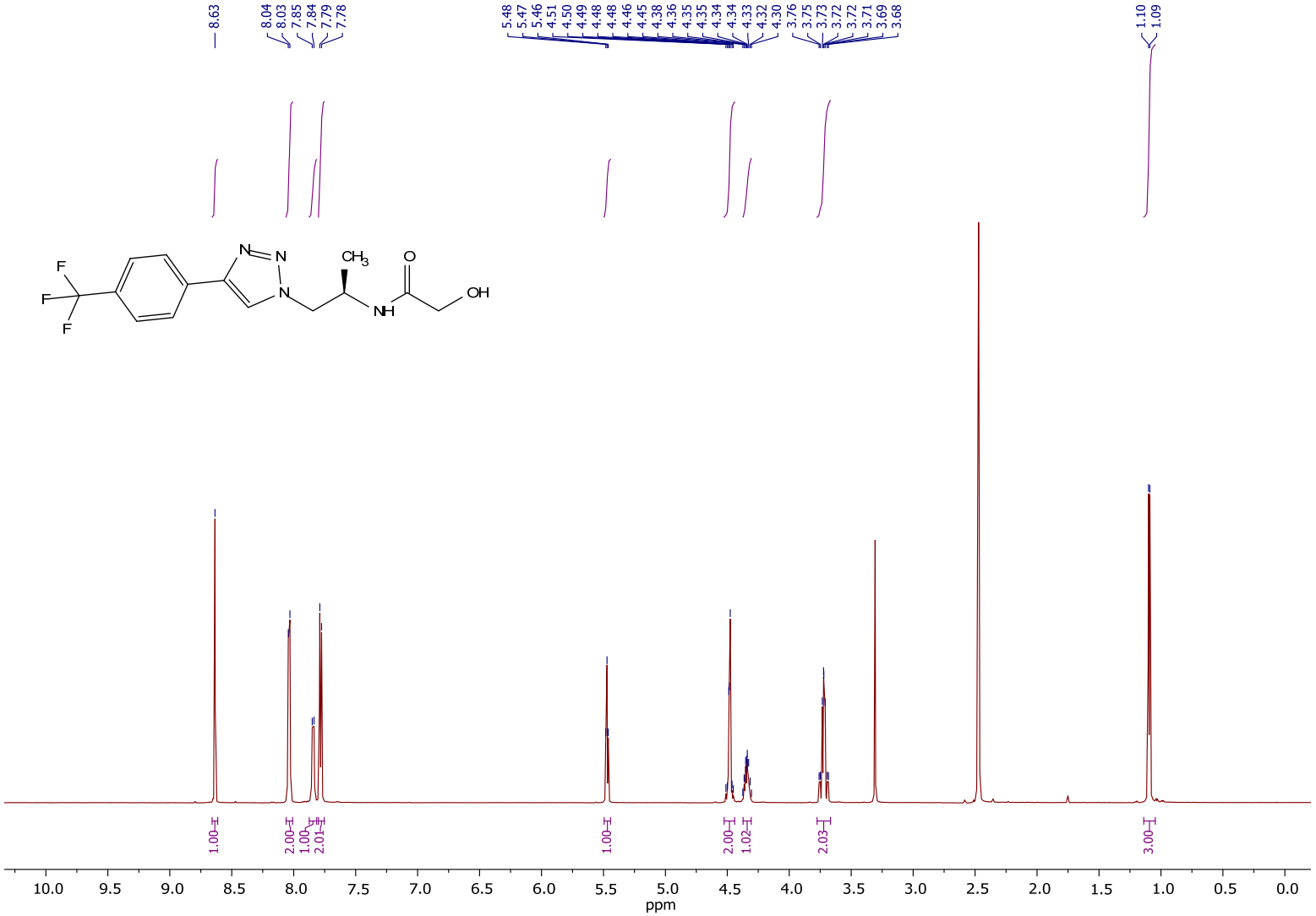
(*R*)-*N*-(1-(4-(4-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)bicyclo[1.1.1]pentane-1-carboxamide (**15**{*2*,*2*,*2*}), ^{19}F NMR (376 MHz, DMSO)



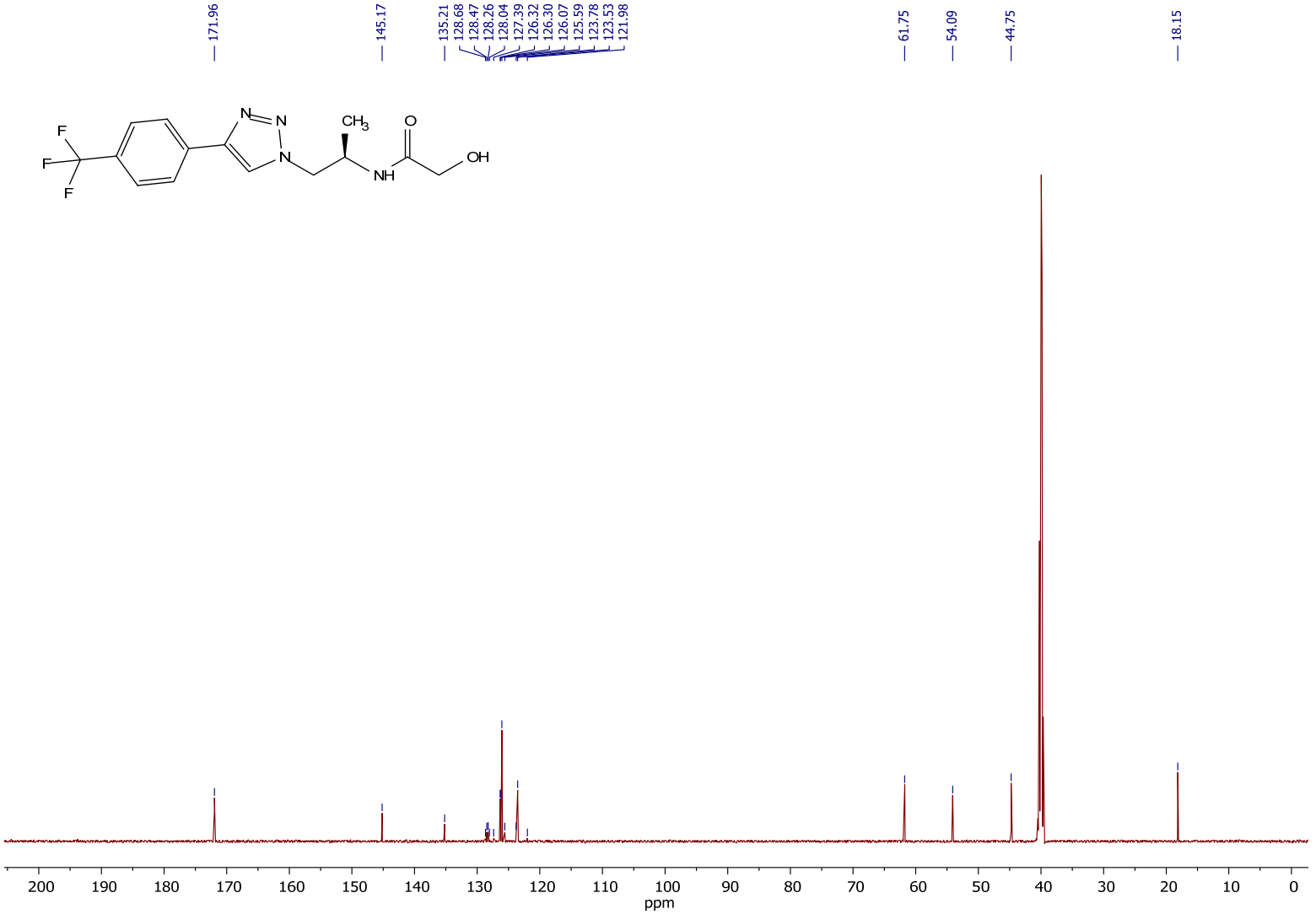
rac-4-((4-((1*R*,2*S*)-2-Hydroxycyclopentyl)-1*H*-1,2,3-triazol-1-yl)methyl)-*N*-(phenyl(thiophen-2-yl)methyl)benzamide (**15**{*1*,*2*,*17*}), ^{1}H NMR (500 MHz, DMSO-d_6)



