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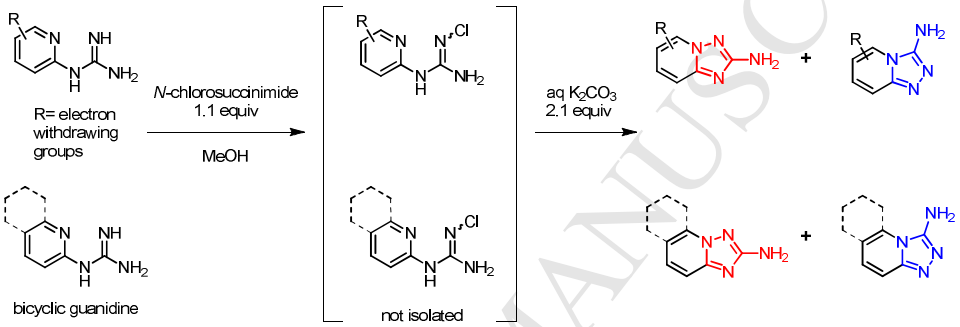

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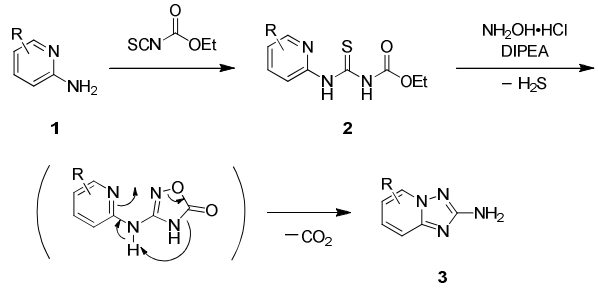
ABSTRACT

Oxidative cyclization of 1-(pyridin-2-yl)guanidine derivatives using *N*-chlorosuccinimide and aqueous potassium carbonate has been investigated. Chlorination of 1-(5-nitropyridin-2-yl)guanidine by *N*-chlorosuccinimide in methanol followed by addition of aqueous potassium carbonate gave rise to cyclization and afforded 6-nitro-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine in one-pot. In the course of studying the scope and limitation of the reaction, it was found that some of the examined 1-(pyridin-2-yl)guanidine derivatives gave not only the desired [1,2,4]triazolo[1,5-*a*]pyridin-2-amines but also unexpected [1,2,4]triazolo[4,3-*a*]pyridin-3-amine products. As plausible reaction mechanisms of this oxidative cyclization, diazirine formation and nitrene formation are presented.

1. Introduction

N-fused heterocycles are one of the important classes of molecules that are found in a variety of natural products and biologically active compounds. Among a diverse array of *N*-fused heterocycles, [1,2,4]triazolo[1,5-*a*]pyridin-2-amine derivatives have attracted much attention due to their significant bioactivities in the field of pharmaceuticals. In fact, a large number of compounds that contain a [1,2,4]triazolo[1,5-*a*]pyridin-2-amine core have been recently reported as drug candidates, including PI3Kγinhibitors,[1] JAK2 inhibitors,[2] CRK3 inhibitors,[3] DNA gyrase /topoisomerase IV inhibitors,[4] PDE10A inhibitors,[5] TYK2 inhibitors,[6] and Src kinase inhibitors[7].

The most common synthetic approach to [1,2,4]triazolo[1,5-*a*]pyridin-2-amines **3** is described in Scheme 1.[8] The reaction of 2-aminopyridines **1** with ethoxycarbonyl isothiocyanate gives thioureas **2**, which are treated with NH_2OH, hydrochloric acid and diisopropylethylamine (DIPEA) to give **3** in good to excellent yield, accompanied by evolution of H_2S and CO_2.[9] This synthesis is so robust that it was applicable to our multi-hundred gram scale synthesis of an intermediate for a VEGFR-2 kinase inhibitor.[10] However, despite the good yield and robustness, the synthesis suffered from the odor, toxicity, corrosivity, and flammability of H_2S generated during the reaction, and an alternative convenient synthesis of **3** was highly desired.



Scheme 1. The most common synthetic approach to [1,2,4]triazolo[1,5-*a*]pyridin-2-amines **3**

2. Results and discussion

Grenda *et al.* reported that *N*-(pyridin-2-yl)benzimidamide was subjected to chlorination when treated with aqueous NaOCl and 1 M HCl, and treatment of the obtained *N*-chloroamidine with aqueous Na_2CO_3 gave rise to cyclization to afford

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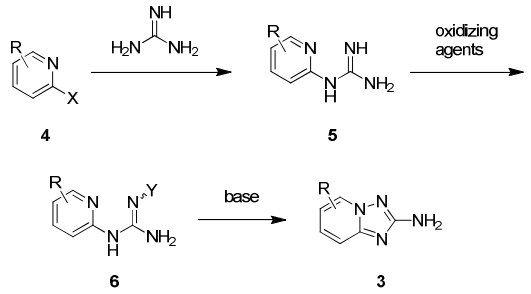
[1,2,4]triazolo[1,5-*a*]pyridine.[11] On the basis of their work, we thought that **3** could be synthesized from 1-(pyridin-2-yl)guanidines **5** using a similar reaction (Scheme 2). The guanidines **5** were envisaged to be prepared by S_NAr reaction of 2-halopyridines **4** with guanidine. It was assumed that oxidation of **5** would give intermediate **6**, and treatment of **6** with a base would lead to cyclization and afford **3**. To the best of our knowledge, oxidation of **5** followed by ring closure with a base has not been hitherto reported. Thus, in order to verify our concept, we first investigated chlorination of a known compound 1-(5-nitropyridin-2-yl)guanidine **5a**[12] (Table 2, entry 1) using *N*-chlorosuccinimide (NCS) and ring closure of the obtained chlorinated intermediate **6a** by aqueous K_2CO_3 (Scheme 3, (a)).



Scheme 2. Proposed synthesis of **3** from 1-(pyridin-2-yl)guanidines **4**

When a slurry of **5a** in MeCN was treated with 1.1 equiv of NCS at 40 ºC, generation of yellow solids was observed in a few minutes. After cooling to room temperature, the yellow solids were isolated by filtration. HRMS and NMR analysis revealed that the structure of the obtained compound was not **6b** but **6a** (Figure 1).[13,14] Fortunately, ring closure of **6a** proceeded smoothly in MeCN by addition of 2.1 equiv of K_2CO_3 in H_2O at 40 °C, affording **3a** in 93% yield. Compound **3a** was also synthesized from 2-amino-5-nitropyridine according to the procedure described in Scheme 1 (See Experimental Section), and we confirmed that the spectral data of **3a** prepared by these two methods was identical.[15]

For the synthesis of **3a**, it was possible to use MeCN as the solvent for both the chlorination of **5a** and the ring closure of **6a**. These results led us to explore the possibility of a convenient one-pot synthesis of **3a** from **5a** in MeCN (Scheme 3, (b)). After **5a** was reacted with 1.1 equiv of NCS in MeCN at 40 °C for 15 min, 2.1 equiv of K_2CO_3 in H_2O was added, and the mixture was stirred for 30 min at the same temperature. Following extraction with EtOAc and washing with 10% aqueous NaCl, the organic layer was analyzed by HPLC using an authentic sample, which showed that **3a** was obtained in 79% yield.

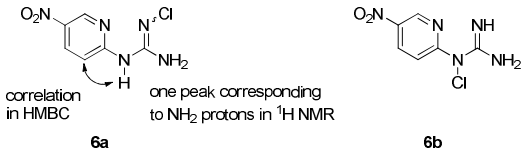
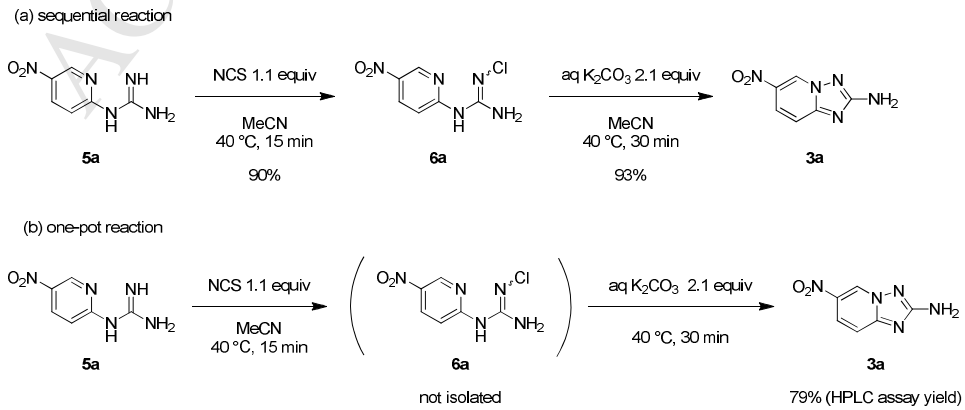


Figure 1. Structure determination of **6a**

With this promising result in hand, optimization of the reaction condition was conducted through a screening of oxidizing agents, bases and solvents (Table 1). Among the screened chlorinating agents, *t*-BuOCl gave **3a** in good yield comparable to NCS (80%, entry 5). Other chlorinating agents such as aqueous NaOCl, chloramine-T, trichloroisocyanuric acid (TCCA), 1,3-dichloro-5,5-dimethylhydantoin (NDDH) all decreased the yield (entries 1–4). The use of other oxidizing agents was also examined. While *N*-bromosuccinimide (NBS) gave the product in low yield (14%, entry 6), *N*-iodosuccinimide (NIS) did not give the product (entry 7). Taking ease of handling and price of the reagent into consideration, NCS was selected as the oxidizing agent for further optimization.

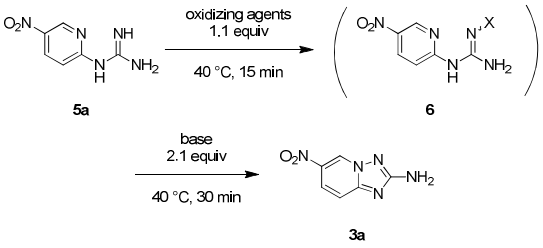
Organic bases such as pyridine, triethylamine and DBU gave the product in lower yield than aqueous K_2CO_3 (entries 8–10). Interestingly, solid K_2CO_3 gave the product in lower yield (34%, entry 11) than aqueous K_2CO_3. The use of 1M NaOH gave the product in comparable yield to aqueous K_2CO_3 (77%, entry 12), whereas the use of aqueous KOAc largely decreased the yield (5%, entry 13). These results indicate that the use of a strong inorganic base and the presence of H_2O are essential for high conversion of **6a** to **3a**.

It was found that alcohol solvents could also be used for this one-pot process (entries 14–16). When alcohol solvents were used for the reaction, precipitation of the product was observed after addition of aqueous K_2CO_3. Following further addition of H_2O to the reaction mixture, **3a** was easily isolated by filtration. The best yield (87% isolated yield) was achieved when MeOH was used as the solvent (entry 14).



Scheme 3. Synthesis of **3a** from **5a** via **6a**

Table 1. Optimization of the reaction condition for the one-pot synthesis of **3a**



entry	oxidizing agent	solvent	base	yield[a] (%)
1	aq NaOCl	MeCN	aq K_2CO_3	41
2	chloramine-T	MeCN	aq K_2CO_3	42
3	TCCA[b]	MeCN	aq K_2CO_3	69
4	NDDH	MeCN	aq K_2CO_3	42
5	*t*-BuOCl	MeCN	aq K_2CO_3	80
6	NBS	MeCN	aq K_2CO_3	13
7	NIS	MeCN	aq K_2CO_3	0
8	NCS	MeCN	pyridine	32
9	NCS	MeCN	triethylamine	15
10	NCS	MeCN	DBU	51
11	NCS	MeCN	K_2CO_3	34
12	NCS	MeCN	1M NaOH	77
13	NCS	MeCN	aq KOAc	5
14	NCS	MeOH	aq K_2CO_3	87[c]
15	NCS	EtOH	aq K_2CO_3	74[c]
16	NCS	*i*-PrOH	aq K_2CO_3	68[c]

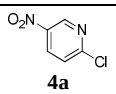
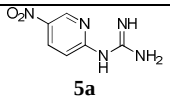
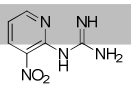
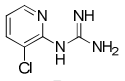
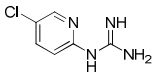
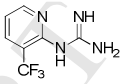
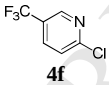
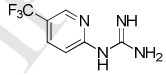
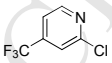
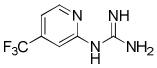
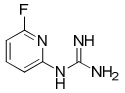
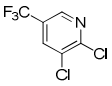
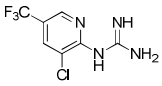
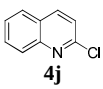
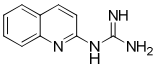
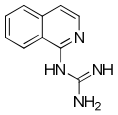
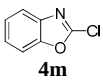
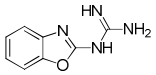
[a] HPLC assay yield.

[b] 0.37 equiv of TCCA was used for the reaction.

[c] Isolated yield.

In order to study the scope and limitation of the reaction, a series of 1-(pyridin-2-yl)guanidine derivatives **5b–5m** were prepared by S_NAr reaction of 2-halopyridine derivatives **4** with guanidine carbonate or guanidine hydrochloride as described in Scheme 2 (Table 2). Although many kinds of 2-halopyridines were examined, the S_NAr reaction proceeded only when 2-halopyridines possessed electron withdrawing groups (entries 1–9). Due to the low solubility of **5** in common organic solvents, isolation of **5** required a rather troublesome work-up and **5** was obtained in low to moderate yields.

Table 2. Preparation of 1-(pyridin-2-yl)guanidine derivatives **5**

entry	reaction condition[a]	substrate	product	yield[b] (%)
1	A	 **4a**	 **5a**	25
2	A	 **4b**	 **5b**	32
3	B	 **4c**	 **5c**	39
4	B	 **4d**	 **5d**	47
5	B	 **4e**	 **5e**	12
6	C	 **4f**	 **5f**[c]	39[c]
7	B	 **4g**	 **5g**	47
8	D	 **4h**	 **5h**	37
9	C	 **4i**	 **5i**	36
10	B	 **4j**	 **5j**	50
11	B	 **4k**	 **5k**	58
12	C	 **4m**	 **5m**	57

[a] Reaction conditions described in the table are as follows:

A guanidine hydrochloride (10 equiv), K_2CO_3 (15 equiv), *t*-BuOH, reflux.

B guanidine carbonate (3 equiv), K_2CO_3 (5 equiv), 1-methylpyrrolidin-2-one (NMP), 120–140 °C.

C guanidine carbonate (1 equiv), K_2CO_3 (3 equiv), NMP, 100–120 °C.

D guanidine carbonate (3 equiv), K_2CO_3 (5 equiv), *N*,*N*-dimethylacetamide, 120 °C.

[b] Isolated yield.

[c] 0.9 NMP solvate was obtained.

With these substrates in hand, the one-pot oxidative cyclization was applied to compounds **5b–5m** (Table 3). When 1-(3-nitropyridin-2-yl)guanidine **5b** was subjected to the above-mentioned one-pot chlorination-cyclization procedure, the product precipitated in the reaction mixture. After addition of

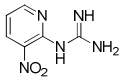
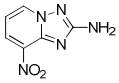
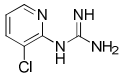
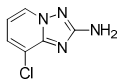
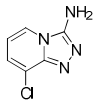
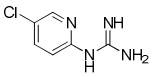
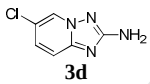
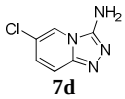
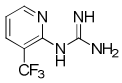
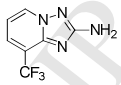
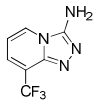
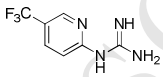
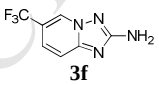
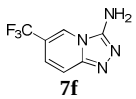
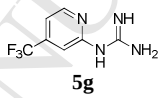
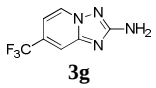
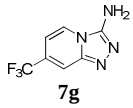
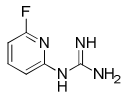
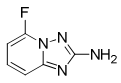
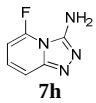
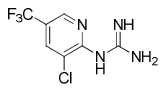
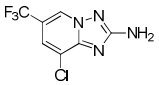
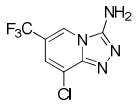
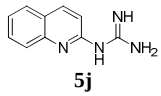
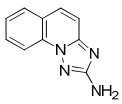
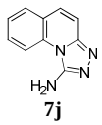
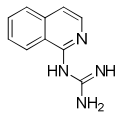
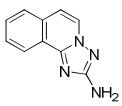
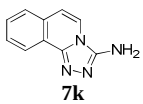
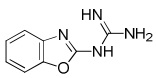
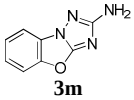
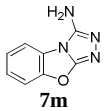
H_2O to the reaction mixture, **3b** was isolated by filtration in 86% yield (entry 1).

The reaction of 1-(3-chloropyridin-2-yl)guanidine **5c**, in contrast, gave a completely different result from the results of the reactions of **5a** and **5b** (entry 2). When **5c** was treated with 1.1 equiv of NCS, chlorination proceeded smoothly to give a single chlorinated product. However, treatment of the chlorinated intermediate with aqueous K_2CO_3 unexpectedly gave two main products with several kinds of byproducts. After isolation by column chromatography, the two products were analyzed by HRMS and NMR. Interestingly, HRMS analysis showed that the two compounds have the same accurate molecular mass corresponding to molecular formula $C_6H_5ClN_4$. In addition, ^1H NMR spectra of the two compounds showed a similar coupling pattern: one triplet-like peak and two doublet-like peaks in the aromatic region, and one peak corresponding to NH_2 protons, whereas the chemical shifts of the corresponding peaks in the two compounds were different. These results implied that treatment of the chlorinated intermediate with aqueous K_2CO_3 gave not only the desired **3c** but a compound having a similar structure to **3c** via an unexpected reaction pathway. Subsequent two-dimensional NMR experiments such as HMBC and NOESY spectra indicated that the structure of the unexpected product was **7c** depicted in Figure 2.[16] The structures of **3c** and **7c** obtained in this one-pot oxidative cyclization were confirmed by comparing the spectral data with that of **3c** and **7c** prepared according to known procedures (Scheme 4).[8, 17]

In the case of 1-(5-chloropyridin-2-yl)guanidine **5d**, compound **7d** was obtained as the main product in 50% yield with a trace amount of **3d** (entry 3). Then 1-(pyridin-2-yl)guanidines bearing a CF_3 group at three different positions were subjected to the reaction. Compound **5e** bearing a 3-CF_3 group gave **3e** as the main product in 44% yield and **7e** as the minor product in 20% yield, respectively (entry 4). On the other hand, in the case of the 4-CF_3 and 5-CF_3 derivatives, compound **7** became the main product. Compound **5f** gave **7f** in 52% yield (entry 5), and **5g** gave **7g** in 50% yield (entry 6), respectively. Interestingly, the reaction of **5h** bearing a 2-F group gave neither **3h** nor **7h** (entry 7). Although the chlorination of **5h** proceeded cleanly, addition of aqueous K_2CO_3 made the reaction mixture a dark purple solution, and generation of several kinds of unidentified products was observed. Compound **5i** bearing a 3-Cl group and a 5-CF_3 group gave **3i** as the main product in 57% yield (entry 8).

The reaction was also applied to guanidines containing a bicyclic ring such as 1-(quinolin-2-yl)guanidine **5j** and 1-(isoquinolin-1-yl)guanidine **5k**. Fortunately, both **5j** and **5k** were successfully chlorinated by NCS, and treatment with aqueous K_2CO_3 gave tricyclic compounds. When **5j** was subjected to the reaction, **7j** was obtained as the main product in 39% yield (entry 9). On the other hand, the reaction of **5k** gave **3k** as the main product in 35% yield (entry 10). Unfortunately, in the case of 1-(benzo[*d*]oxazol-2-yl)guanidine **5m**, the cyclized products were not obtained (entry 11).

Table 3. One-pot oxidative cyclization of 1-(pyridin-2-yl)guanidine derivatives **5**[a]

entry	substrate	product	
		5b	**3b**	**7b**
1			86%	N.D.[b]
2	 **5c**	 **3c** 27%	 **7c** 19%
3	 **5d**	 **3d** trace	 **7d** 50%
4	 **5e**	 **3e** 44%	 **7e** 20%
5[c]	 **5f**	 **3f** 23%	 **7f** 52%
6	 **5g**	 **3g** 16%	 **7g** 50%
7	 **5h**	 **3h** N.D.	 **7h** N.D.
8	 **5i**	 **3i** 57%	 **7i** 9%
9	 **5j**	 **3j** 20%	 **7j** 39%
10	 **5k**	 **3k** 35%	 **7k** 13%
11	 **5m**	 **3m** N.D.	 **7m** N.D.

[a] The substrates in MeOH were treated with 1.1 equiv of NCS at 40 °C for 15 min. Then 2.1 equiv of K_2CO_3 in H_2O was added, and the reaction mixture was stirred at 40 °C for 30 min.

[b] Not Detected.

[c] 0.9 NMP solvate of **5f** was used as the substrate.

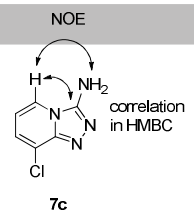
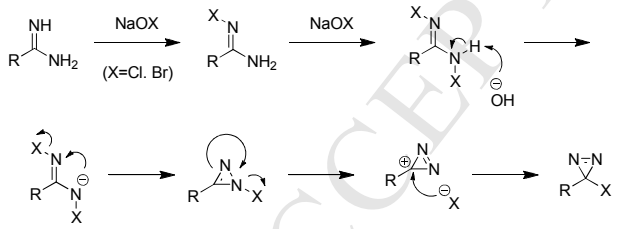


Figure 2. Structure determination of **7c**

In Table 3, the substrates having an electron withdrawing group at 3-position of the pyridine ring (**5b**, **5c**, **5e**) gave **3** as the major product. Meanwhile, while **5d** and **5f**, which have an electron withdrawing group at 5-position, mainly gave **7**, compound **5a** with a strong electron withdrawing group (NO_2) at 5-position gave exclusively compound **3**. Interestingly, although compound **5f** gave mainly compound **7**, compound **5i**, which have one more additional electron withdrawing group (Cl) at 3-position, showed a different reactivity from **5f** and gave mainly compound **3**. These results may indicate that the type, position and number of substituents affect the reaction pathway.[18]

As mentioned previously, oxidation of 1-(pyridin-2-yl)guanidine derivatives **5** and their ring closure with a base has not been previously reported. Meanwhile, a literature survey shows that treatment of amidines with aqueous NaOCl/NaOBr gives 3-halo-3-substituted diazirines via an interesting reaction mechanism (Scheme 5).[19] In this diazirine formation reported first by Graham, intermediates other than *N*-chloro and *N*,*N*'-dichloroamidines have not been directly observed.[20] Thus, it is not clear whether the diazirine formation proceeds via direct displacement of a halogen atom with a nitrogen anion or via formation of iminonitrene. Moss *et al.* intensively studied this reaction and reported that dichlorination of amidines is prerequisite for the base promoted diazirine formation, while *N*-chloro and *N*,*N*',*N*'-trichloroamidines did not afford diazirine.[21] Probably, the second chlorination of a NH_2 group would be essential because the chlorine atom acts as an electron withdrawing group and promotes deprotonation of the NH proton by a base.



Scheme 5. Formation of 3-halo-3-substituted diazirines by Graham's procedure (ref 19)

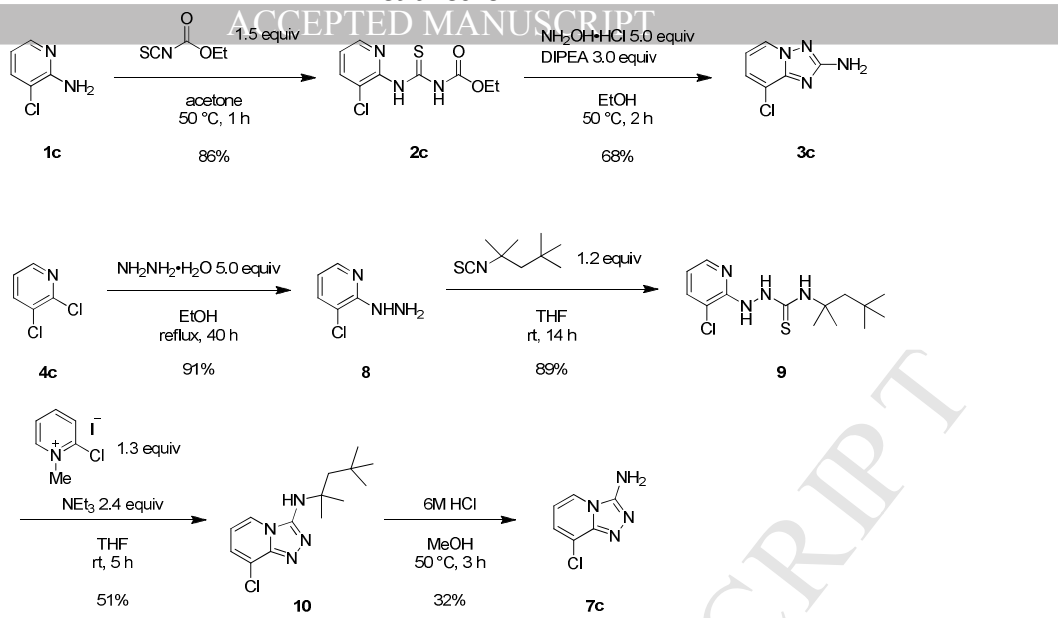
In the case of **5**, an electron deficient pyridine ring is thought to increase acidity of the neighboring NH proton, which would cause base promoted formation of diazirine **12** via **11** (Scheme 6, (a)). Ring opening of **12** is assumed to proceed in two different pathways. The attack of a nitrogen atom of a pyridine ring to the nitrogen atom of the diazirine would give **3** via N-N bond cleavage (path A), while the attack of the nitrogen atom of the pyridine ring to the carbon atom of the C=N double bond of the diazirine would give **7** via C-N bond cleavage (path B).

An alternative possible reaction mechanism is the one involving nitrene formation (Scheme 6, (b)).[22] Anion **11** could generate nitrene **13** by loss of a chlorine atom, and ring closure of **13** would give **3** (path C).[11] At the same time, there is a possibility that nitrene **14**, which is an isomer of **13**, could give carbodiimide **15** via Curtius-type rearrangement.[23, 24] The attack of the nitrogen atom of the pyridine ring to the carbon atom of the carbodiimide would give **7** (path D).

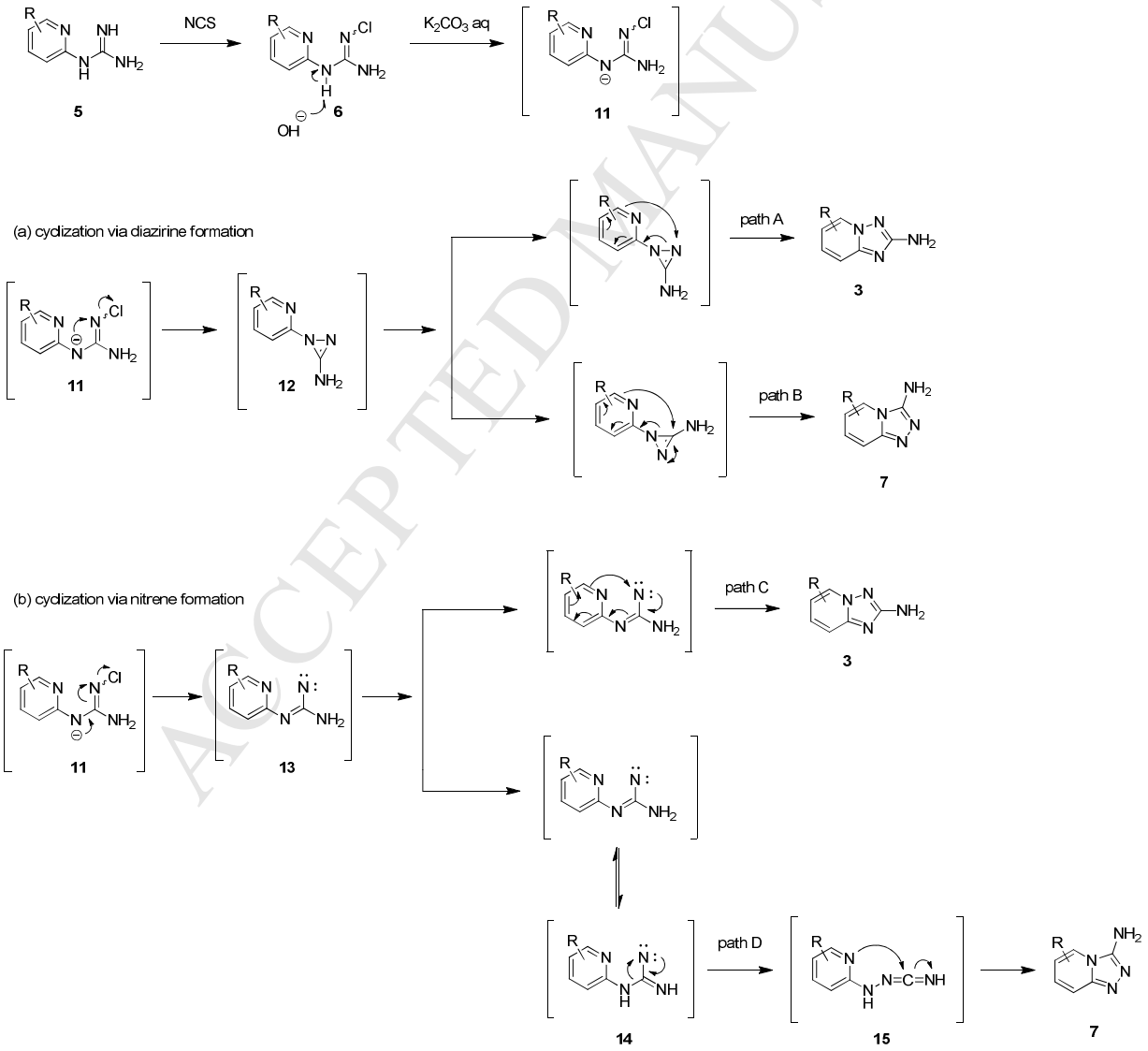
At present, it is difficult to predict which reaction pathway mainly works in each substrate. Further detailed investigation is required to elucidate the factors (substituent, oxidizing agent, temperature, base and solvent) that control the dominant reaction pathway.

3. Conclusions

We have shown that chlorination of 1-(5-nitropyridin-2-yl)guanidine **5a** by NCS followed by treatment with aqueous K_2CO_3 gives rise to cyclization and affords 6-nitro-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine **3a**. It was possible to conduct this reaction sequence in one-pot by using MeOH as the solvent. In the course of studying the scope and limitation of this one-pot oxidative cyclization, it was found that some of the 1-(pyridin-2-yl)guanidine derivatives **5** gave not only [1,2,4]triazolo[1,5-*a*]pyridin-2-amines **3** but [1,2,4]triazolo[4,3-*a*]pyridin-3-amines **7**. Although we proposed plausible reaction mechanisms based on the diazirine formation and the nitrene formation, the precise reaction mechanism remains to be elucidated. A more detailed study on this reaction is to be performed in the future.



Scheme 4. Preparation of **3c** and **7c** according to known procedures



Scheme 6. Plausible reaction mechanisms of the oxidative cyclization of **5**

4. Experimental section

4.1. General

All materials were purchased from commercial suppliers and used without any additional purification. NH silica gel (CHROMATOREX) was purchased from Fuji Silysia Chemical Ltd. Melting points were determined on a Büchi Melting Point B-540 and on a Stanford Research Systems OptiMelt MPA 100, and are uncorrected unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER AVANCE 500 spectrometer and on a BRUKER AVANCE 600 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are shown in ppm. HPLC analysis of the compounds and reaction monitoring was carried out on a Shimadzu LC-2010C_{HT}. High-resolution mass spectrometry (HRMS) data was obtained on a Shimadzu Prominence UFLC system with a Thermofisher LTQ Orbitrap Discovery. IR spectra were recorded on a Thermo Electron FT-IR Nicolet 4700 (ATR). Elemental analyses were recorded on an Elementar vario MICRO cube. HPLC conditions are as follows: Inertsil ODS-3 column, 5 µm, 250 mm × 4.6 mm i.d.; UV detector at 254 nm; isocratic elution with CH_3CN/50 mM aqueous KH_2PO_4 (pH 7) (30:70) at 1.0 mL/min flow rate; column temperature: 25 °C. Retention times: **5a** (3.9 min), **3a** (4.9 min).

4.2. General procedure for the one-pot oxidative cyclization

To a solution of 1-(3-chloropyridin-2-yl)guanidine **5c** (1.00 g, 5.86 mmol) in MeOH (100 mL) was added *N*-chlorosuccinimide (861 mg, 6.45 mmol) at 40 °C, and the mixture was stirred at the same temperature for 15 min. To the resulting slurry was added K_2CO_3 (1.70 g, 12.3 mmol) in H_2O (20 mL) at 40 °C, and the mixture was stirred at the same temperature for 30 min. After cooling to room temperature, the solvent was concentrated *in vacuo*. To the residue were added EtOAc (100 mL) and 10% aqueous NaCl (50 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 100 mL), and the combined organic layer was washed with 10% aqueous K_2CO_3 (2 × 50 mL) and 10% aqueous NaCl (50 mL). The organic layer was concentrated *in vacuo* and the residue was purified by column chromatography (NH silica gel, 1:4 EtOAc/hexane to 3:97 MeOH/EtOAc) to give crude **3c** (275 mg) and **7c** (190 mg, 19%, pale brown solid). Crude **3c** (150 mg) was triturated with EtOAc/hexnae (1:1, 2 mL) and filtered to give **3c** (148 mg, 27%) as a pale brown solid.

*4.3. Syntheses of 1-(pyridin-2-yl)guanidine derivatives **5***

*4.3.1. 1-(5-Nitropyridin-2-yl)guanidine (**5a**)*[12]

To a suspension of 2-chloro-5-nitropyridine **4a** (5.00 g, 31.5 mmol) and guanidine hydrochloride (30.1 g, 315 mmol) in *t*-BuOH (250 mL) was added K_2CO_3 (65.3 g, 473 mmol), and the mixture was refluxed for 50 h. The solvent was removed by evaporation, and H_2O (200 mL) was added to the residue. The slurry was stirred at room temperature for 1 h and then filtered. The wet cake was washed with H_2O (2 × 10 mL). The resulting solids were suspended in EtOH/H_2O (1:6, 11 mL), and the mixture was stirred at 60 °C for 1 h. The mixture was cooled by ice bath and stirred for 1 h, and then filtered. The wet cake was washed with H_2O (3 × 2 mL) and dried *in vacuo* to give the crude product (3.69 g). The crude product (3.00 g) was suspended in EtOAc/hexane (1:2, 27 mL), and the mixture was stirred at 50 °C for 30 min. The mixture was cooled to room temperature and stirred for 1 h, and then filtered. The obtained solids were suspended in EtOAc/hexane (1:1, 12 mL), and the mixture was stirred at 50 °C for 30 min. The mixture was cooled to room temperature and stirred for 1 h, and then filtered to give **5a** as an orange solid (1.16 g, 25%). mp 228 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.58 (d, J = 9.5 Hz, 1H), 7.30 (br s, 4H), 8.10 (dd, J = 9.3, 3.0 Hz, 1H), 8.93 (d, J = 2.8 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 118.0, 131.3, 134.8, 144.6, 159.7, 167.2; IR (ATR) 3406, 3033, 1664, 1599, 1563, 1509, 1461, 1412, 1313, 1262, 1111, 992, 947, 934, 864, 836, 771, 726, 713, 531, 496, 452, 420 cm^{-1}; HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_6H_8N_5O_2$, 182.0678; found, 182.0673.

*4.3.2. 1-(3-Nitropyridin-2-yl)guanidine (**5b**)*

To a suspension of 2-chloro-3-nitropyridine **4b** (5.00 g, 31.5 mmol) and guanidine hydrochloride (30.1 g, 315 mmol) in *t*-BuOH (150 mL) was added K_2CO_3 (65.4 g, 473 mmol), and the mixture was refluxed for 40 h. The solvent was removed by evaporation, and EtOAc (500 mL) was added to the residue. The suspension was filtered through a pad of NH silica gel, and the pad was washed with EtOAc (2 × 100 mL). The combined filtrate was washed with saturated brine (3 × 15 mL) and 10% aqueous NaCl (2 × 15 mL), and concentrated *in vacuo*. The resulting solids were suspended in EtOAc/hexane (1:2, 45 mL) and stirred at 50 °C for 1 h. The mixture was cooled to room temperature and stirred for 1 h, and then filtrated to give the crude product (3.99 g). The crude product (1.00 g) was suspended in EtOAc/hexane (1:2, 9 mL), and the mixture was stirred at 50 °C for 30 min. The mixture was cooled to room temperature and stirred for 1 h, and then filtrated to give **5b** as a yellow solid (462 mg, 32%). mp 140–141 °C (lit.[25] mp 143–144 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.73 (dd, J = 7.6, 5.0 Hz, 1H), 6.96 (br s, 4H), 7.86 (dd, J = 7.9, 1.9 Hz, 1H), 8.21 (dd, J = 4.7, 1.9 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 111.9, 130.8, 140.3, 148.8, 154.7, 158.4; IR (ATR) 3458, 3412, 3128, 2362, 1651, 1581, 1536, 1491, 1417, 1348, 1325, 1257, 1044, 877, 837, 760, 730, 714, 586, 555, 527, 447 cm^{-1}; HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_6H_8N_5O_2$, 182.0678; found, 182.0670.

*4.3.3. 1-(3-Chloropyridin-2-yl)guanidine (**5c**)*

To a suspension of 2,3-dichloropyridine **4c** (4.50 g, 30.4 mmol) and guanidine carbonate (16.4 g, 91.2 mmol) in 1-methylpyrrolidin-2-one (NMP) (40 mL) was added K_2CO_3 (21.0 g, 152 mmol), and the mixture was heated to 140 °C and stirred for 30 h. The mixture was filtered through a glass filter at approximately 100 °C, and the cake was washed with EtOAc (5 × 90 mL). The combined filtrate was washed with H_2O (45 mL) and 10% aqueous NaCl (3 × 45 mL), and concentrated *in vacuo*. The residue was suspended in EtOAc/hexane (1:2, 45 mL), and the mixture was stirred at 50 °C for 1 h. The mixture was cooled by ice bath and stirred for 1 h, and then filtered. The obtained solids were suspended in H_2O (45 mL), and the slurry was stirred at 50 °C for 1 h. The mixture was cooled by ice bath and stirred for 1 h, and then filtered to give **5c** (2.01 g, 39%) as a white solid. mp 138 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.63 (dd, J = 7.7, 4.9 Hz, 1H), 6.83 (br s, 4H), 7.61 (dd, J = 7.7, 1.7 Hz, 1H), 7.98 (dd, J = 4.9, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 113.8, 123.0, 136.9, 144.1, 157.8, 159.2; IR (ATR) 3474, 3365, 3148, 2357, 1609, 1555, 1512, 1421, 1311, 1230, 1154, 1121, 1036, 997, 951, 855, 764, 731, 668, 646, 558, 523, 476, 455, 431, 405 cm^{-1}; HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_6H_8ClN_4$, 171.0437; found, 171.0432.

*4.3.4. 1-(5-Chloropyridin-2-yl)guanidine (**5d**)*

To a suspension of 5-chloro-2-fluoropyridine **4d** (5.00 g, 38.0 mmol) and guanidine carbonate (20.5 g, 114 mmol) in NMP (50 mL) was added K_2CO_3 (26.3 g, 190 mmol), and the mixture was heated to 130 °C and stirred for 8 h. To the mixture at room temperature were added EtOAc (100 mL) and H_2O (200 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 100 mL), and the combined organic layer was

washed with 10% aqueous NaCl (3 × 50 mL) and concentrated *in vacuo*. To the resulting residue was added EtOAc (500 mL), and the solution was filtered through a pad of NH silica gel. The filtrate was evaporated, and the residue was suspended in EtOAc/hexane (1:3, 40 mL). The mixture was stirred at 40 °C for 1 h. The mixture was cooled to room temperature and stirred for 1 h, and then filtered. The obtained solids were dissolved into H_2O (15 mL) at 50 °C, and the solution was gradually cooled to room temperature. The slurry was stirred at room temperature for 1 h, and then filtered to give **5d** (3.03 g, 47%) as a white solid. mp 162–163 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.60 (dd, J = 8.8, 0.6 Hz, 1H), 6.75 (br s, 4H), 7.48 (dd, J = 8.8, 2.8 Hz, 1H), 8.04 (d, J = 2.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 119.3, 120.0, 136.5, 143.7, 157.6, 162.1; IR (ATR) 3468, 3414, 2362, 1627, 1573, 1543, 1518, 1463, 1370, 1314, 1278, 1229, 1133, 1110, 1004, 914, 857, 834, 756, 730, 614, 572, 520 459, 436, 405 cm^{-1}; HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_6H_8ClN_4$ 171.0437; found, 171.0432.

*4.3.5. 1-(3-(Trifluoromethyl)pyridin-2-yl)guanidine (**5e**)*

To a suspension of 2-chloro-3-(trifluoromethyl)pyridine **4e** (10.0 g, 55.3 mmol) and guanidine carbonate (29.9 g, 166 mmol) in NMP (100 mL) was added K_2CO_3 (38.2 g, 277 mmol), and the mixture was heated to 120 °C and stirred for 40 h. The mixture was filtered through a glass filter at approximately 100 °C, and the cake was washed with EtOAc (5 × 200 mL). The combined filtrate was washed with H_2O (100 mL) and 10% aqueous NaCl (3 × 100 mL), and concentrated *in vacuo*. The residue was purified by column chromatography (NH silica gel, EtOAc/hexane 1:10 to 2:3) to give the crude product. To the crude product in EtOAc (200 mL) was added activated carbon (500 mg), and the mixture was stirred at room temperature for 30 min. The activated carbon was filtered off, and the filtrate was concentrated *in vacuo*. The residue was dissolved into EtOAc (100 mL), and 4M HCl in EtOAc (14 mL, 55.3 mmol) was added at 5 °C. The mixture was stirred at 5 °C for 30 min, and then filtered. To the obtained solids were added EtOAc (200 mL) and aqueous 5% $NaHCO_3$ (50 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (100 mL), and the combined organic layer was concentrated *in vacuo*. To the residue was added EtOAc/hexane (1:3, 10 mL), and the slurry was stirred at 5 °C for 1 h, and then filtered to give **5e** (1.31 g, 12%) as a white solid. mp 128–130 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.72 (dd, J = 7.4, 4.9 Hz, 1H), 6.87 (br s, 4H), 7.78 (dd, J = 7.6, 1.9 Hz, 1H), 8.23 (dd, J = 5.0, 1.6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 111.9, 115.8 (q, $^2J_{CF}$ = 28.8 Hz), 124.3 (q, $^1J_{CF}$ = 270.0 Hz), 135.1 (q, $^3J_{CF}$ = 6.3 Hz), 149.7, 157.7, 160.5; IR (ATR) 3483, 3449, 3384, 3164, 1614, 1592, 1561, 1513, 1430, 1334, 1301, 1256, 1226, 1158, 1127, 1102, 1070, 1027, 965, 859, 806, 779, 742, 695, 615, 583, 543, 483, 471, 448, 435, 422 cm^{-1}; HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_7H_8F_3N_4$, 205.0701; found, 205.0696.

*4.3.6. 1-(5-(Trifluoromethyl)pyridin-2-yl)guanidine 0.9 1-methylpyrrolidin-2-one solvate (**5f**)*

To a suspension of 2-chloro-5-(trifluoromethyl)pyridine **4f** (8.00 g, 44.1 mmol) and guanidine carbonate (7.94 g, 44.1 mmol) in NMP (80 mL) was added K_2CO_3 (18.3 g, 132 mmol), and the mixture was heated to 120 °C and stirred for 7 h. The mixture was filtered through a glass filter at approximately 100 °C, and the cake was washed with EtOAc (5 × 160 mL). The combined filtrate was washed with H_2O (80 mL) and 10% aqueous NaCl (3 × 80 mL), and concentrated *in vacuo*. To the residue was added EtOAc/hexane (1:2, 40 mL), and the mixture was stirred at 50 °C for 1 h. The mixture was cooled by ice bath and stirred for 1 h, and then filtered to give the crude product (6.13 g). The crude product (1.00 g) was suspended in EtOAc/hexane (1:2, 9 mL), and the mixture was stirred at 50 °C for 1 h. The mixture was cooled to room temperature and stirred for 1 h, and then filtered to give **5f** (829 mg, 39%) as a white solid. mp 95–97 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.85–1.96 (m, 1.8H, NMP), 2.18 (t, J = 8.0 Hz, 1.8H, NMP), 2.70 (s, 2.7H, NMP), 3.30 (t, J = 6.9 Hz, 1.8H, NMP), 6.66 (d, J = 8.8 Hz, 1H), 7.01 (br s, 4H), 7.67 (dd, J = 8.8, 2.5 Hz, 1H), 8.35 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 17.2 (NMP), 28.9 (NMP), 30.1 (NMP), 48.4 (NMP), 113.9 (q, $^2J_{CF}$ = 32.1 Hz), 118.3, 124.9 (q, $^1J_{CF}$ = 268.3 Hz), 133.1 (q, $^3J_{CF}$ = 2.5 Hz), 143.5 (q, $^3J_{CF}$ = 5.0 Hz), 158.8, 166.1, 173.7 (NMP); IR (ATR) 3483, 3449, 3384, 3163, 1614, 1591, 1561, 1512, 1430, 1334, 1301, 1256, 1226, 1158, 1127, 1102, 1070, 1027, 965, 859, 806, 779, 742, 695, 651, 614, 584, 542, 480, 470, 448, 435, 422, 410 cm^{-1}; HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_7H_8F_3N_4$, 205.0701; found, 205.0694; Anal. Calcd for $C_{11.5}H_{15.1}N_{4.9}F_3O_{0.9}$: C, 47.08; H, 5.19; N, 23.39. Found: C, 46.96 H, 5.13; N, 23.17.

*4.3.7. 1-(4-(Trifluoromethyl)pyridin-2-yl)guanidine (**5g**)*

To a suspension of 2-chloro-4-(trifluoromethyl)pyridine **4g** (4.50 g, 24.8 mmol) and guanidine carbonate (13.4 g, 74.4 mmol) in NMP (45 mL) was added K_2CO_3 (17.1 g, 124 mmol), and the mixture was heated to 120 °C and stirred for 18 h. The mixture was filtered through a glass filter at approximately 100 °C, and the cake was washed with EtOAc (5 × 90 mL). The combined filtrate was washed with H_2O (45 mL) and 10% aqueous NaCl (3 × 45 mL), and concentrated *in vacuo*. The residue was suspended in EtOAc/hexane (1:2, 23 mL), and the mixture was stirred at 50 °C for 1 h. The mixture was cooled by ice bath and stirred for 1 h, and then filtered. The obtained solids were suspended in H_2O (13 mL) and the slurry was stirred at 50 °C for 1 h. The mixture was gradually cooled by ice bath and stirred for 1 h, and then filtered to give **5g** (2.39 g, 47%) as a white solid. mp 141–142 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.75 (s, 1H), 6.85 (dd, J = 5.4, 1.6 Hz, 1H), 6.92 (br s, 4H), 8.25 (d, J = 5.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 107.5 (q, $^3J_{CF}$ = 2.5 Hz), 113.9 (q, $^3J_{CF}$ = 3.8 Hz), 123.2 (q, $^1J_{CF}$ = 271.3 Hz), 137.3 (q, $^2J_{CF}$ = 32.5 Hz), 147.7, 158.3, 164.2; IR (ATR) 3388, 3045, 1663, 1595, 1527, 1411, 1335, 1293, 1271, 1171, 1145, 1122, 1078, 980, 871, 817, 793, 758, 731, 689, 667, 561, 536, 467, 444, 421, 401 cm^{-1}; HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_7H_8F_3N_4$, 205.0701; found, 205.0693.

*4.3.8. 1-(6-Fluoropyridin-2-yl)guanidine (**5h**)*

To a suspension of 2,6-difluoropyridine **4h** (4.00 g, 34.8 mmol) and guanidine carbonate (12.5 g, 69.6 mmol) in *N*,*N*-dimethylacetamide (80 mL) was added K_2CO_3 (14.4 g, 104 mmol), and the mixture was heated to 120 °C and stirred for 6 h. At this point, guanidine carbonate (6.27 g, 34.8 mmol) and K_2CO_3 (9.62 g, 69.6 mmol) were added, and the mixture was stirred at 120 °C for an additional 3 h. After cooling to room temperature, EtOAc (160 mL) and H_2O (240 mL) were added, and the layers were separated. The aqueous layer was extracted with EtOAc (5 × 40 mL), and the combined organic layer was washed with saturated brine (2 × 40 mL) and 10% aqueous NaCl (3 × 40 mL), and concentrated *in vacuo*. The resulting residue was purified by column chromatography (NH silica gel, EtOAc/hexane 1:1). The obtained solids were suspended in EtOAc/hexane (1:2, 36 mL), and the mixture was stirred at 50 °C for 1 h. The mixture was cooled to room temperature and stirred for 1 h, and then filtered. The obtained solids were suspended in H_2O (12 mL), and the mixture was stirred at 50 °C for 1 h. The mixture was cooled to room temperature and stirred for 1 h, and then filtered to give the crude product (2.31 g). The crude product (1.00 g) was suspended in EtOAc/hexane (1:3, 5 mL),

and the slurry was stirred at 50 °C for 1 h. The mixture was gradually cooled to room temperature and stirred for 1 h, and then filtered to give **5h** (866 mg, 37%) as a white solid. mp 121–122 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.27 (dd, J = 7.6, 2.2 Hz, 1H), 6.48 (dd, J = 8.0, 2.1 Hz, 1H), 6.67 (br s, 4H), 7.56 (dt, J = 9.8, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 96.4 (d, ^2J = 36.3 Hz), 115.6 (d, $^4J_{HF}$ = 5.0 Hz), 141.5 (d, $^3J_{HF}$ = 6.3 Hz), 158.0, 161.2 (d, $^1J_{HF}$ = 233.8 Hz), 162.6 (d, $^3J_{HF}$ = 12.6 Hz); IR (ATR) 3485, 3310, 3137, 2255, 2179, 1709, 1635, 1608, 1564, 1537, 1487, 1464, 1416, 1334, 1260, 1243, 1222, 1151, 1055, 1035, 988, 957, 866, 781, 726, 696, 673, 596, 572, 555, 472, 422, 404 cm^{-1}; HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_6H_8FN_4$, 155.0733; found, 155.0725.

*4.3.9. 1-(3-Chloro-5-(trifluoromethyl)pyridin-2-yl)guanidine (**5i**)*

To a suspension of 2,3-dichloro-5-(trifluoromethyl)pyridine **4i** (10.0 g, 46.3 mmol) and guanidine carbonate (8.34 g, 46.3 mmol) in NMP (100 mL) was added K_2CO_3 (19.2 g, 139 mmol), and the mixture was heated to 100 °C and stirred for 5 h. The mixture was filtered through a glass filter at approximately 100 °C, and the cake was washed with EtOAc (200 mL). To the combined filtrate was added 10% aqueous NaCl (100 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with 10% aqueous NaCl (3 × 100 mL) and concentrated *in vacuo*. To the residue was added EtOAc (100 mL), and the solution was cooled by ice bath. To the solution was added 4M HCl in EtOAc (23 mL, 92.6 mmol), and the mixture was stirred for 2 h, and then filtered. To the obtained solids were added EtOAc (200 mL), H_2O (50 mL) and 8M NaOH (12 mL, 92.6 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layer was concentrated *in vacuo*. The residue was purified by column chromatography (NH silica gel, EtOAc/hexane 1:3 to 1:1) to give the crude product. To the crude product was added H_2O (10 mL), and the mixture was stirred at 60 °C for 1 h. The mixture was cooled to room temperature and stirred for 1 h, and then filtered to give **5i** (4.02 g, 36%) as a white solid. mp 146–149 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.14 (br s, 4H), 7.91 (d, J = 2.2 Hz, 1H), 8.30 (dd, J = 2.4, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 113.9 (q, $^2J_{CF}$ = 32.5 Hz), 122.8, 124.0 (q, $^1J_{CF}$ = 268.8 Hz), 132.9 (q, $^3J_{CF}$ = 2.5 Hz), 141.7 (q, $^3J_{CF}$ = 5.0 Hz), 159.2, 161.5; IR (ATR) 3511, 3457, 3405, 3324, 1624, 1600, 1542, 1519, 1461, 1405, 1382, 1331, 1307, 1257, 1153, 1112, 1088, 1054, 999, 937, 910, 878, 809, 773, 721, 670, 641, 598, 543, 481, 465, 421, 405 cm^{-1}; HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_7H_7ClF_3N_4$, 239.0311; found, 239.0309.

*4.3.10. 1-(Quinolin-2-yl)guanidine (**5j**)*

To a suspension of 2-chloroquinoline **4j** (4.50 g, 27.5 mmol) and guanidine carbonate (14.9 g, 82.5 mmol) in NMP (45 mL) was added K_2CO_3 (19.0 g, 138 mmol), and the mixture was heated to 120 °C and stirred for 17 h. After cooling to room temperature, EtOAc (90 mL) was added, and the mixture was filtered through a glass filter. The cake was washed with EtOAc (4 × 90 mL). To the combined filtrate was added H_2O (45 mL), and the layers were separated. The organic layer was washed with 10% aqueous NaCl (2 × 45 mL) and concentrated *in vacuo*. The residue was suspended in EtOAc/hexane (1:2, 45 mL), and the mixture was stirred at 50 °C for 1 h. The mixture was cooled to room temperature and stirred for 1 h, and then filtered. The obtained solids were suspended in H_2O (14 mL), and the mixture was stirred at 50 °C for 1 h. The mixture was cooled by ice bath and stirred for 1 h, and then filtered to give **5j** (2.54 g, 50%) as a white solid. mp 218–219 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.80 (d, J = 8.8 Hz, 1H), 7.18 (br s, 4H), 7.22 (td, J = 7.4, 1.3 Hz, 1H), 7.43–7.53 (m, 1H) 7.59 (d, J = 8.5 Hz, 1H), 7.65 (dd, J = 8.0, 1.1 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H),; ^{13}C NMR (125 MHz, DMSO-d_6) δ 121.7, 122.2, 123.4, 125.7, 127.1, 128.6, 135.9, 146.4, 158.9, 162.9; IR (ATR) 3411, 2997, 1657, 1620, 1585, 1535, 1491, 1444, 1417, 1378, 1349, 1309, 1284, 1246, 1212, 1142, 1119, 1016, 1003, 974, 944, 929, 828, 788, 763, 752, 684, 640, 593, 550, 478, 467, 447, 416 cm^{-1}; HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{10}H_{11}N_4$, 187.0984; found, 187.0976.

*4.3.11. 1-(Isoquinolin-1-yl)guanidine (**5k**)*

To a suspension of 1-chloroisoquinoline **4k** (4.50 g, 27.5 mmol) and guanidine carbonate (14.9 g, 82.5 mmol) in NMP (45 mL) was added K_2CO_3 (19.0 g, 138 mmol), and the mixture was heated to 120 °C and stirred for 15 h. The mixture was filtered through a glass filter at approximately 100 °C, and the cake was washed with EtOAc (5 × 90 mL). To the combined filtrate was added H_2O (45 mL) and the layers were separated. The organic layer was washed with 10% aqueous NaCl (3 × 45 mL) and concentrated *in vacuo*. The residue was purified by column chromatography (NH silica gel, EtOAc/hexane 1:1). The obtained solids were suspended in H_2O (45 mL) and the slurry was stirred at 50 °C for 1 h. The mixture was cooled to room temperature and stirred for 1 h, and then filtered to give the crude product (3.30 g). The crude product (700 mg) was suspended in EtOAc/hexane (1:2, 11 mL), and the mixture was stirred at 50 °C for 1 h. The mixture was cooled to room temperature and stirred for 1 h, and then filtered to give **5k** (0.627 g, 58%) as a white solid. mp 193–194 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.98 (d, J = 6.0 Hz, 1H), 7.11 (br s, 4H), 7.43 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.58 (ddd, J = 7.6, 7.6, 1.3 Hz, 1H), 7.61–7.67 (m, 1H), 7.90 (d, J = 5.7 Hz, 1H), 8.62 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 111.3, 125.5, 125.6, 126.0, 126.8, 130.0, 137.3, 140.4, 158.9, 162.0; IR (ATR) 3382, 3046, 2179, 1586, 1519, 1489, 1443, 1390, 1363, 1315, 1277, 1211, 1139, 1089, 1020, 964, 950, 877, 810, 797, 757, 728, 682, 658, 584, 520, 463, 425, 404 cm^{-1}; HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{10}H_{11}N_4$, 187.0984; found, 187.0976.

*4.3.12. 1-(Benzo[d]oxazol-2-yl)guanidine (**5m**)*

To a suspension of 2-chlorobenzo[*d*]oxazole **4m** (4.50 g, 29.3 mmol) and guanidine carbonate (5.28 g, 29.3 mmol) in NMP (90 mL) was added K_2CO_3 (12.1 g, 87.9 mmol), and the mixture was heated to 100 °C and stirred for 1 h. After cooling to room temperature, EtOAc (135 mL) and H_2O (225 mL) were added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 90 mL). The combined organic layer was washed with 10% aqueous NaCl (3 × 23 mL) and concentrated *in vacuo*. The residue was purified by column chromatography (NH silica gel, EtOAc/hexane 1:3 to 1:1). The obtained solids were suspended in H_2O (23 mL) and the mixture was stirred at 40 °C for 1 h. The mixture was cooled by ice bath and stirred for 1 h, and then filtered to give the crude product (3.83 g). The crude product (700 mg) was suspended in EtOAc/hexane (1:2, 11 mL), and the mixture was stirred at 50 °C for 1 h. The mixture was cooled to room temperature and stirred for 1 h, and then filtered to give **5m** as a white solid (535 mg, 57%). mp 185–186 °C (lit.[26] 186 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.03 (dd, J = 7.7, 1.1 Hz, 1H), 7.07–7.20 (m, 1H), 7.18 (br s, 4H), 7.20–7.30 (m, 1H), 7.30–7.40 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 108.5, 115.3, 120.8, 123.0, 142.5, 146.6, 159.8, 166.4; IR (ATR) 3448, 3340, 3196, 3056, 1609, 1547, 1455, 1344, 1316, 1251, 1177, 1101, 1029, 1007, 962, 919, 755, 728, 504, 434, 416, 409 cm^{-1}; HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_8H_9N_4O$, 177.0776; found, 177.0768.

*4.4. 2-Chloro-1-(5-nitropyridin-2-yl)guanidine (**6a**)*

To a suspension of **5a** (544 mg, 3.00 mmol) in MeCN (27 mL) was added *N*-chlorosuccinimide (NCS, 441 mg, 3.30 mmol) at 40 °C, and the mixture was stirred at this temperature for 15 min. The mixture was cooled by ice bath and stirred for 30 min, and then filtered to give **6a** (584 mg, 90%) as a pale yellow solid. mp 154–155 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.35 (d, J = 9.5 Hz, 1H), 7.58 (br s, 2H), 8.44 (dd, J = 9.5, 2.8 Hz, 1H), 9.05 (d, J = 2.5 Hz, 1H), 10.3 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 111.2, 133.7, 137.8, 144.5, 157.5, 157.9; IR (ATR) 3461, 3228, 3056, 1659, 1599, 1562, 1523, 1478, 1413, 1322, 1287, 1243, 1159, 1111, 1014, 978, 954, 889, 850, 833, 756, 723, 697, 609, 528, 499, 416 cm^{-1}; HRMS (ESI): [M+H$^+$] calcd for $C_6H_7N_5O_2Cl$, 216.0288; found, 216.0287.

*4.5. Syntheses of [1,2,4]triazolo[1,5-a]pyridin-2-amines **3** and [1,2,4]triazolo[4,3-a]pyridin-3-amines **7***

*4.5.1. 6-Nitro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (**3a**)*

*4.5.1.1. Synthesis from **6a***

To a suspension of **6a** (431 mg, 2.00 mmol) in MeCN (22 mL) was added K_2CO_3 (581 mg, 4.20 mmol) in H_2O (9 mL) at 40 °C, and the mixture was stirred at this temperature for 30 min. After cooling to room temperature, H_2O (35 mL) was added, and the mixture was cooled by ice bath and stirred for 30 min, and then filtered to give **3a** (332 mg, 93%) as a yellow solid. mp 311–312 °C (lit.[15] mp 310 °C); ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.68 (s, 2H), 7.47 (d, J = 9.5 Hz, 1H), 8.16 (dd, J = 9.4, 2.3 Hz, 1H), 9.64 (d, J = 1.9 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 110.9, 123.8, 126.9, 135.1, 152.6, 168.7; IR (ATR) 3449, 3320, 3237, 3110, 3070, 3033, 1633, 1561, 1522, 1488, 1448, 1422, 1328, 1290, 1256, 1205, 1139, 1081, 1038, 946, 888, 831, 760, 744, 725, 697, 610, 582, 550, 489, 424 cm^{-1}; HRMS (ESI): [M+H$^+$] calcd for $C_6H_6N_5O_2$, 180.0521; found, 180.0514.

*4.5.1.2. One-pot synthesis from **5a***

To a suspension of **5a** (362 mg, 2.00 mmol) in MeOH (36 mL) was added NCS (294 mg, 2.20 mmol) at 40 °C, and the mixture was stirred at this temperature for 15 min. To the resulting slurry was added K_2CO_3 (581 mg, 4.20 mmol) in H_2O (7 mL) at 40 °C, and the mixture was stirred at this temperature for 30 min. After cooling to room temperature, H_2O (29 mL) was added, and the mixture was stirred for 30 min, and then filtered to give **3a** (312 mg, 87%) as a yellow solid.

*4.5.2. 8-Nitro[1,2,4]triazolo[1,5-a]pyridin-2-amine (**3b**)*

Compound **3b** was synthesized from **5b** (544 mg, 3.00 mmol) according to the procedure described for the one-pot synthesis of **3a**. Yellow solid, 461 mg, 86% yield. mp 350 °C (decompose); ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.71 (s, 2H), 7.04 (dd, J = 7.5, 7.5 Hz, 1H), 8.41 (dd, J = 8.3, 1.1 Hz, 1H), 8.99 (dd, J = 6.4, 1.1 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 109.2, 127.2, 132.7, 133.4, 145.2, 167.7; IR (ATR) 3361, 3309, 3220, 3173, 3101, 1631, 1561, 1519, 1442, 1413, 1340, 1272, 1194, 1149, 1077, 1038, 984, 898, 841, 835, 795, 752, 738, 686, 596, 563, 543, 474, 452 cm^{-1}; HRMS (ESI): [M+H$^+$] calcd for $C_6H_6N_5O_2$, 180.0521; found, 180.0513.

*4.5.3. 8-Chloro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (**3c**)*

mp 225 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.25 (s, 2H), 6.86 (dd, J = 7.7, 6.6 Hz, 1H), 7.60 (dd, J = 7.7, 0.9 Hz, 1H), 8.55 (dd, J = 6.8, 1.1 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 110.9, 116.9, 126.7, 128.1, 148.4, 166.1; IR (ATR) 3323, 3164, 1641, 1627, 1544, 1506, 1407, 1308, 1221, 1203, 1136, 1121, 1062, 1029, 962, 907, 794, 779, 772, 749, 675, 635, 579, 561, 537, 408 cm^{-1}; HRMS (ESI): [M+H$^+$] calcd for $C_6H_6ClN_4$, 169.0281; found, 169.0273.

*4.5.4. 8-Chloro-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**7c**)*

mp 270-271 °C (decompose) (lit.[16] 275–276 °C); ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.56 (s, 2H), 6.75 (dd, J = 7.0, 7.0 Hz, 1H), 7.28 (d, J = 7.1 Hz, 1H), 8.06 (dd, J = 6.8, 0.8 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 111.2, 120.0, 121.6, 124.0, 143.2, 149.8; IR (ATR) 3265, 3106, 1658, 1629, 1575, 1517, 1500, 1439, 1414, 1378, 1331, 1154, 1128, 1043, 1036, 943, 935, 882, 868, 781, 758, 727, 687, 651, 568, 557, 539, 510, 409, 404 cm^{-1}; HRMS (ESI): [M+H$^+$] calcd for $C_6H_6ClN_4$, 169.0281; found, 169.0273.

*4.5.5. 6-Chloro-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**7d**)*

Compound **5d** (512 mg, 3.00 mmol) in MeOH (51 mL) was treated with NCS (441 mg, 3.30 mmol) and K_2CO_3 (871 mg, 6.3 mmol) in H_2O (10 mL), and work-up was conducted according to the general procedure. The residue obtained after evaporation of the organic layer was purified by column chromatography (NH silica gel, EtOAc/hexane 1:1 to EtOAc) to give crude **7d** (262 mg). Crude **7d** (150 mg) was triturated with EtOAc/hexane (2:1, 2 mL) and filtered to give **7d** (145 mg, 50%) as a pale yellow solid. mp 256 °C (decompose); ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.48 (s, 2H), 7.08 (dd, J = 9.8, 1.9 Hz, 1H), 7.50 (dd, J = 9.8, 0.8 Hz, 1H), 8.34 (dd, J = 1.7, 0.9 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 116.5, 118.3, 120.1, 125.8, 144.1, 148.5; IR (ATR) 3248, 3094, 1664, 1630, 1578, 1509, 1447, 1391, 1359, 1337, 1165, 1137, 1034, 928, 851, 824, 817, 790, 734, 676, 572, 540, 416 cm^{-1}; HRMS (ESI): [M+H$^+$] calcd for $C_6H_6ClN_4$, 169.0281; found, 169.0279.

*4.5.6. 8-(Trifluoromethyl)[1,2,4]triazolo[1,5-a]pyridin-2-amine (**3e**)*

Compound **5e** (817 mg, 4.00 mmol) in MeOH (82 mL) was treated with NCS (588 mg, 4.40 mmol) and K_2CO_3 (1.16 g, 8.40 mmol) in H_2O (16 mL), and work-up was conducted according to the general procedure. The residue obtained after evaporation of the organic layer was purified by column chromatography (NH silica gel, EtOAc/hexane 1:4 to EtOAc) to give crude **3e** (473 mg) and crude **7e** (189 mg). Crude **3e** (200 mg) was purified by column chromatography (NH silica gel, EtOAc/hexane 1:4 to 1:1), and the obtained solids were triturated with EtOAc/hexane (1:1, 1 mL) and filtered to give **3e** (151 mg, 44%) as a white solid. mp 221 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.44 (s, 2H), 7.00 (t, J = 7.2 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 8.84 (d, J = 6.8 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 109.9, 112.6 (q, $^2J_{CF}$ = 33.0 Hz), 122.9 (q, $^1J_{CF}$ = 270.0 Hz), 127.2 (q, $^3J_{CF}$ = 4.5 Hz), 131.2, 146.8, 166.8; IR (ATR) 3342, 3209, 1640, 1582, 1524, 1509, 1460, 1421, 1352, 1330, 1303, 1226, 1199, 1166, 1112, 1068, 1028, 959, 929, 906, 807, 794, 762, 717, 667, 593, 526, 507 cm^{-1}; HRMS (ESI): [M+H$^+$] calcd for $C_7H_6F_3N_4$, 203.0545; found, 203.0540.

*4.5.7. 8-(Trifluoromethyl)[1,2,4]triazolo[4,3-a]pyridin-3-amine (**7e**)*

Crude **7e** (100 mg) was triturated with EtOAc/hexane (1:1, 1 mL) and filtered to give **7e** (87 mg, 20%) as a yellow solid. mp 258 °C (decompose); ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.64 (s, 2H), 6.88 (t, J = 7.0 Hz, 1H), 7.58 (d, J = 6.8 Hz, 1H), 8.30 (d, J = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 109.9, 115.9 (q, $^2J_{CF}$ = 33.0 Hz), 122.5 (q, $^1J_{CF}$ = 270.0 Hz), 125.0 (q, $^3J_{CF}$ = 6.0 Hz), 126.6, 140.6, 149.2; IR (ATR) 3304, 3153, 1661, 1637, 1585, 1558, 1508, 1450, 1424, 1390, 1338, 1313, 1240, 1163,

1139, 1114, 1046, 1031, 946, 872, 773, 742, 733, 690, 642, 611, 564, 520, 504 cm^{-1}; HRMS (ESI): $[M+H^+]$ calcd for $C_7H_6F_3N_4$, 203.0545; found, 203.0540.

*4.5.8. 6-(Trifluoromethyl)[1,2,4]triazolo[1,5-a]pyridin-2-amine (**3f**)*

Compound **5f** (1.17 g, 4.00 mmol) in MeOH (117 mL) was treated with NCS (588 mg, 4.40 mmol) and K_2CO_3 (1.16 g, 8.40 mmol) in H_2O (23 mL), and work-up was conducted according to the general procedure. The residue obtained after evaporation of the organic layer was purified by column chromatography (NH silica gel, EtOAc/hexane 1:1 to 4:1) to give **3f** (184 mg, 23%) as a white solid and crude **7f** (454 mg). mp 182 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.37 (s, 2H), 7.52 (d, J = 9.4 Hz, 1H), 7.68 (dd, J = 9.1, 1.9 Hz, 1H), 9.18 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 112.8, 113.4 (q, $^2J_{CF}$ = 33.5 Hz), 123.7 (q, $^1J_{CF}$ = 269.0 Hz), 124.9 (q, $^3J_{CF}$ = 3.0 Hz), 126.6 (q, $^3J_{CF}$ = 4.5 Hz), 151.4, 167.5; IR (ATR) 3343, 3172, 2360, 2341, 1648, 1564, 1543, 1522, 1428, 1358, 1331, 1307, 1181, 1120, 1058, 1034, 938, 864, 809, 761, 740, 674, 639, 562, 537, 438, 415 cm^{-1}; HRMS (ESI): $[M+H^+]$ calcd for $C_7H_6F_3N_4$, 203.0545; found, 203.0538.

*4.5.9. 6-(Trifluoromethyl)[1,2,4]triazolo[4,3-a]pyridin-3-amine (**7f**)*

Crude **7f** (200 mg) was dissolved in EtOAc and washed with 5% aqueous K_2CO_3. After evaporation of the solvent, the obtained solids were triturated with EtOAc/hexane (1:1, 2 mL) and filtered to give **7f** (184 mg, 52%) as a yellow solid. mp 249 °C (decompose); ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.72 (s, 2H), 7.23 (dd, J = 9.8, 1.5 Hz, 1H), 7.63 (d, J = 9.8 Hz, 1H), 8.77 (d, J = 1.5 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 114.0 (q, $^2J_{CF}$ = 33.5 Hz), 117.0, 119.8 (q, $^3J_{CF}$ = 3.0 Hz), 123.2 (q, $^3J_{CF}$ = 6.0 Hz), 123.6 (q, $^1J_{CF}$ = 269.0 Hz), 144.7, 149.5; IR (ATR) 3257, 3105, 1666, 1650, 1588, 1531, 1450, 1405, 1376, 1322, 1170, 1119, 1031, 930, 889, 833, 801, 777, 743, 651, 633, 584, 566, 542, 522, 425, 410 cm^{-1}; HRMS (ESI): $[M+H^+]$ calcd for $C_7H_6F_3N_4$, 203.0545; found, 203.0539.

*4.5.10. 7-(Trifluoromethyl)[1,2,4]triazolo[1,5-a]pyridin-2-amine (**3g**)*

Compound **5g** (817 mg, 4.00 mmol) in MeOH (82 mL) was treated with NCS (588 mg, 4.40 mmol) and K_2CO_3 (1.16 g, 8.40 mmol) in H_2O (16 mL), and work-up was conducted according to the general procedure. The residue obtained after evaporation of the organic layer was purified by column chromatography (NH silica gel, EtOAc/hexane 1:4 to 10:1) to give **3g** (131 mg, 16%) as a pale yellow solid and crude **7g** (496 mg). mp 167–168 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.35 (s, 2H), 7.15 (dd, J = 7.0, 2.1 Hz, 1H), 7.82 (s, 1H), 8.78 (d, J = 7.2, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 106.7 (q, $^3J_{CF}$ = 3.0 Hz), 109.7 (q, $^3J_{CF}$ = 3.8 Hz), 123.3 (q, $^1J_{CF}$ = 270.8 Hz), 128.7 (q, $^2J_{CF}$ = 33.0 Hz), 128.7, 149.5, 167.4; IR (ATR) 3327, 3166, 1650, 1556, 1523, 1509, 1483, 1326, 1272, 1256, 1211, 1180, 1119, 1057, 1035, 951, 860, 789, 758, 740, 673, 582, 568, 544, 443, 413 cm^{-1}; HRMS (ESI): $[M+H^+]$ calcd for $C_7H_6F_3N_4$, 203.0545; found, 203.0539.

*4.5.11. 7-(Trifluoromethyl)[1,2,4]triazolo[4,3-a]pyridin-3-amine (**7g**)*

Crude **7g** (200 mg) was dissolved in EtOAc and washed with 10% aqueous NH_4Cl and H_2O. After evaporation of the solvent, the obtained solids were triturated with EtOAc/hexane (1:1, 4 mL) and filtered to give **7g** (162 mg, 50%) as a white solid. mp 275 °C (decompose); ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.71 (s, 2H), 6.99 (dd, J = 7.6, 1.5 Hz, 1H), 7.99 (s, 1H), 8.25 (d, J = 7.6 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 106.6 (q, $^3J_{CF}$ = 3.0 Hz), 114.6 (q, $^3J_{CF}$ = 5.5 Hz), 123.3 (q, $^1J_{CF}$ = 270.5 Hz), 124.1, 124.8 (q, $^2J_{CF}$ = 33.0 Hz), 143.9, 149.4; IR (ATR) 3272, 3081, 1651, 1572, 1509, 1481, 1428, 1371, 1336, 1293, 1263, 1145, 1050, 1035, 937, 887, 826, 793, 779, 741, 731, 688, 674, 639, 606, 576, 526, 459, 433, 407 cm^{-1} ; HRMS (ESI): $[M+H^+]$ calcd for $C_7H_6F_3N_4$, 203.0545; found, 203.0540.

*4.5.12. 8-Chloro-6-(trifluoromethyl)[1,2,4]triazolo[1,5-a]pyridin-2-amine (**3i**)*

Compound **5i** (716 mg, 3.00 mmol) in MeOH (72 mL) was treated with NCS (441 mg, 3.30 mmol) and K_2CO_3 (871 mg, 6.30 mmol) in H_2O (14 mL), and work-up was conducted according to the general procedure. The residue obtained after evaporation of the organic layer was purified by column chromatography (NH silica gel, EtOAc/hexane 1:5 to 5:1) to give crude **3i** (420 mg) and crude **7i** (129 mg). Crude **3i** (200 mg) was triturated with EtOAc/hexane (1:1, 2 mL) and filtered to give **3i** (193 mg, 57%) as a white solid. mp 238–239 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.62 (s, 2H), 7.99 (d, J = 1.5 Hz, 1H), 9.22 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 113.3 (q, $^2J_{CF}$ = 34.5 Hz), 117.5, 123.1 (q, $^1J_{CF}$ = 268.5 Hz), 124.2 (q, $^3J_{CF}$ = 1.5 Hz), 125.9 (q, $^3J_{CF}$ = 4.5 Hz), 149.5, 167.3; IR (ATR) 3379, 3299, 3165, 3111, 1627, 1542, 1401, 1351, 1321, 1306, 1219, 1170, 1116, 1074, 1031, 975, 920, 883, 869, 841, 758, 691, 652, 628, 551, 532, 502, 449, 410 cm^{-1}; HRMS (ESI): $[M+H^+]$ calcd for $C_7H_5ClF_3N_4$, 237.0155; found, 237.0148.

*4.5.13. 8-Chloro-6-(trifluoromethyl)[1,2,4]triazolo[4,3-a]pyridin-3-amine (**7i**)*

Crude **7i** (129 mg) was triturated with EtOAc/hexane (1:1, 1 mL) and filtered to give **7i** (72 mg, 9%) as a white solid. mp 266 °C (decompose); ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.89 (s, 2H), 7.58 (d, J = 1.1 Hz, 1H), 8.79 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 113.9 (q, $^2J_{CF}$ = 34.0 Hz), 119.0 (q, $^3J_{CF}$ = 2.7 Hz), 121.7, 122.6 (q, $^3J_{CF}$ = 6.0 Hz), 123.0 (q, $^1J_{CF}$ = 269.5 Hz), 142.5, 150.9; IR (ATR) 3472, 3297, 3228, 3104, 2998, 1647, 1572, 1542, 1518, 1441, 1377, 1345, 1312, 1234, 1163, 1115, 1069, 1037, 948, 905, 884, 873, 865, 831, 754, 732, 685, 651, 630, 550, 446, 424 cm^{-1}; HRMS (ESI): $[M+H^+]$ calcd for $C_7H_5ClF_3N_4$, 237.0155; found, 237.0151.

*4.5.14. [1,2,4]Triazolo[1,5-a]quinolin-2-amine (**3j**)*

Compound **5j** (745 mg, 4.00 mmol) in MeOH (75 mL) was treated with NCS (588 mg, 4.40 mmol) and K_2CO_3 (1.16 g, 8.40 mmol) in H_2O (15 mL), and work-up was conducted according to the general procedure. The residue obtained after evaporation of the organic layer was purified by column chromatography (NH silica gel, EtOAc/hexane 1:5 to EtOAc/MeOH 99:5) to give crude **3j** (168 mg) and crude **7j** (370 mg). Crude **3j** (130 mg) was purified by column chromatography (NH silica gel, EtOAc/hexane 1:2), and the obtained solids were triturated with EtOAc/hexane (1:3, 3 mL) and filtered to give **3j** (115 mg, 20%) as a pale pink solid. mp 196 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.09 (s, 2H), 7.45–7.54 (m, 2H), 7.78 (t, J = 7.9 Hz, 1H), 7.94 (d, J = 9.4 Hz, 1H), 8.02 (d, J = 7.6 Hz, 1H), 8.15 (d, J = 8.3 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 113.2, 114.5, 121.9, 124.0, 129.0, 129.7, 130.2, 132.5, 148.5, 165.6; IR (ATR) 3328, 3178, 1651, 1611, 1561, 1530, 1449, 1418, 1392, 1355, 1330, 1215, 1092, 1054, 810, 767, 756, 745, 691, 643, 615, 554, 522, 508, 477, 424, 409 cm^{-1}; HRMS (ESI): $[M+H^+]$ calcd for $C_{10}H_9N_4$, 185.0827; found, 185.0820.

*4.5.15. [1,2,4]Triazolo[4,3-a]quinolin-1-amine (**7j**)*

Crude **7j** (300 mg) was purified by column chromatography (NH silica gel, EtOAc), and the obtained solids were triturated with EtOAc/hexane (1:1, 3 mL) and filtered to give **7j** (231 mg,

39%) as a pink solid. mp 255–256 (lit.[27] mp 175–177 °C, lit.[28] mp 250–253 °C); ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.31 (br s, 2H), 7.40 (d, *J* = 9.4 Hz, 1H), 7.45–7.55 (m, 2H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 8.52 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 115.1, 115.9, 124.0, 125.3, 127.4, 128.5, 128.6, 131.9, 146.1, 151.5; IR (ATR) 3292, 3126, 1654, 1612, 1567, 1546, 1539, 1471, 1449, 1440, 1390, 1341, 1329, 1278, 1214, 1171, 1150, 1126, 1065, 1039, 1008, 968, 930, 879, 854, 803, 754, 739, 691, 680, 609, 565, 536, 509, 440, 418 cm^{-1}; HRMS (ESI): [M+H$^+$] calcd for $C_{10}H_9N_4$, 185.0827; found, 185.0820.

*4.5.16. [1,2,4]Triazolo[5,1-a]isoquinolin-2-amine (**3k**)*

Compound **5k** (745 mg, 4.00 mmol) in MeOH (75 mL) was treated with NCS (588 mg, 4.40 mmol) and K_2CO_3 (1.16 g, 8.40 mmol) in H_2O (15 mL), and work-up was conducted according to the general procedure. The residue obtained after evaporation of the organic layer was purified by column chromatography (NH silica gel, EtOAc/hexane 1:2 to EtOAc/MeOH 98:2) to give crude **3k** (361 mg) and crude **7k** (141 mg). Crude **3k** (300 mg) was purified by column chromatography (NH silica gel, EtOAc/hexane 1:2), and the obtained solids were triturated with EtOAc/hexane (2:1, 9 mL) and filtered to give **3k** (212 mg, 35%) as an orange solid. mp 193–195 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.03 (s, 2H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.70 (td, *J* = 7.5, 1.3 Hz, 2H), 7.95 (d, *J* = 7.5 Hz, 1H), 8.29 (d, *J* = 7.7 Hz, 1H), 8.37 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 110.7, 120.1, 123.1, 124.6, 127.3, 127.7, 129.2, 131.0, 148.1, 165.3; IR (ATR) 3320, 3175, 1638, 1556, 1537, 1523, 1486, 1434, 1400, 1370, 1330, 1298, 1258, 1137, 1095, 1058, 904, 823, 778, 747, 704, 682, 659, 613, 570, 548, 509, 416 cm^{-1}; HRMS (ESI): [M+H$^+$] calcd for $C_{10}H_9N_4$, 185.0827; found, 185.0820.

*4.5.17. [1,2,4]Triazolo[3,4-a]isoquinolin-3-amine (**7k**)*

Crude **7k** (141 mg) was purified by column chromatography (NH silica gel, EtOAc/hexane 1:1 to EtOAc), and the obtained solids were triturated with EtOAc/hexane (1:1, 2 mL) and filtered to give **7k** (98 mg, 13%) as an orange solid. mp 263 °C (decompose); ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.47 (s, 2H), 7.07 (d, *J* = 7.2 Hz, 1H), 7.63 (dt, *J* = 7.7 Hz , 2H), 7.79 (d, *J* = 7.0 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 8.31 (d, *J* = 7.1 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 112.1, 119.8, 121.6, 122.0, 127.3, 128.5, 129.0 (2C), 143.7, 149.9; IR (ATR) 3311, 3139, 1644, 1567, 1557, 1525, 1480, 1459, 1437, 1370, 1325, 1303, 1132, 1044, 982, 926, 896, 783, 769, 750, 741, 708, 700, 679, 636, 560, 507, 484, 471, 462, 443, 432, 421, 405 cm^{-1}; HRMS (ESI): [M+H$^+$] calcd for $C_{10}H_9N_4$, 185.0827; found, 185.0821.

*4.6. Synthesis of **3a** from 5-nitropyridin-2-amine*

To a stirred solution of 5-nitropyridin-2-amine (1.00 g, 7.19 mmol) in acetone (10 mL) was added ethoxycarbonyl isothiocyanate (1.41 g, 10.8 mmol), and the mixture was stirred at 50 °C for 22 h. After cooling to room temperature, H_2O (10 mL) was slowly added to the mixture. The slurry was stirred at room temperature for 1 h and then filtered to give ethyl [(5-nitropyridin-2-yl)carbamothioyl]carbamate (1.46 g, 75%) as a brown solid. mp 178–179 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.28 (t, *J* = 7.2 Hz, 3H), 4.25 (q, *J* = 7.2 Hz, 2H), 8.69 (dd, *J* = 9.2, 3.0 Hz, 1H), 8.90 (d, *J* = 9.4 Hz, 1H), 9.22 (d, *J* = 2.6 Hz, 1H), 12.0 (br s, 1H), 12.5 (br s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 14.0, 62.5, 113.9, 134.2, 140.8, 144.6, 153.3, 155.2, 177.9; IR (ATR) 3162, 2994, 1720, 1579, 1529, 1508, 1455, 1355, 1311, 1243, 1192, 1143, 1110, 1038, 1004, 949, 870, 840, 799, 757, 734, 714, 700, 628, 596, 525, 501, 436, 412 cm^{-1}; HRMS (ESI): [M+H$^+$] calcd for $C_9H_{11}N_4O_4S$, 271.0501; found, 271.0497.

To a stirred solution of ethyl [(5-nitropyridin-2-yl)carbamothioyl]carbamate (1.00 g, 3.70 mmol) in EtOH (10 mL) were added *N*,*N*-diisopropylethylamine (1.43 g, 11.1 mmol) and hydroxylamine hydrochloride (1.29 g, 18.5 mmol), and the mixture was stirred at 50 °C for 1.5 h. After cooling to room temperature, H_2O (10 mL) was slowly added to the mixture. The slurry was stirred at room temperature for 1 h and then filtered. The wet solids were suspended in EtOAc/*n*-heptane (1:1, 10 mL), and the mixture was stirred at 50 °C for 30 min. The mixture was cooled to room temperature and stirred for 1 h, and then filtered to give **3a** (587 mg, 89%) as a yellow solid.

*4.7. Synthesis of **3c** from 3-chloropyridin-2-amine **1c***

*4.7.1. Ethyl [(3-Chloropyridin-2-yl)carbamothioyl]carbamate (**2c**)*

To a stirred solution of 3-chloropyridin-2-amine **1c** (800 mg, 6.22 mmol) in acetone (8 mL) was added ethoxycarbonyl isothiocyanate (1.22 g, 9.33 mmol), and the mixture was stirred at 50 °C for 1 h. After cooling to room temperature, H_2O (16 mL) was slowly added, and the mixture was stirred at 40 °C for 30 min. The mixture was cooled to room temperature and stirred for 1 h, and then filtered to give **2c** (1.39 g, 86%) as a white solid. mp 126–128 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.27 (t, *J* = 7.2 Hz, 3H), 4.23 (q, *J* = 7.2 Hz, 2H), 7.42 (dd, *J* = 8.1, 4.7 Hz, 1H), 8.04 (dd, *J* = 7.9, 1.5 Hz, 1H), 8.45 (dd, *J* = 4.5, 1.5 Hz, 1H), 11.4–11.5 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 14.1, 62.1, 124.4, 128.5, 138.7, 147.1, 148.5, 153.4, 180.0; IR (ATR) 3152, 2989, 1723, 1578, 1510, 1474, 1447, 1423, 1370, 1321, 1266, 1235, 1171, 1137, 1068, 1041, 1031, 870, 795, 769, 753, 736, 708, 680, 647, 598, 551, 534, 418 cm^{-1}; HRMS (ESI): [M+H$^+$] calcd for $C_9H_{11}ClN_3O_2S$, 260.0261; found, 260.0258.

*4.7.2. Synthesis of **3c** from **2c***

To a stirred solution of **2c** (1.00 g, 3.85 mmol) in EtOH (10 mL) were added *N*,*N*-diisopropylethylamine (1.49 g, 11.6 mmol) and hydroxylamine hydrochloride (1.34 g, 19.3 mmol), and the mixture was stirred at 50 °C for 2 h. After cooling to room temperature, H_2O (10 mL) was slowly added to the mixture. The slurry was stirred at room temperature for 1 h and then filtered. The wet solids were suspended in EtOAc/*n*-heptane (1:1, 10 mL), and the mixture was stirred at 50 °C for 30 min. The mixture was cooled to room temperature and stirred for 1 h, and then filtered to give **3c** (443 mg, 68%) as a white solid.

*4.8. Synthesis of **7c** from 2,3-dichloropyridine **4c***

*4.8.1. 3-Chloro-2-hydrazinylpyridine (**8**)[29]*

To a stirred solution of **4c** (5.00 g, 33.8 mmol) in EtOH (25 mL) was added hydrazine monohydrate (6.77 g, 135 mmol), and the mixture was heated to reflux for 20 h. At this point, additional hydrazine monohydrate (1.69 g, 33.8 mmol) was added, and the mixture was heated to reflux for 20 h. The mixture was cooled by ice bath and stirred for 1 h, and then filtered to give **8** (4.40 g, 91%) as a white solid. mp 164–166 °C (lit.[25] mp 163–164 °C); ^{1}H NMR (600 MHz, DMSO-d_6) δ 4.22 (br s, 2H), 6.61 (dd, *J* = 7.6, 4.9 Hz, 1H), 7.52– 7.64 (m, 2H), 8.05 (dd, *J* = 4.7, 1.3 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 113.2, 113.6, 136.2, 145.7, 155.7; IR (ATR) 3284, 3195, 1592, 1494, 1455, 1412, 1343, 1264, 1122, 1033, 991, 968, 957, 930, 787, 761, 750, 726, 634, 610, 543, 497, 438, 423, 416 cm^{-1}; HRMS (ESI): [M+H$^+$] calcd for $C_5H_7ClN_3$, 144.0328; found, 144.0323.

*4.8.2. 2-(3-Chloropyridin-2-yl)-N-(2,4,4-trimethylpentan-2-yl)hydrazinecarbothioamide (**9**)*

To a stirred solution of **8** (3.00 g, 20.9 mmol) in THF (150 mL) was added 2-isothiocyanato-2,4,4-trimethylpentane (4.30 g, 25.1 mmol), and the mixture was stirred at room temperature for 14 h. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (EtOAc/hexane 1:5) to give the crude product. The crude product was suspended in hexane (35 mL), and the mixture was stirred at 50 °C for 30 min. The mixture was cooled to room temperature and stirred for 1 h, and then filtered to give **9** (5.84 g, 89%) as a white solid. mp 105–106 °C; ^{1}H NMR (600 MHz,$CDCl_3$) δ 0.93 (s, 9H), 1.60 (s, 6H), 1.91 (s, 2H), 6.86 (m, 2H), 7.11 (br s, 1H), 7.52–7.63 (m, 2H), 8.18 (d, J = 4.5 Hz, 1H); ^{13}C NMR (150 MHz,$CDCl_3$) δ 28.9 (2C), 31.4 (3C), 31.5, 52.3, 57.6, 116.3, 118.1, 137.3, 146.5, 152.5, 181.9; IR (ATR) 3360, 3332, 3208, 2954, 1586, 1567, 1533, 1503, 1472, 1454, 1402, 1387, 1365, 1323, 1266, 1225, 1156, 1127, 1101, 1065, 1034, 1005, 979, 791, 754, 735, 668, 596, 553, 441, 412, 401 cm^{-1}; HRMS (ESI): [M+H$^+$] calcd for $C_{14}H_{24}ClN_4S$, 315.1410; found, 315.1405.

*4.8.3. 8-Chloro-N-(2,4,4-trimethylpentan-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**10**)*

To a stirred solution of **9** (3.80 g, 12.1 mmol) in THF (114 mL) were added triethylamine (4.01 g, 29.0 mmol) and 2-chloro-1-methylpyridinium iodide (4.01 g, 15.7 mmol), and the mixture was stirred at room temperature for 5 h. To the mixture were added EtOAc (228 mL) and H_2O (38 mL), and the layers were separated. The organic layer was washed with 5% aqueous $NaHCO_3$ (2 × 38 mL) and H_2O (2 × 38 mL). To the organic layer was added activated carbon (380 mg), and the mixture was stirred at room temperature for 30 min. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography twice (EtOAc/hexane 1:10 to 1:1, then EtOAc/hexane 1:3) to give the crude product. The crude product was suspended in EtOAc/*n*-hexane (1:5, 114 mL), and the mixture was stirred at 50 °C for 30 min. The mixture was cooled to room temperature and stirred for 1 h, and then filtered to give **10** (1.72 g, 51%) as a pale brown solid. mp 182–183 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.92 (s, 9H), 1.51 (s, 6H), 1.93 (s, 2H), 6.22 (s, 1H), 6.73 (t, J = 7.0 Hz, 1H), 7.29 (d, J = 6.8 Hz, 1H), 8.26 (d, J = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 29.4 (3C), 31.1 (2C), 31.4, 49.9, 55.3, 110.9, 120.0, 121.8, 124.3, 142.9, 148.3; IR (ATR) 3360, 3332, 3209, 2953, 1586, 1567, 1533, 1503, 1471, 1454, 1402, 1387, 1365, 1323, 1266, 1225, 1156, 1127, 1101, 1065, 1033, 1005, 979, 791, 754, 735, 667, 593, 553, 442, 413 cm^{-1}; HRMS (ESI): [M+H$^+$] calcd for $C_{14}H_{22}ClN_4$, 281.1533; found, 281.1530.

*4.8.4. Synthesis of **7c** from **10***

To a stirred solution of **10** (500 mg, 1.78 mmol) in MeOH (2.5 mL) was added 6M HCl (2.5 mL), and the mixture was stirred at 50 °C for 5 h. At this point, MeOH (2.5 mL) and 6M HCl (2.5 mL) were added, and the mixture was stirred at 50 °C for 2 h. Then additional MeOH (2.5 mL) and 6M HCl (2.5 mL) were added, and the mixture was stirred at 50 °C for 1.5 h. The mixture was concentrated *in vacuo*. To the residue were added EtOAc (100 mL) and 5% aqueous $NaHCO_3$ (50 mL), and the layers were separated. The aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic layer was washed with 5% aqueous $NaHCO_3$ (2 × 20 mL) and 10% aqueous NaCl (20 mL) and concentrated *in vacuo*. The resulting residue was suspended in EtOAc/*n*-hexane (1:1, 10 mL), and the mixture was stirred at 50 °C for 30 min. The mixture was cooled to room temperature and stirred for 1 h, and then filtered to give **7c** (97.0 mg, 32%) as a white solid.