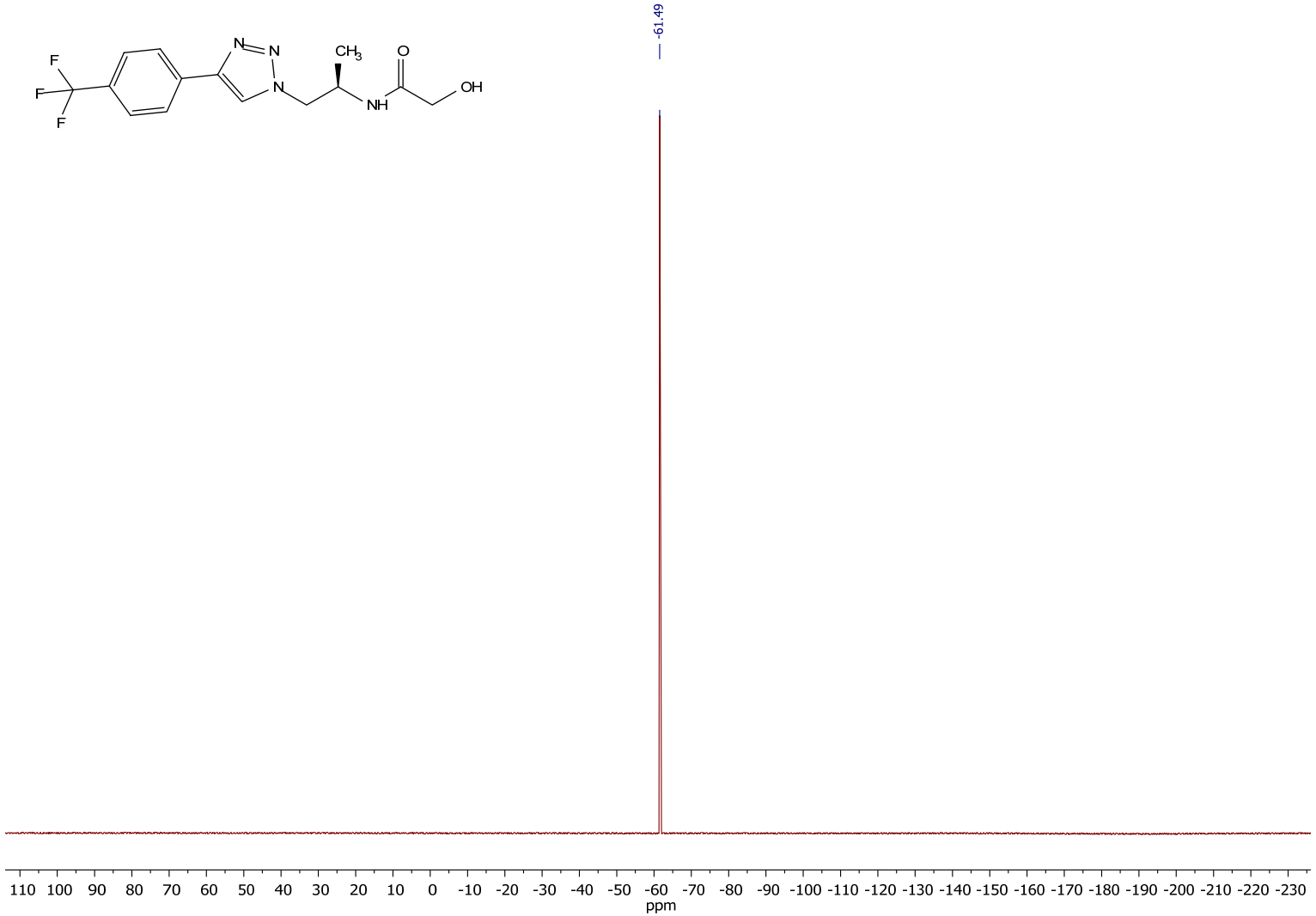
rac-4-((4-((1*R*,2*S*)-2-Hydroxycyclopentyl)-1*H*-1,2,3-triazol-1-yl)methyl)-*N*-(phenyl(thiophen-2-yl)methyl)benzamide (**15**{*1*,*2*,*17*}), ^{13}C NMR (126 MHz, DMSO-d_6)