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Supplementary data

Copies of ^{1}H NMR and ^{13}C NMR data for all products in this article, HMBC spectrum of **6a**, HMBC and NOESY spectra of **3a**, **3b**, **3c**, **7c**, **7d**, **3e**, **7e**, **3f**, **7f**, **3g**, **7g**, **3i**, **7i**, **3j**, **7j**, **3k** and **7k**. Supplementary data associated with this article can be found in the online version, at

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Supporting Information

Oxidative Cyclization of 1-(Pyridin-2-yl)guanidine Derivatives: A Synthesis of [1,2,4]Triazolo[1,5-*a*]pyridin-2-amines and An Unexpected Synthesis of [1,2,4]Triazolo[4,3-*a*]pyridin-3-amines

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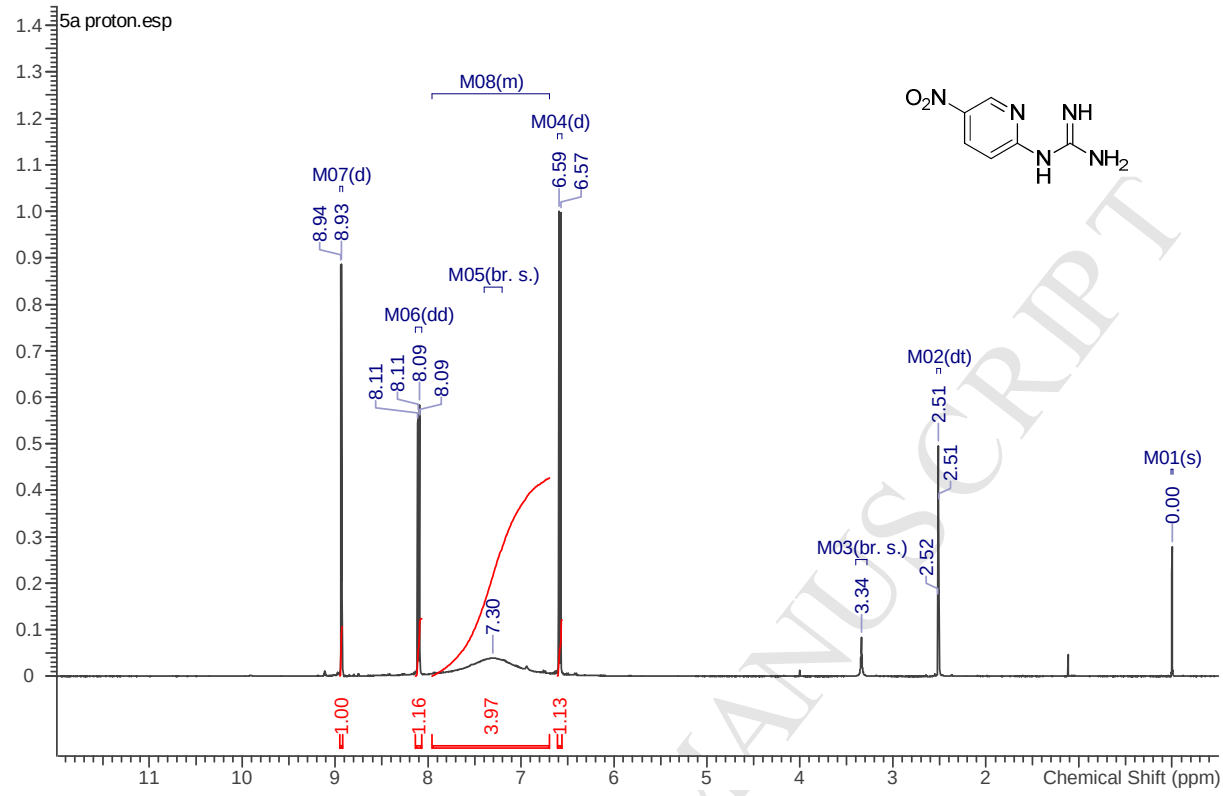
Table of Contents

1-(5-nitropyridin-2-yl)guanidine (**5a**)

^{1}H NMR spectrum



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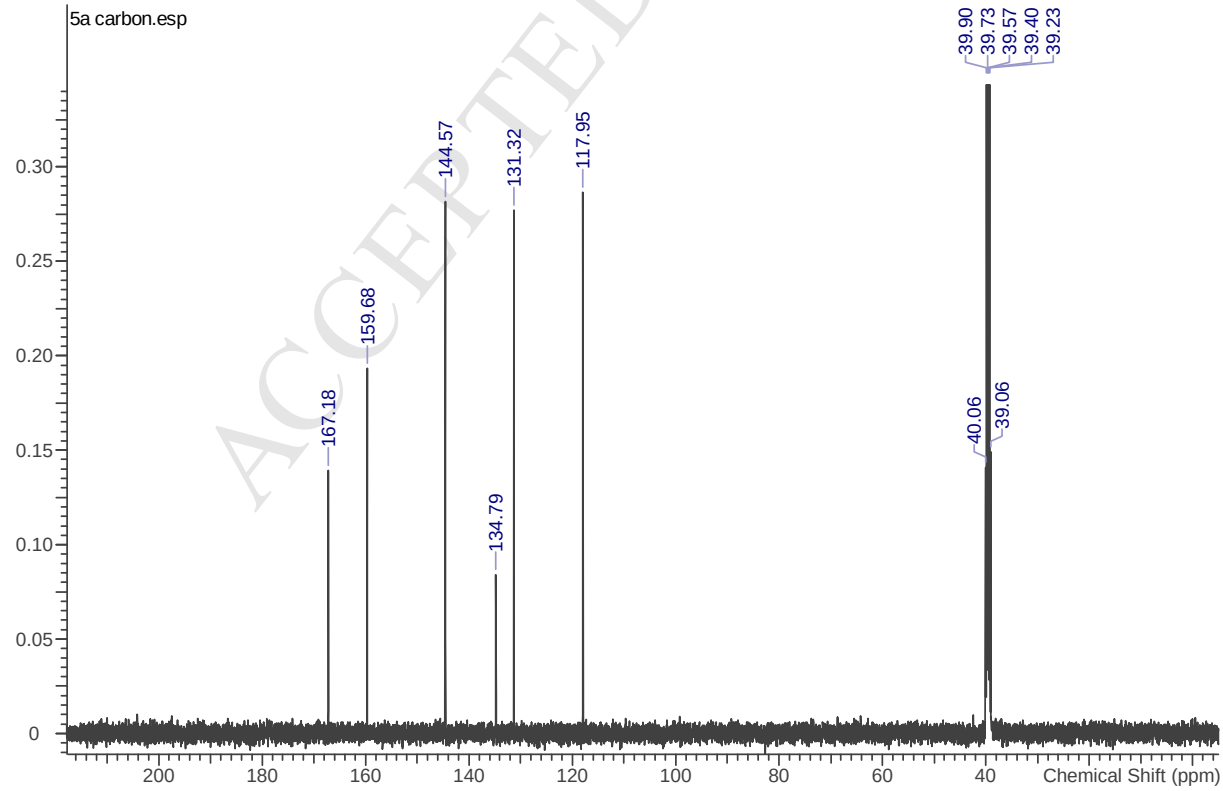

1-(3-nitropyridin-2-yl)guanidine (**5b**)

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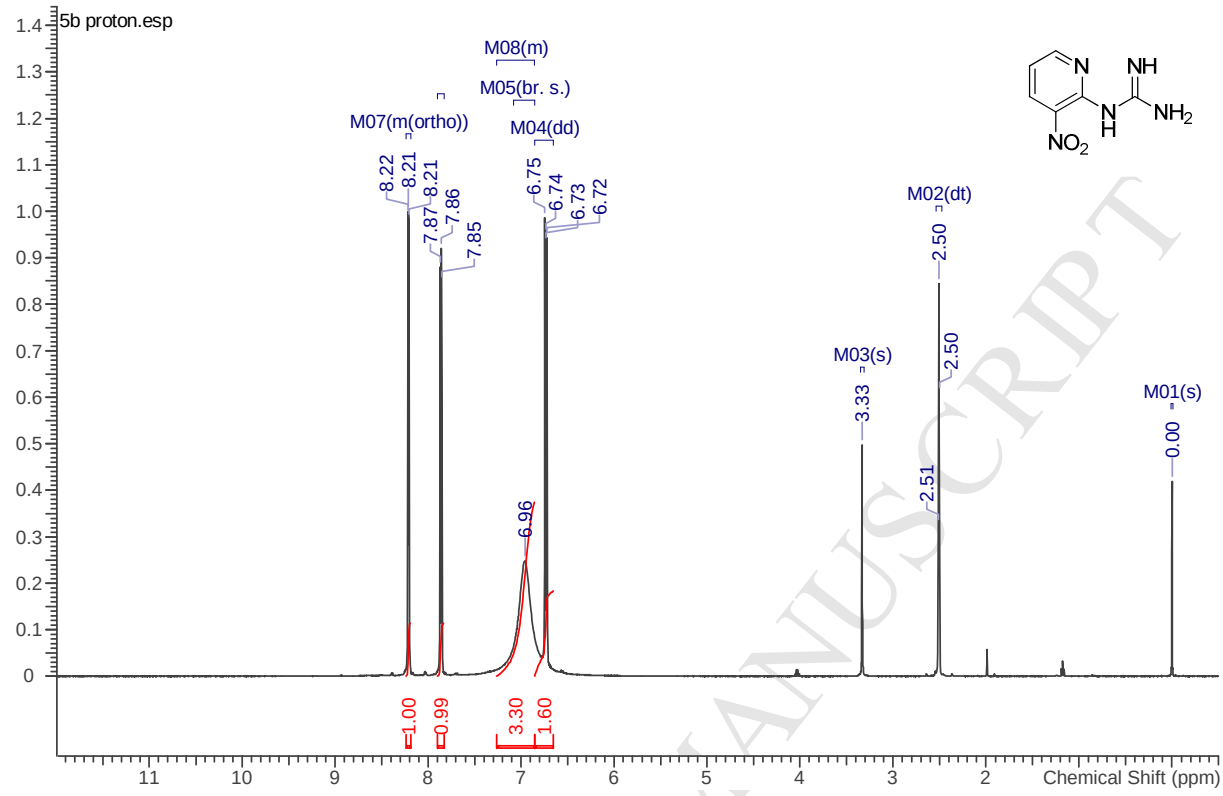

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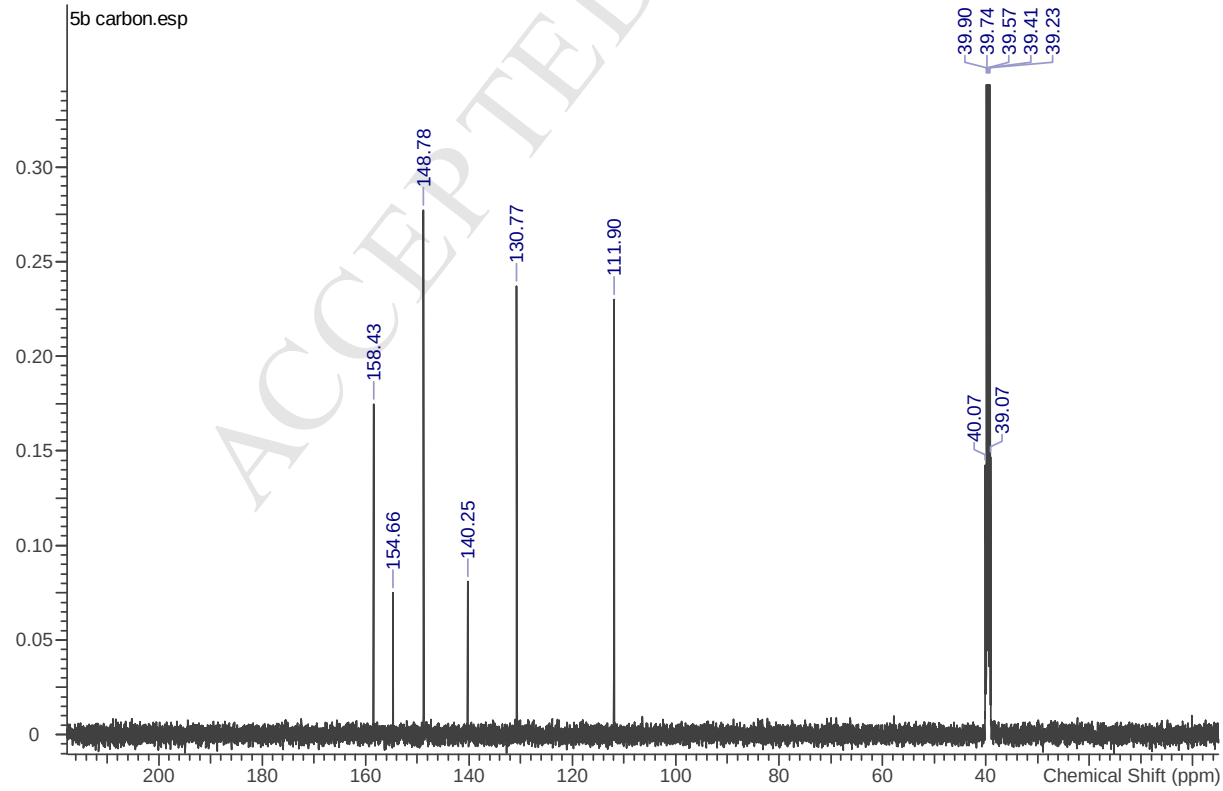

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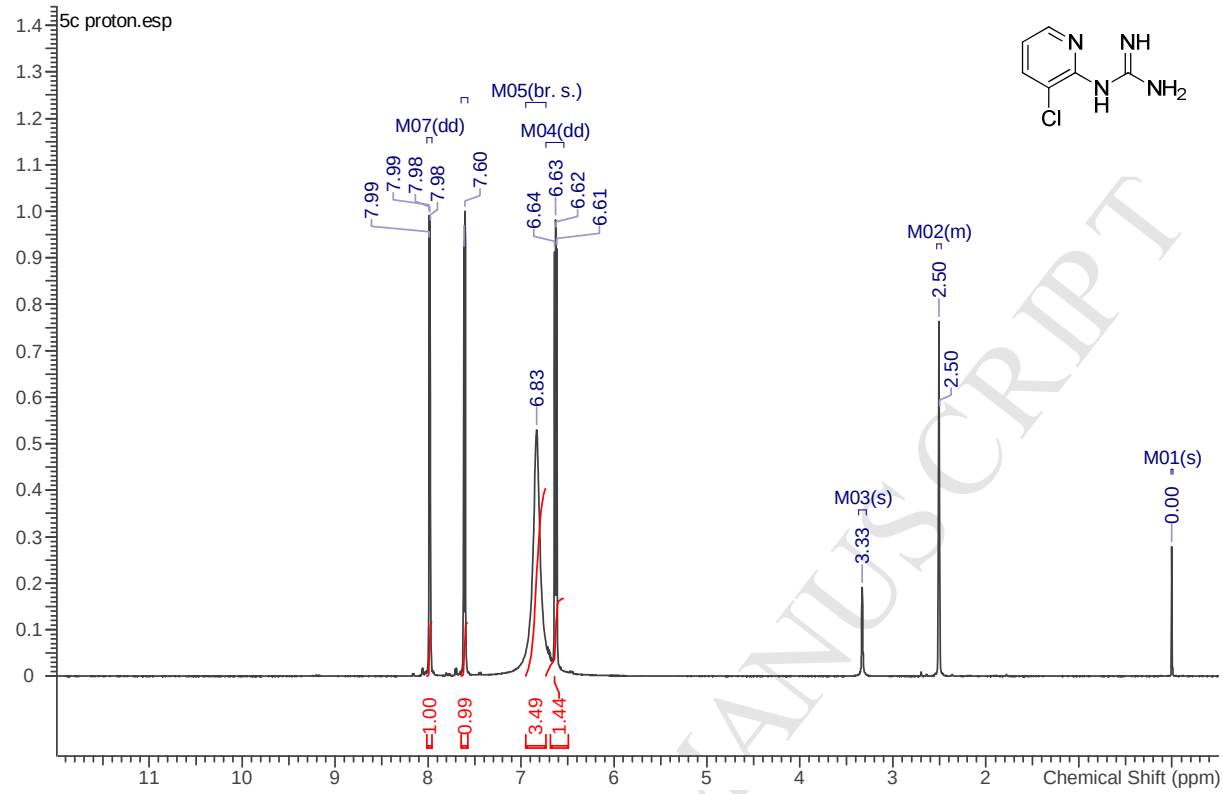

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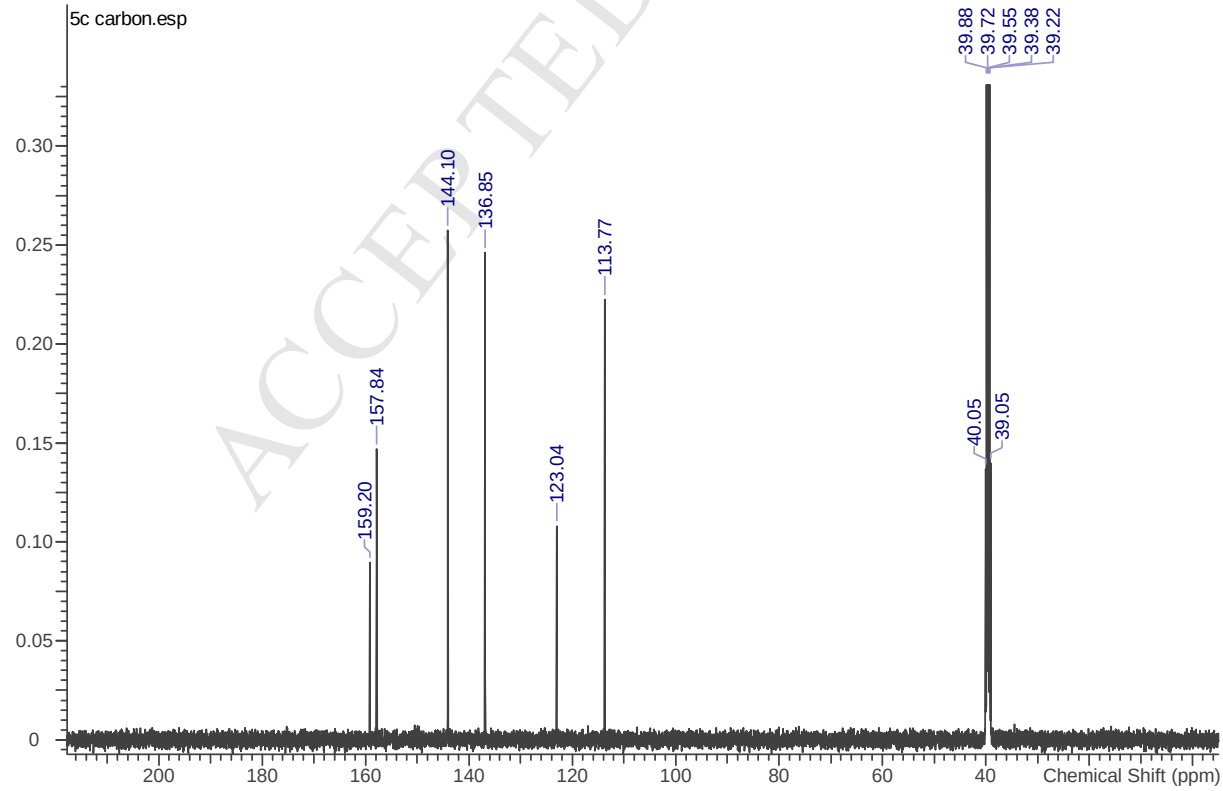

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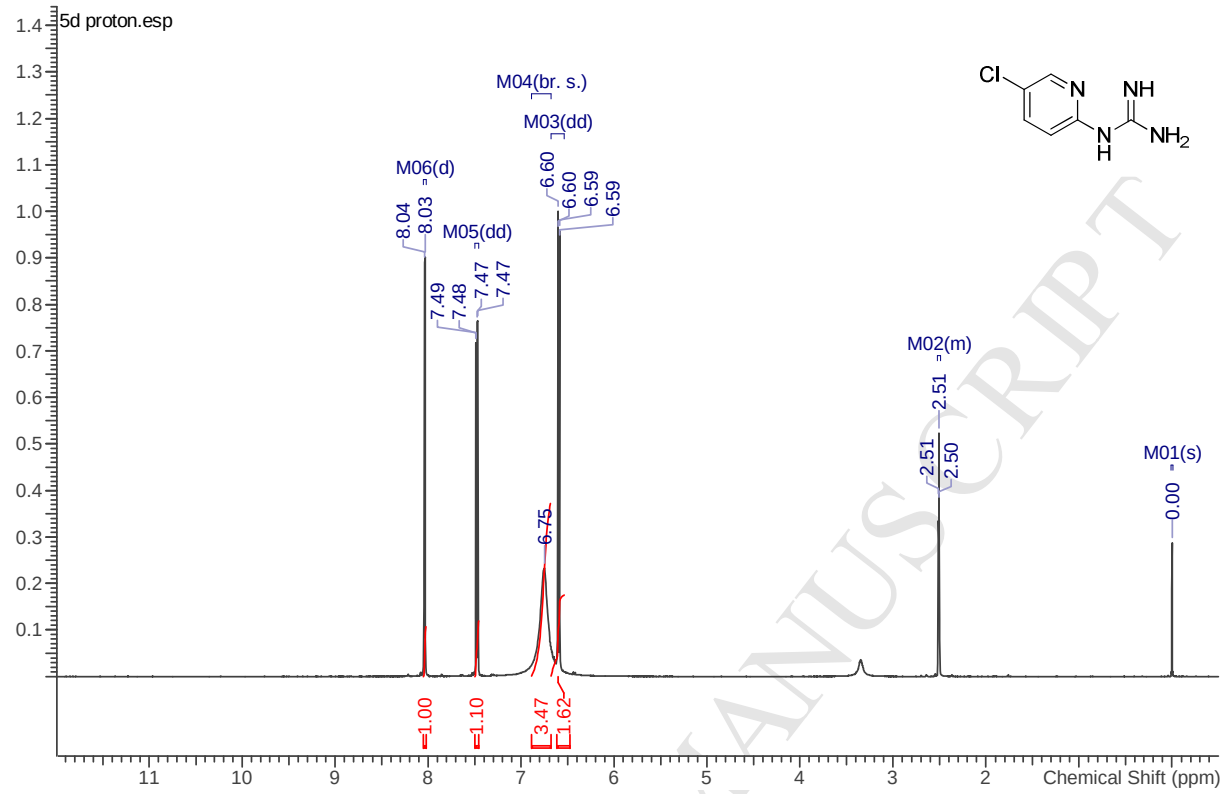

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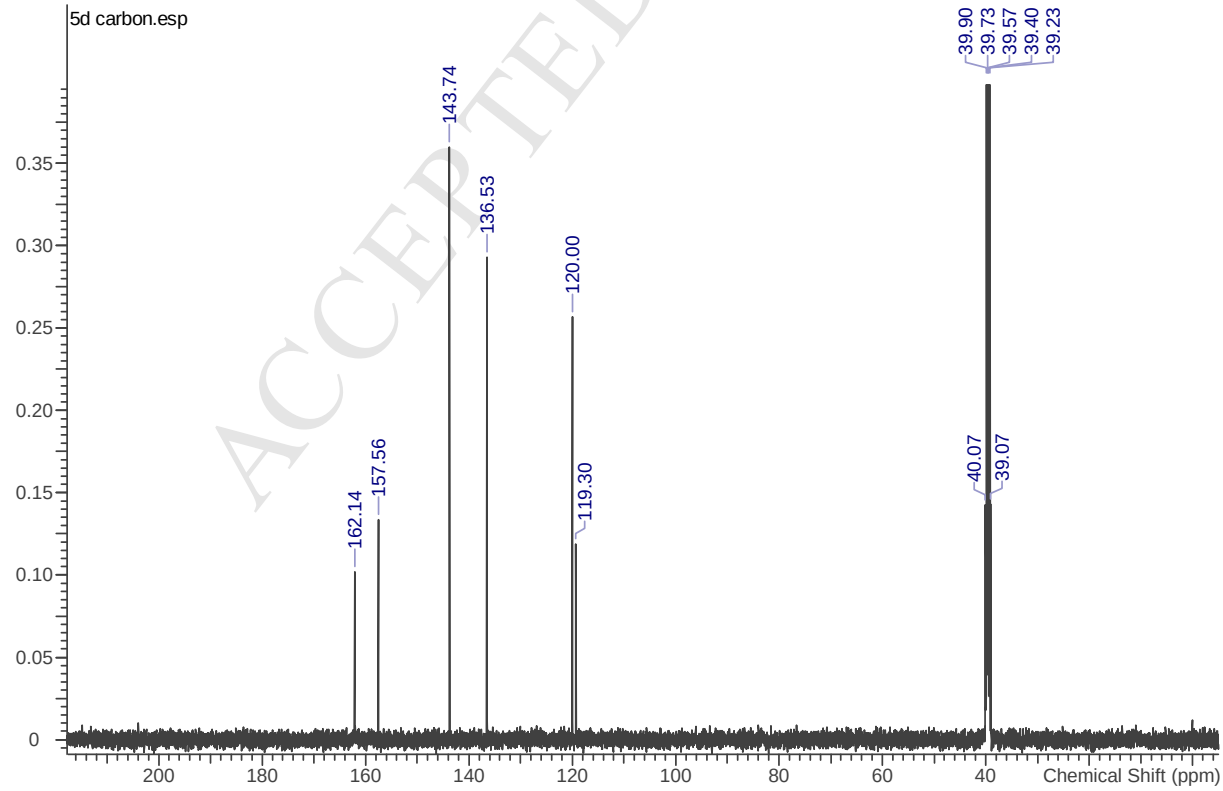

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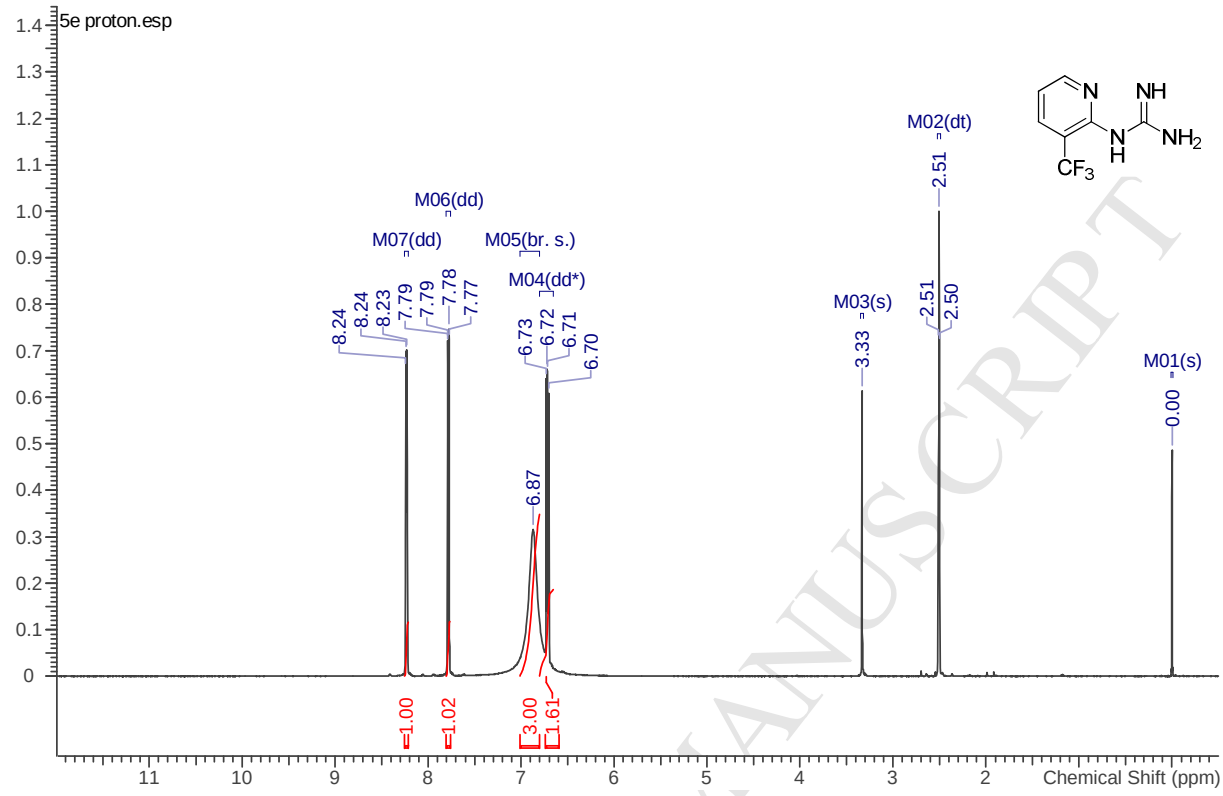

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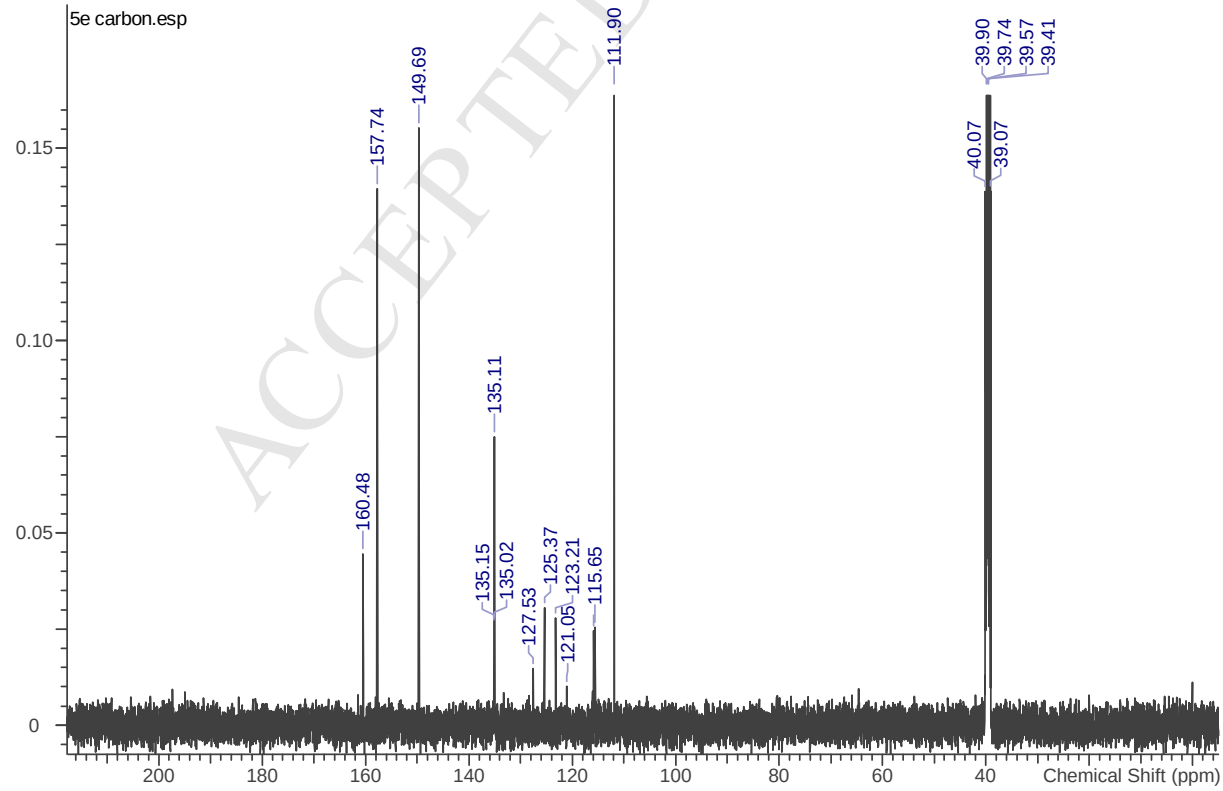

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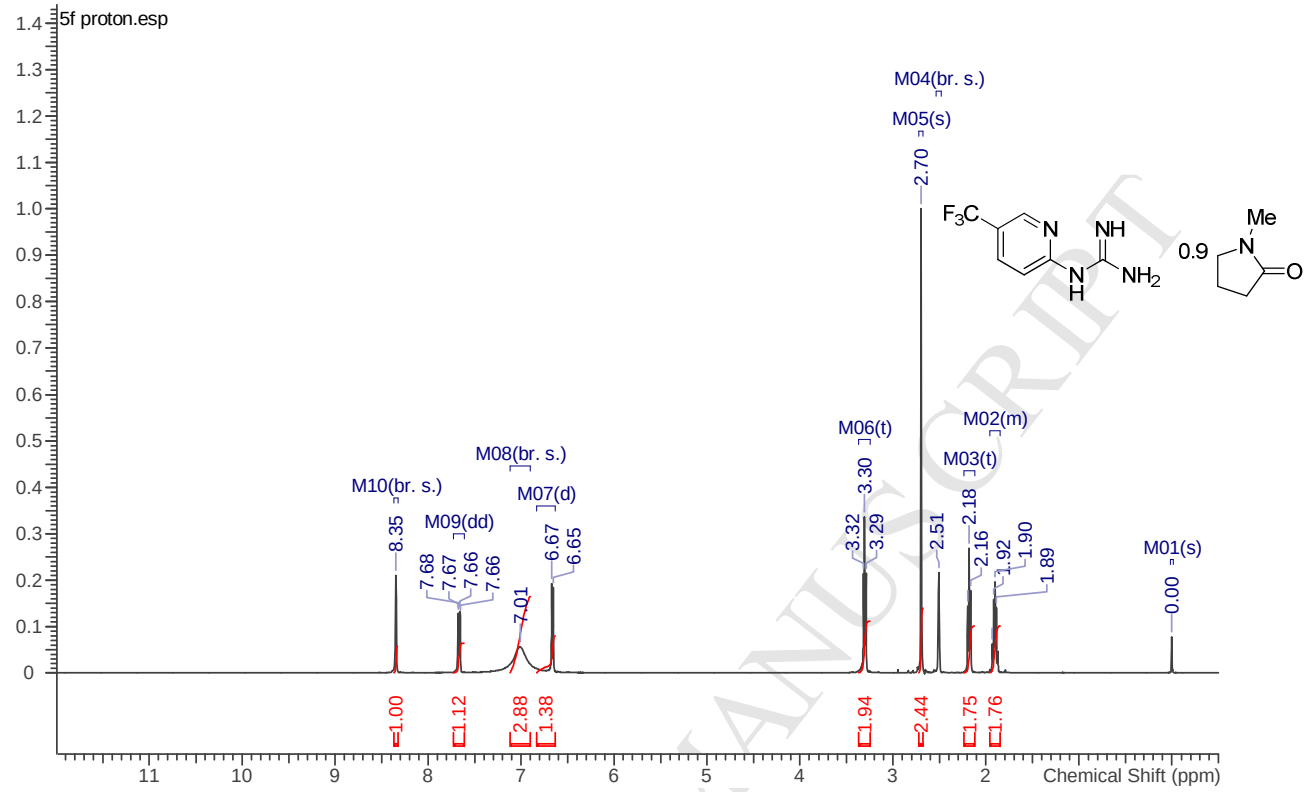

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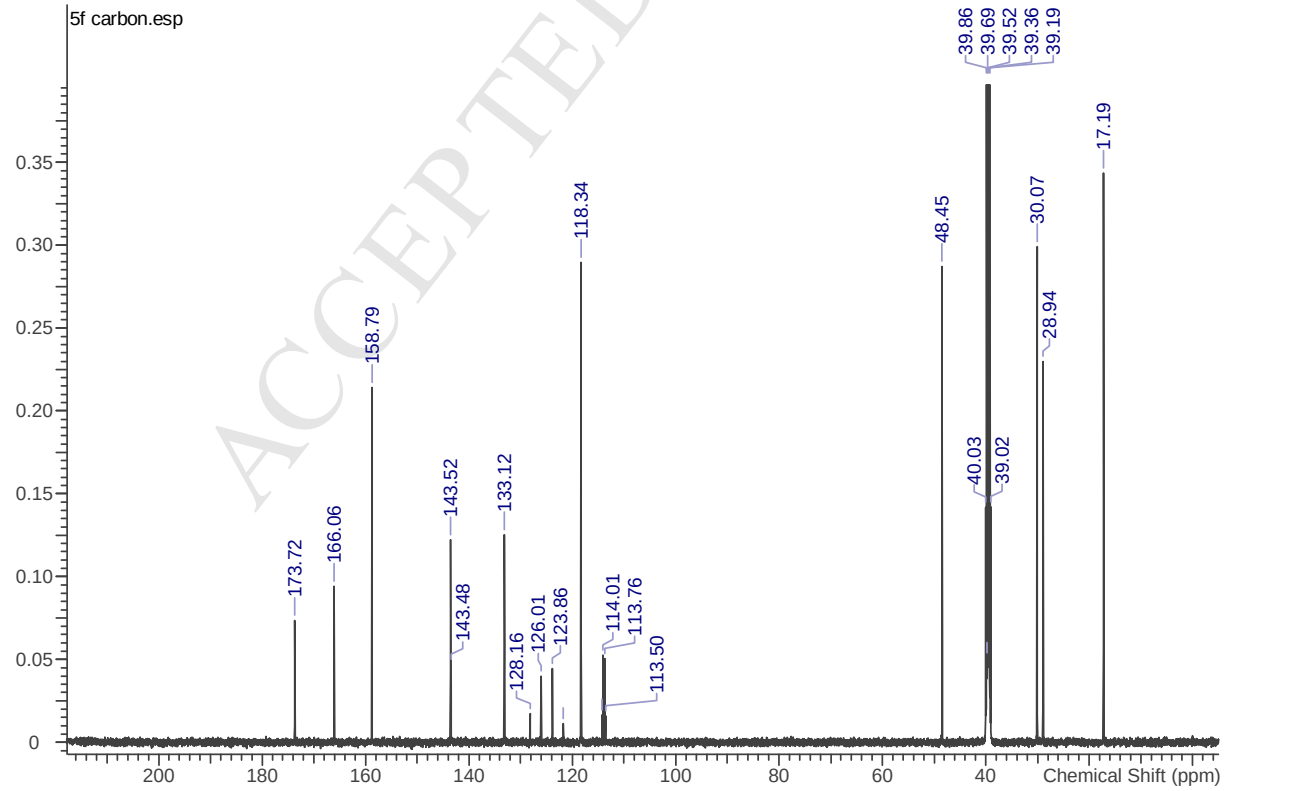
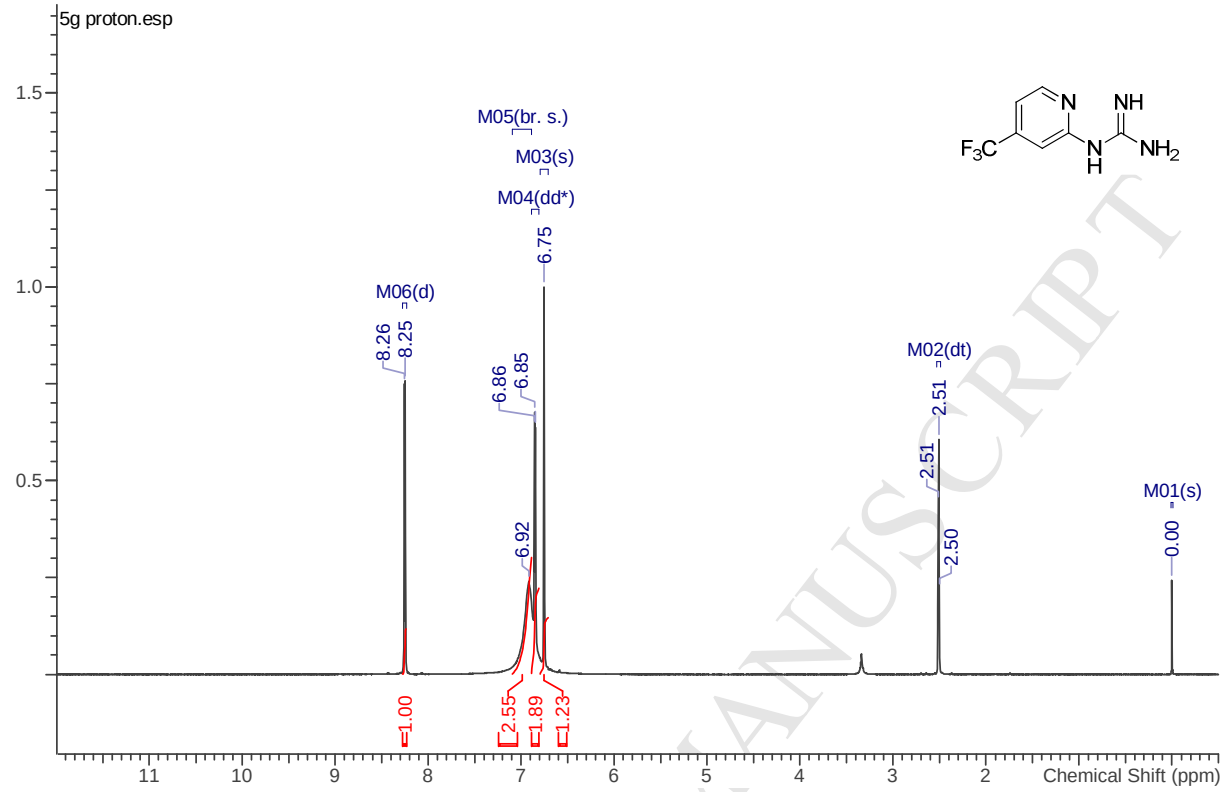
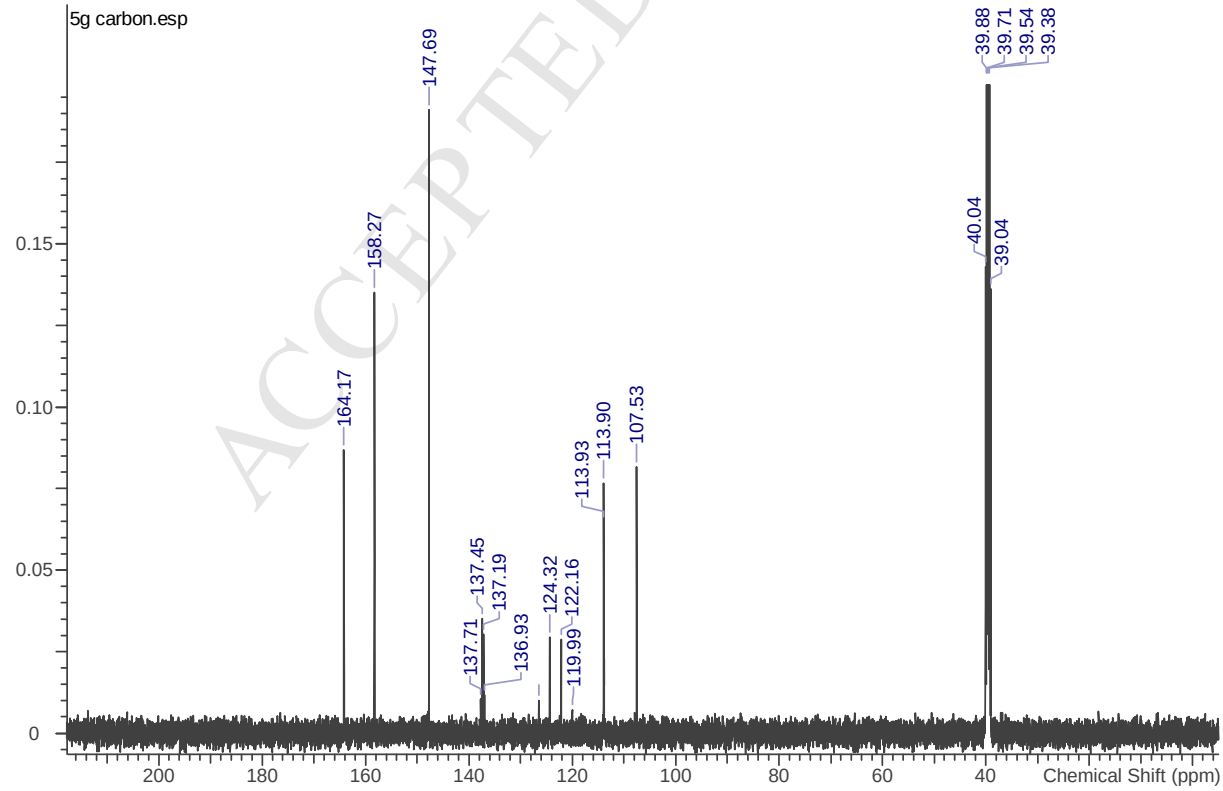


1-(4-(trifluoromethyl)pyridin-2-yl)guanidine (**5g**)

^{1}H NMR spectrum

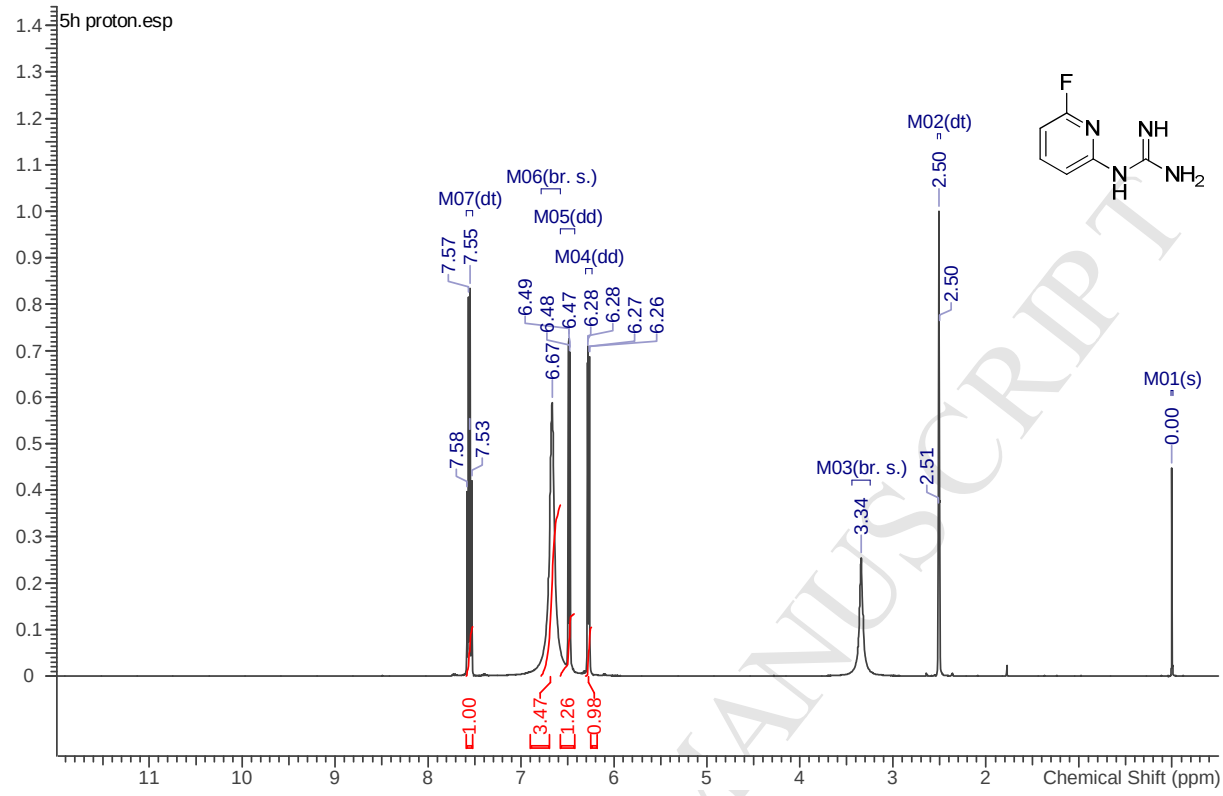


^{13}C NMR spectrum

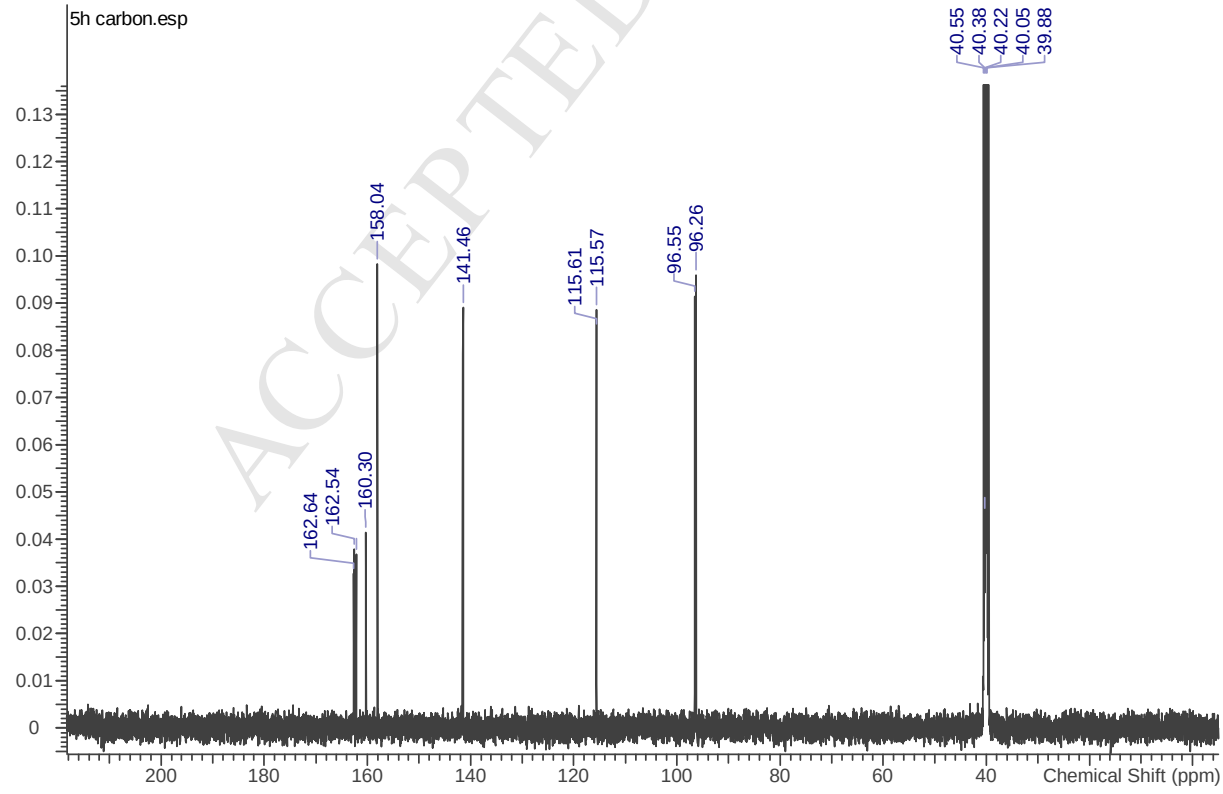


1-(6-fluoropyridin-2-yl)guanidine (**5h**)