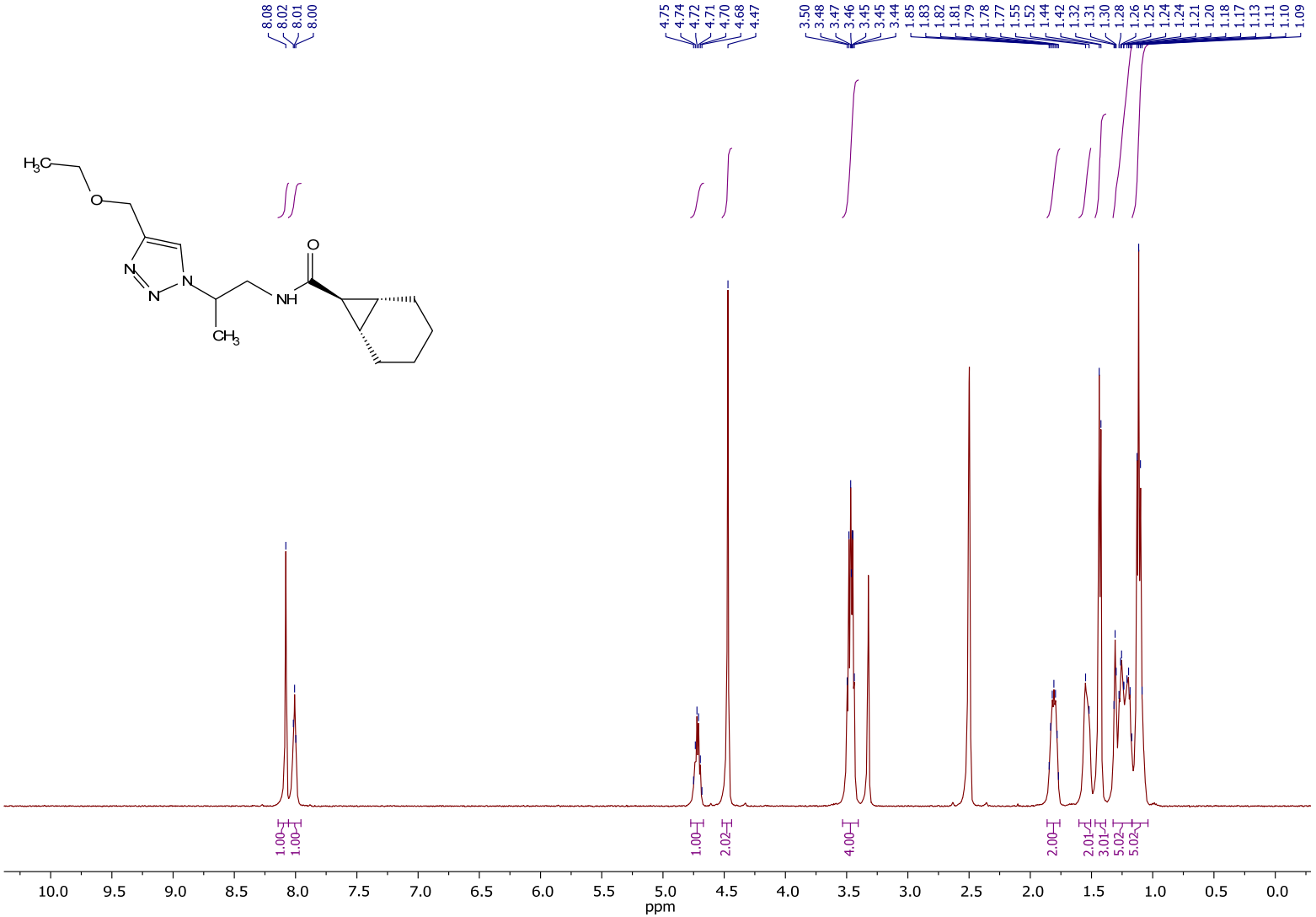
(*R*)-2-Hydroxy-*N*-(1-(4-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)acetamide **15**{*2*,*30*,*29*}, ^{1}H NMR (600 MHz, DMSO-d_6)



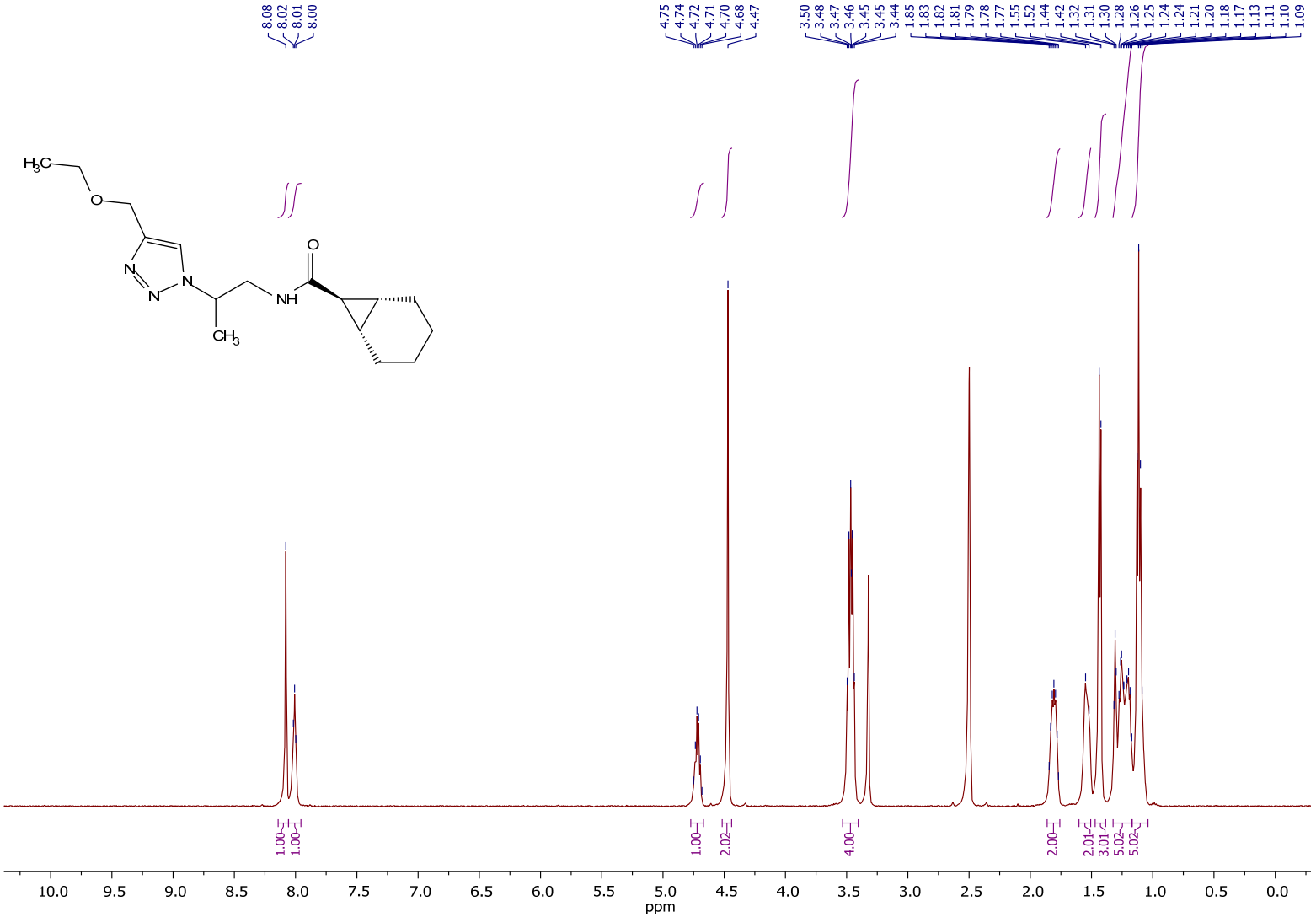
(*R*)-2-Hydroxy-*N*-(1-(4-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)acetamide **15**{*2*,*30*,*29*}, ^{13}C NMR (151 MHz, DMSO-d_6)



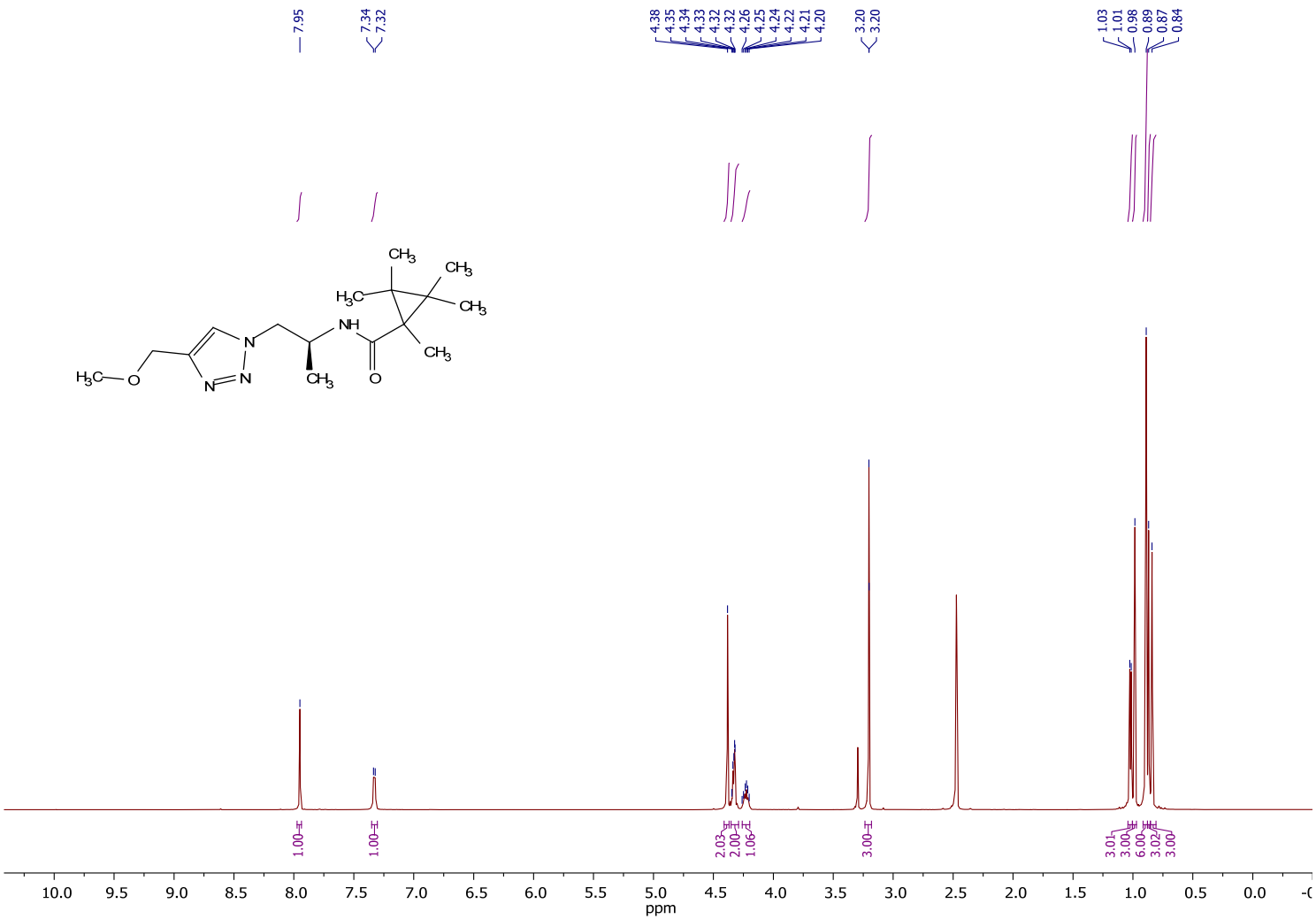
(*R*)-2-Hydroxy-*N*-(1-(4-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)acetamide **15**{*2*,*30*,*29*},^{19}F NMR (376 MHz, DMSO-d_6)



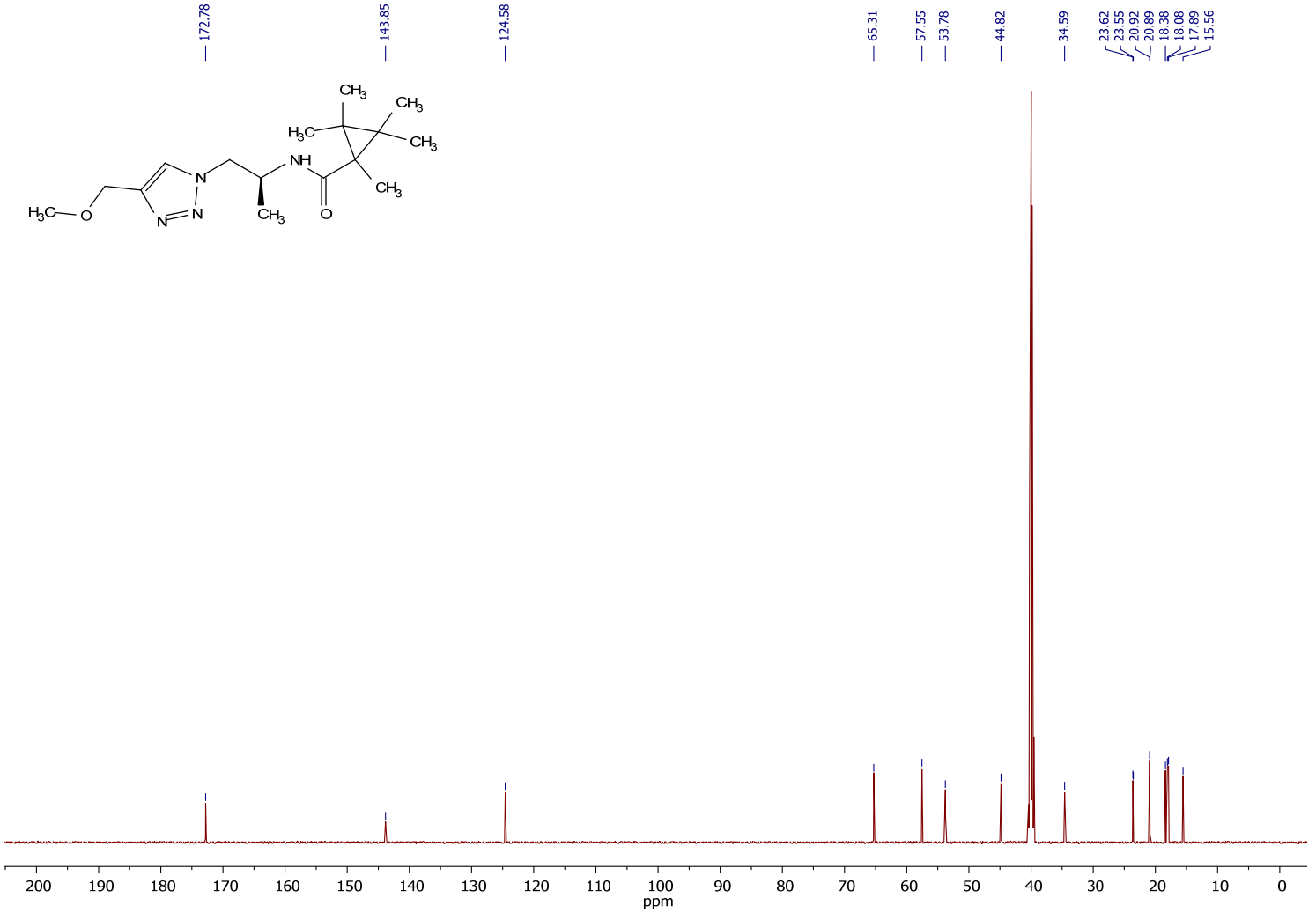
(1*R*,6*S*,7*r*)-*N*-(2-(4-(Ethoxymethyl)-1*H*-1,2,3-triazol-1-yl)propyl)bicyclo[4.1.0]heptane-7-carboxamide (**15**{*4*,*15*,*14*}), ^{1}H NMR (500 MHz, DMSO-d_6)