^{1}H NMR spectrum

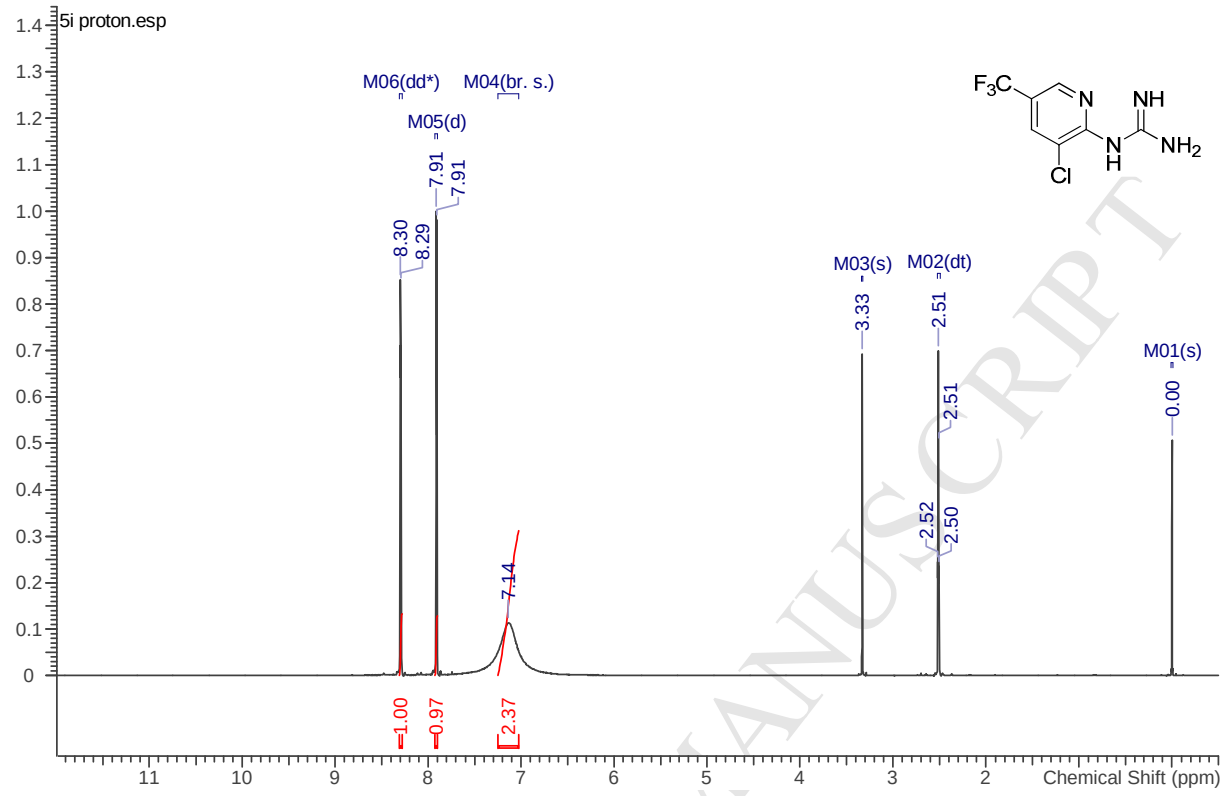


^{13}C NMR spectrum

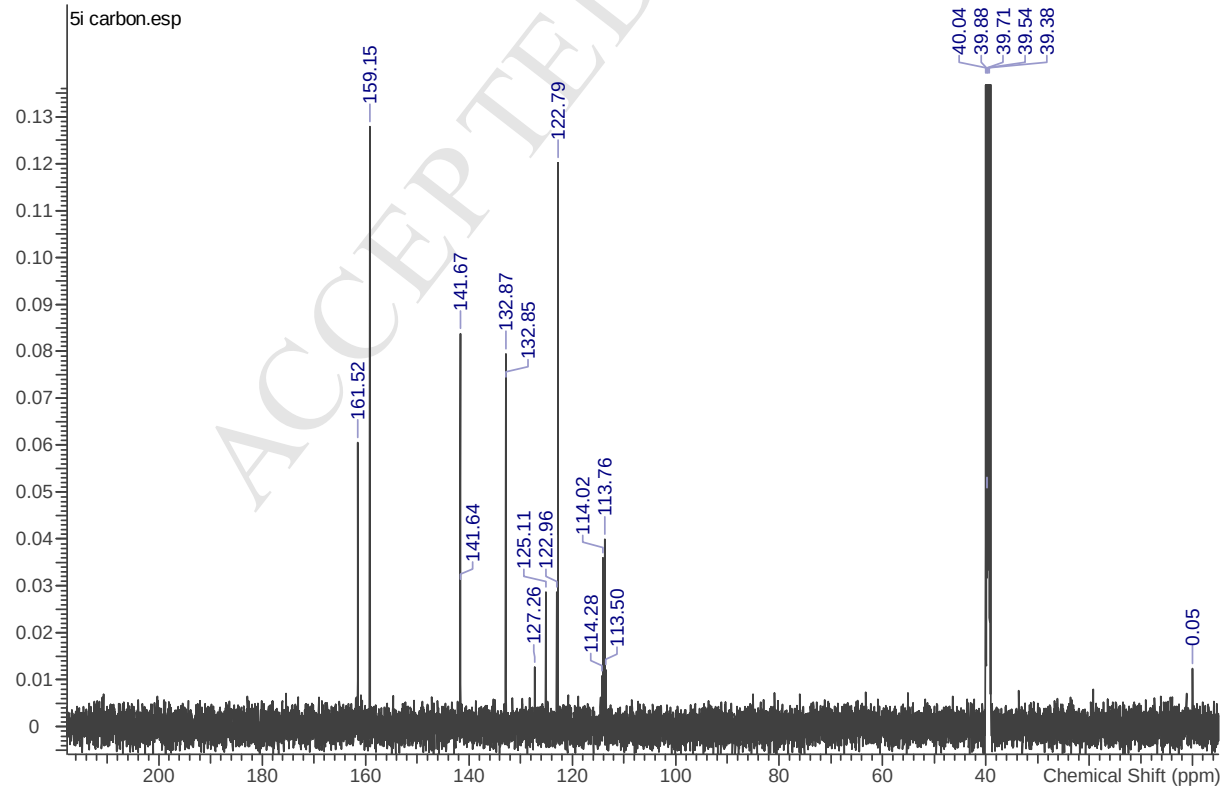


1-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)guanidine (**5i**)

^{1}H NMR spectrum

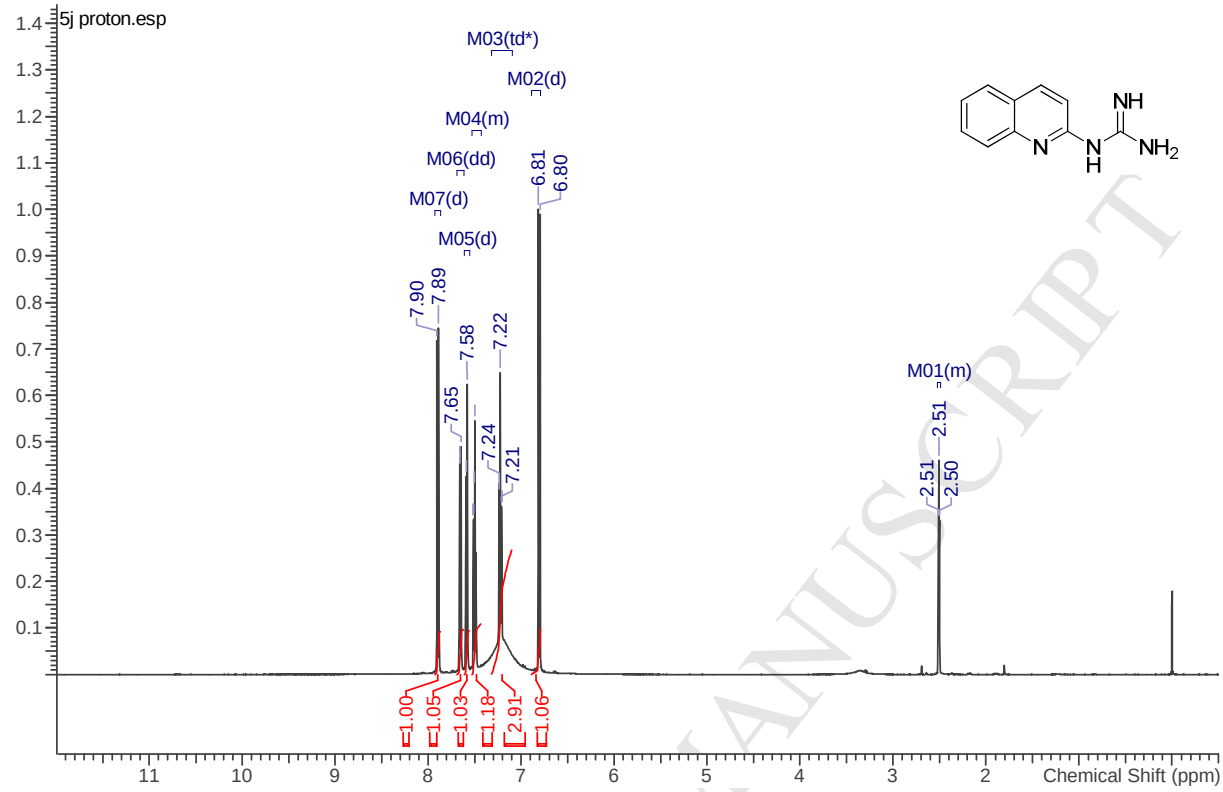


^{13}C NMR spectrum

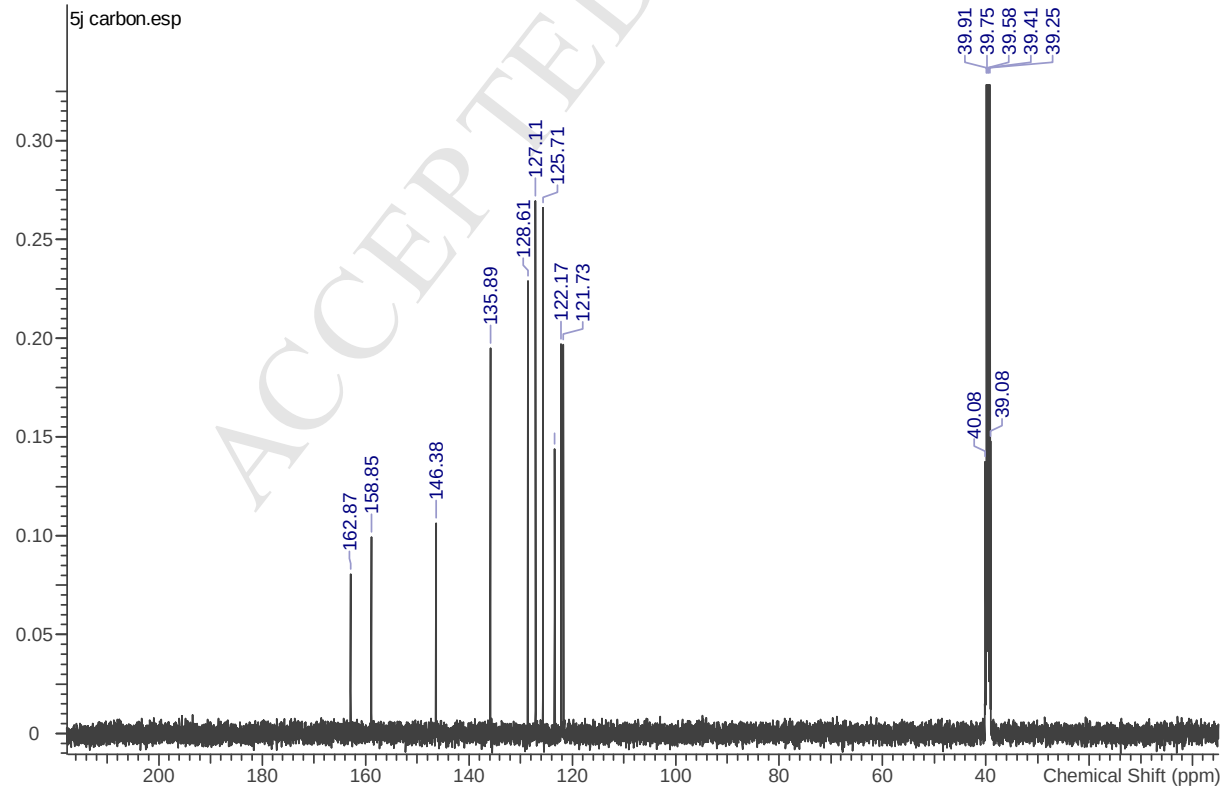


1-(quinolin-2-yl)guanidine (**5j**)

^{1}H NMR spectrum

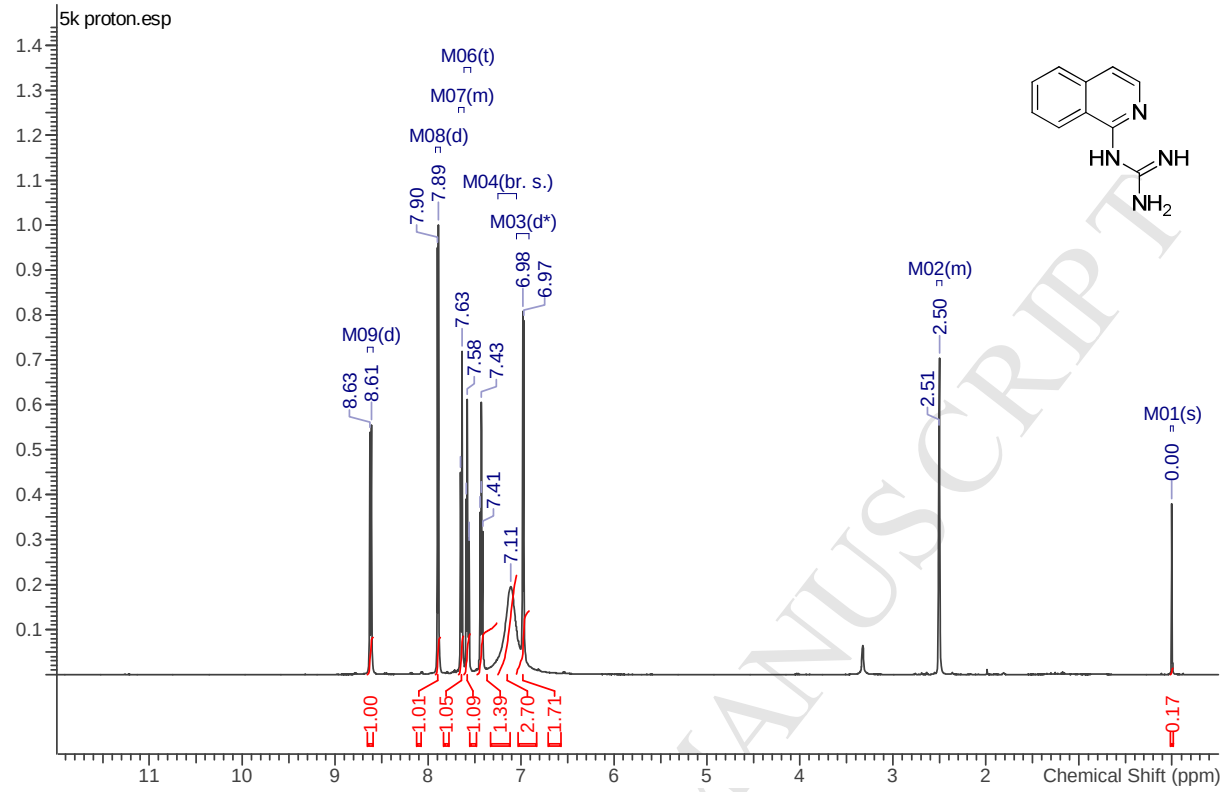


^{13}C NMR spectrum

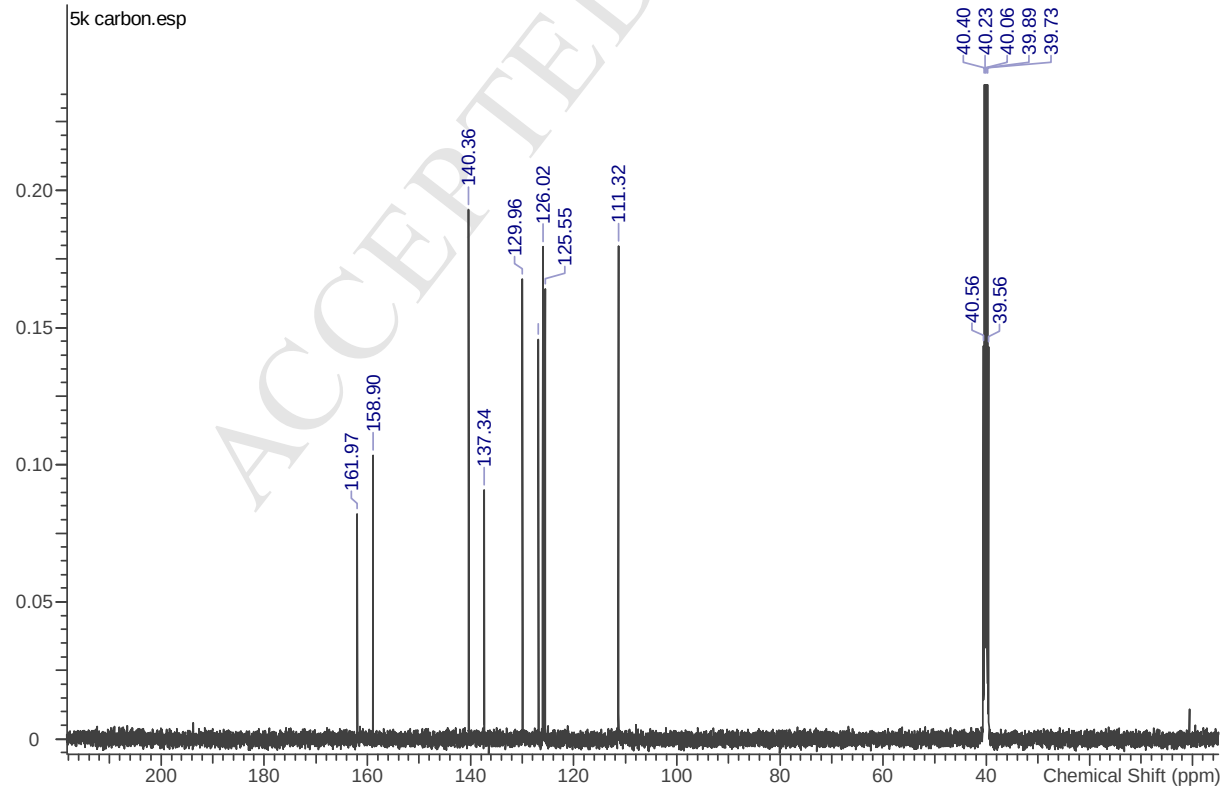


1-(isoquinolin-1-yl)guanidine (**5k**)

[1]H NMR spectrum

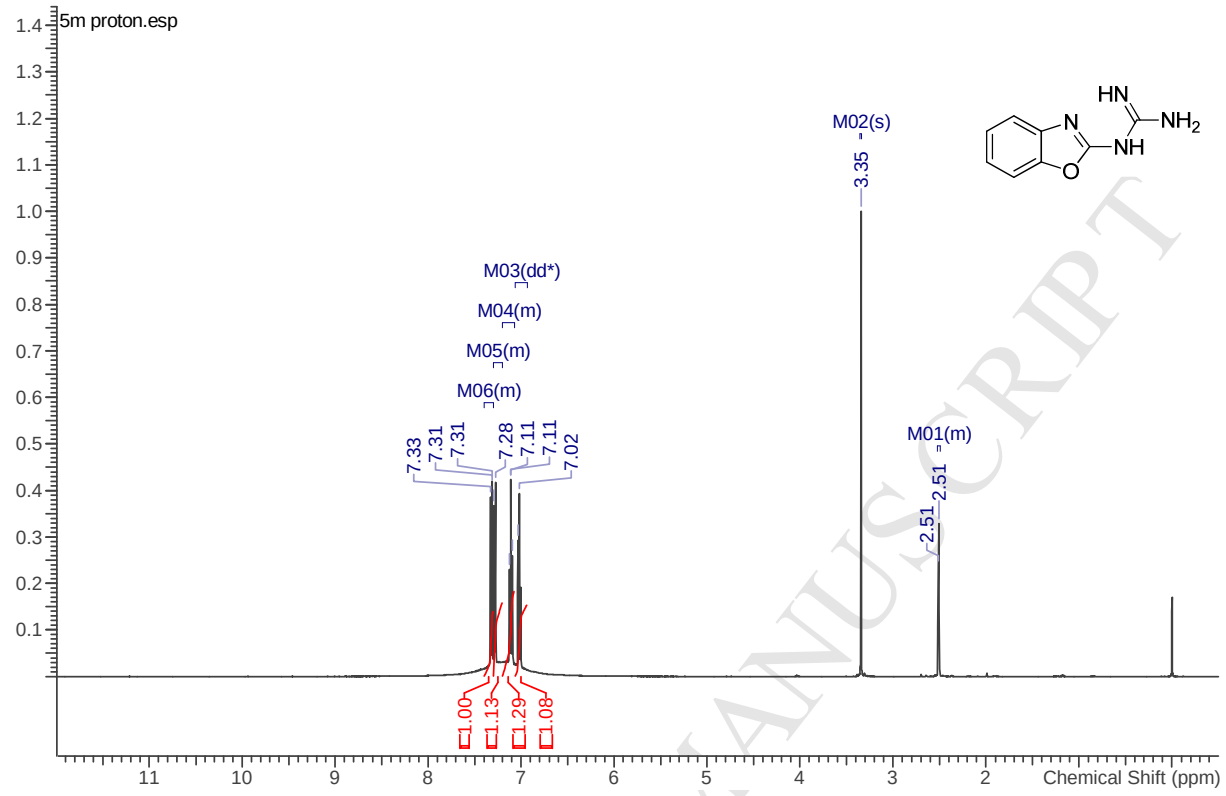


[13]C NMR spectrum

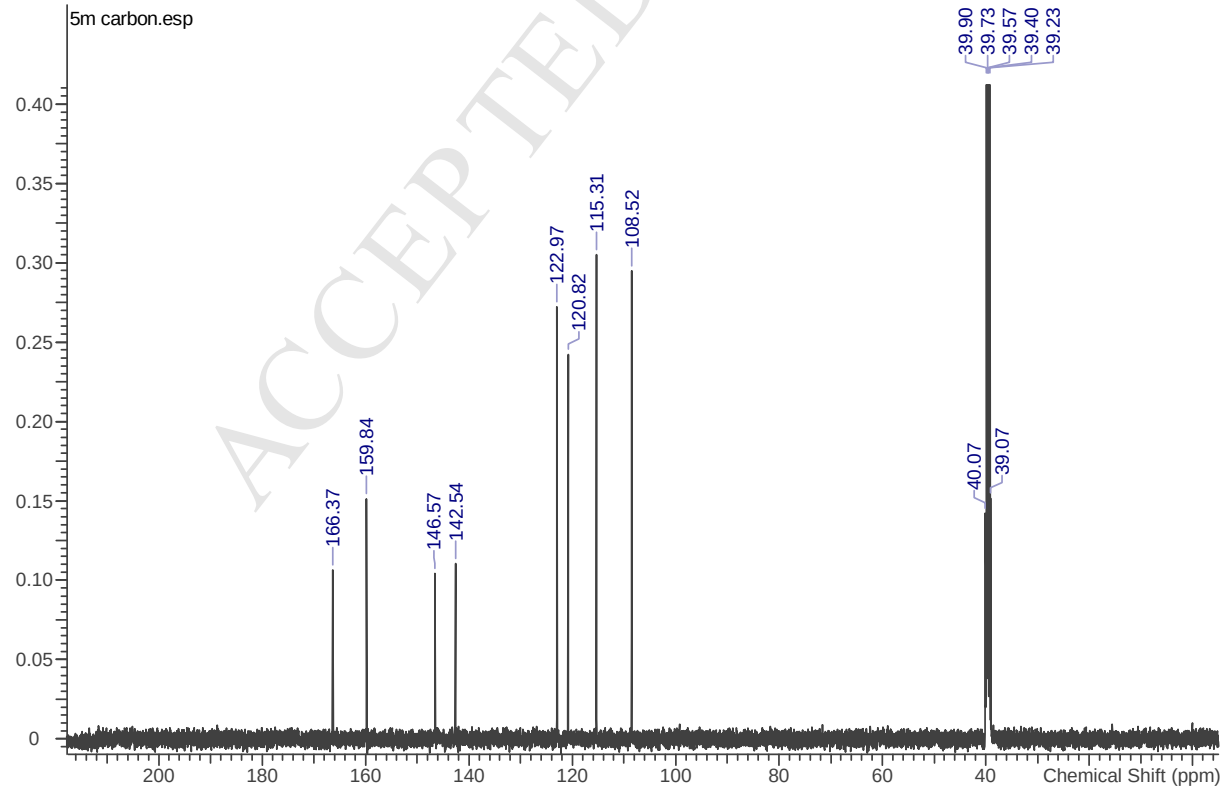


1-(benzo[d]oxazol-2-yl)guanidine (**5m**)

^{1}H NMR spectrum

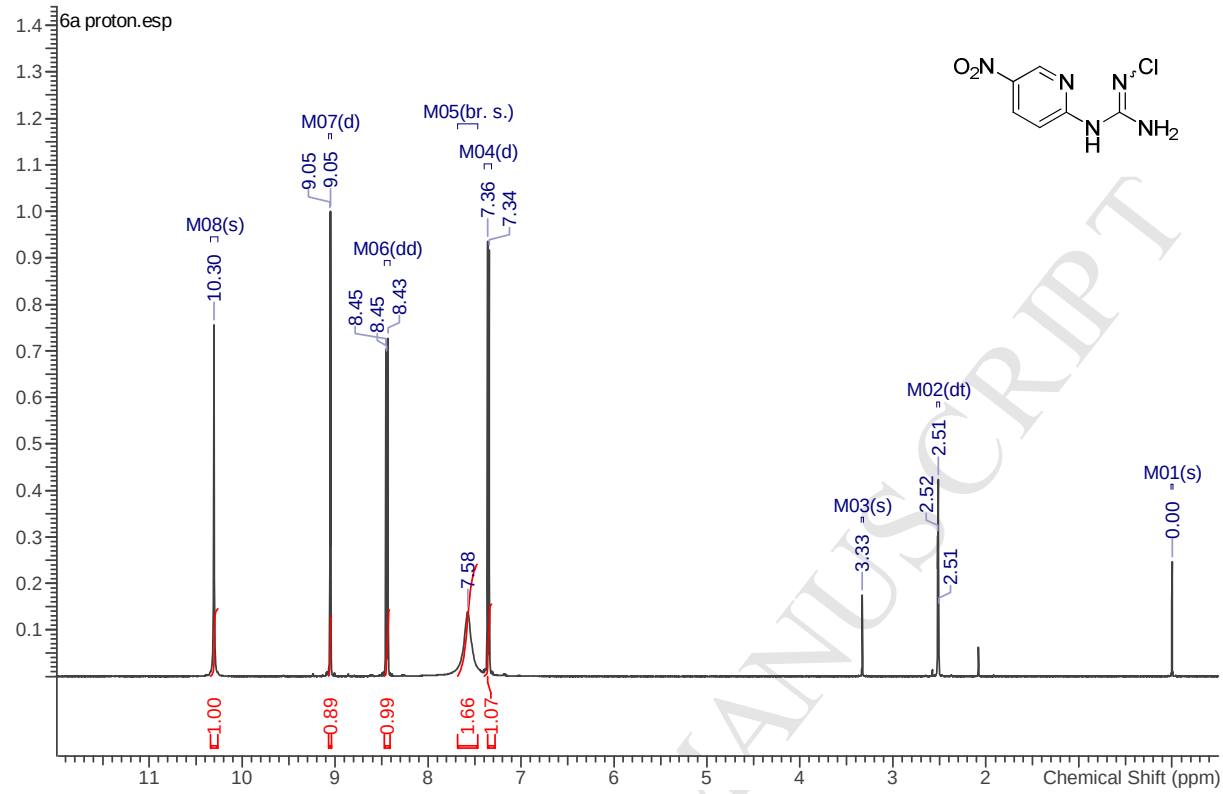


^{13}C NMR spectrum

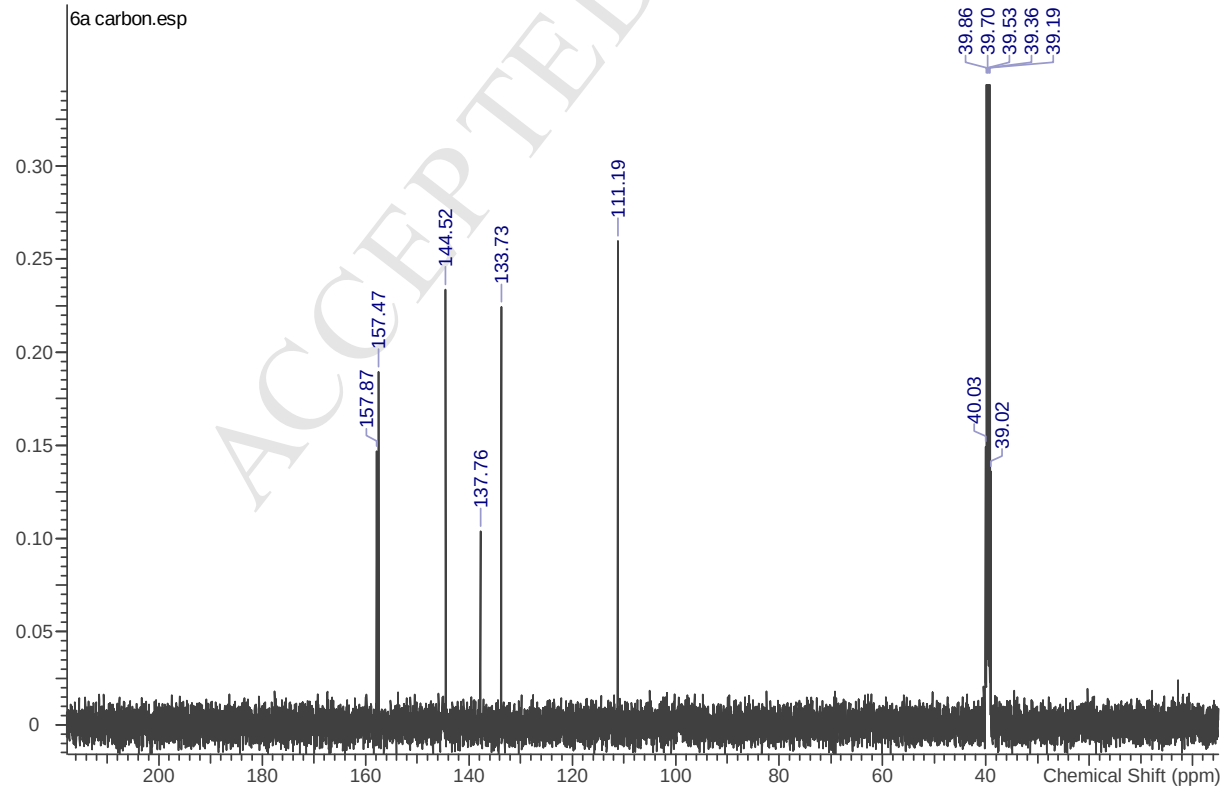


2-chloro-1-(5-nitropyridin-2-yl)guanidine (**6a**)

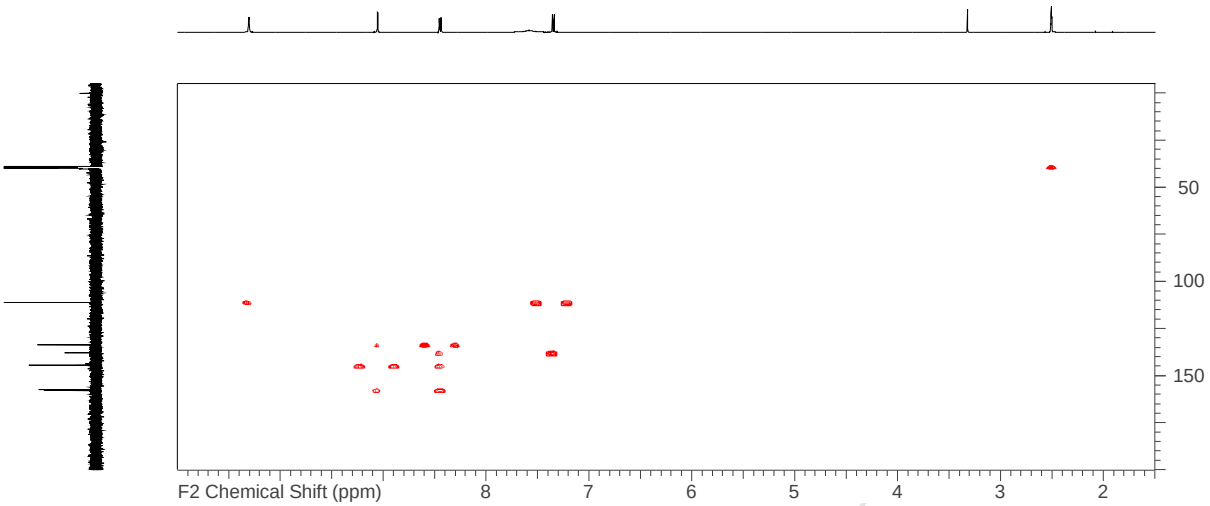
[1]H NMR spectrum



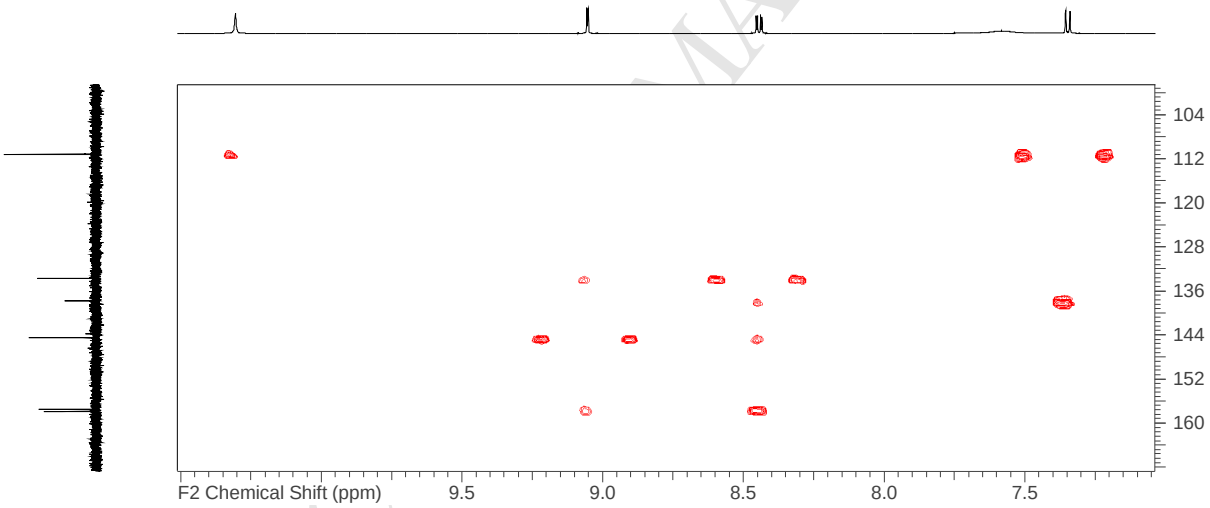
[13]C NMR spectrum



HMBC spectrum

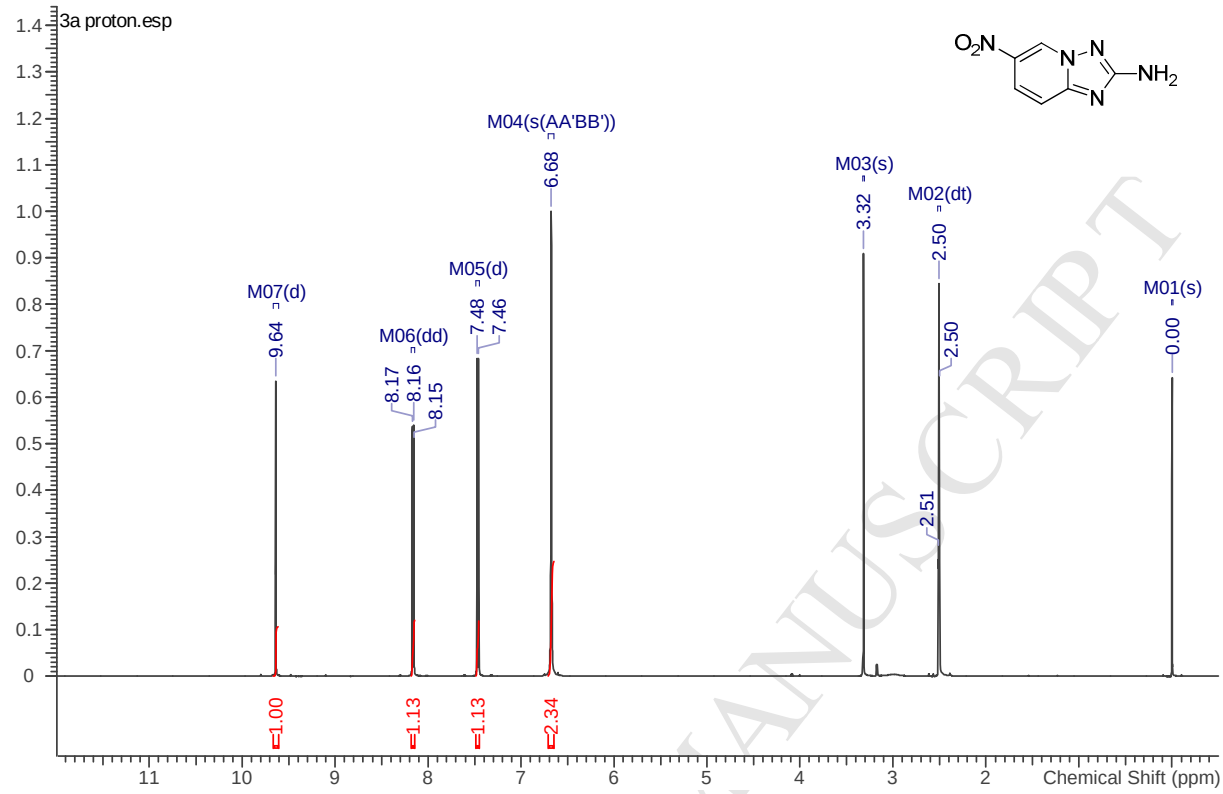


HMBC spectrum (expansion of aromatic region)

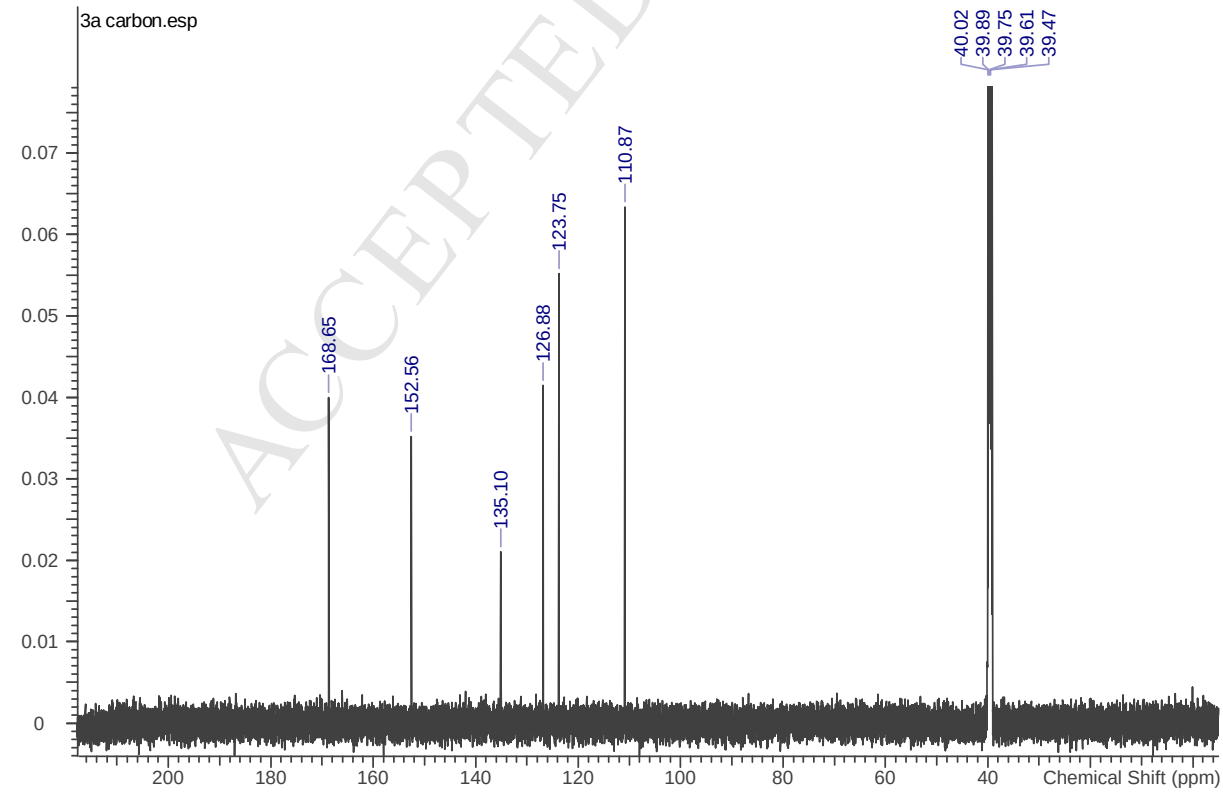


6-nitro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (**3a**)