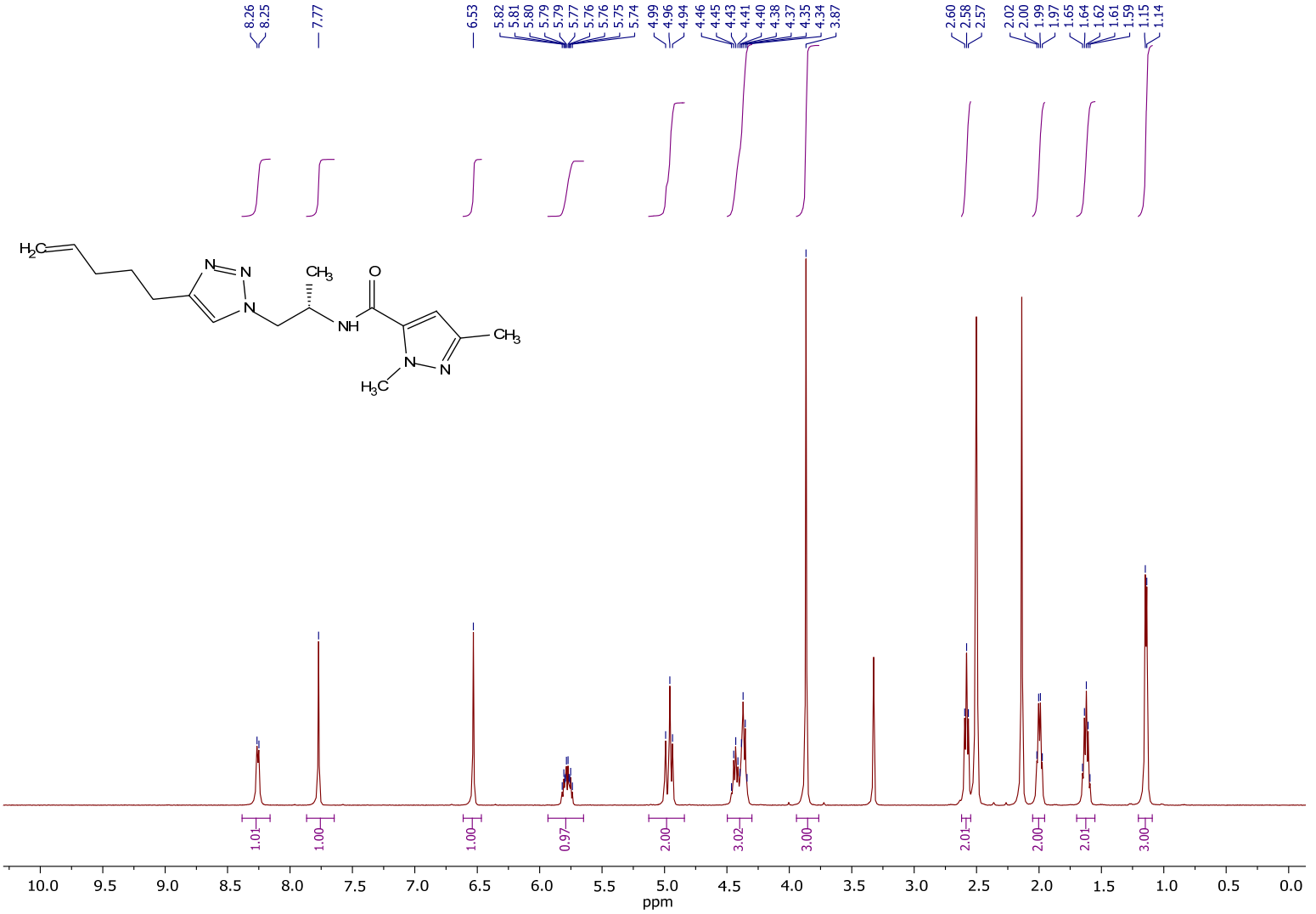
(1*R*,6*S*,7*r*)-*N*-(2-(4-(Ethoxymethyl)-1*H*-1,2,3-triazol-1-yl)propyl)bicyclo[4.1.0]heptane-7-carboxamide (**15**{*4*,*15*,*14*}), ^{13}C NMR (126 MHz, DMSO-d_6)