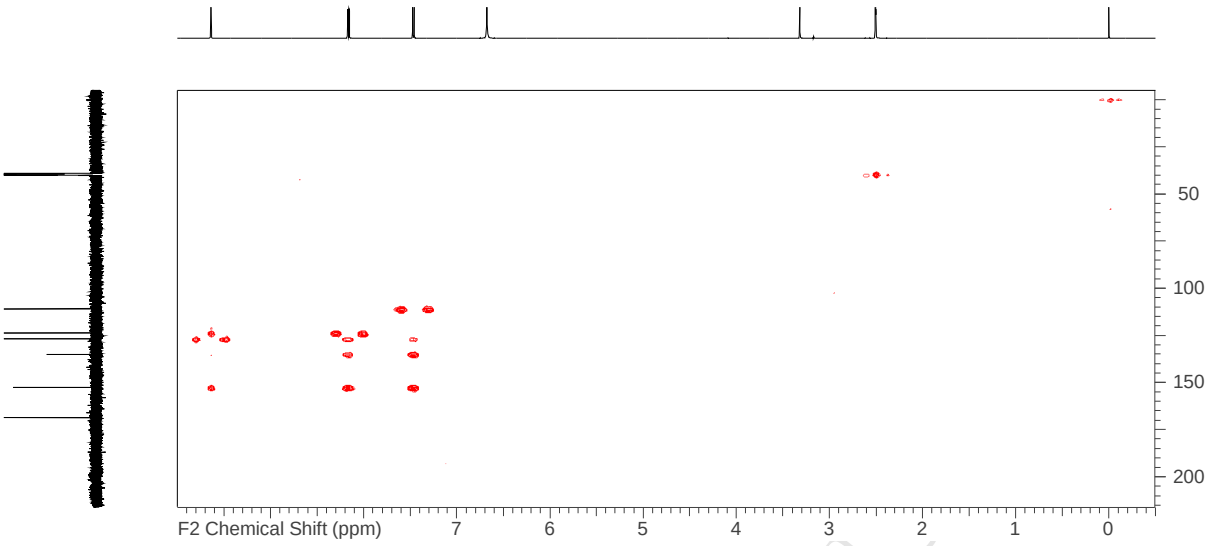
^{1}H NMR spectrum



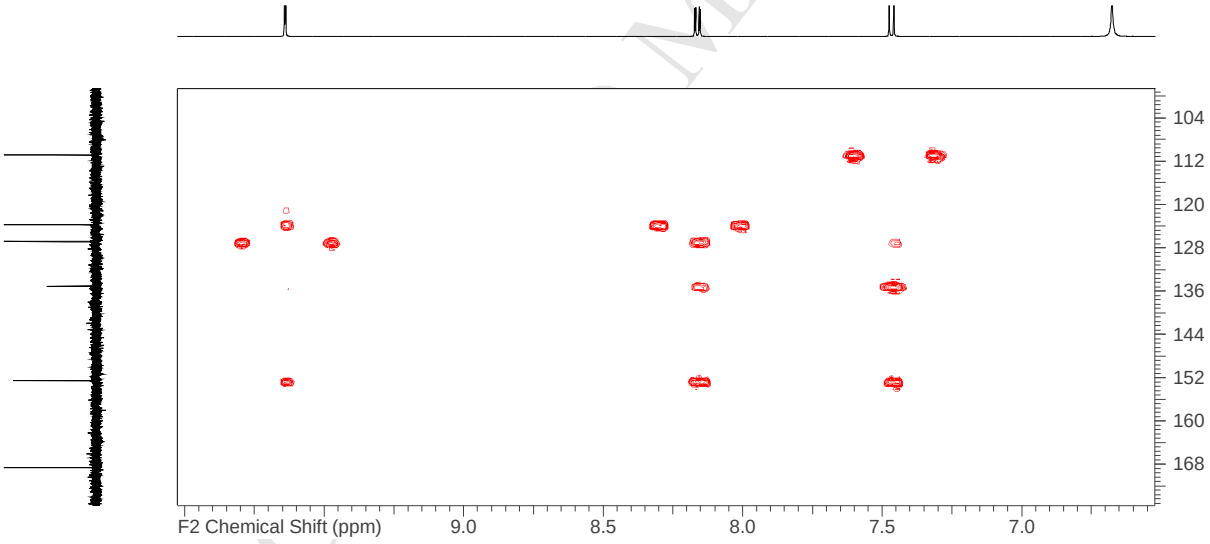
^{13}C NMR spectrum



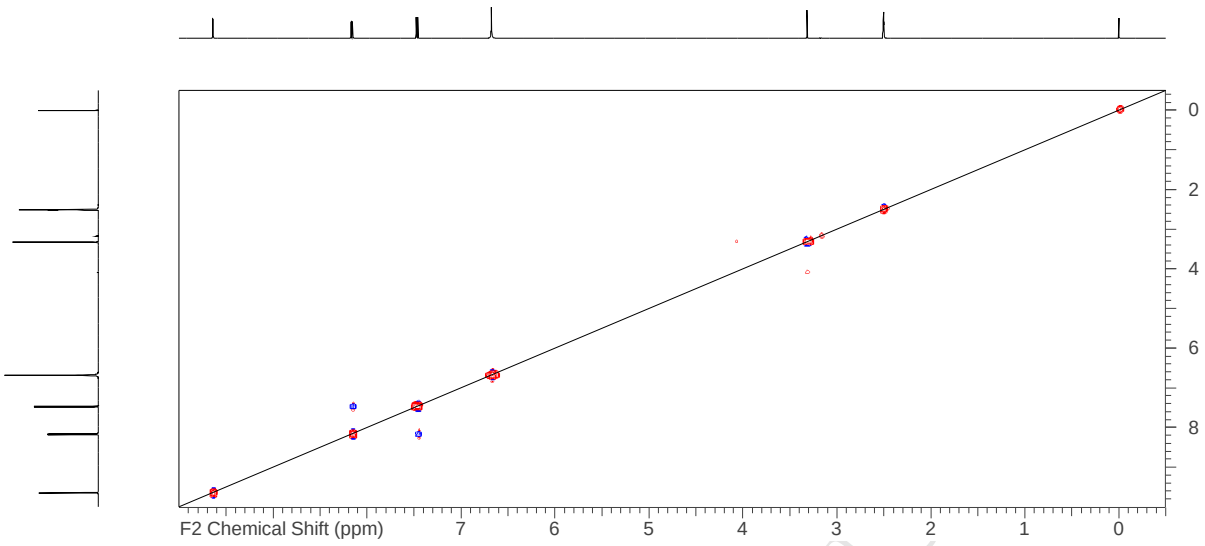
HMBC spectrum



HMBC spectrum (expansion of aromatic region)

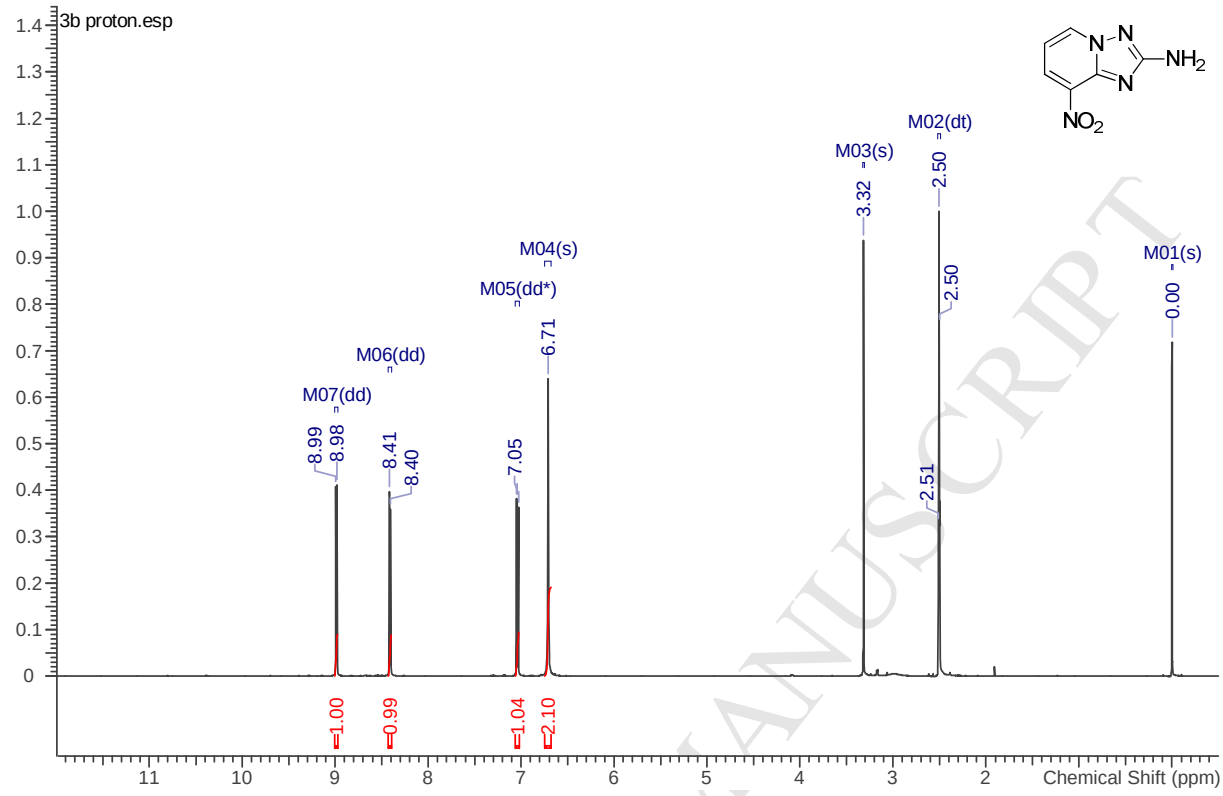


NOESY spectrum

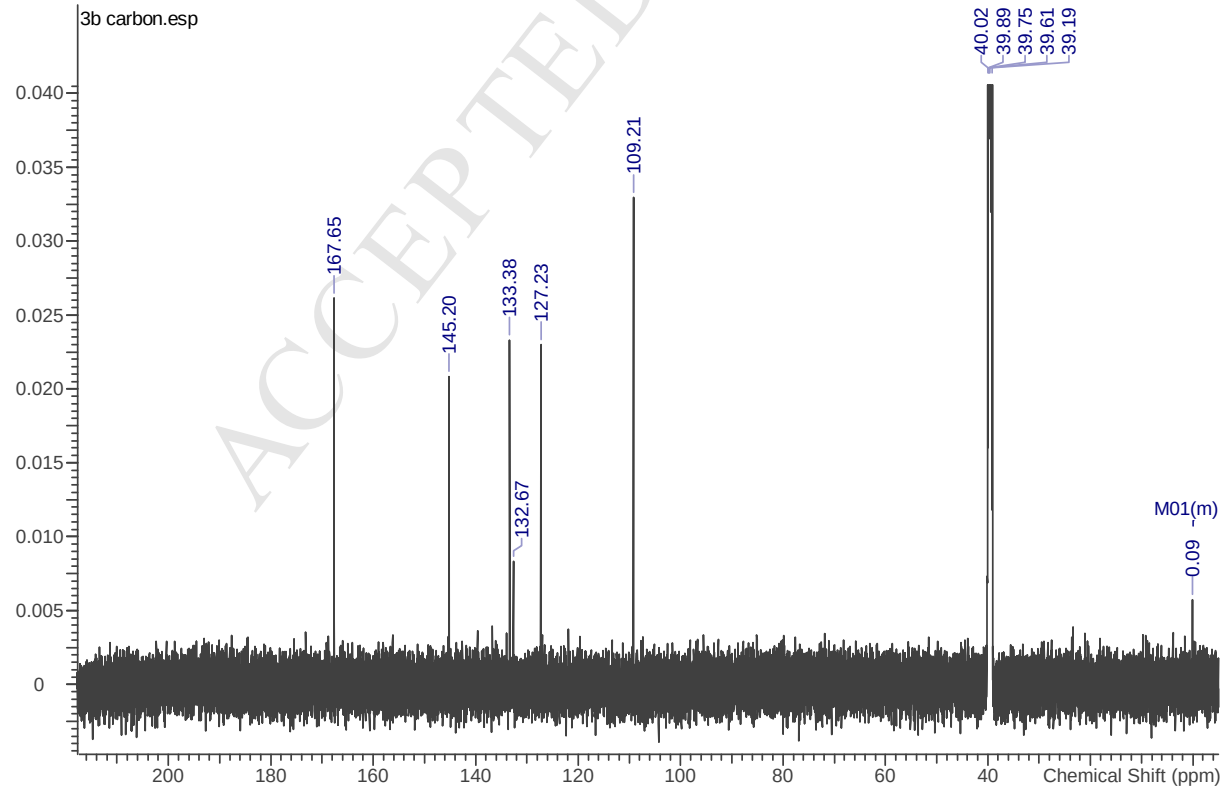


8-nitro[1,2,4]triazolo[1,5-a]pyridin-2-amine (**3b**)

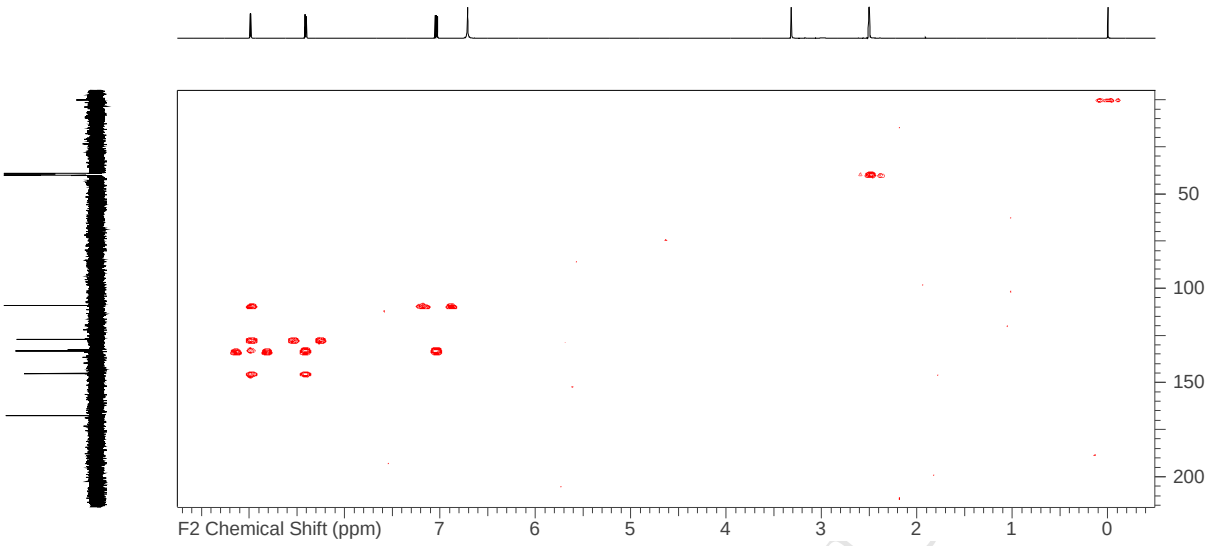
^{1}H NMR spectrum



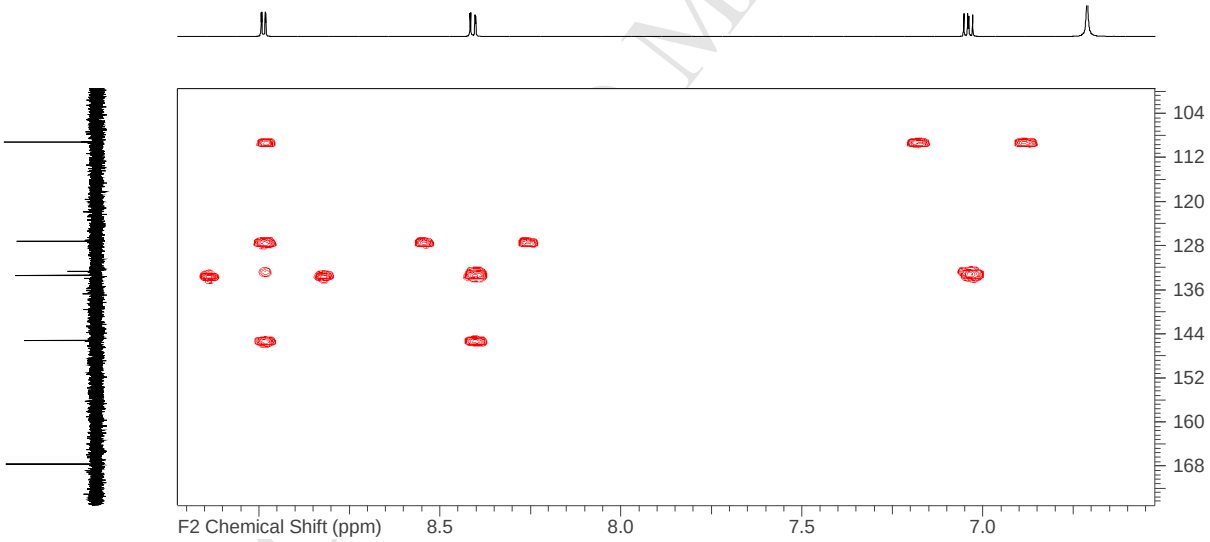
^{13}C NMR spectrum



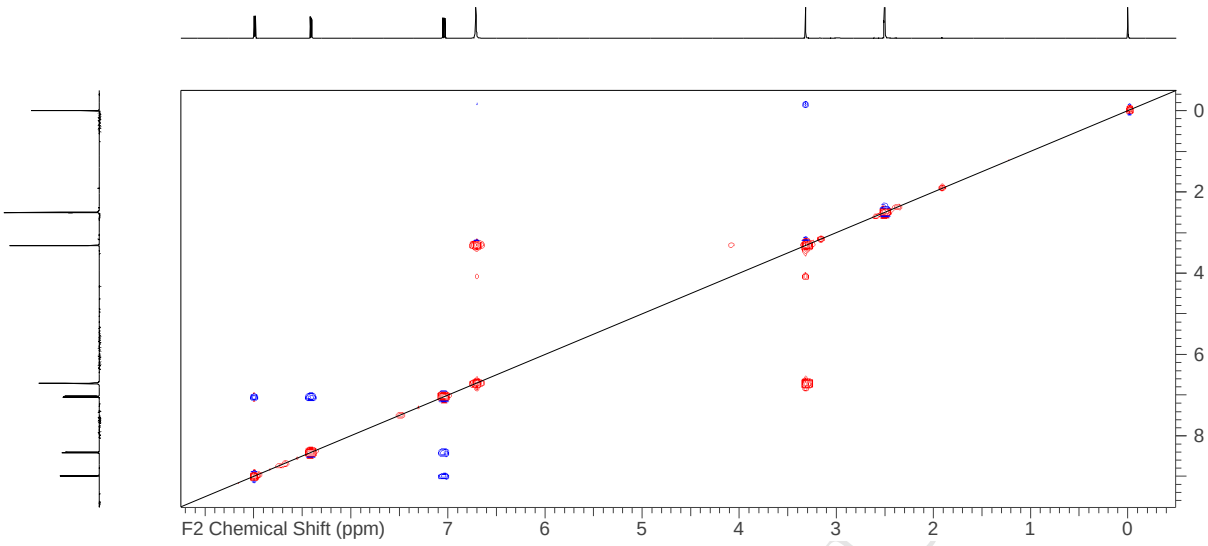
HMBC spectrum



HMBC spectrum (expansion of aromatic region)

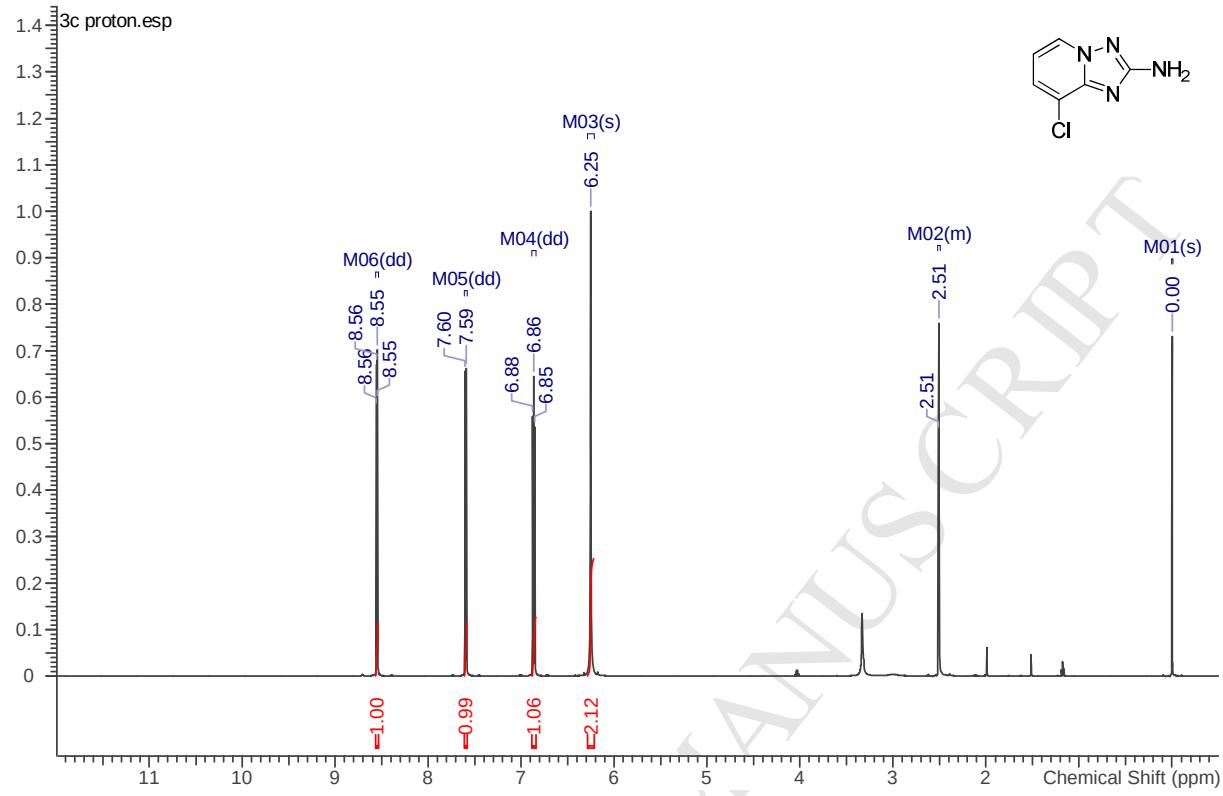


NOESY spectrum

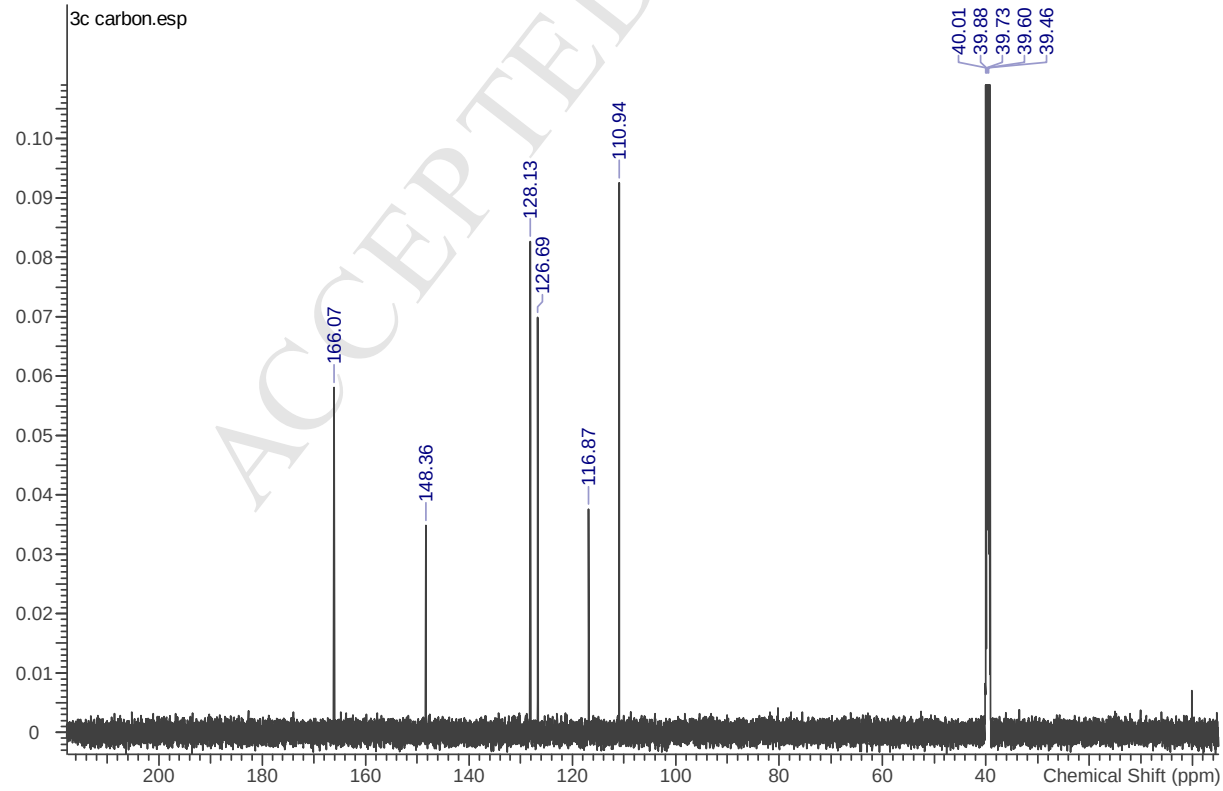


8-chloro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (**3c**)

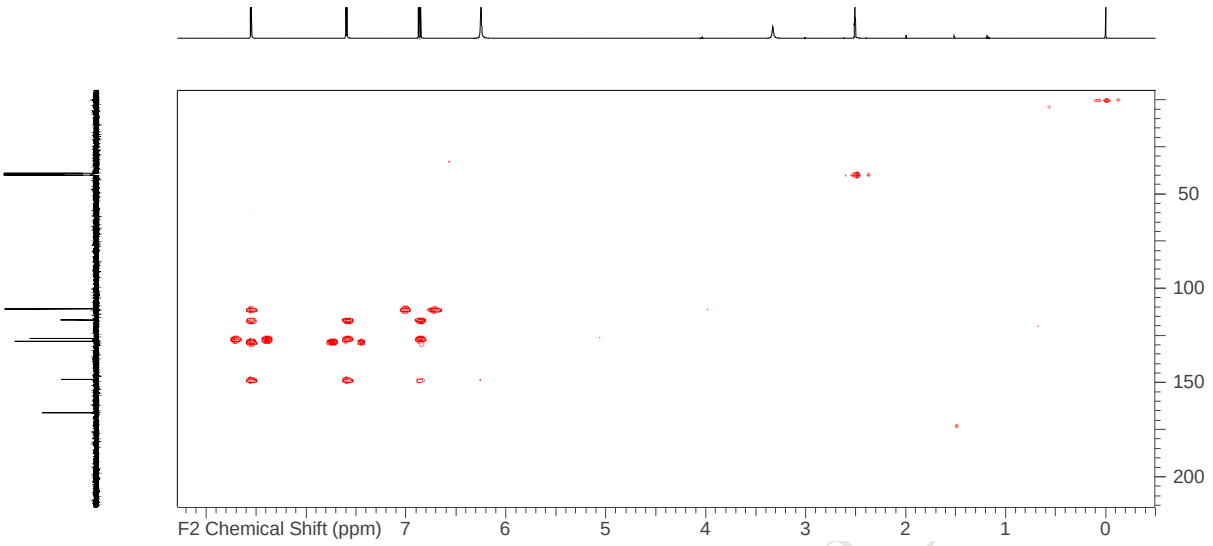
^{1}H NMR spectrum



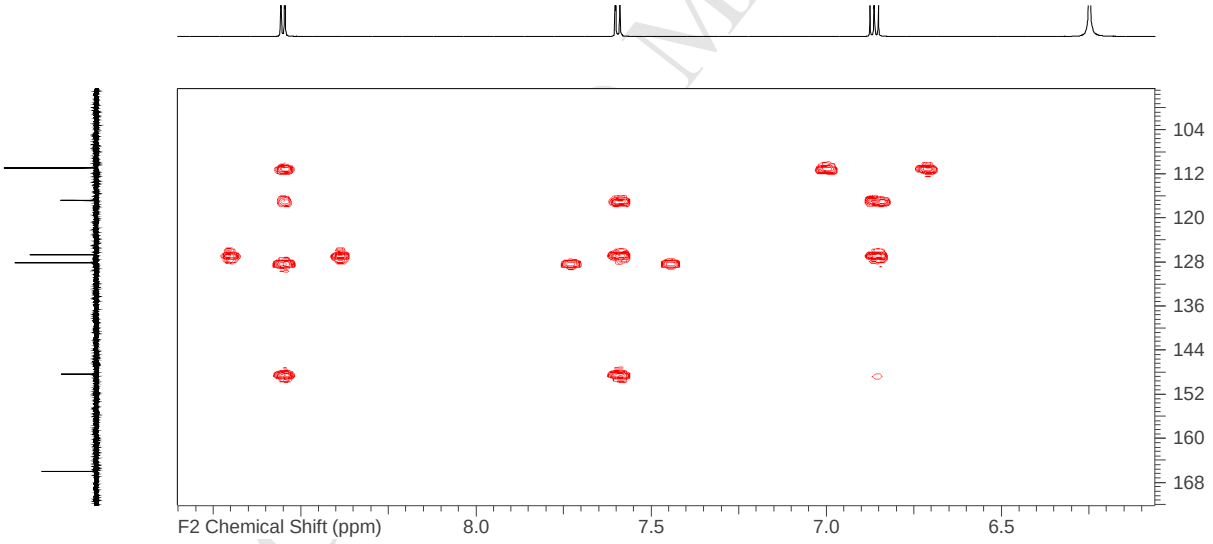
^{13}C NMR spectrum



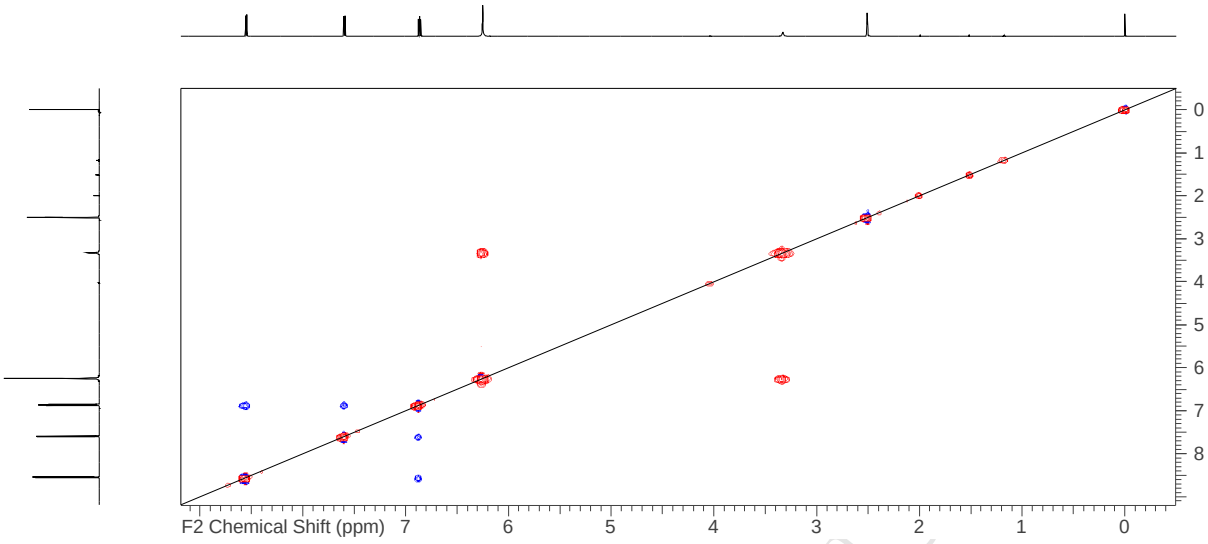
HMBC spectrum



HMBC spectrum (expansion of aromatic region)

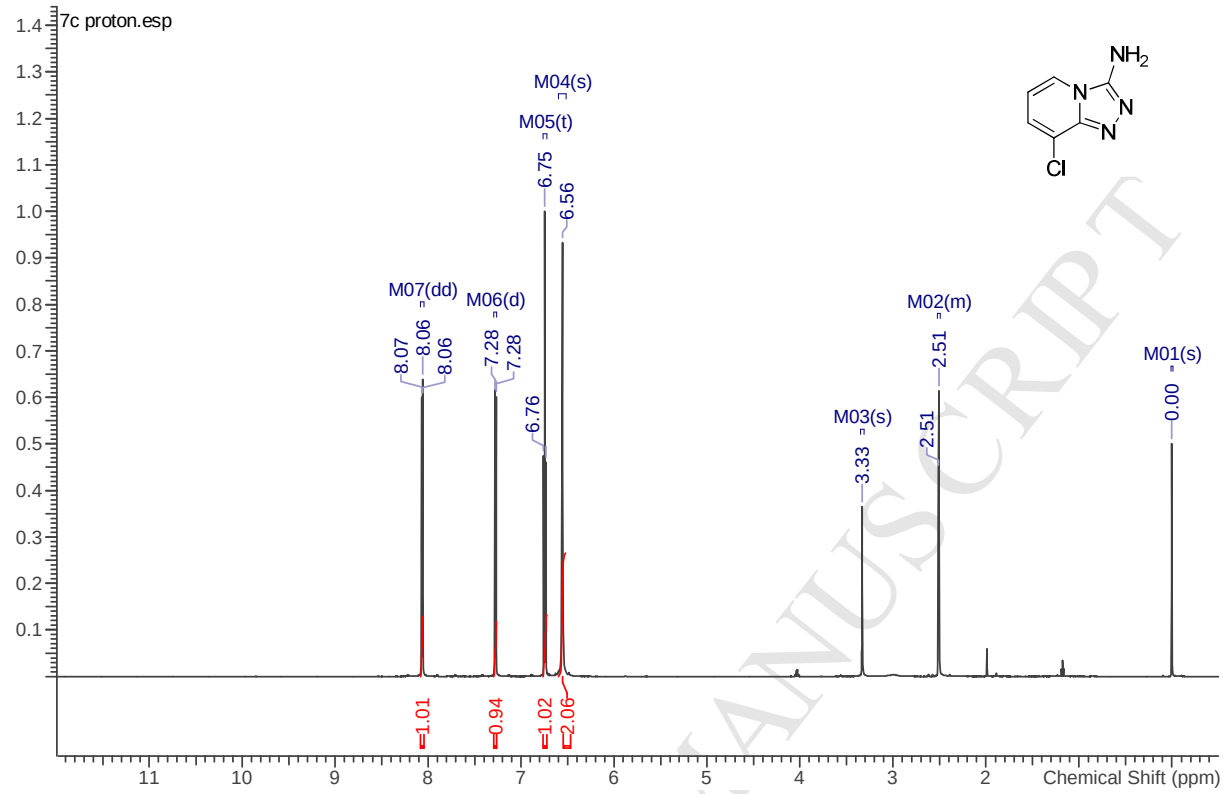


NOESY spectrum

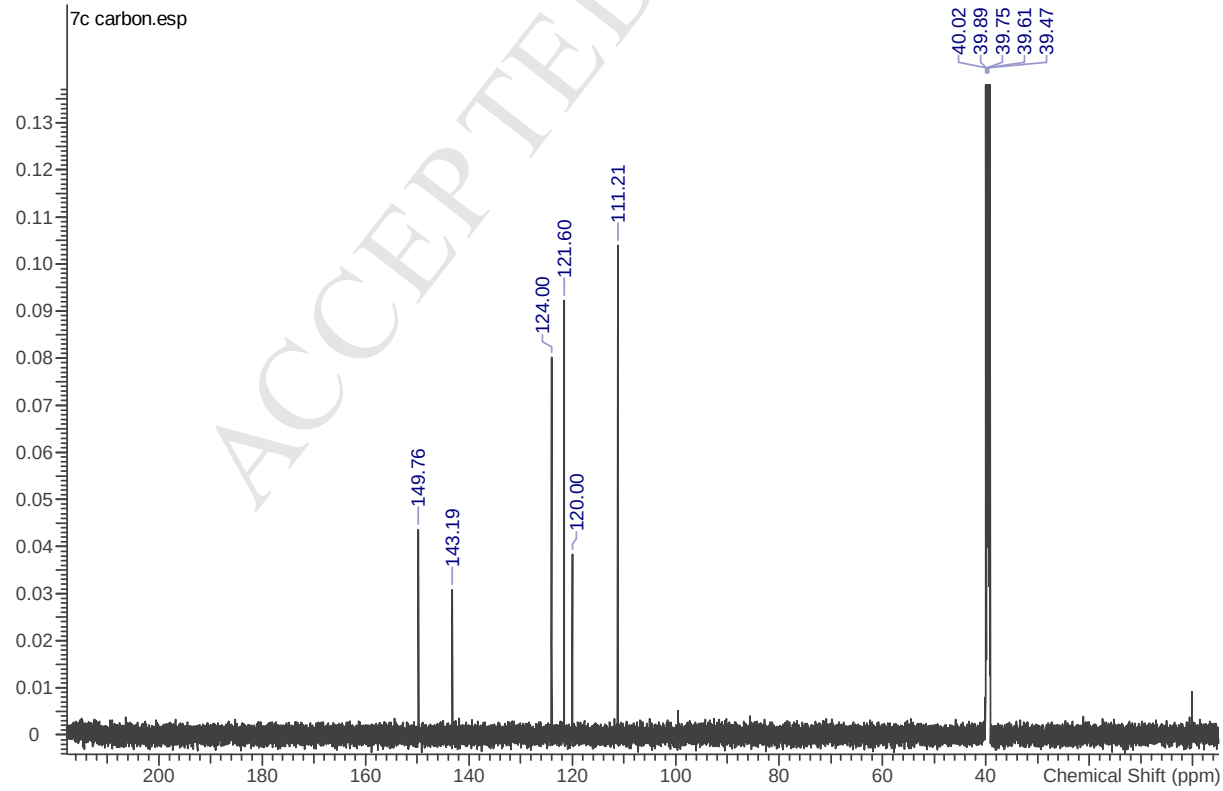


8-chloro-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**7c**)

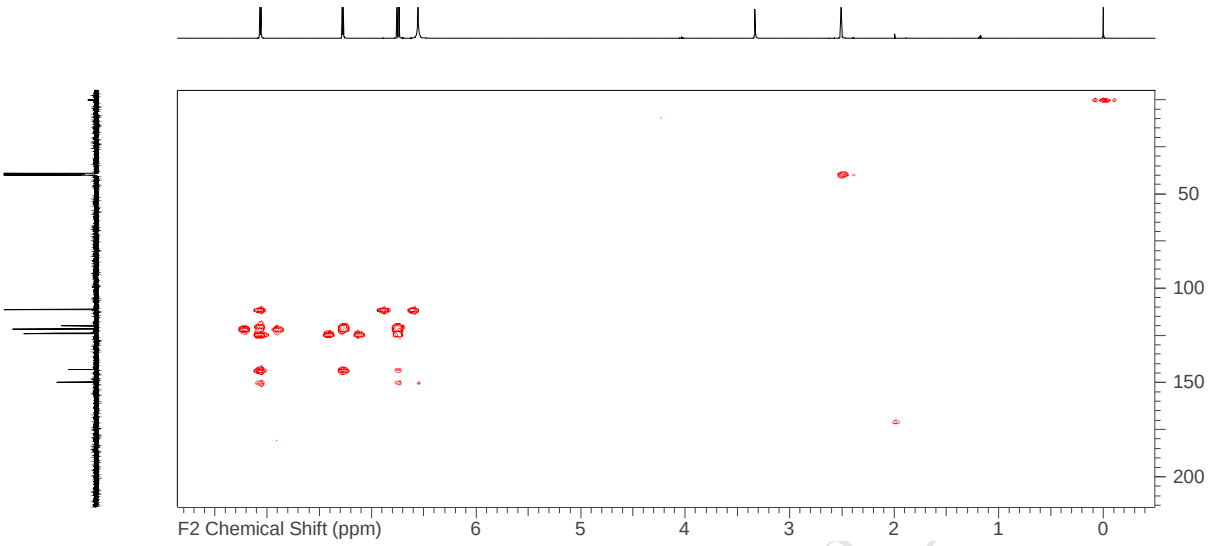
^{1}H NMR spectrum



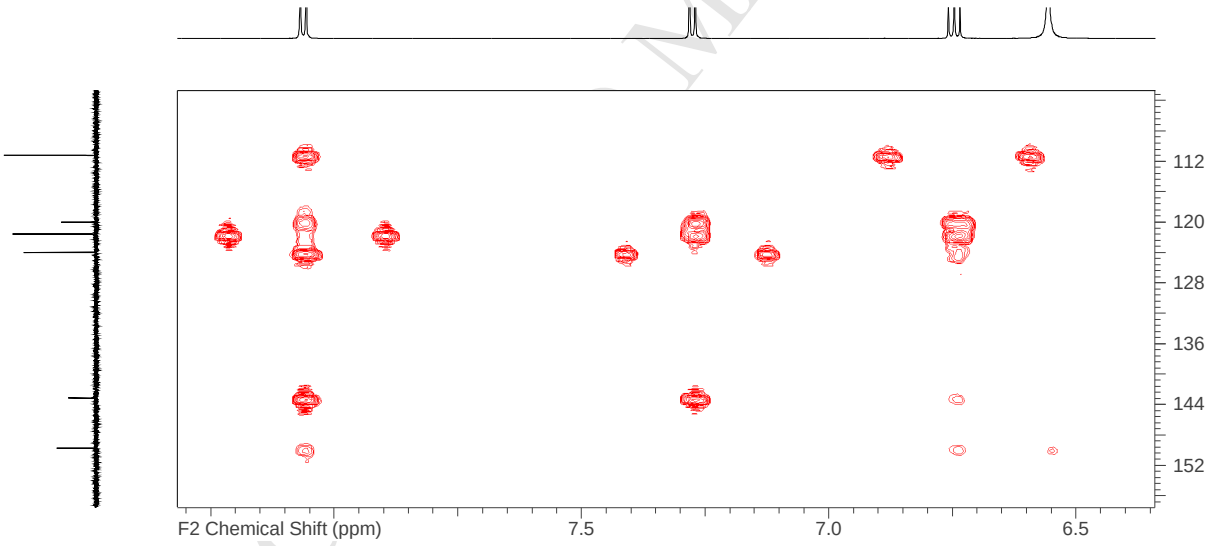
^{13}C NMR spectrum



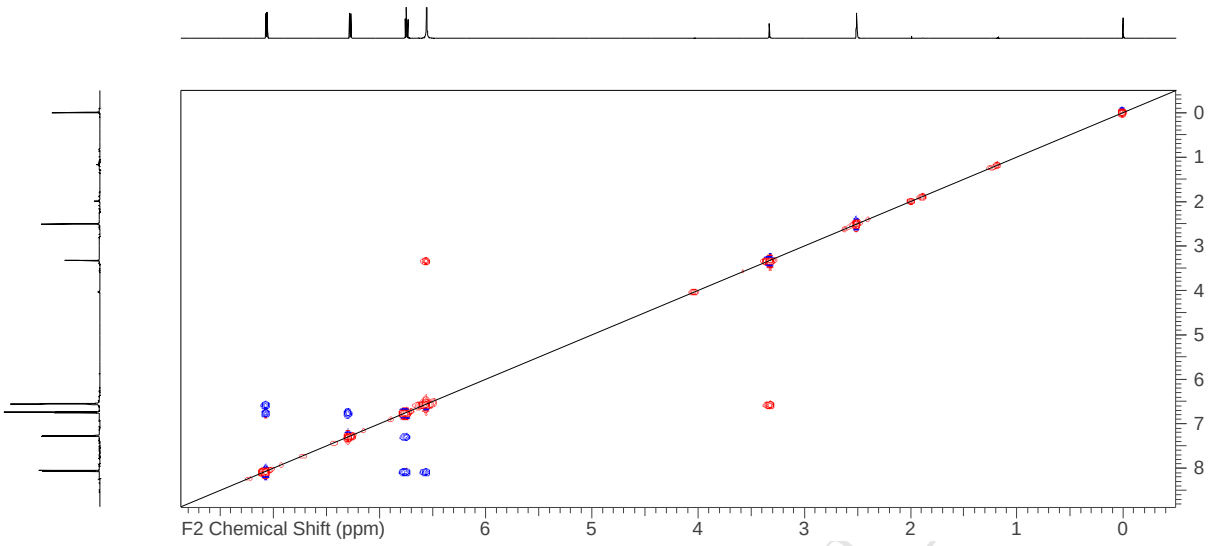
HMBC spectrum



HMBC spectrum (expansion of aromatic region)

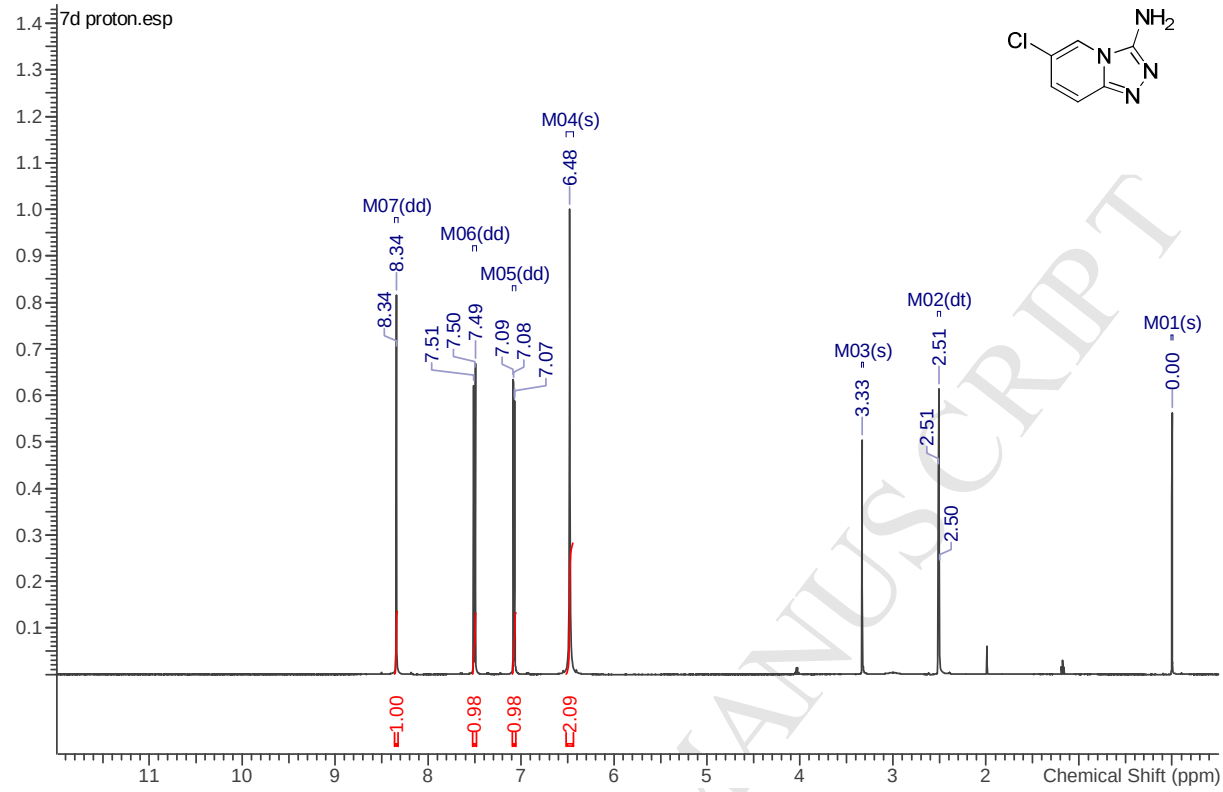


NOESY spectrum

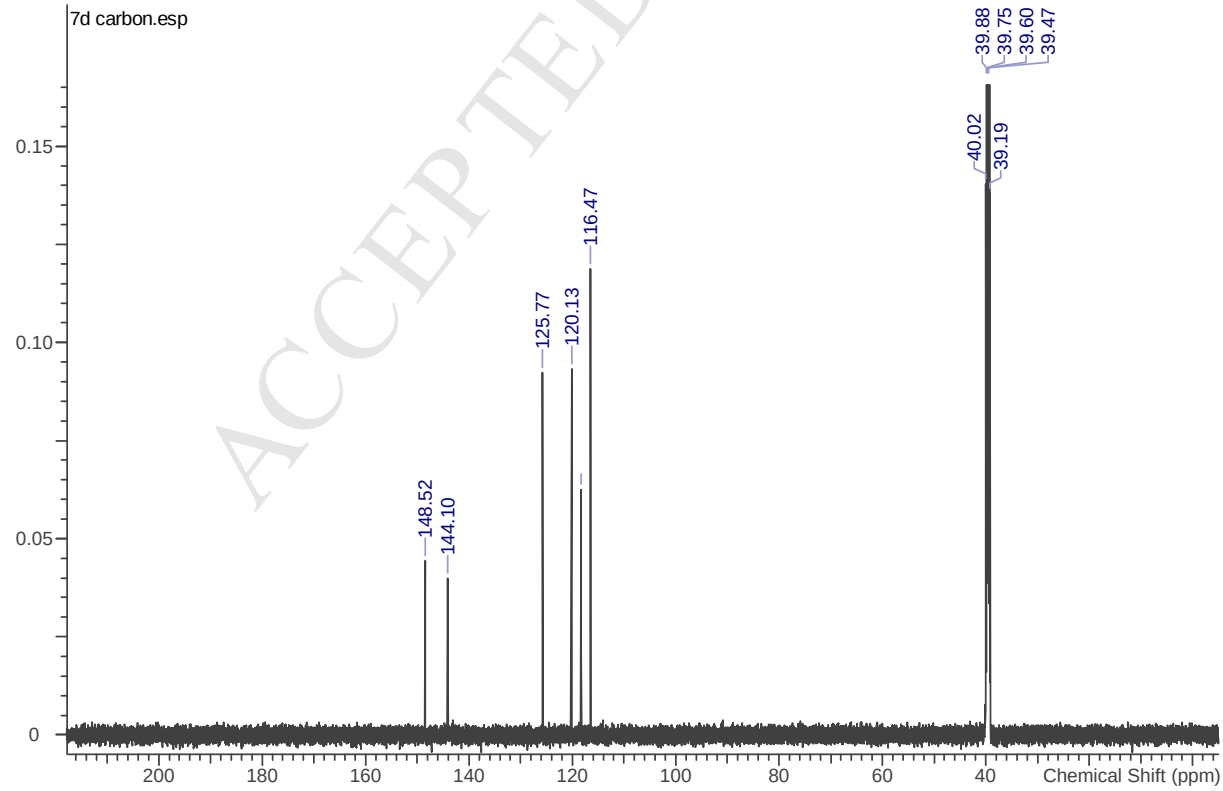


6-chloro-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**7d**)