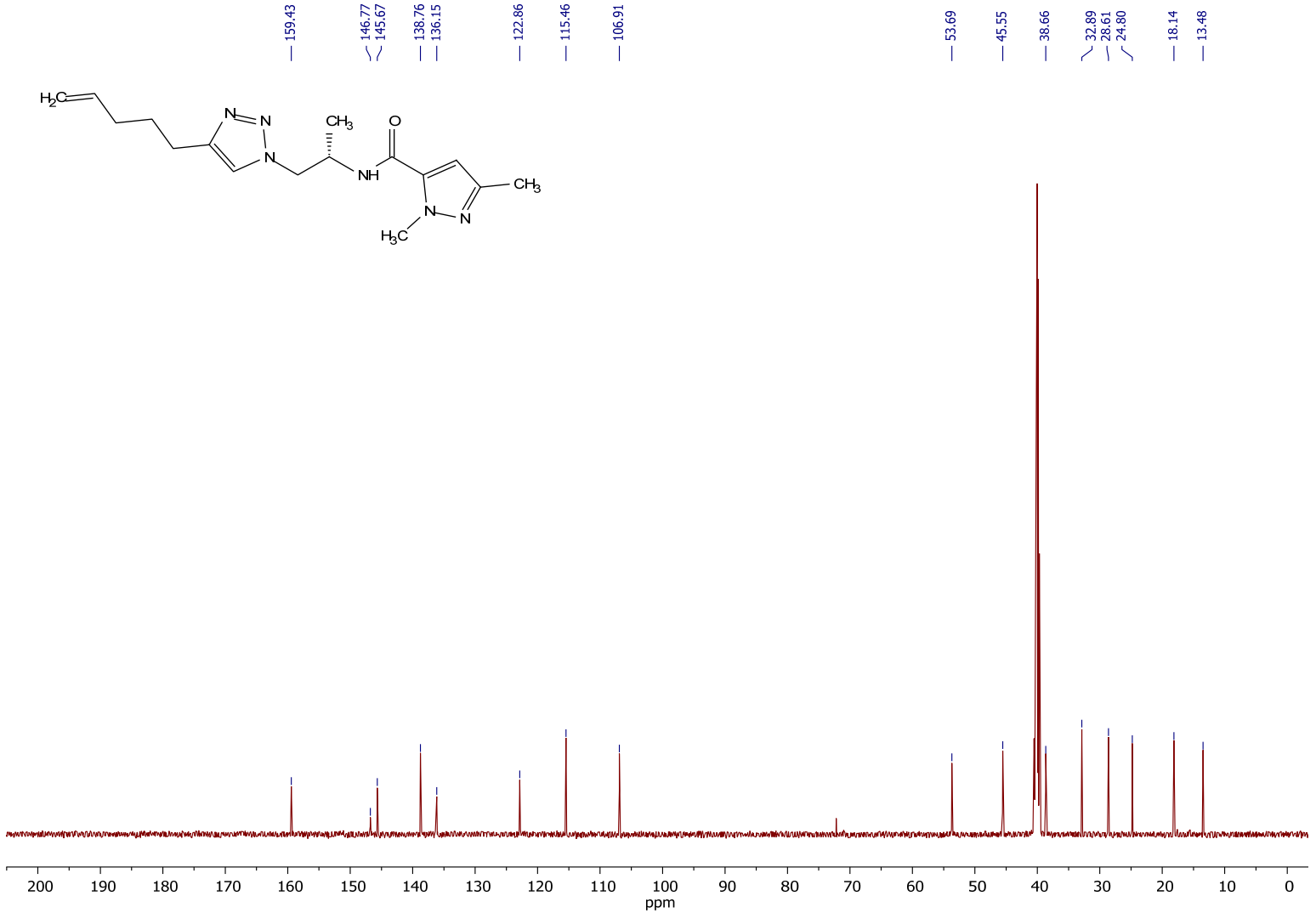
(*S*)-*N*-(1-(4-(Methoxymethyl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)-1,2,2,3,3-pentamethylcyclopropanecarboxamide (**15**{*6*,*14*,*13*}), ^{1}H NMR (600 MHz, DMSO-d_6)



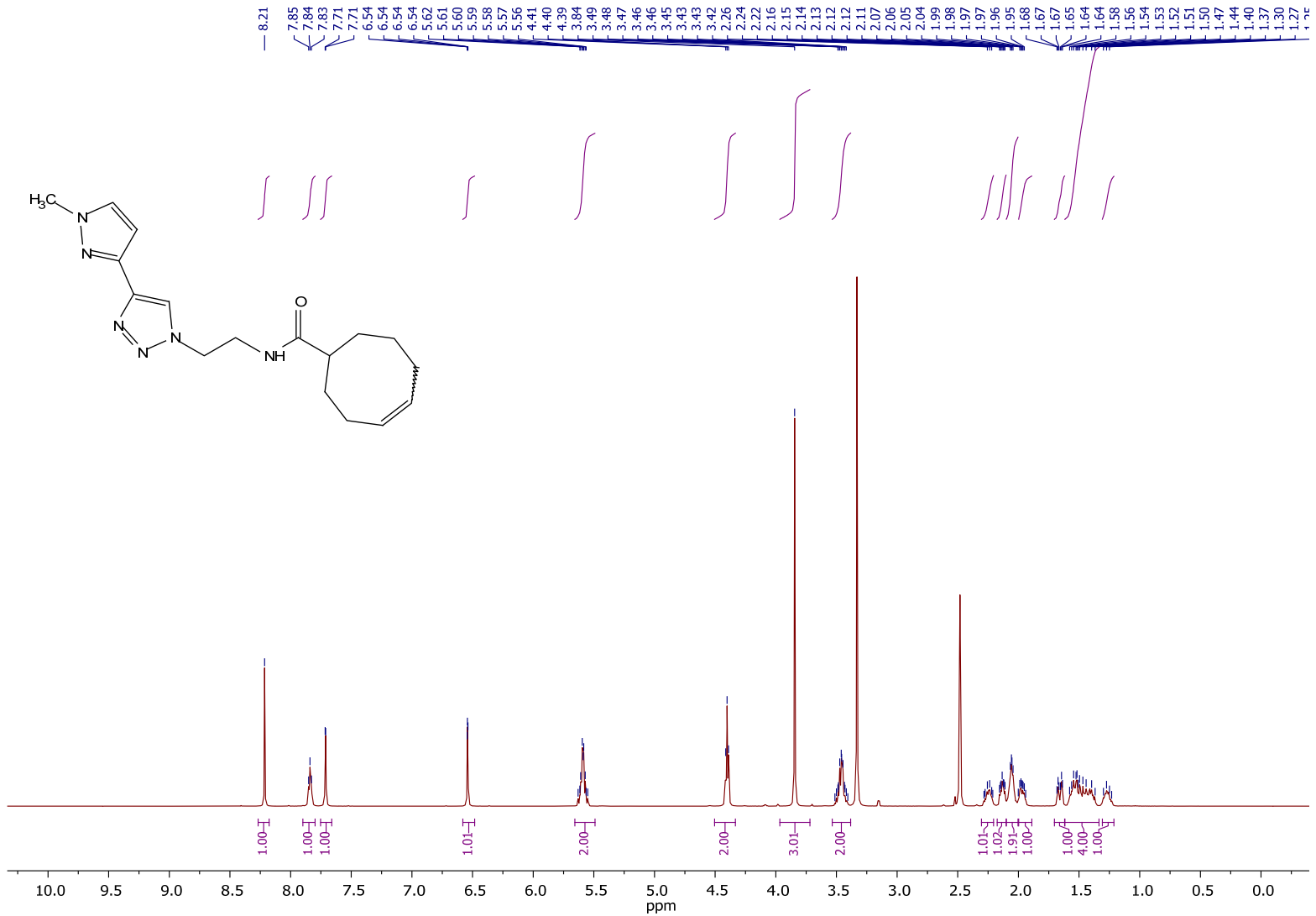
(*S*)-*N*-(1-(4-(Methoxymethyl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)-1,2,2,3,3-pentamethylcyclopropanecarboxamide (**15**{*6*,*14*,*13*}), ^{13}C NMR (151 MHz, DMSO-d_6)