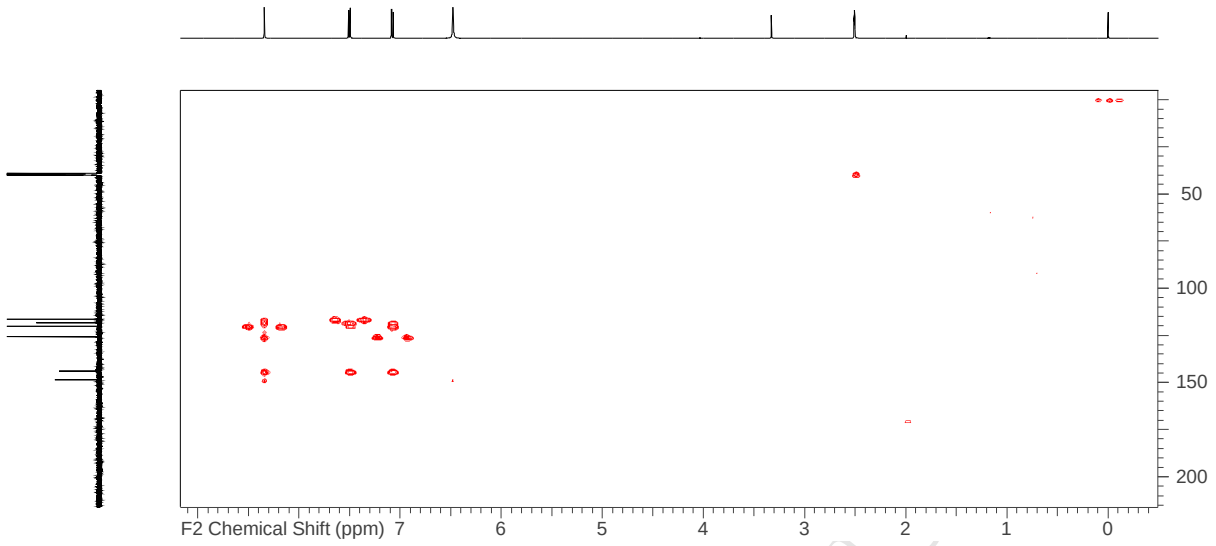
^{1}H NMR spectrum



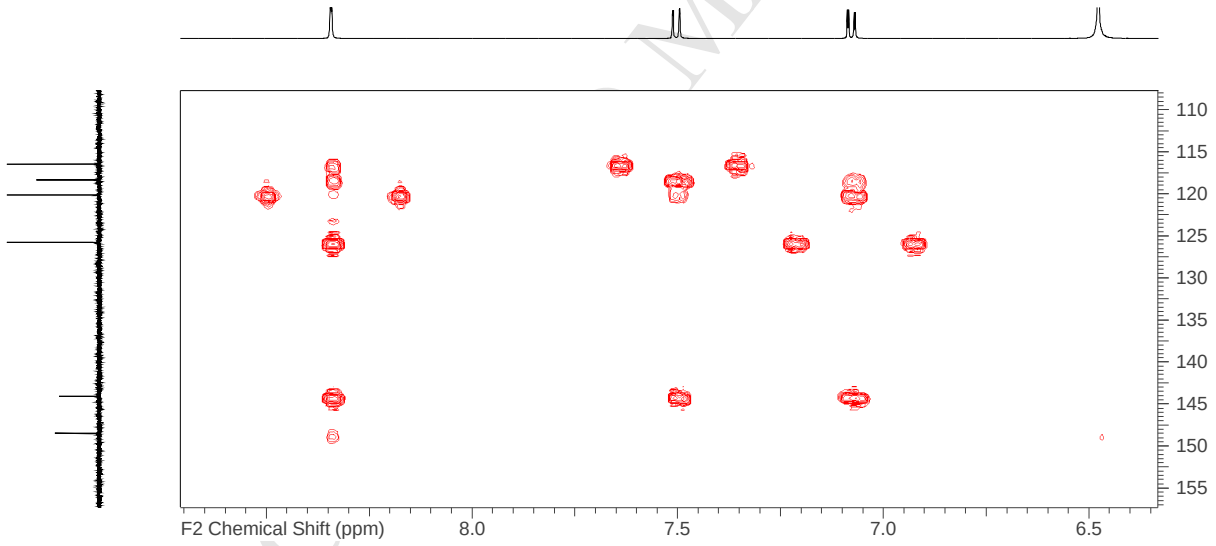
^{13}C NMR spectrum



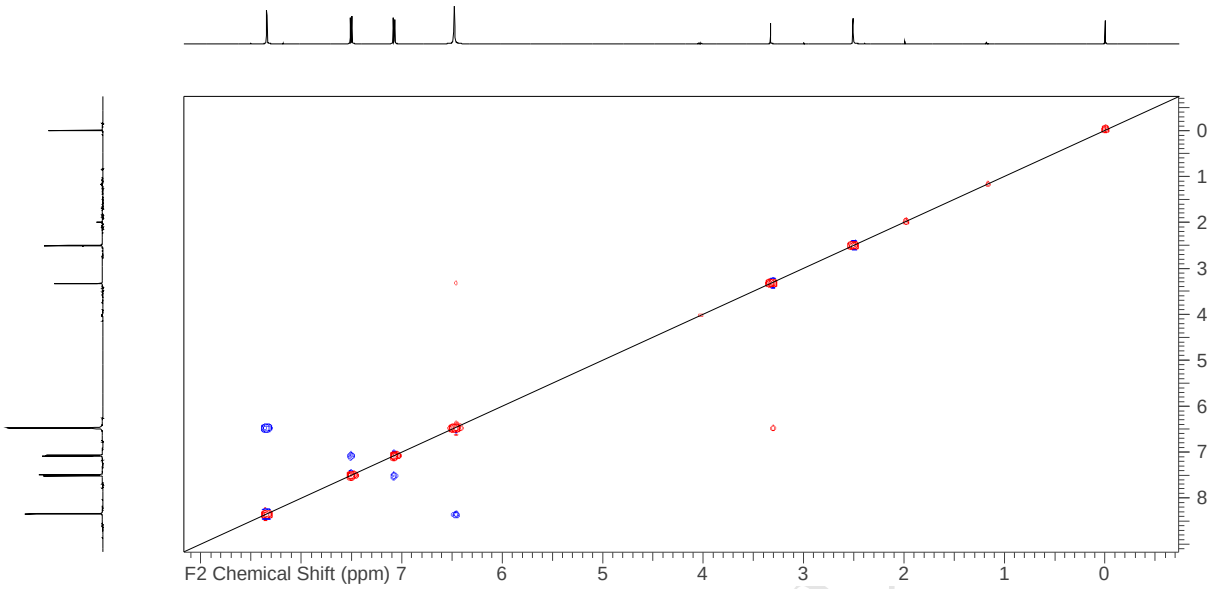
HMBC spectrum



HMBC spectrum (expansion of aromatic region)

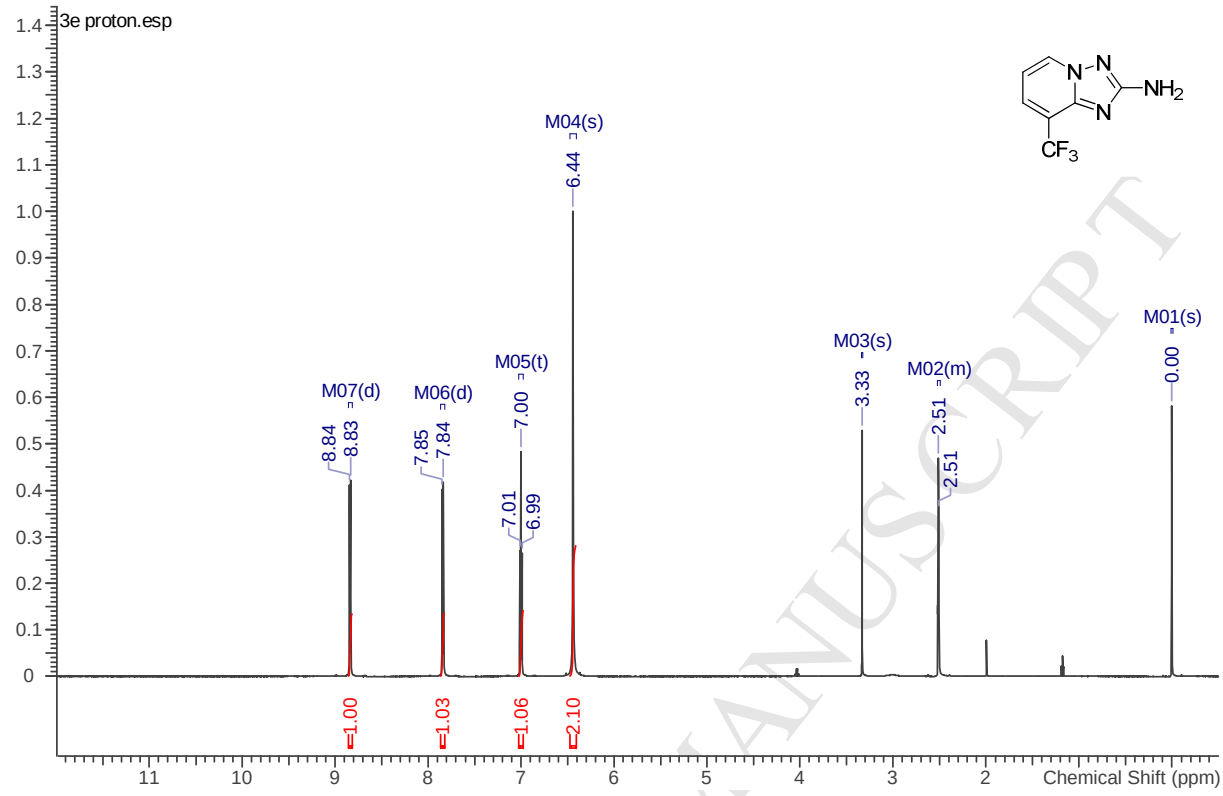


NOESY spectrum

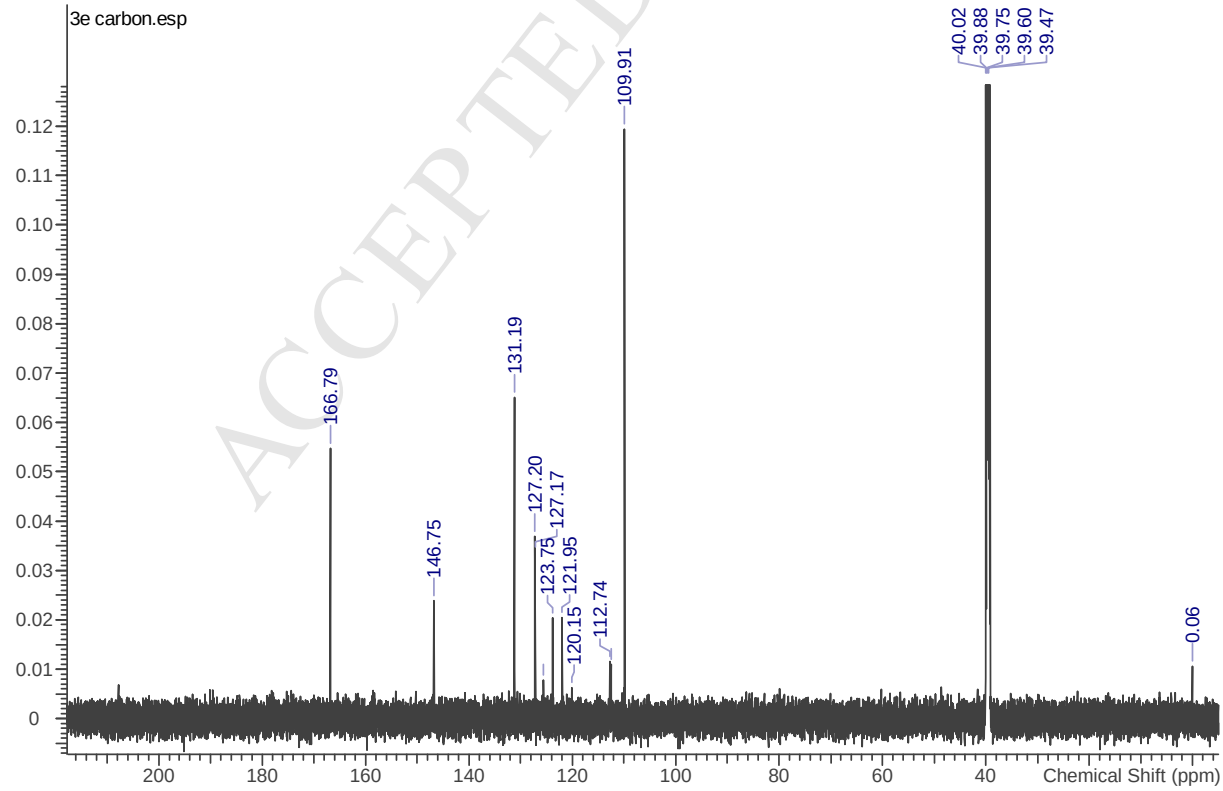


8-(trifluoromethyl)[1,2,4]triazolo[1,5-a]pyridin-2-amine (**3e**)

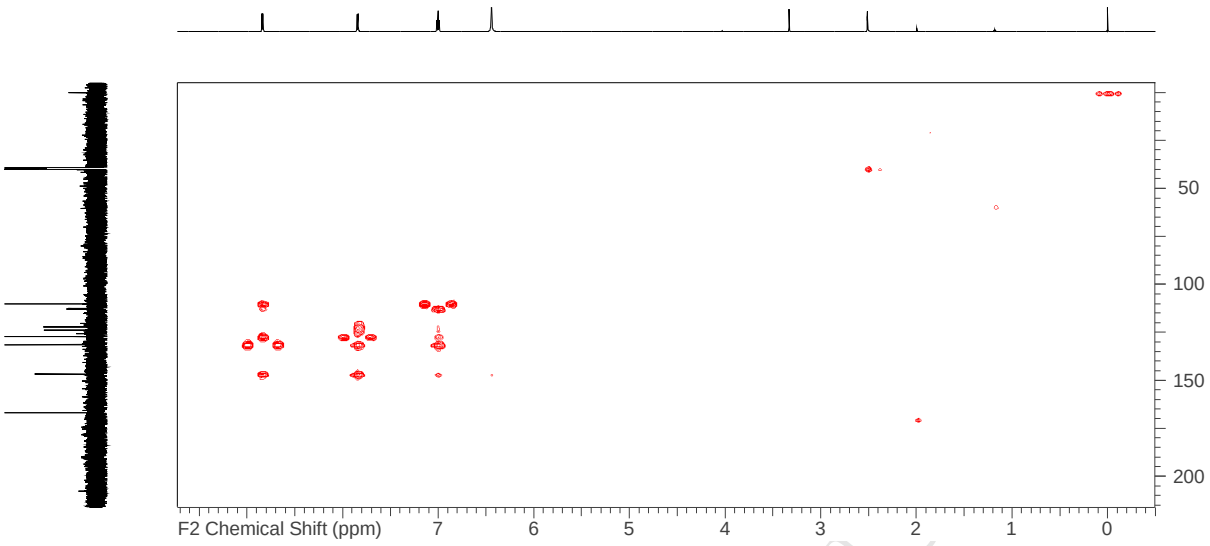
^{1}H NMR spectrum



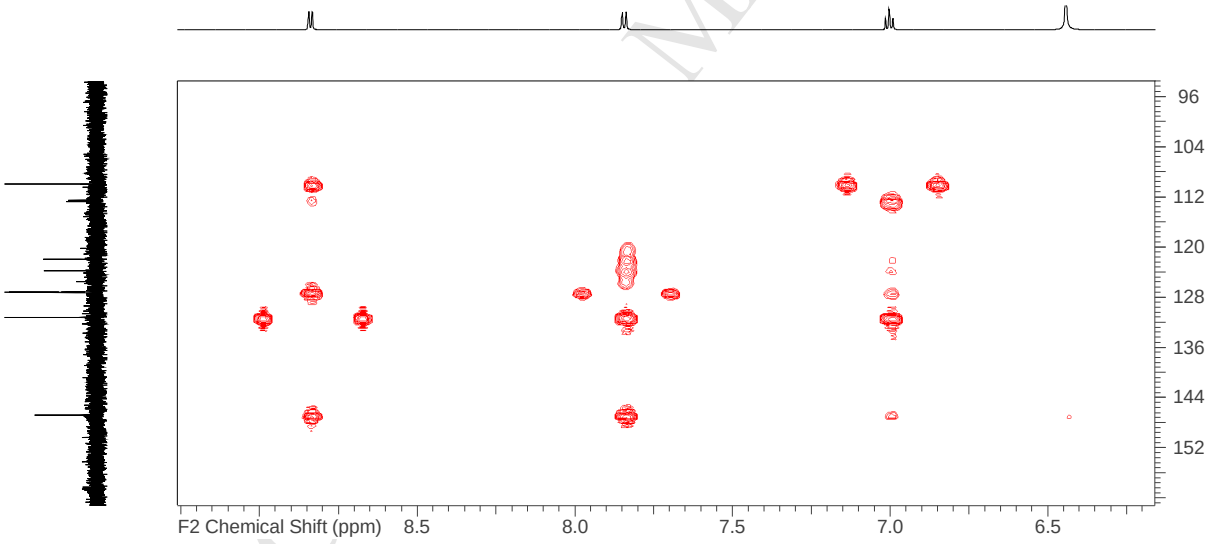
^{13}C NMR spectrum



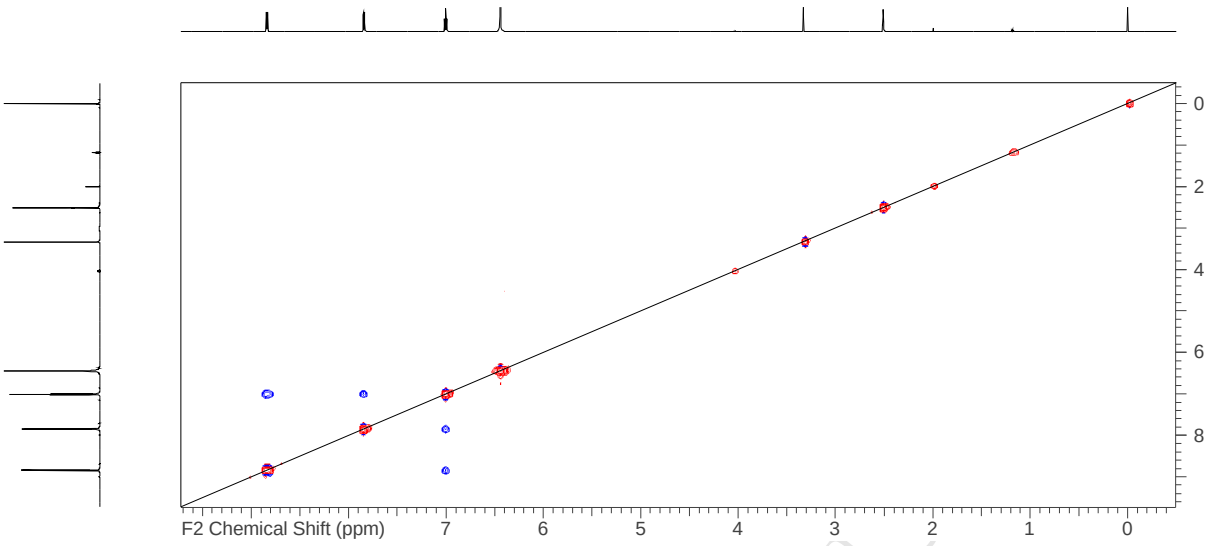
HMBC spectrum



HMBC spectrum (expansion of aromatic region)

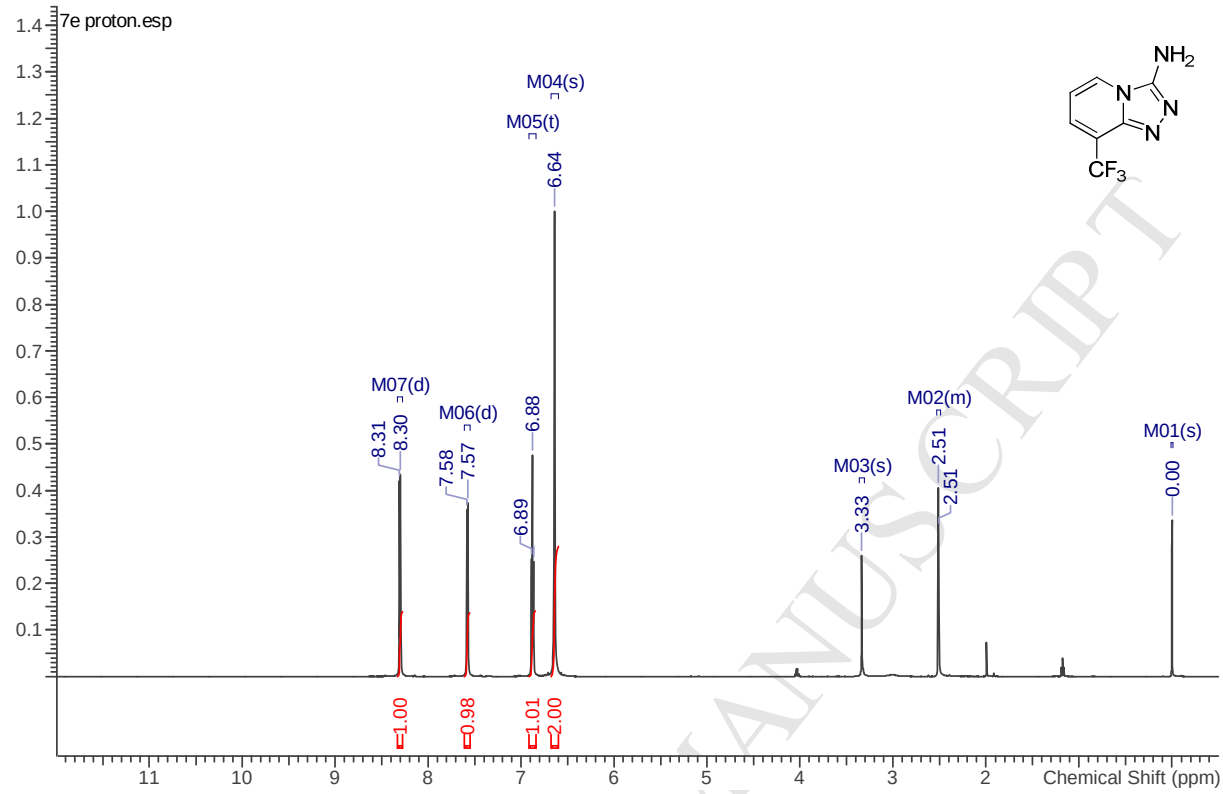


NOESY spectrum

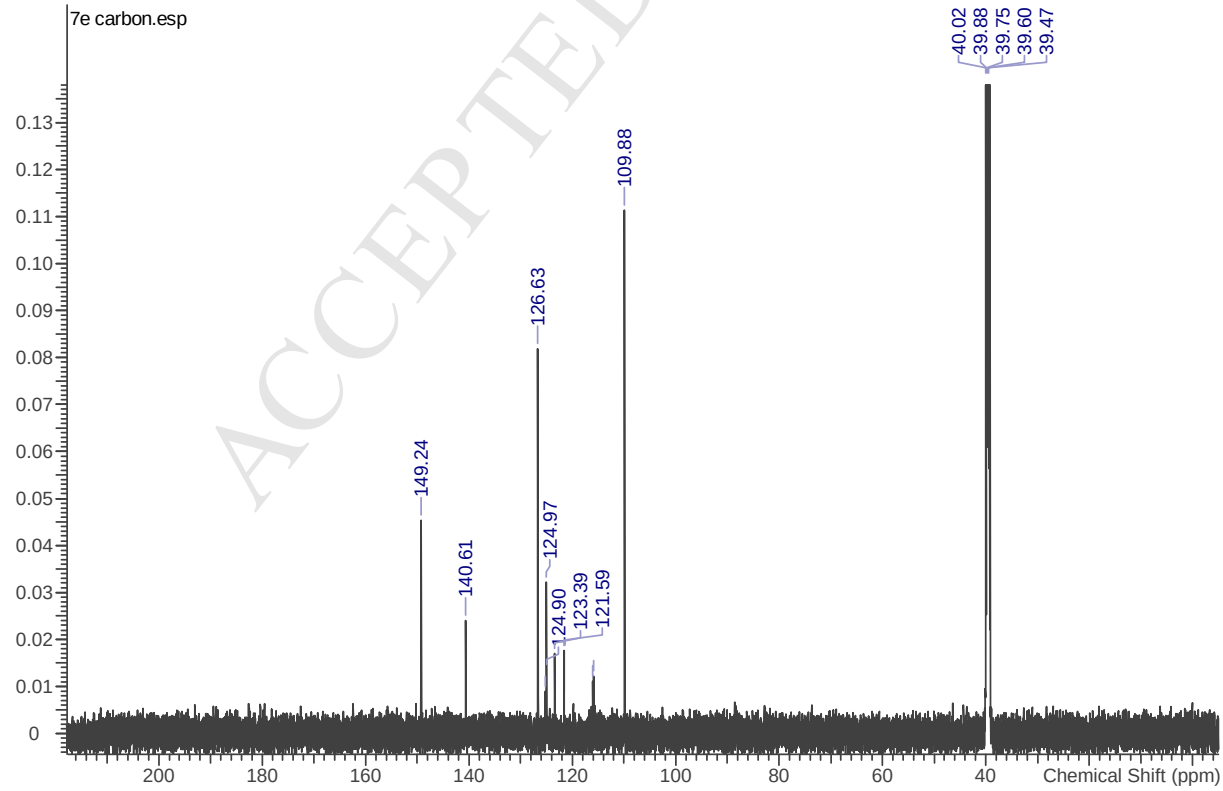


8-(trifluoromethyl)[1,2,4]triazolo[4,3-a]pyridin-3-amine (**7e**)

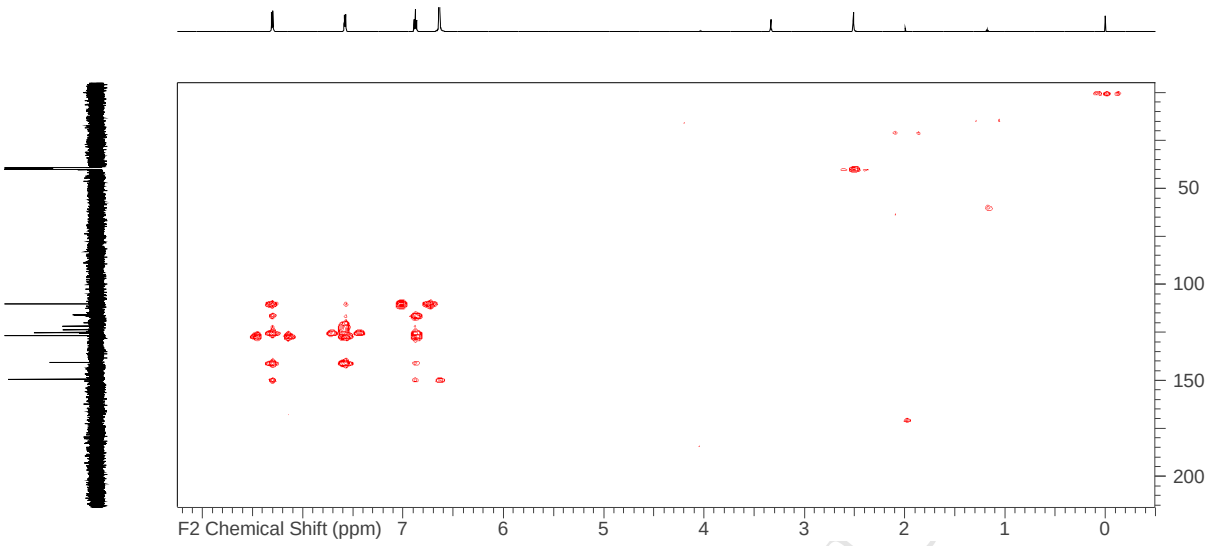
^{1}H NMR spectrum



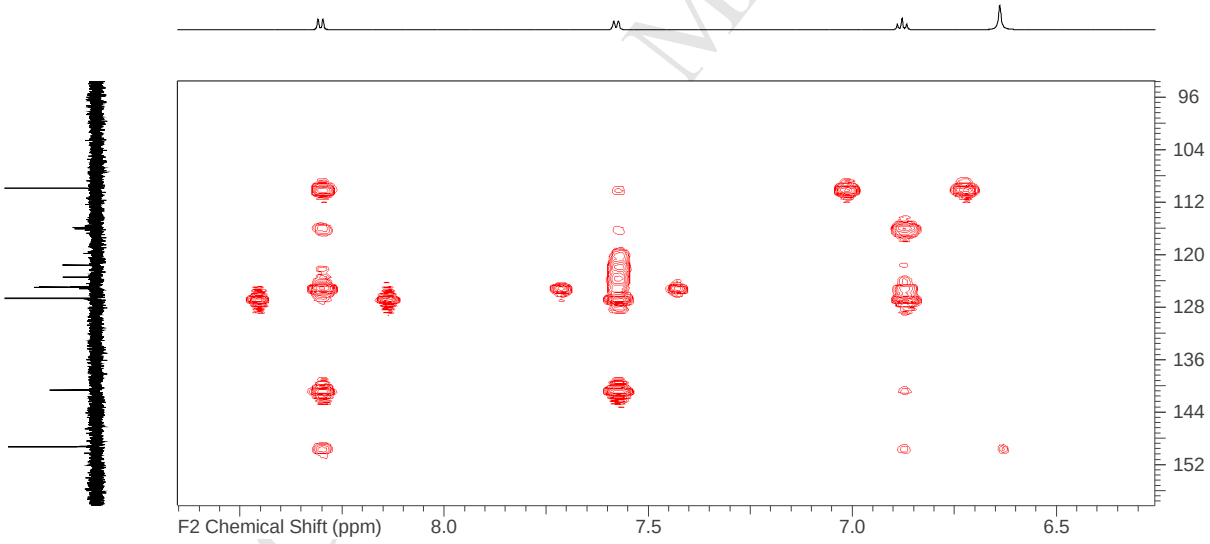
^{13}C NMR spectrum



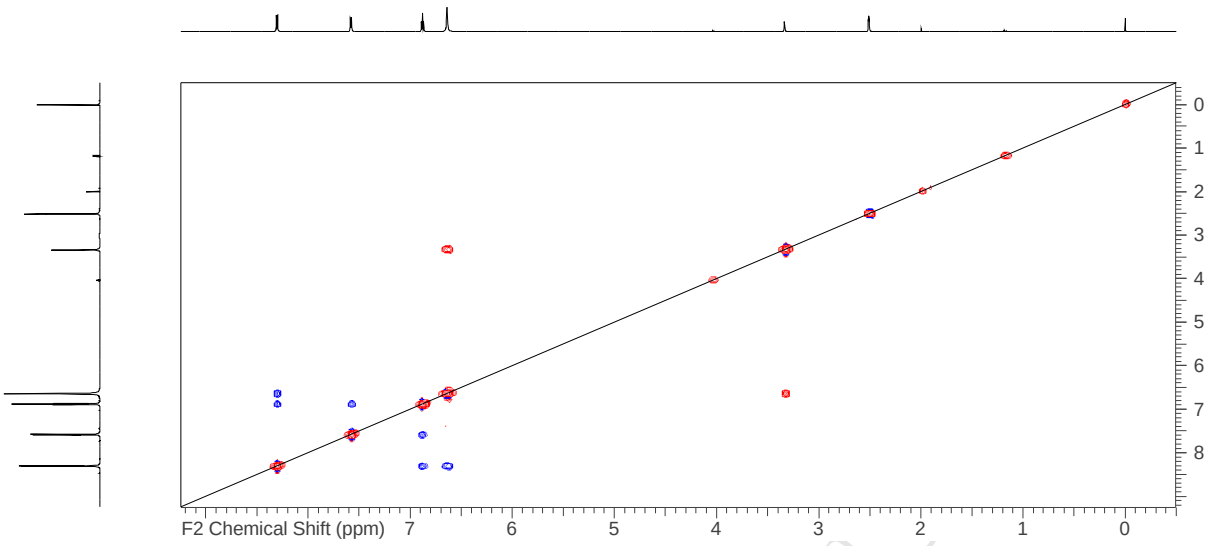
HMBC spectrum



HMBC spectrum (expansion of aromatic region)

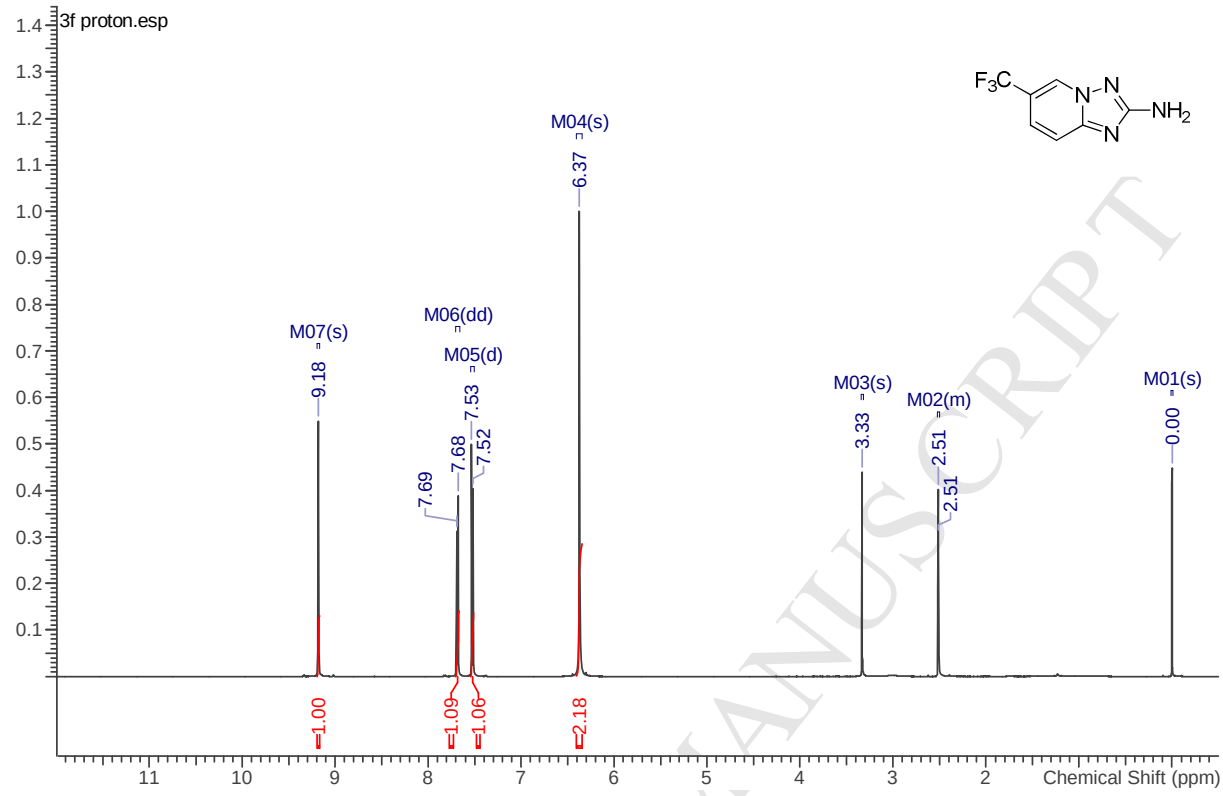


NOESY spectrum

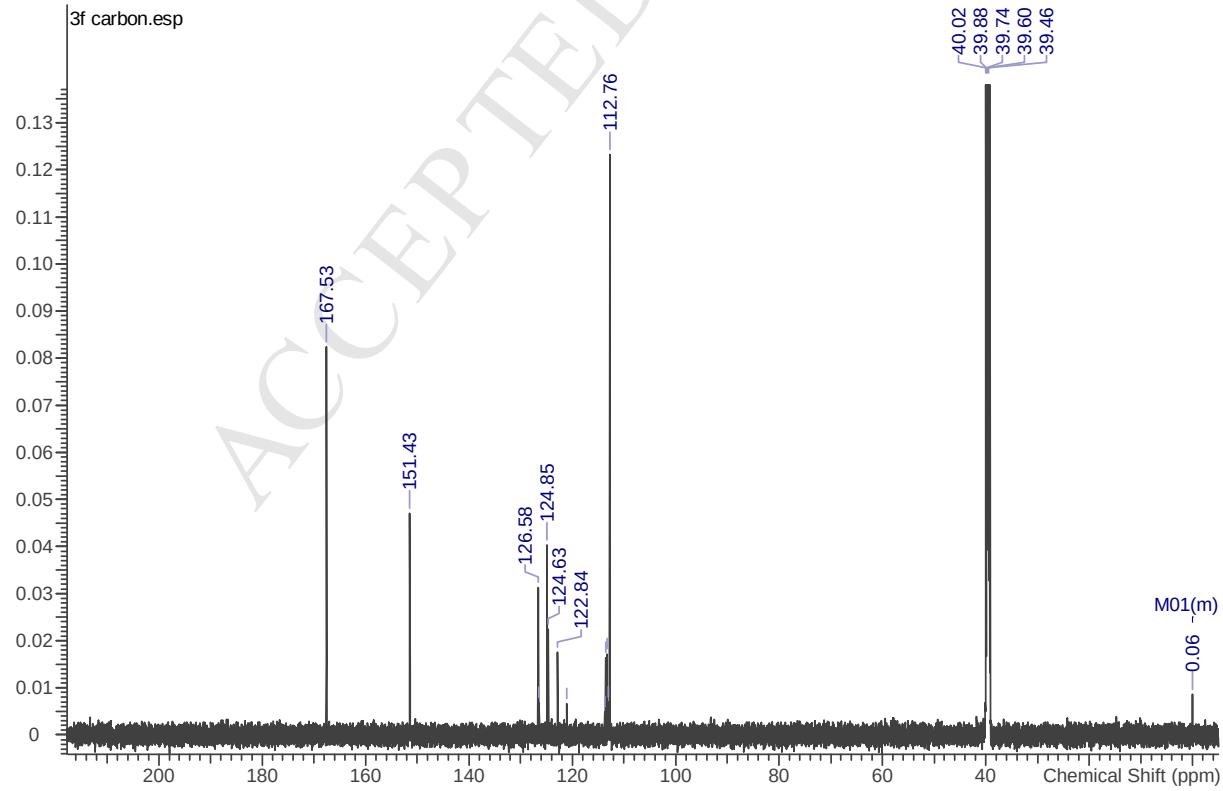


6-(trifluoromethyl)[1,2,4]triazolo[1,5-a]pyridin-2-amine (**3f**)

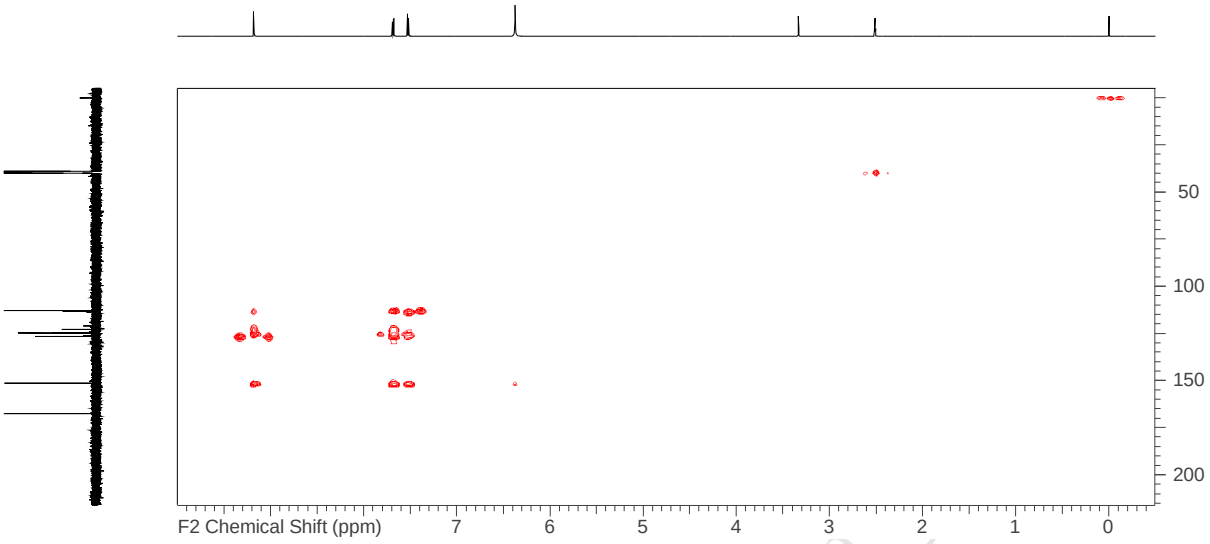
^{1}H NMR spectrum



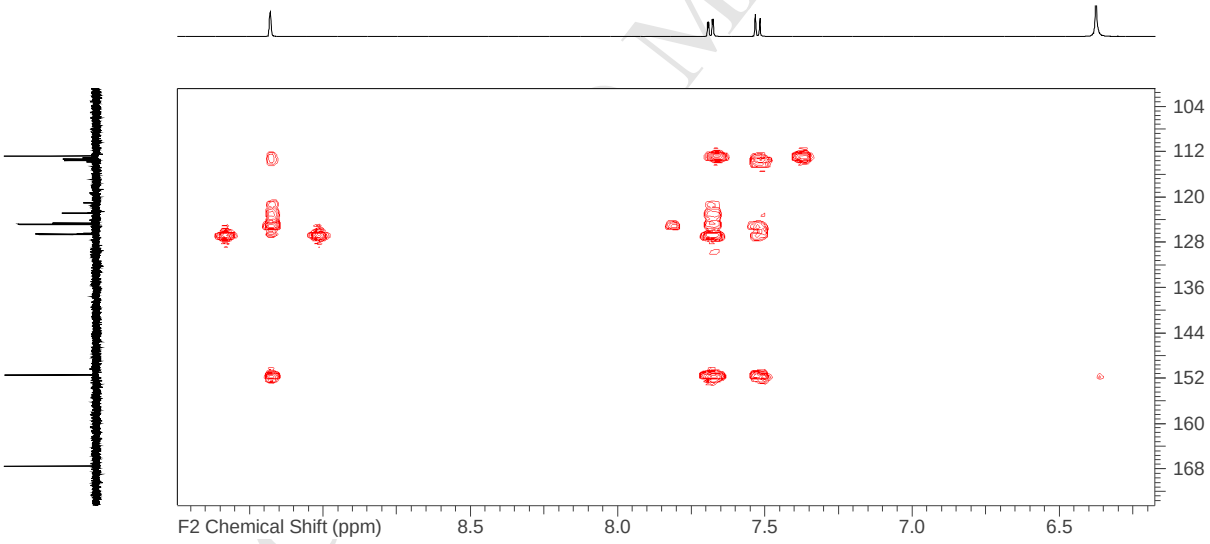
^{13}C NMR spectrum



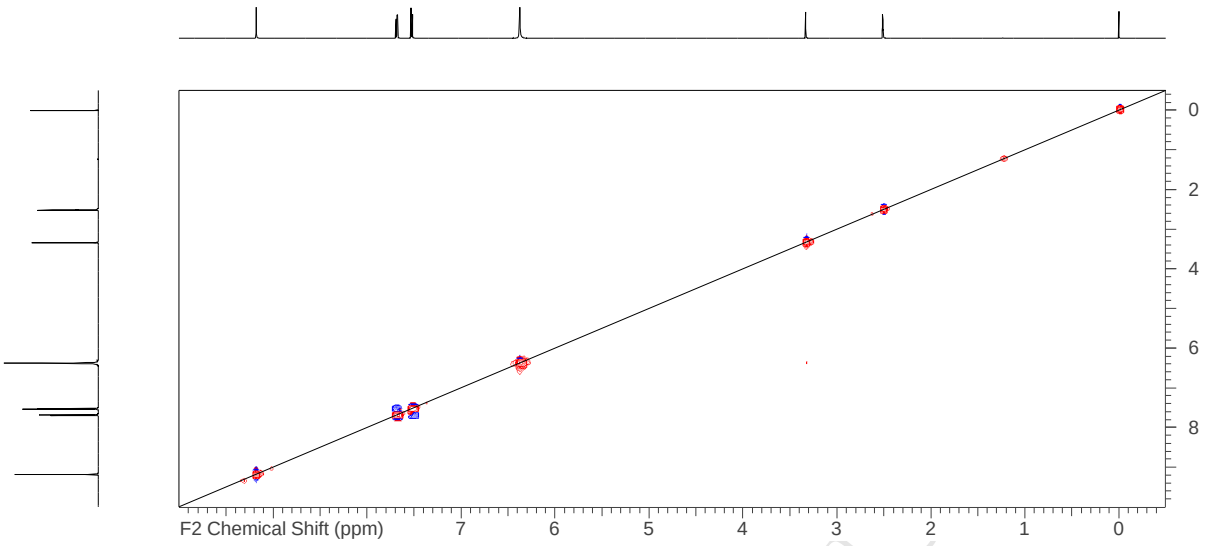
HMBC spectrum



HMBC spectrum (expansion of aromatic region)