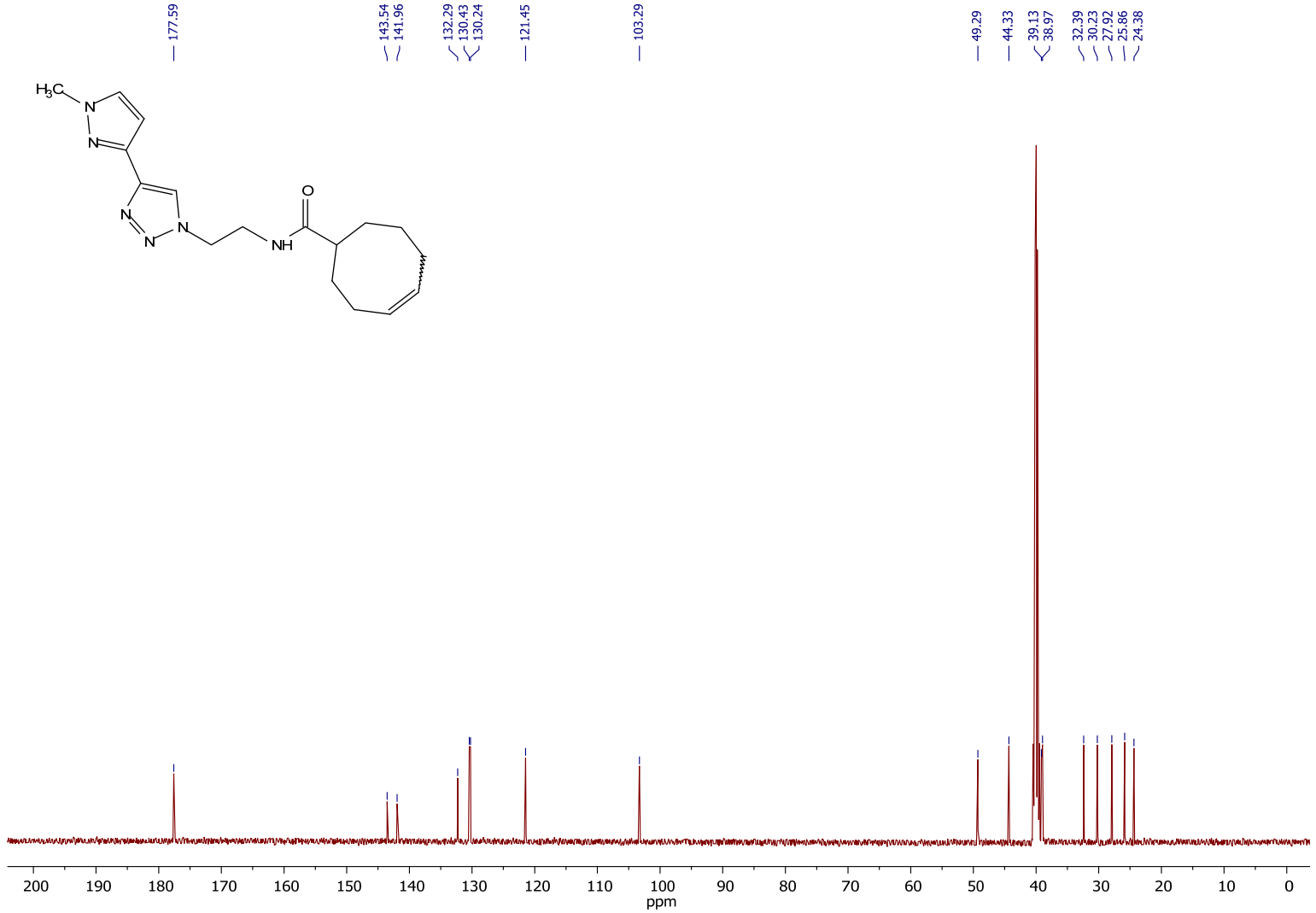
(*S*)-1,3-Dimethyl-*N*-(1-(4-(pent-4-en-1-yl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)-1*H*-pyrazole-5-carboxamide **15**{*6*,*9*,*9*}, ^{1}H NMR (500 MHz, DMSO-d_6)



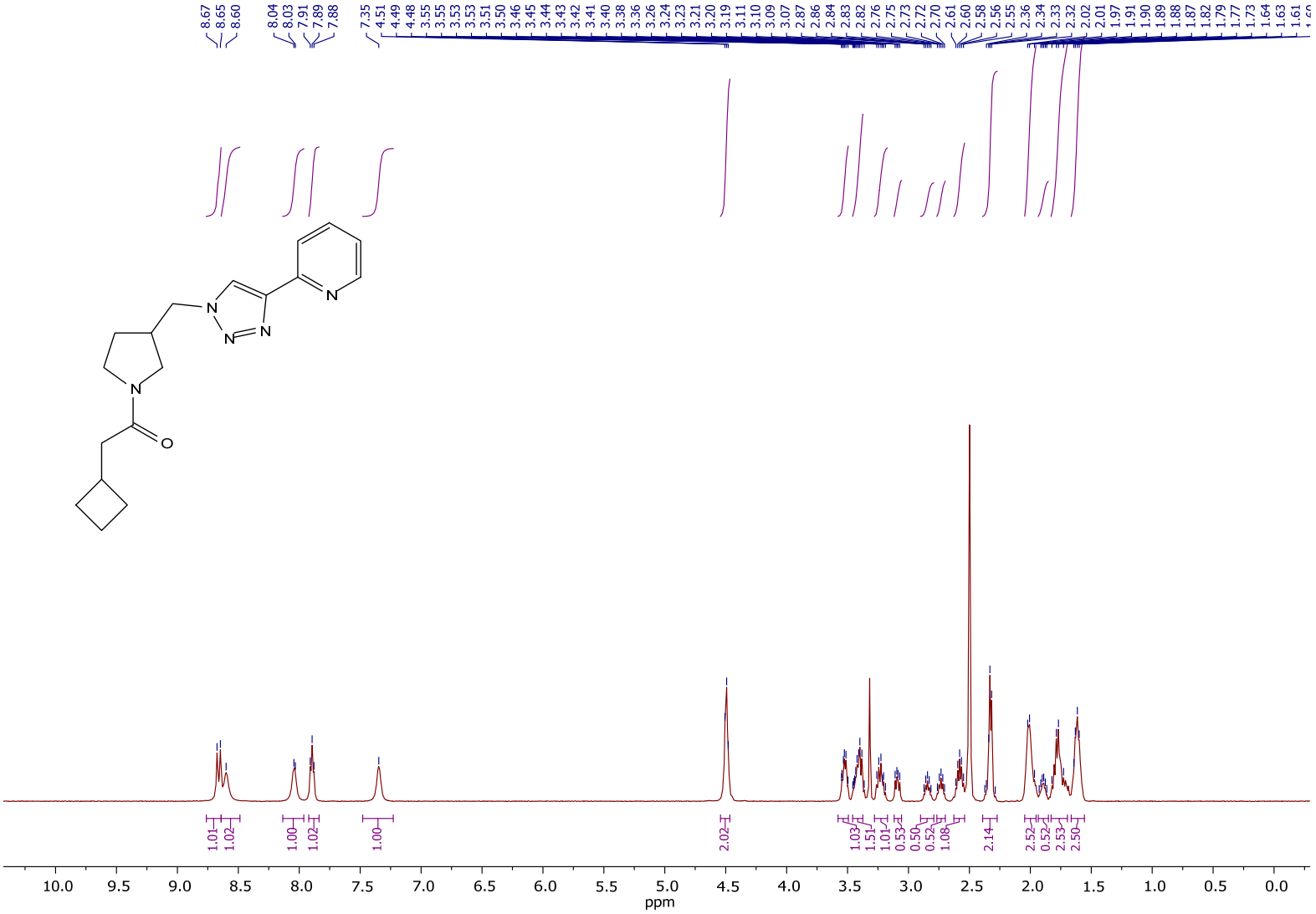
(*S*)-1,3-Dimethyl-*N*-(1-(4-(pent-4-en-1-yl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl)-1*H*-pyrazole-5-carboxamide **15**{*6*,*9*,*9*}, ^{13}C NMR (126 MHz, DMSO-d_6)