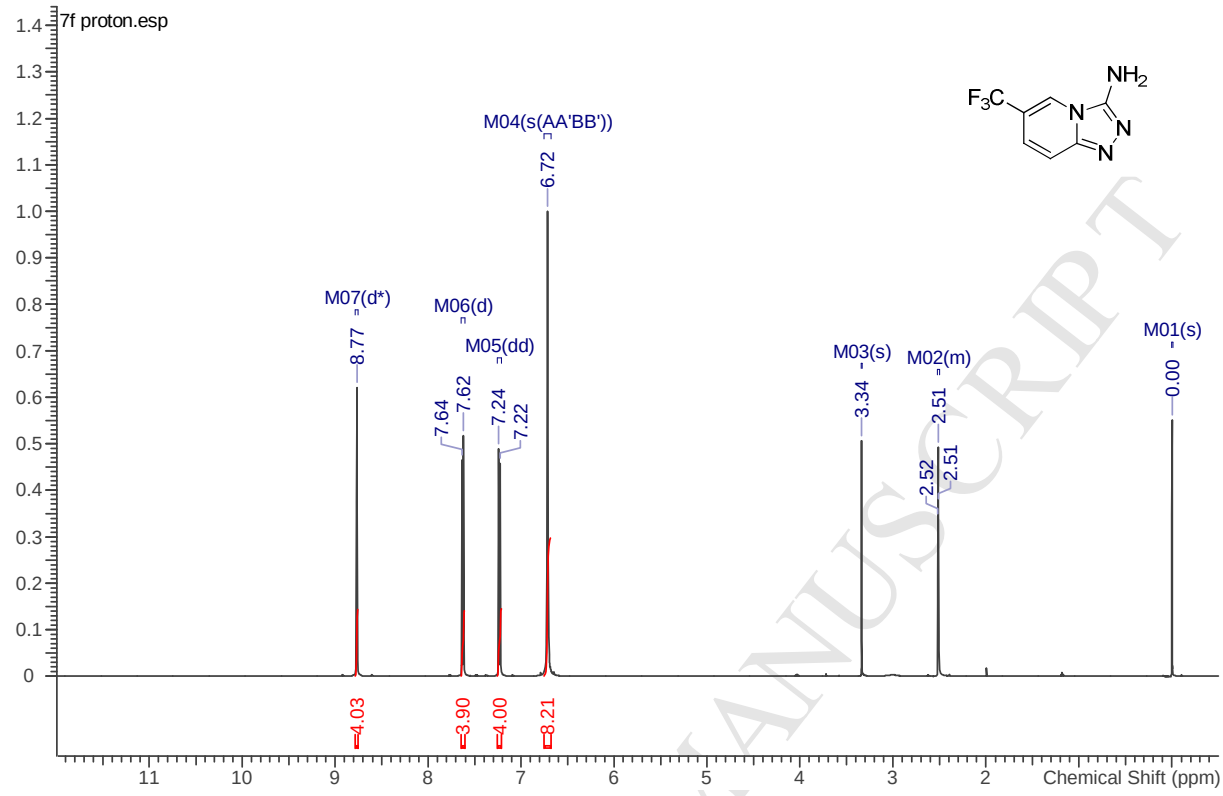


NOESY spectrum

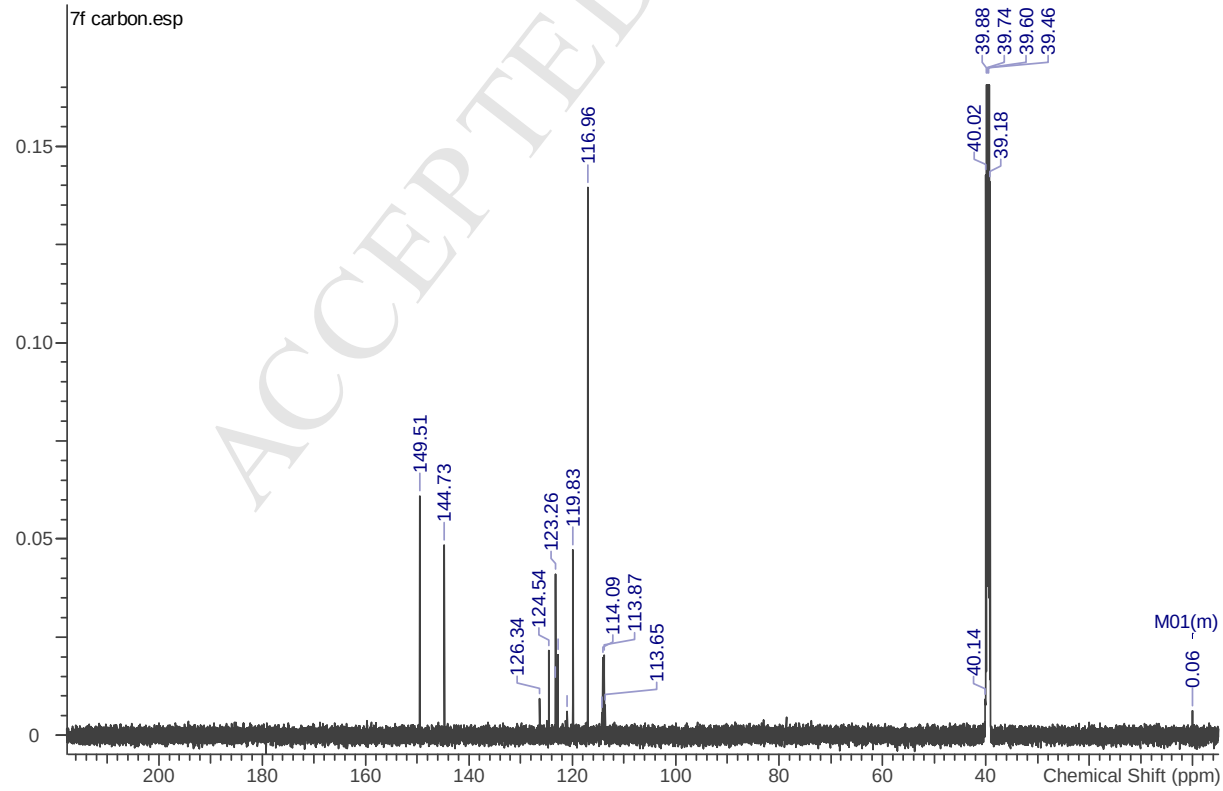


6-(trifluoromethyl)[1,2,4]triazolo[4,3-a]pyridin-3-amine (**7f**)

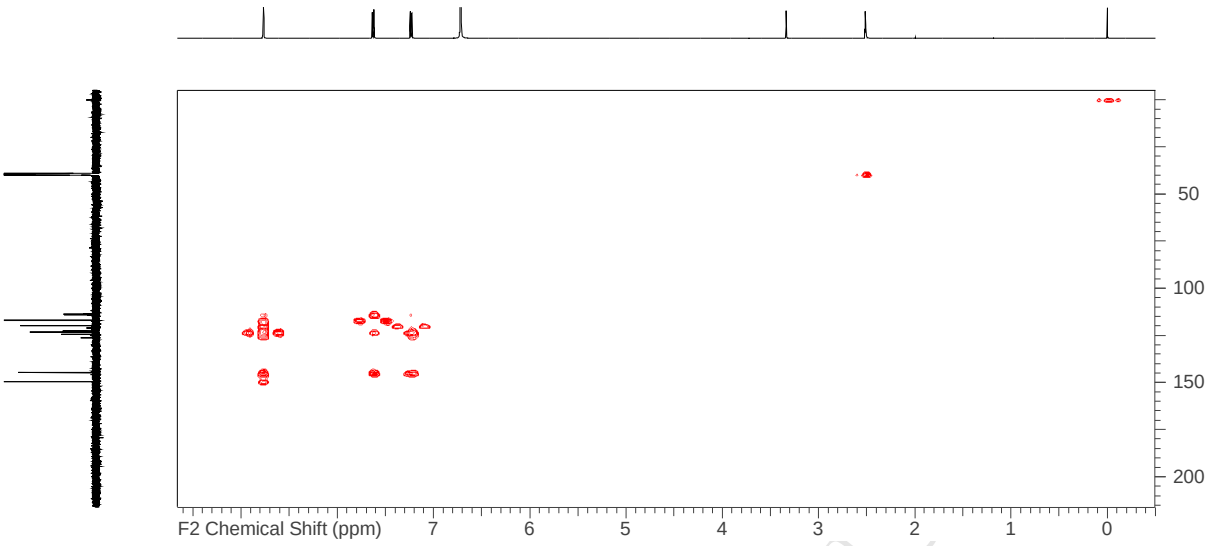
^{1}H NMR spectrum



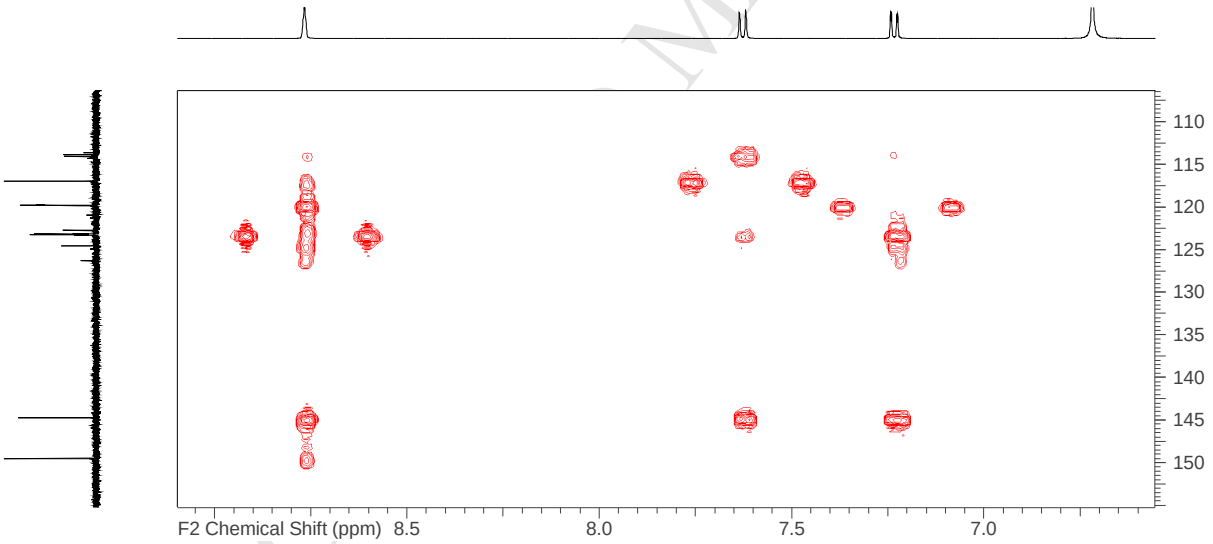
^{13}C NMR spectrum



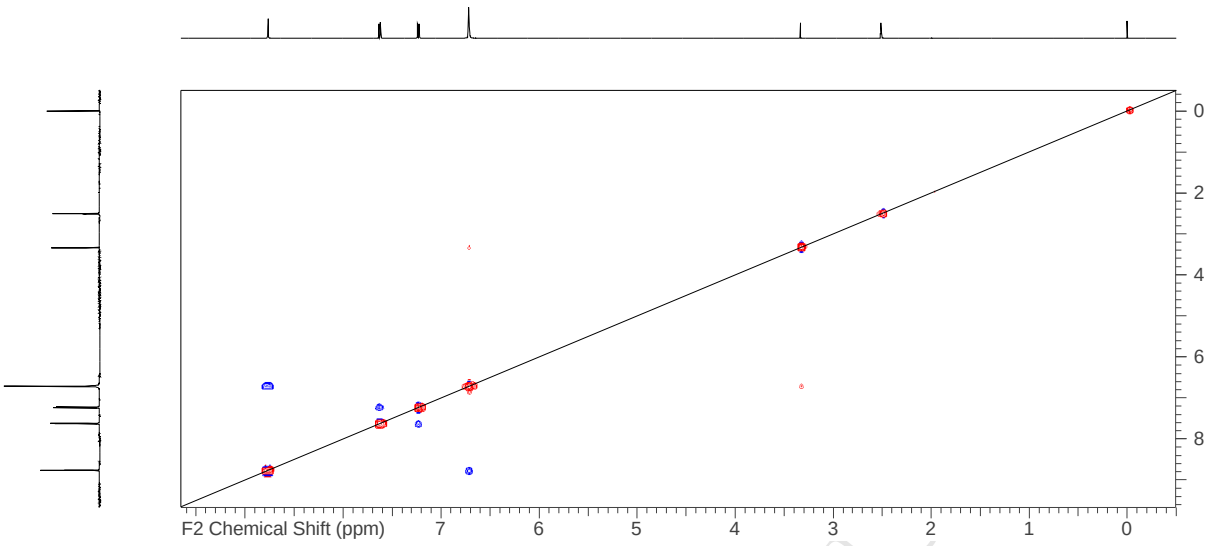
HMBC spectrum



HMBC spectrum (expansion of aromatic region)

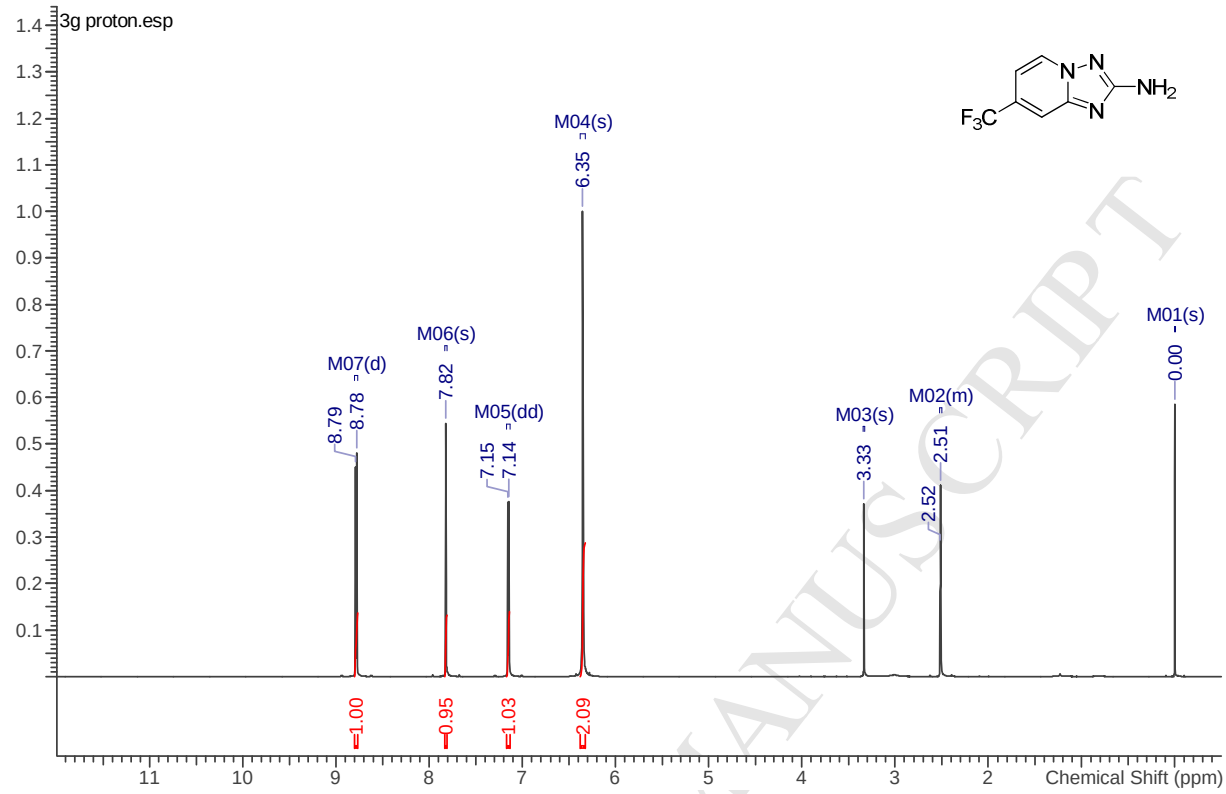


NOESY spectrum

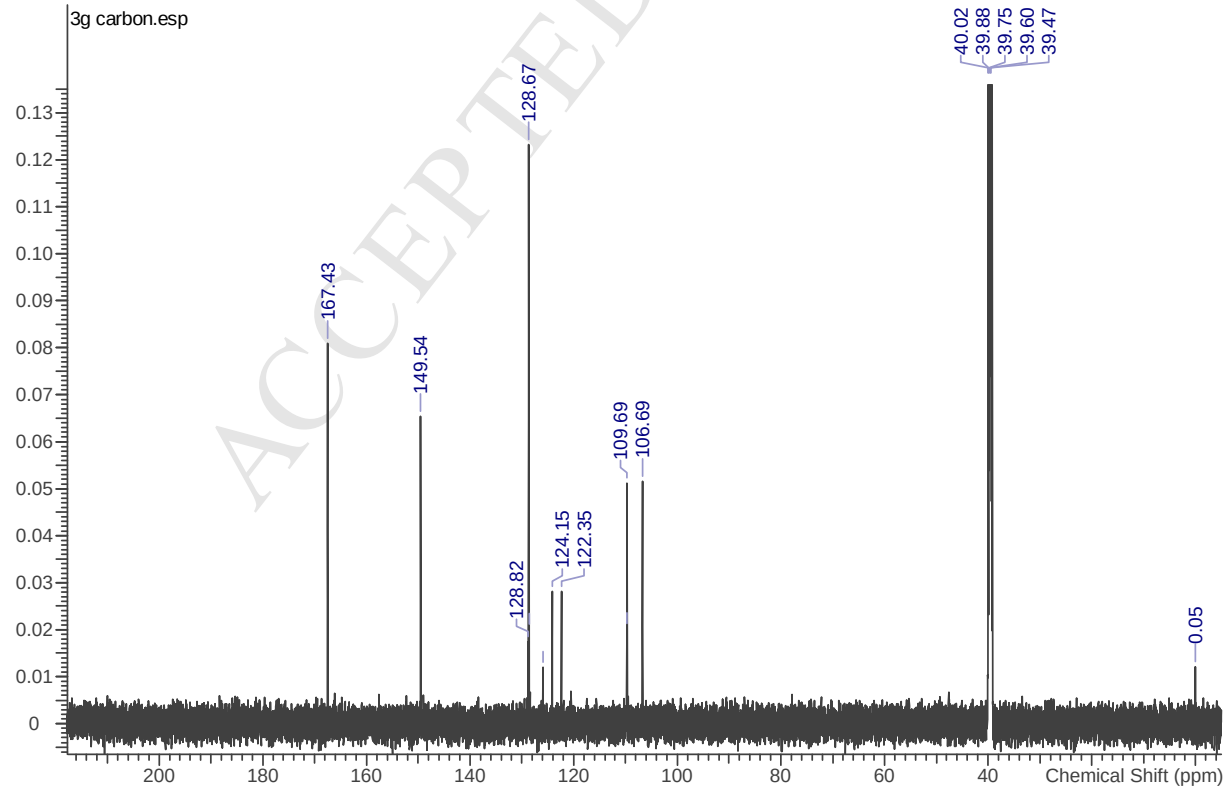


7-(trifluoromethyl)[1,2,4]triazolo[1,5-a]pyridin-2-amine (**3g**)

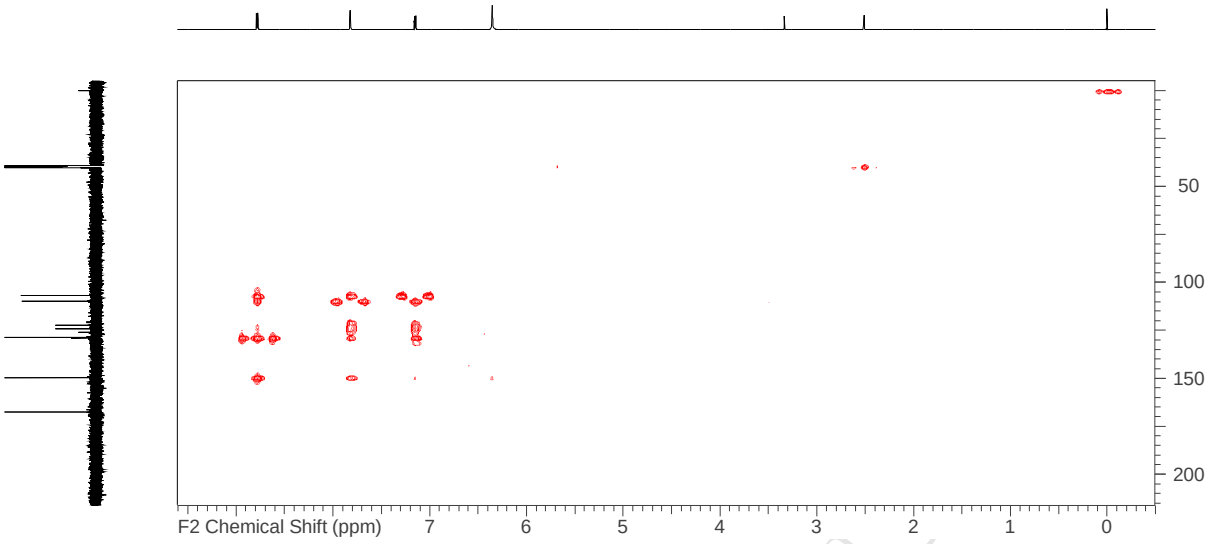
^{1}H NMR spectrum



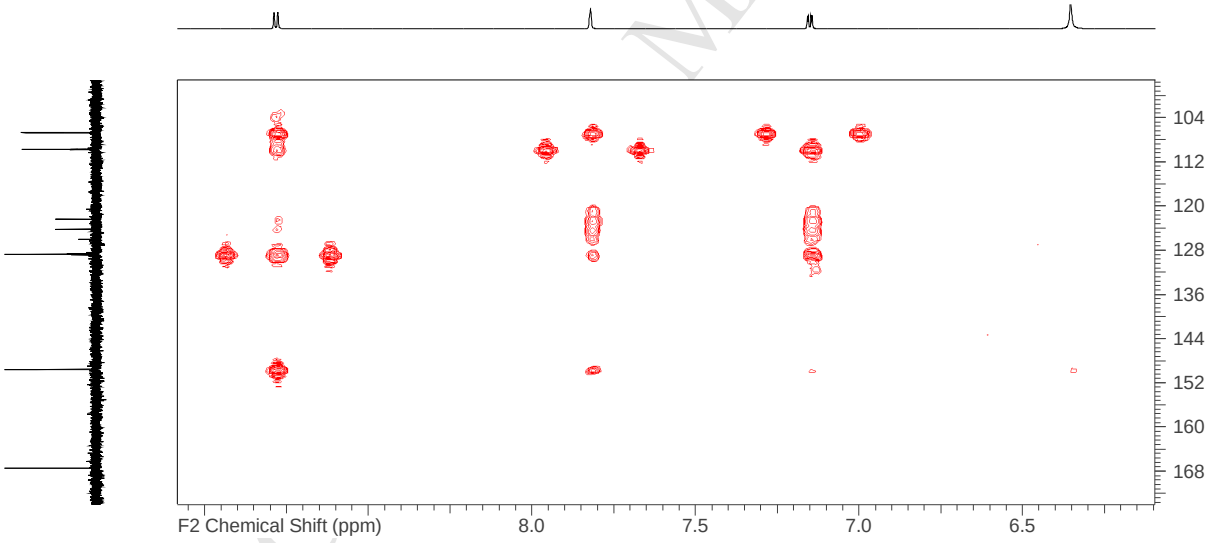
^{13}C NMR spectrum



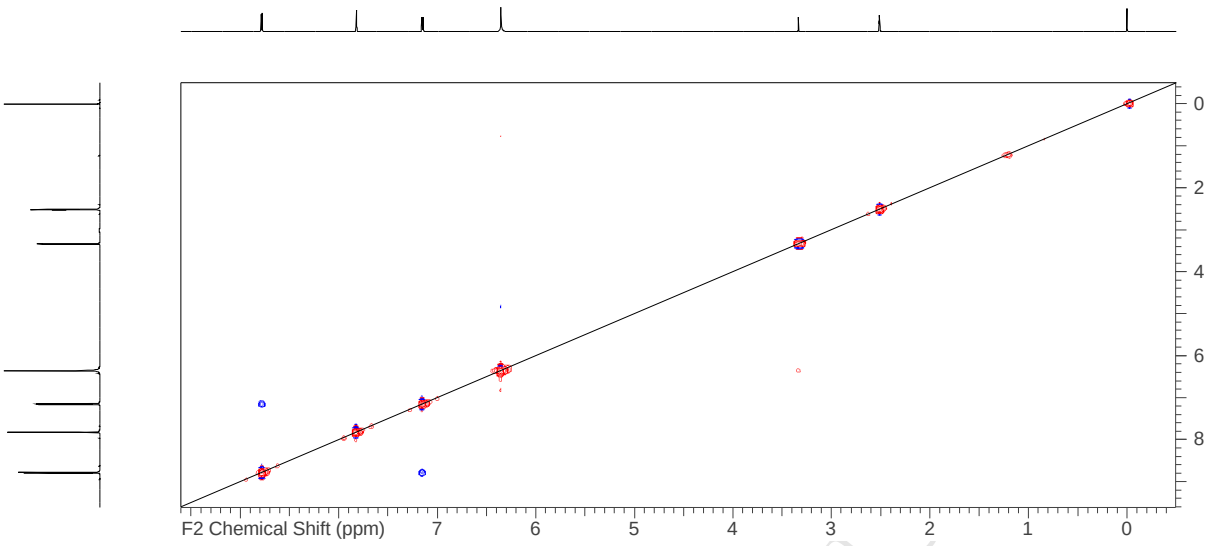
HMBC spectrum



HMBC spectrum (expansion of aromatic region)

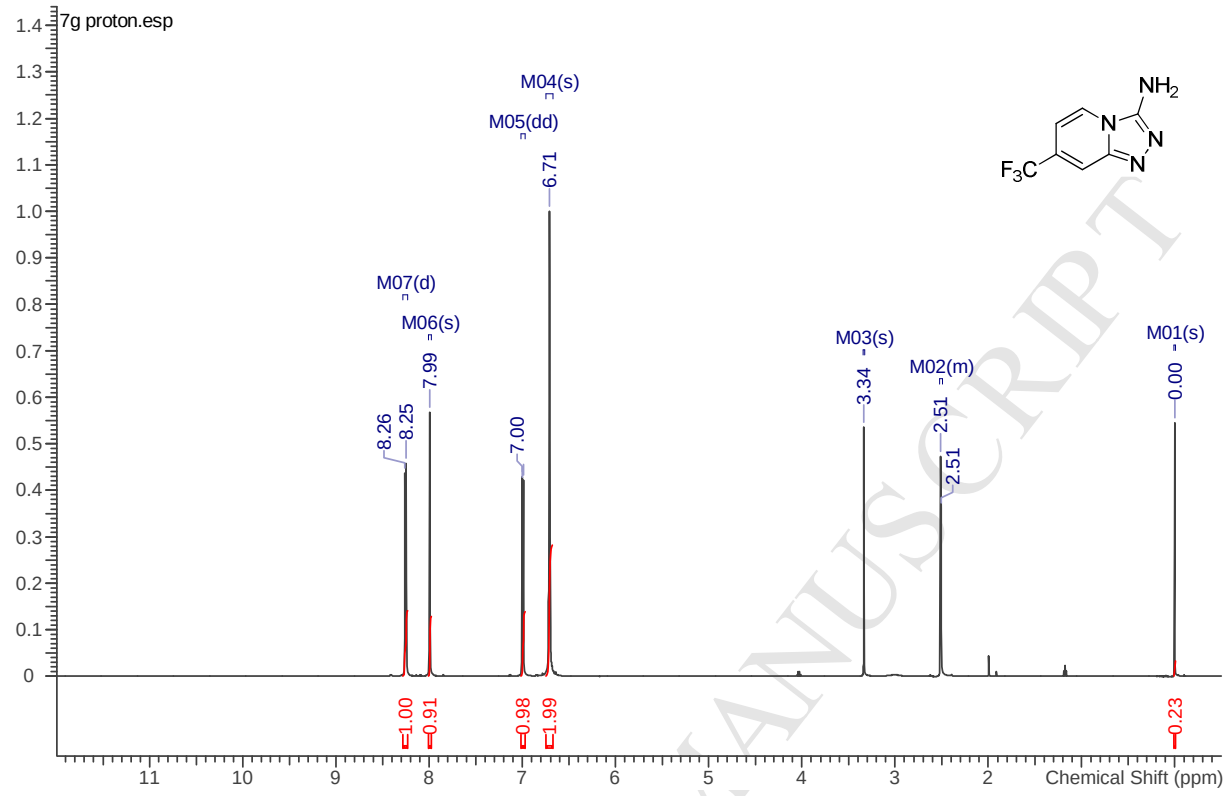


NOESY spectrum

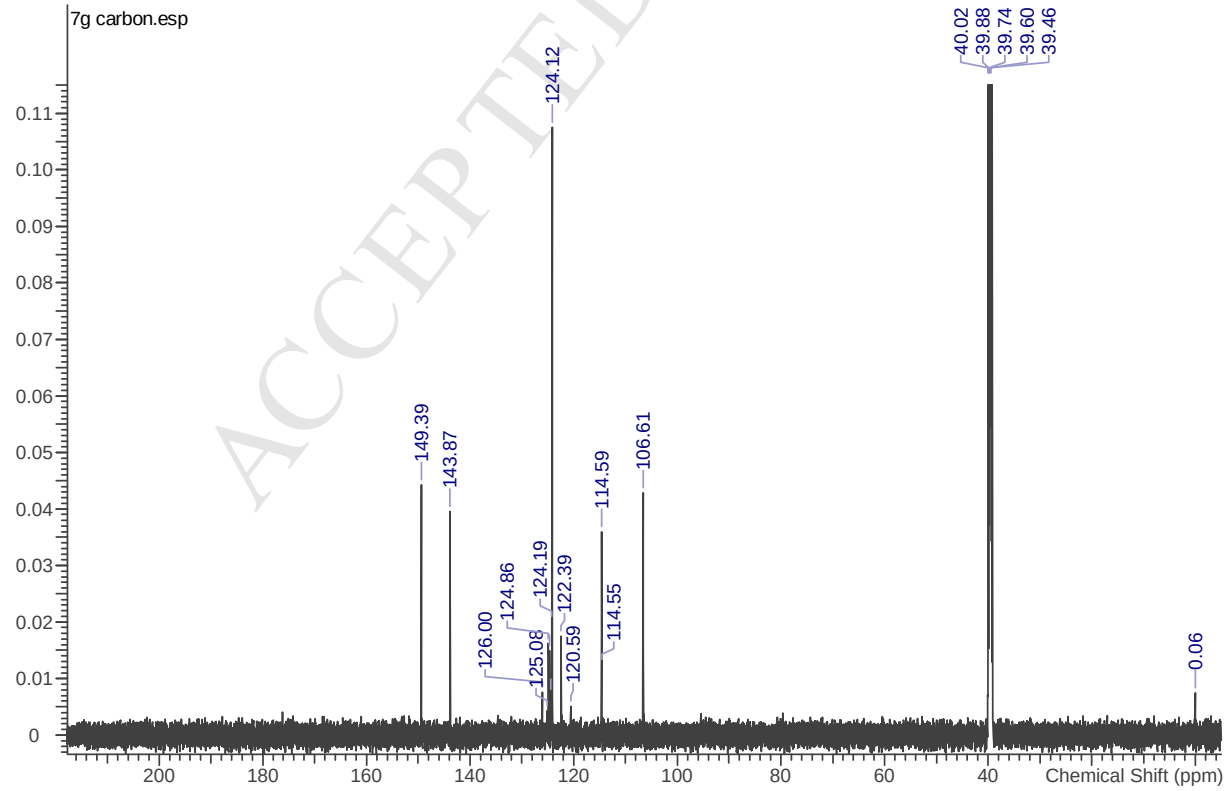


7-(trifluoromethyl)[1,2,4]triazolo[4,3-a]pyridin-3-amine (**7g**)

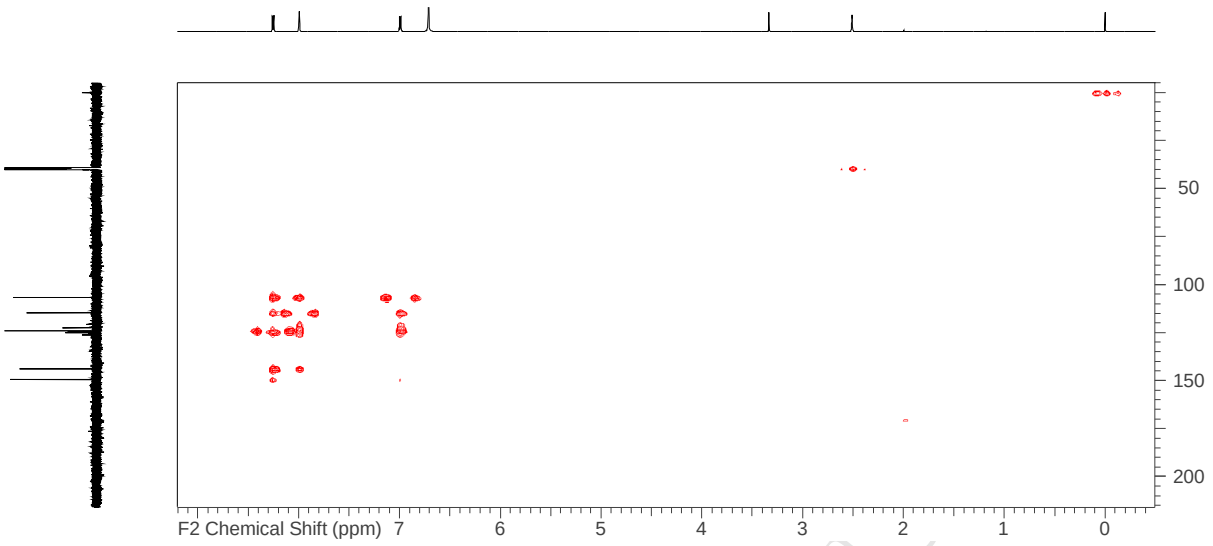
^{1}H NMR spectrum



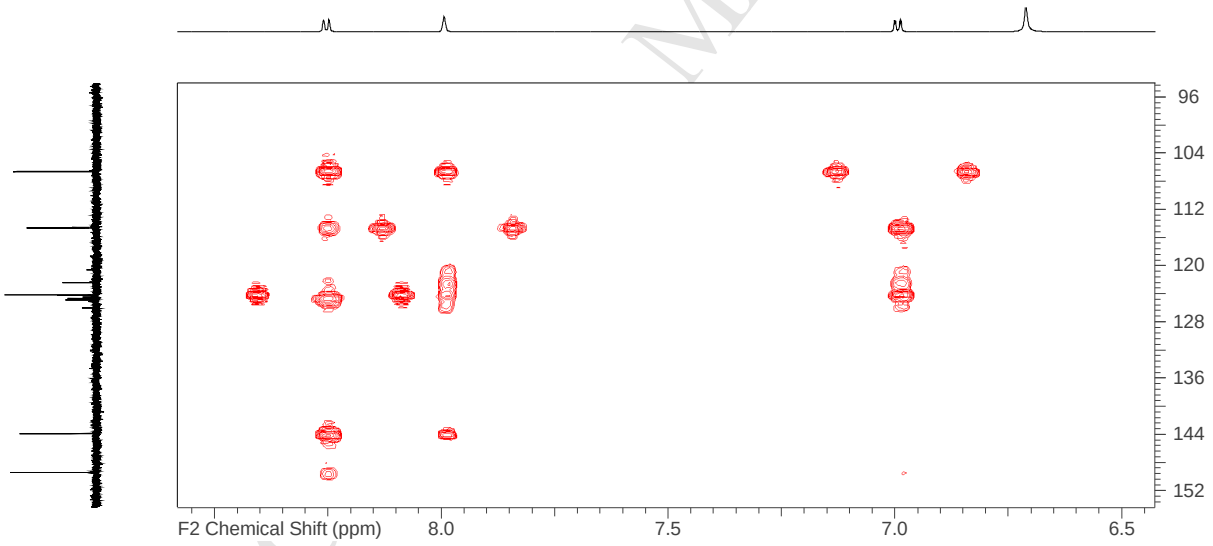
^{13}C NMR spectrum



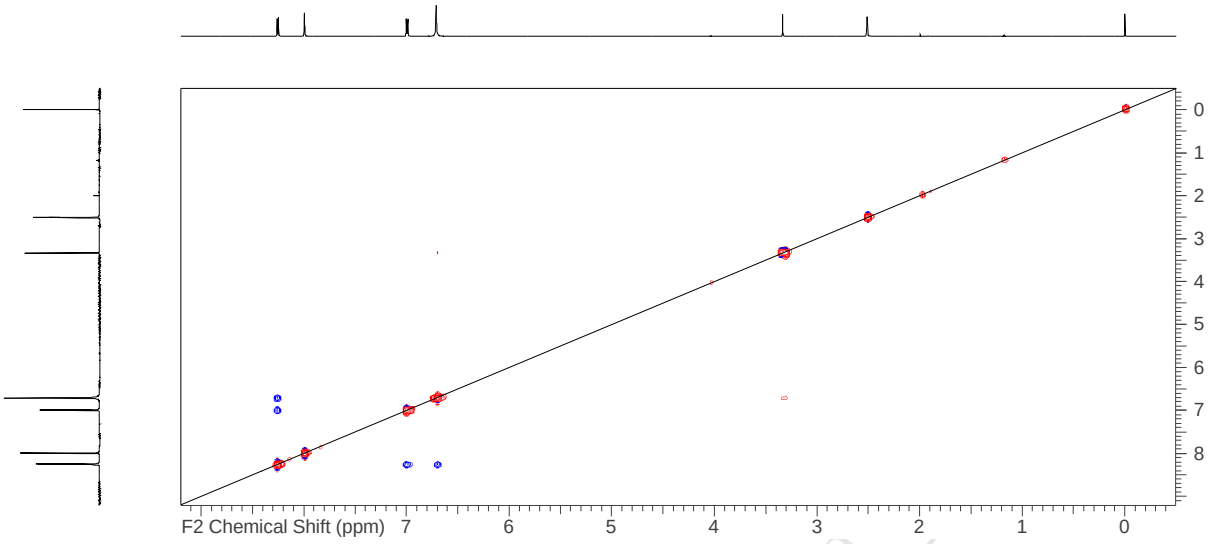
HMBC spectrum



HMBC spectrum (expansion of aromatic region)

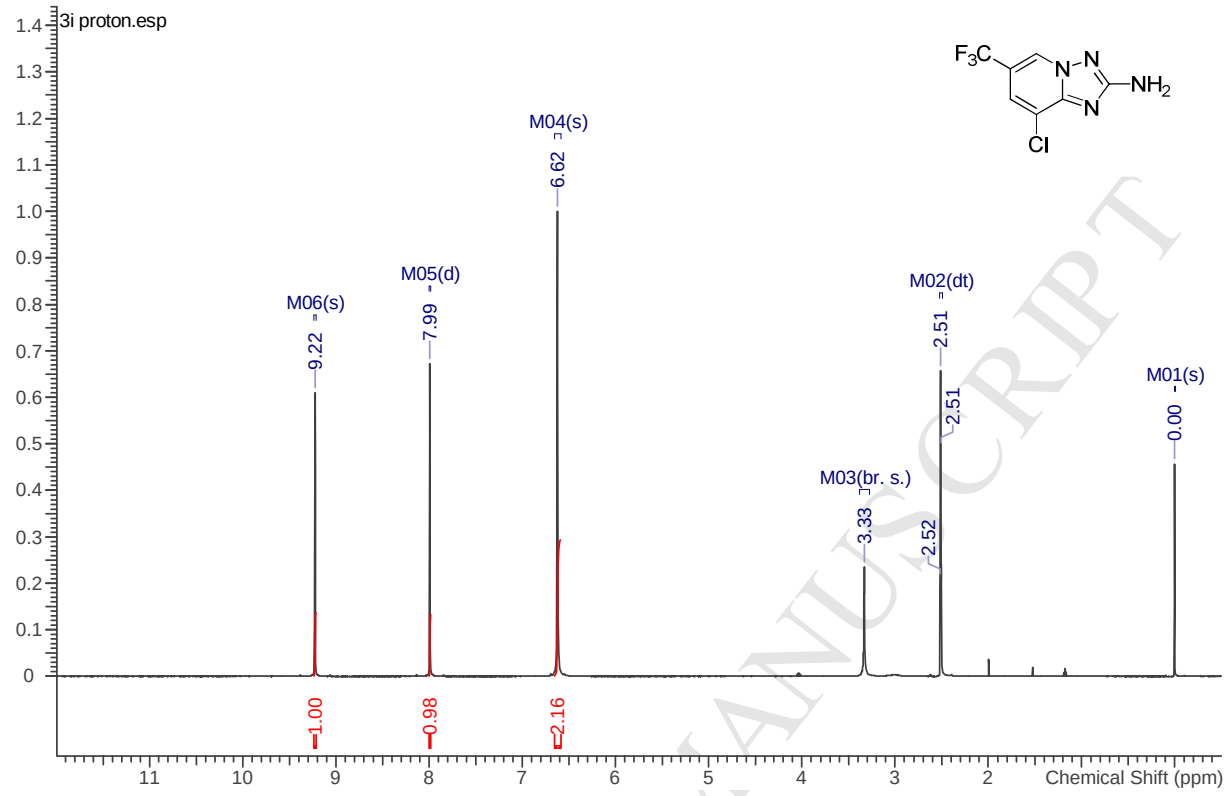


NOESY spectrum

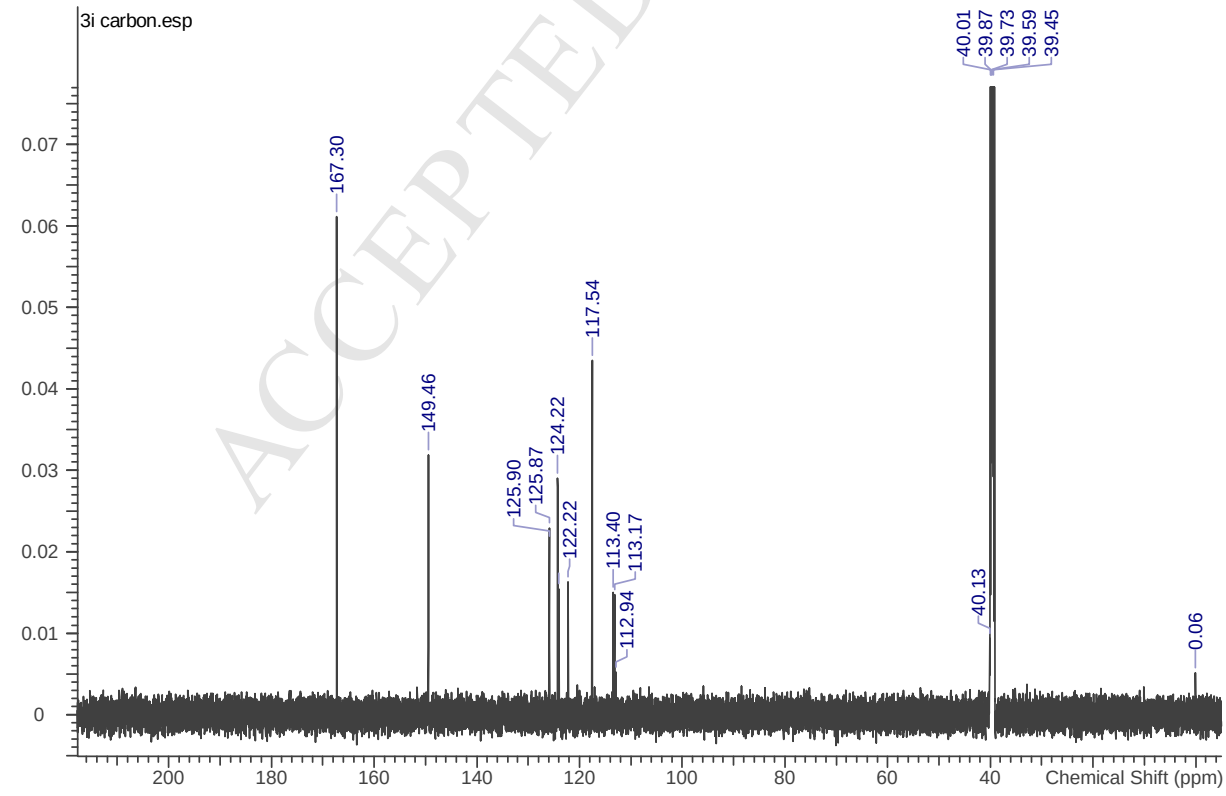


8-chloro-6-(trifluoromethyl)[1,2,4]triazolo[1,5-a]pyridin-2-amine (**3i**)