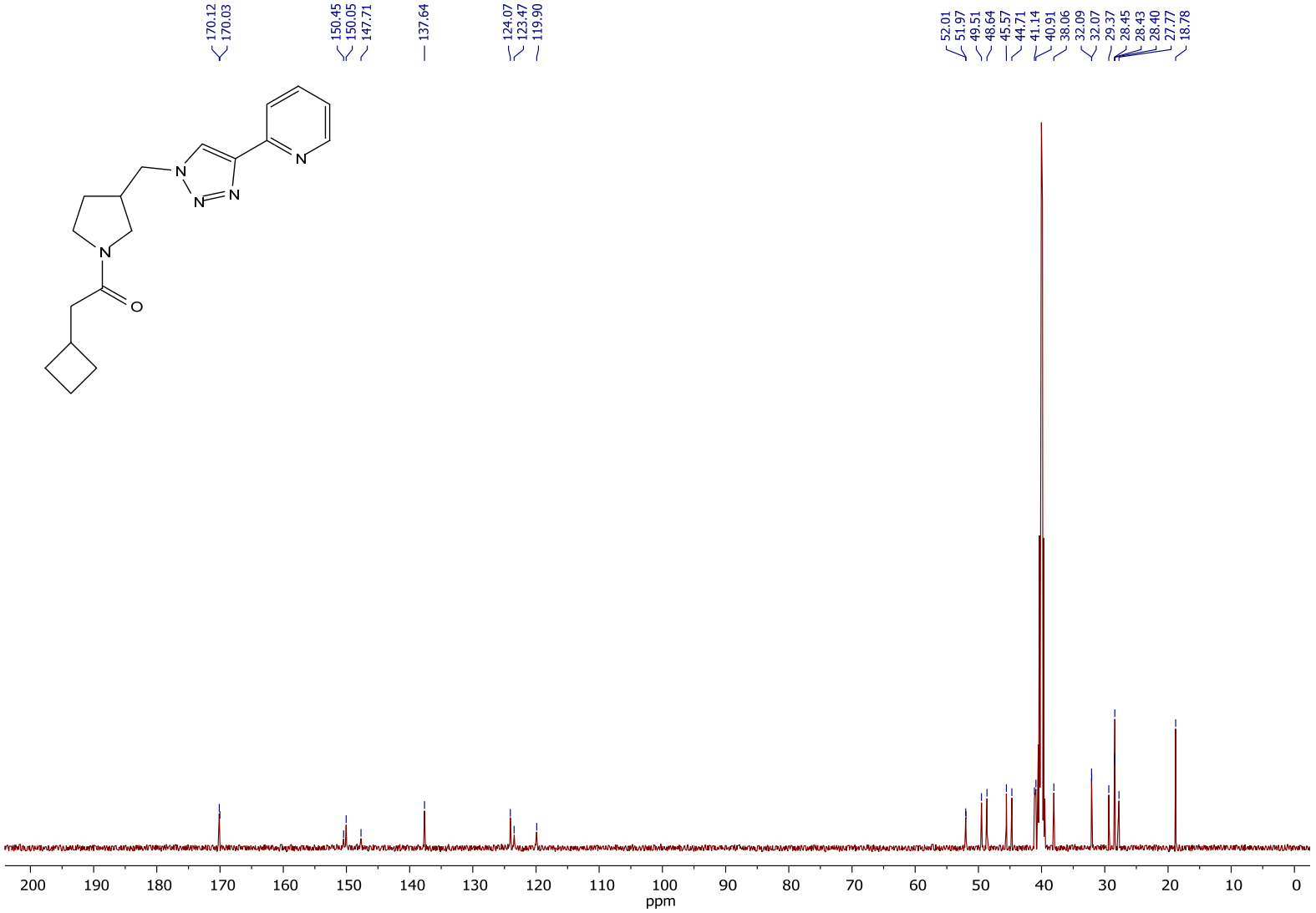
N-(2-(4-(1-Methyl-1*H*-pyrazol-3-yl)-1*H*-1,2,3-triazol-1-yl)ethyl)cyclooct-4-enecarboxamide **15**{*3*,*3*,*3*}, ^{1}H NMR (500 MHz, DMSO-d_6)



N-(2-(4-(1-Methyl-1*H*-pyrazol-3-yl)-1*H*-1,2,3-triazol-1-yl)ethyl)cyclooct-4-enecarboxamide **15**{*3*,*3*,*3*}, ^{13}C NMR (126 MHz, DMSO-d_6)



2-Cyclobutyl-1-(3-((4-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidin-1-yl)ethanone (**15**{*8*,*10*,*10*}), ^{1}H NMR (500 MHz, DMSO-d_6)



2-Cyclobutyl-1-(3-((4-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl)pyrrolidin-1-yl)ethanone (**15**{*8*,*10*,*10*}), ^{13}C NMR (126 MHz, DMSO-d_6)