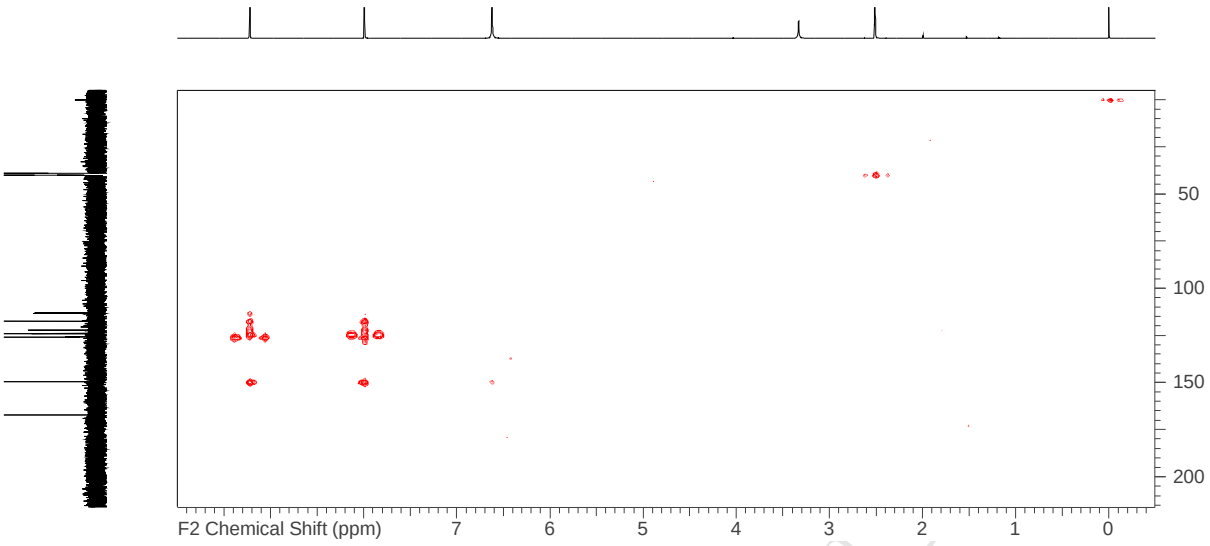
^{1}H NMR spectrum



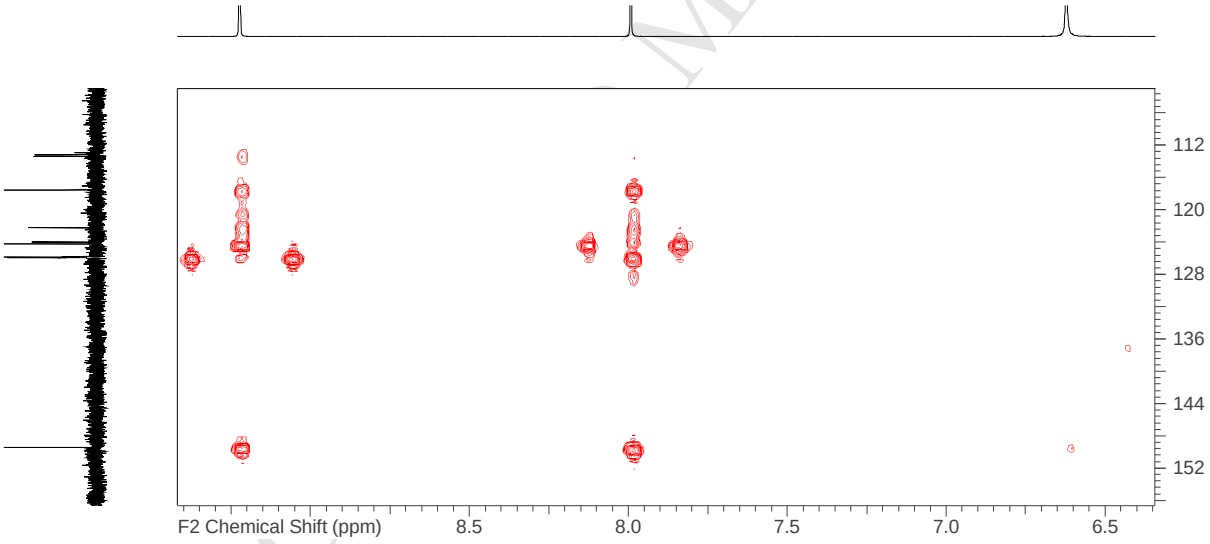
^{13}C NMR spectrum



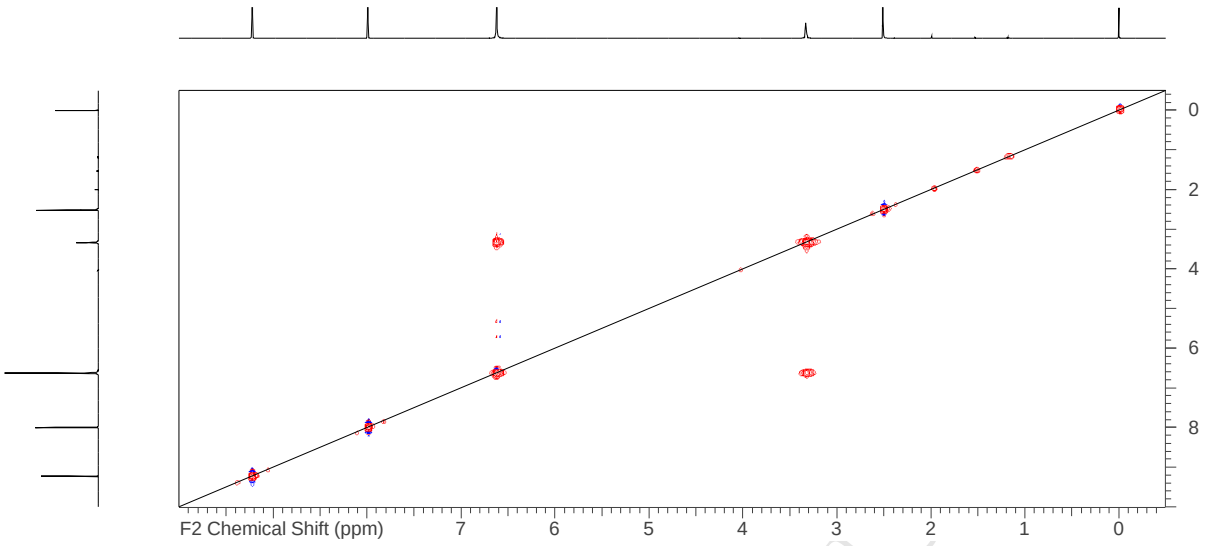
HMBC spectrum



HMBC spectrum (expansion of aromatic region)

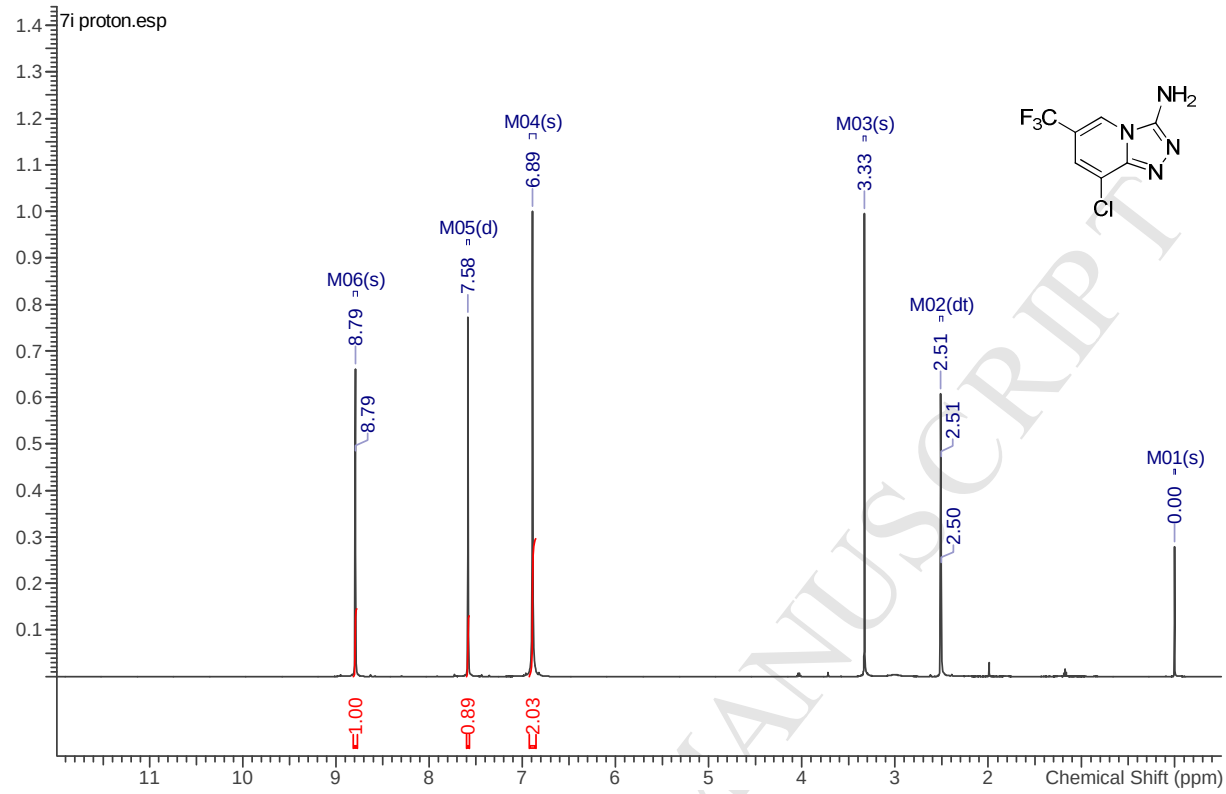


NOESY spectrum

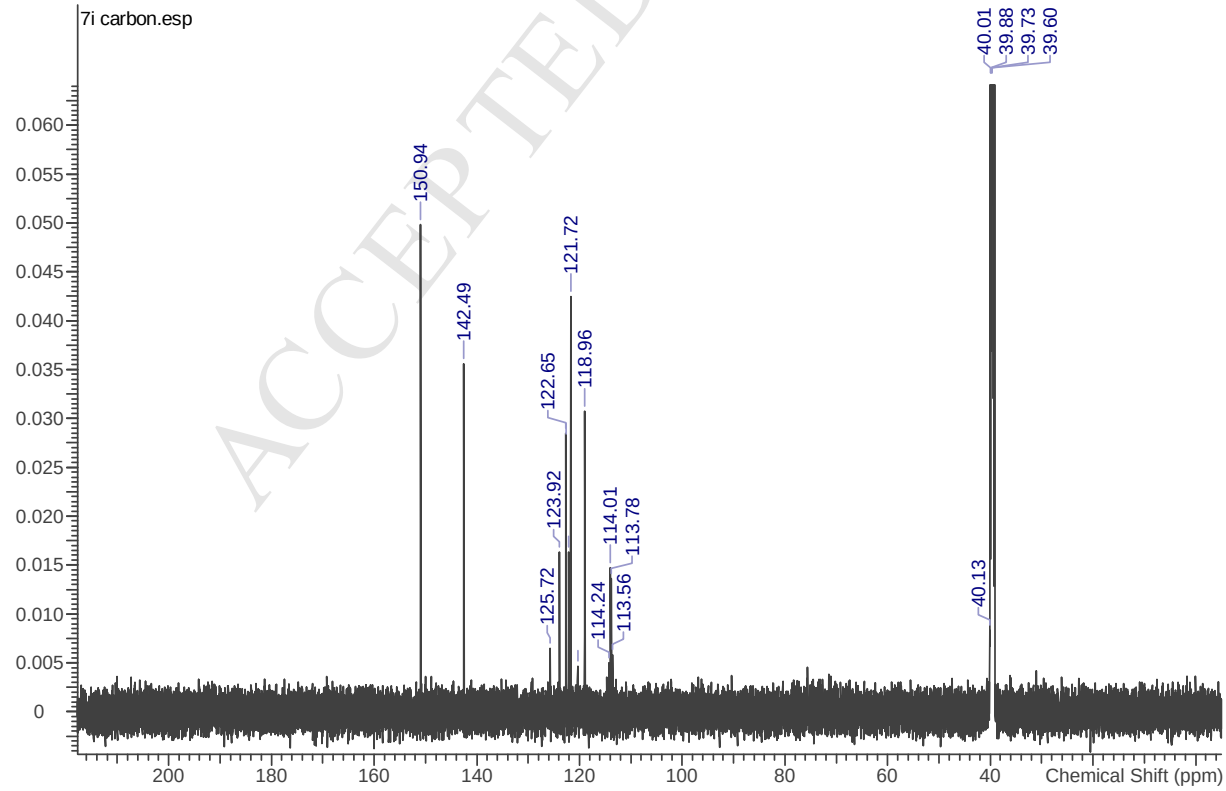


8-chloro-6-(trifluoromethyl)[1,2,4]triazolo[4,3-a]pyridin-3-amine (**7i**)

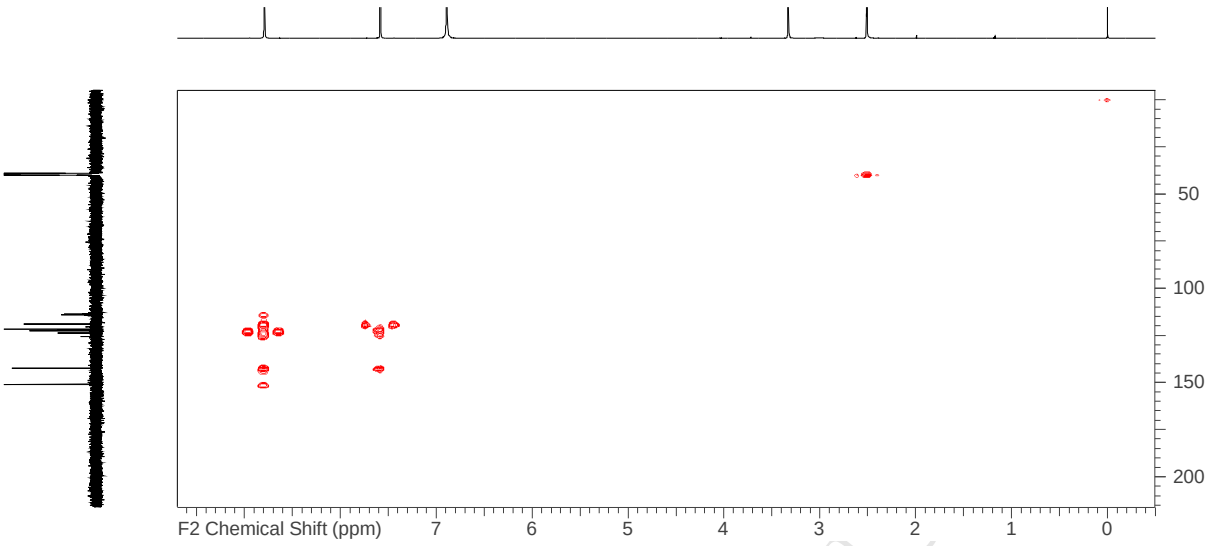
^{1}H NMR spectrum



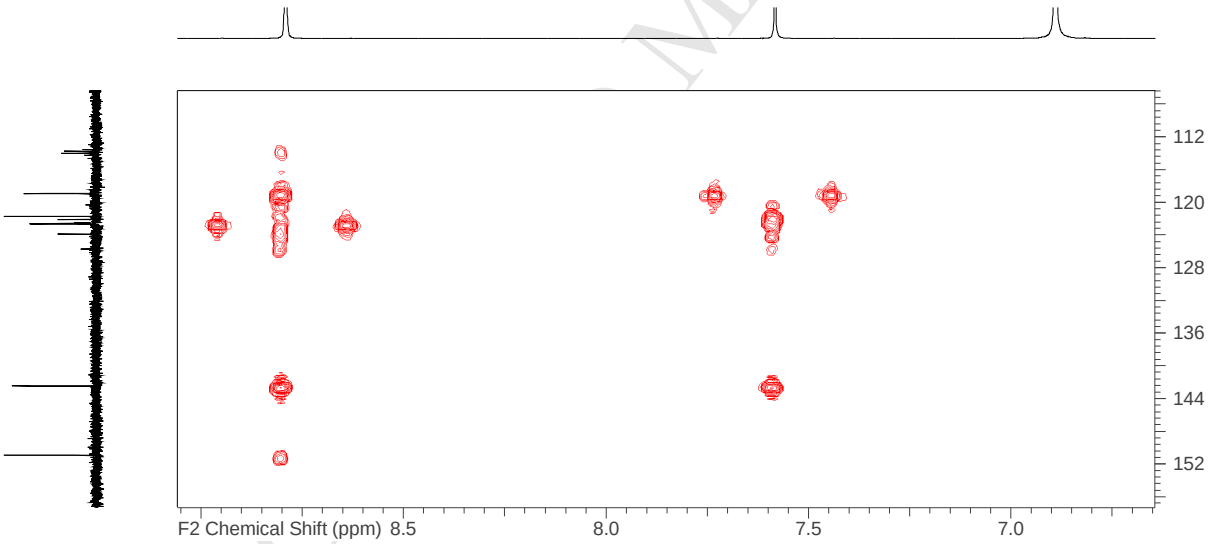
^{13}C NMR spectrum



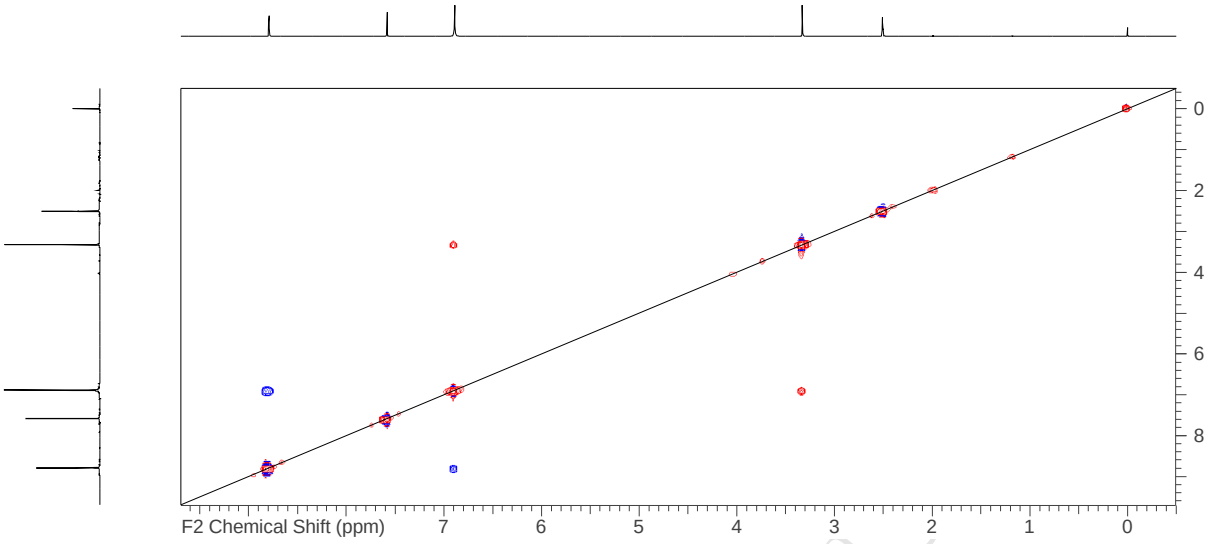
HMBC spectrum



HMBC spectrum (expansion of aromatic region)

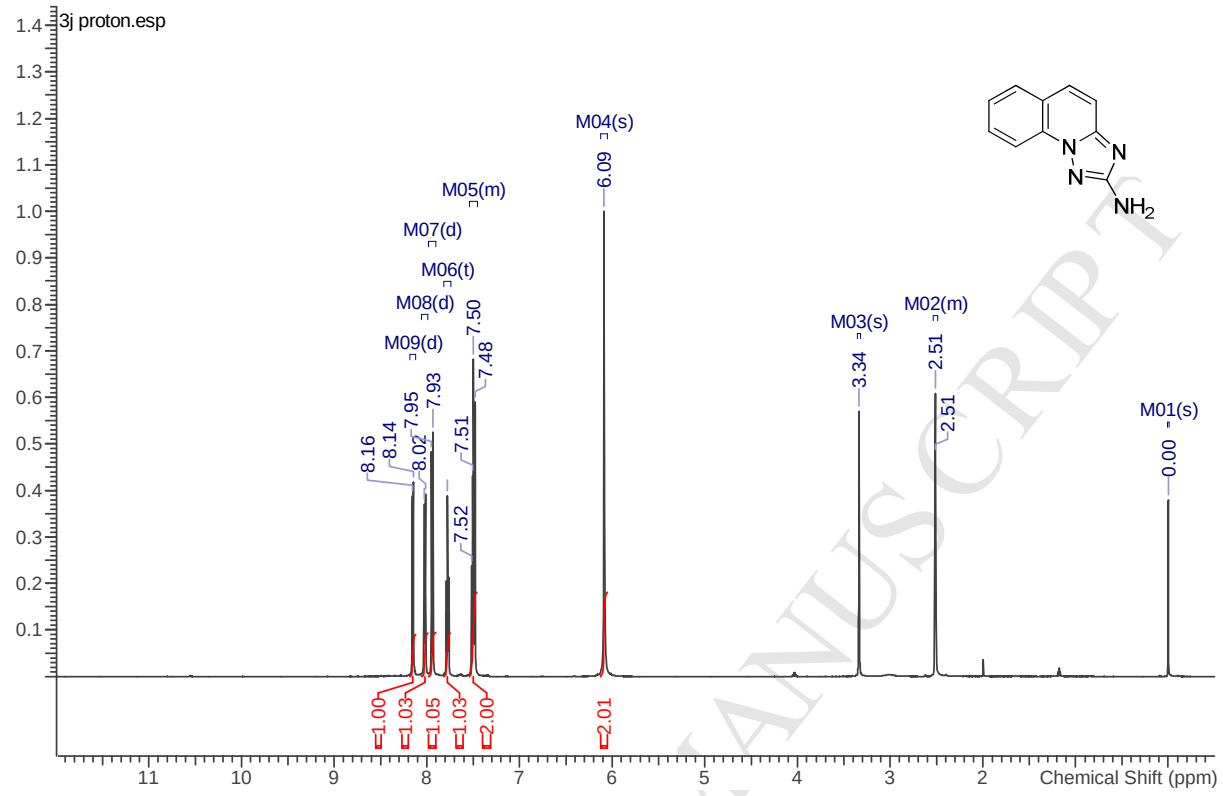


NOESY spectrum

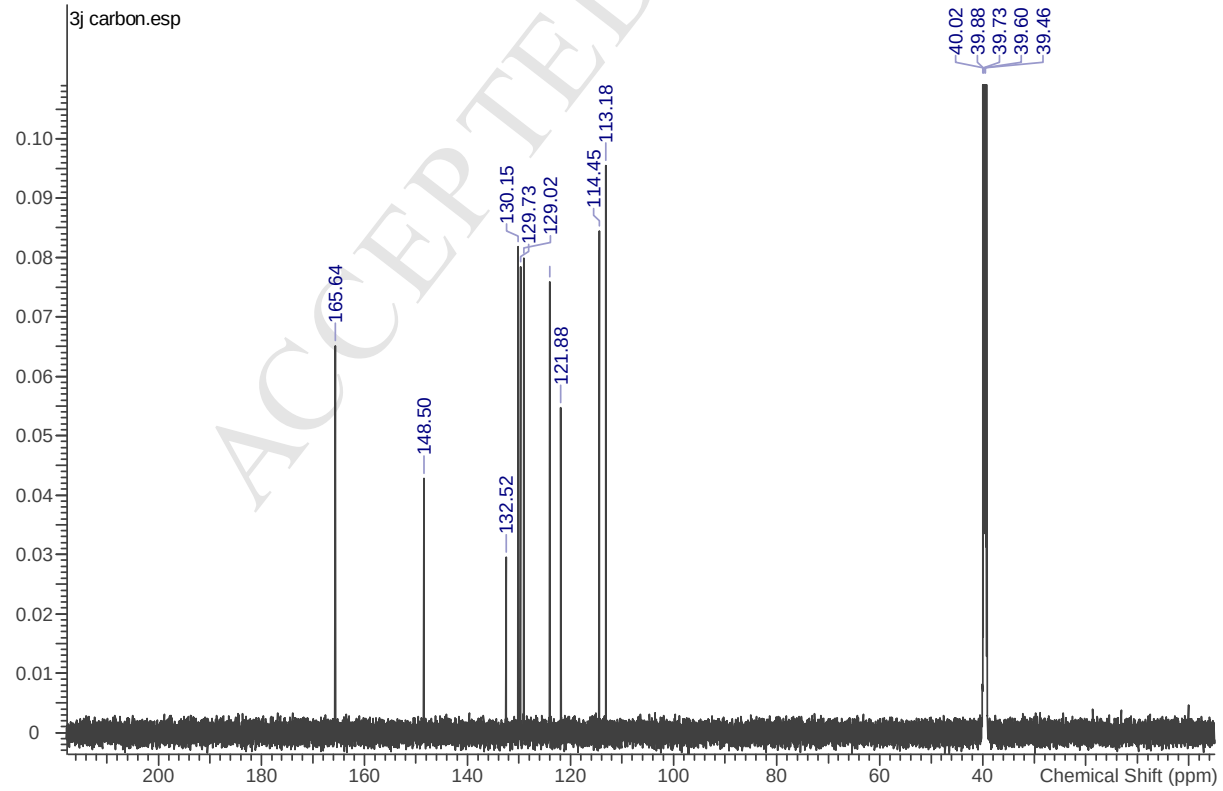


[1,2,4]triazolo[1,5-a]quinolin-2-amine (**3j**)

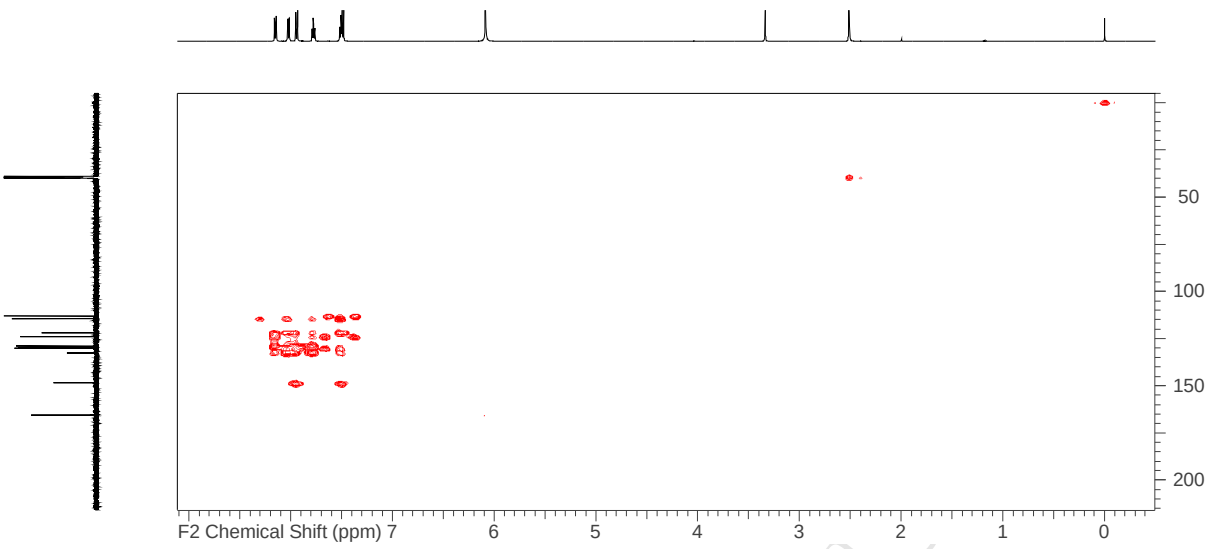
^{1}H NMR spectrum



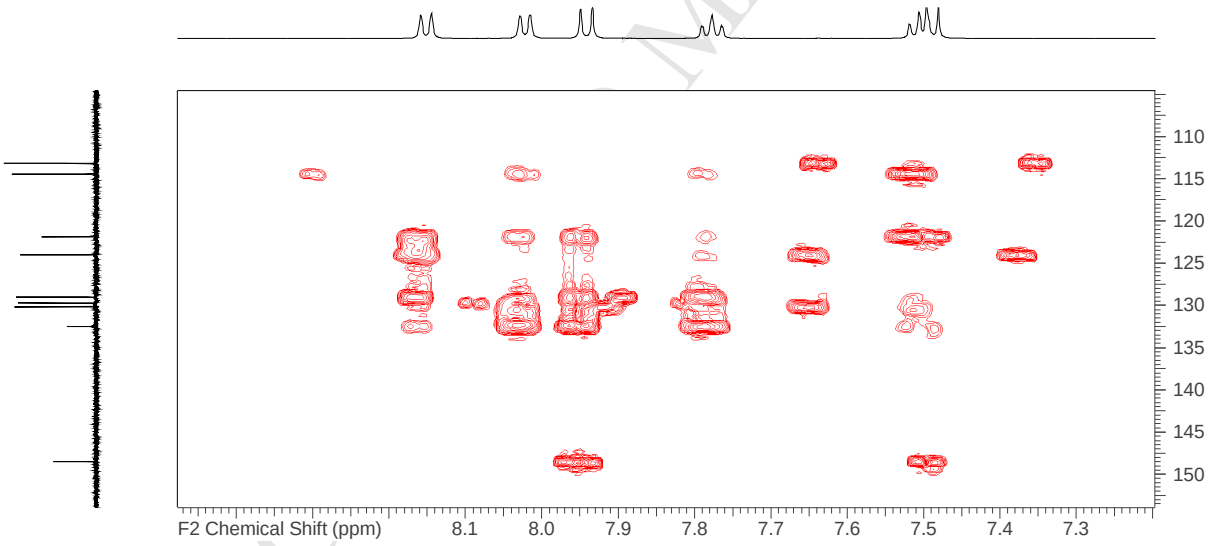
^{13}C NMR spectrum



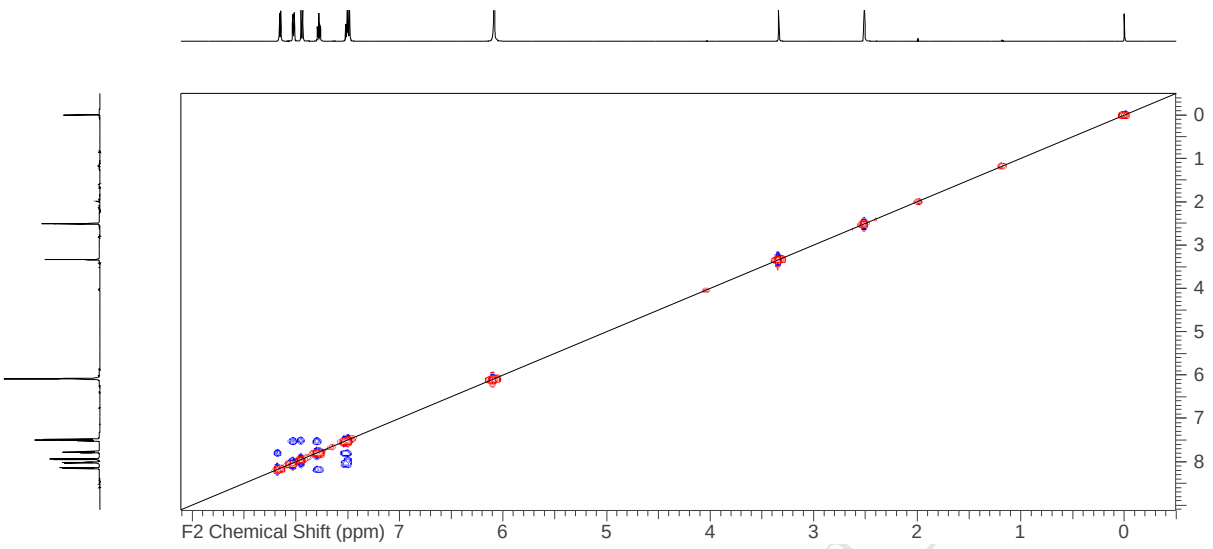
HMBC spectrum



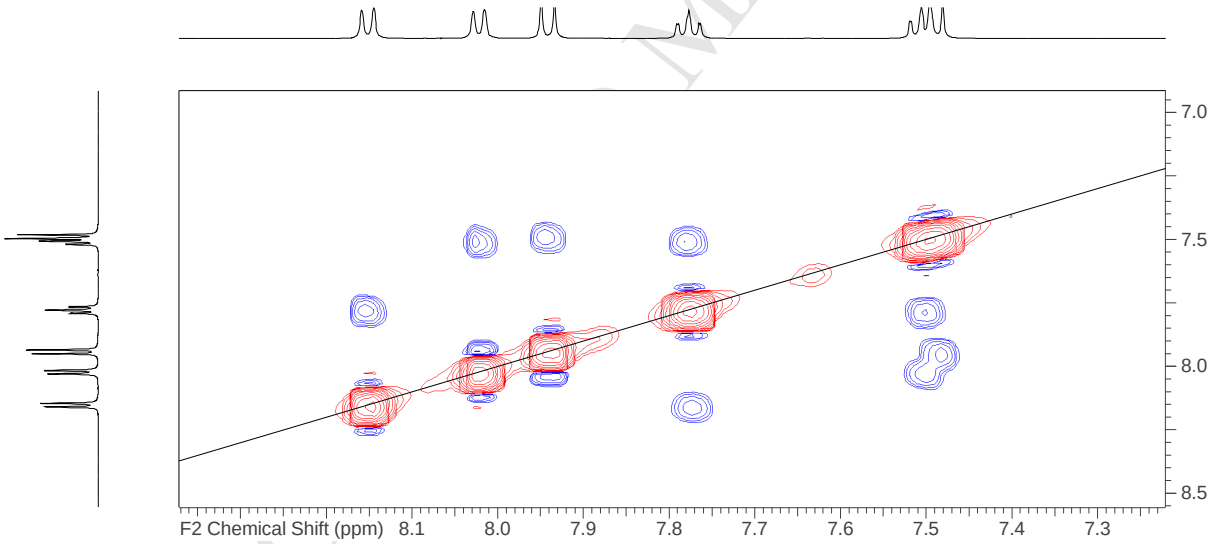
HMBC spectrum (expansion of aromatic region)



NOESY spectrum

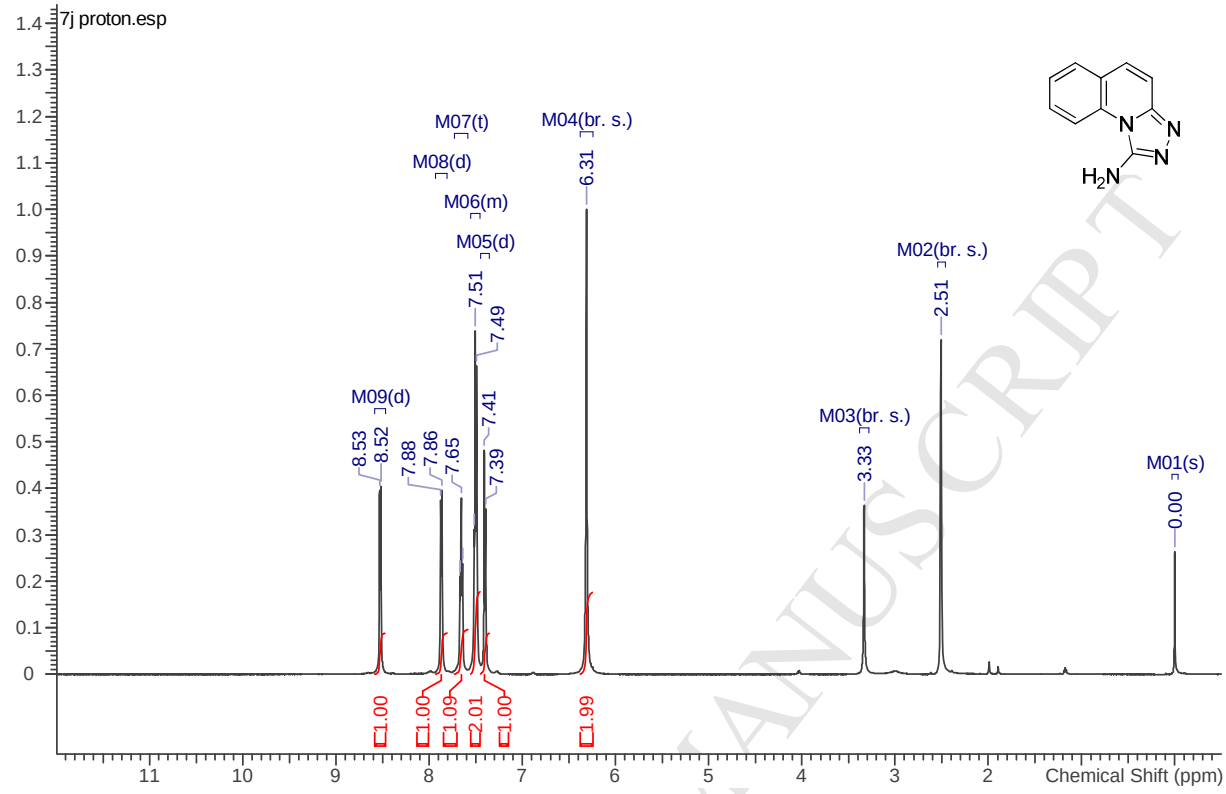


NOESY spectrum (expansion of aromatic region)

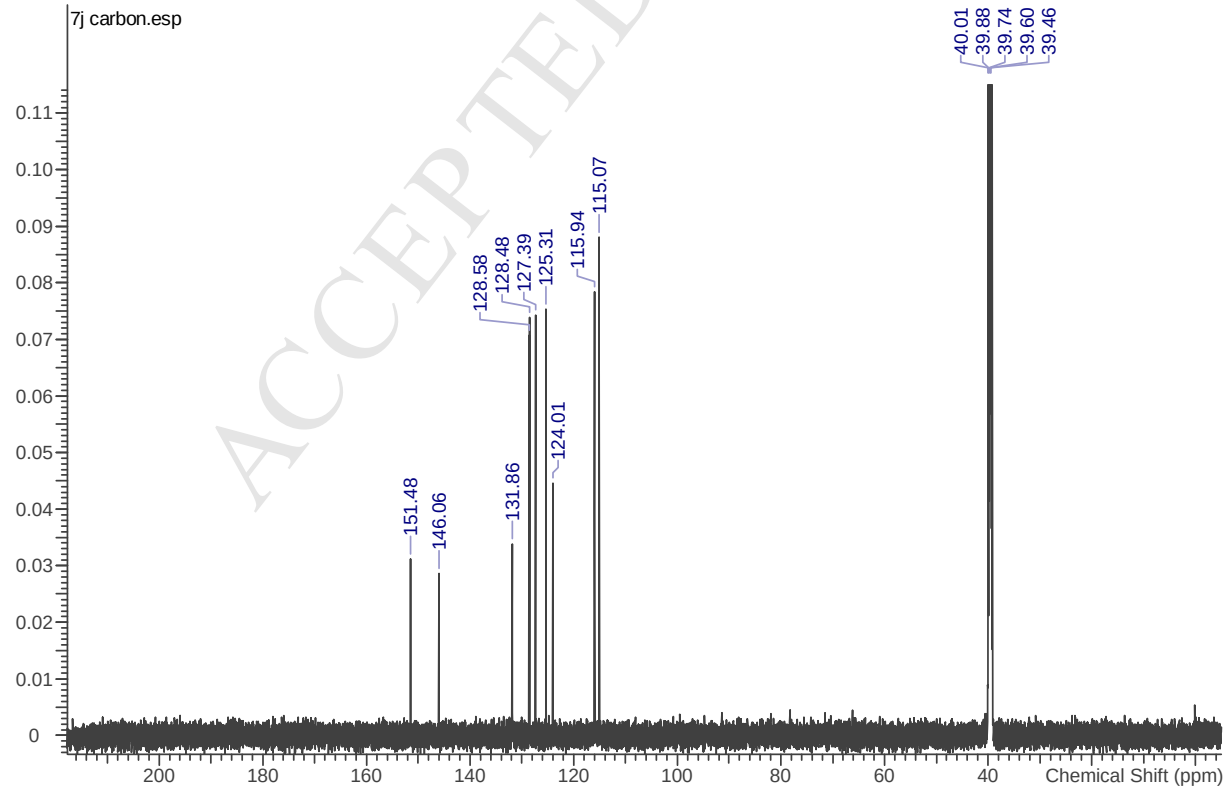


[1,2,4]triazolo[4,3-a]quinolin-1-amine (**7j**)

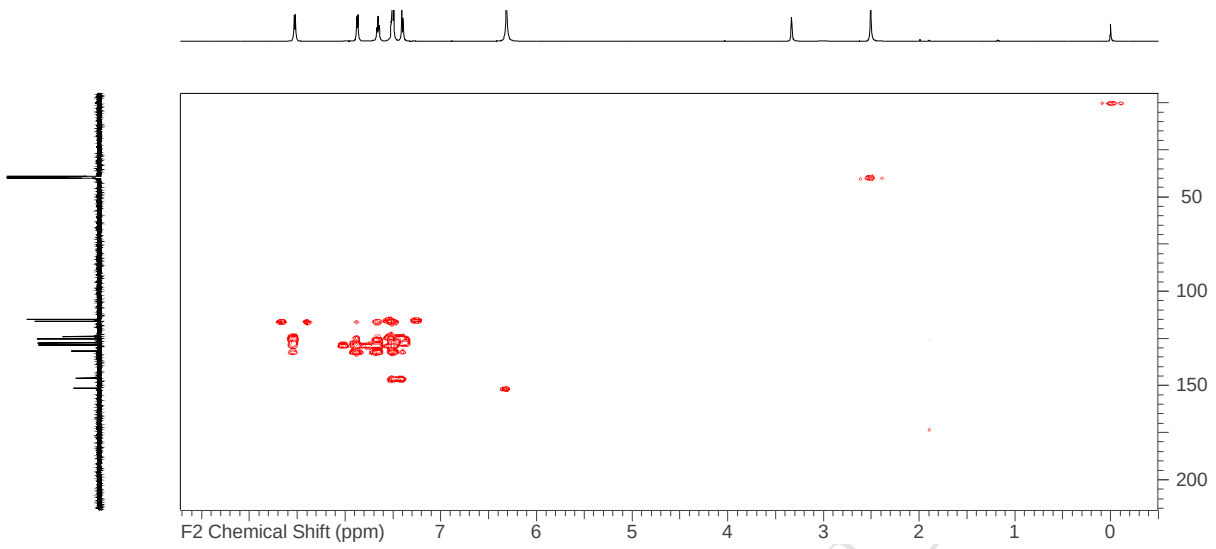
^{1}H NMR spectrum



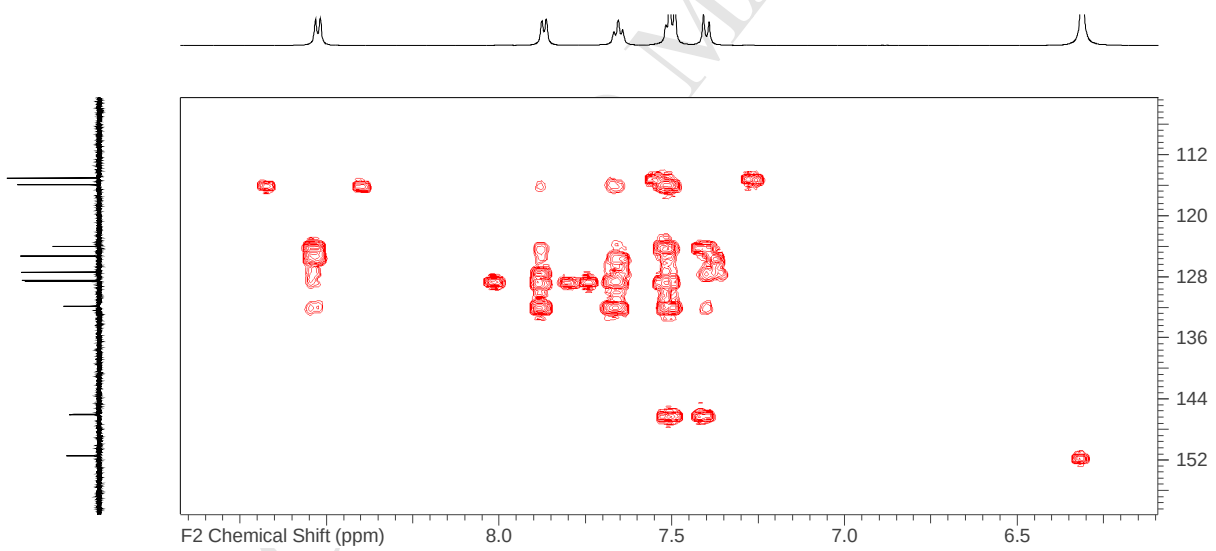
^{13}C NMR spectrum



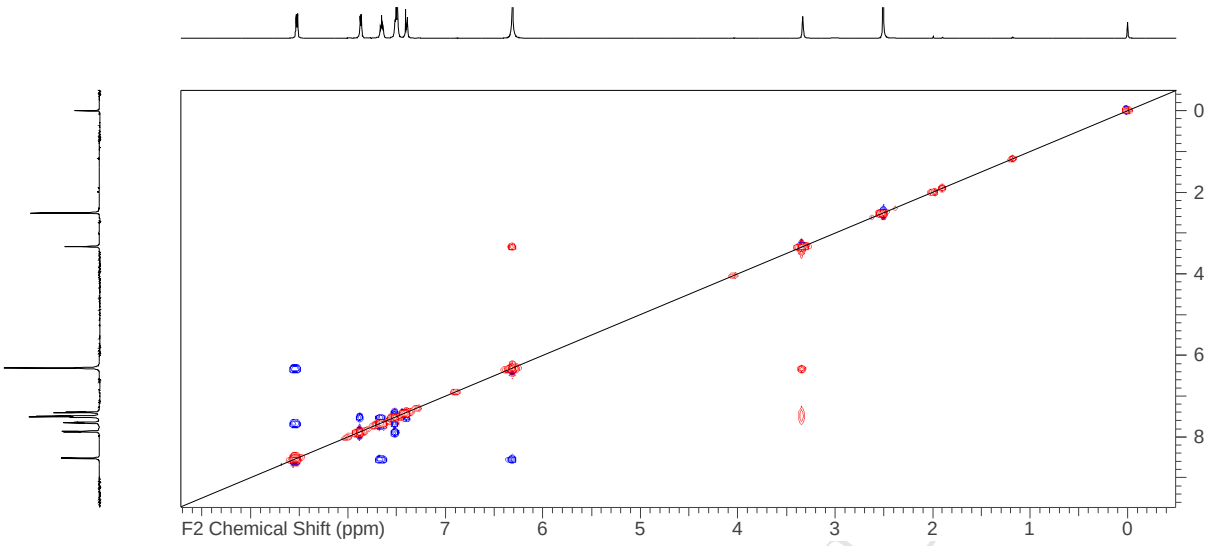
HMBC spectrum



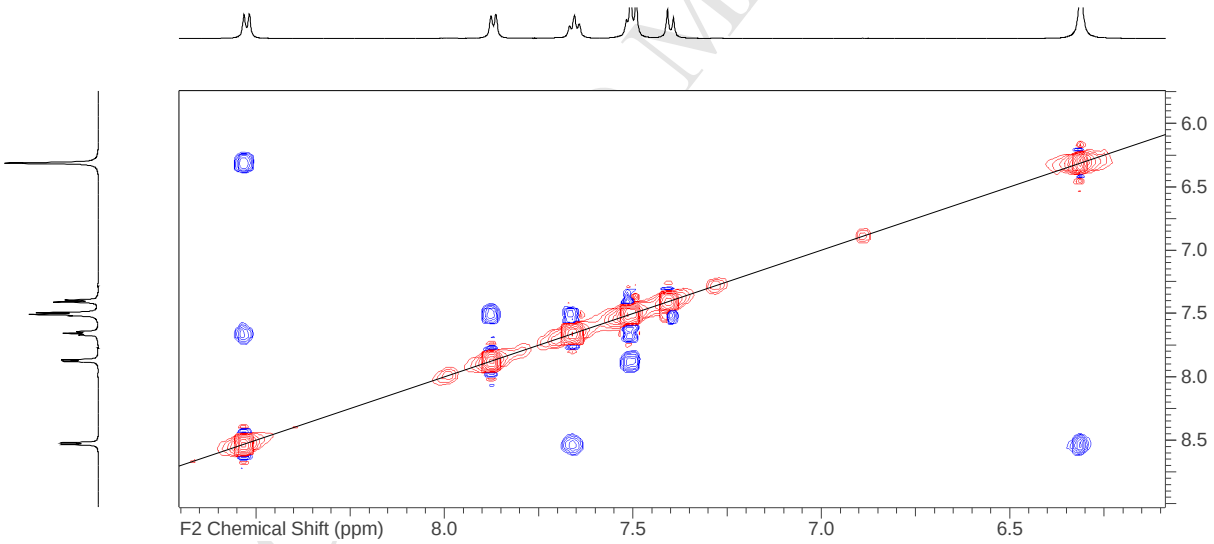
HMBC spectrum (expansion of aromatic region)



NOESY spectrum

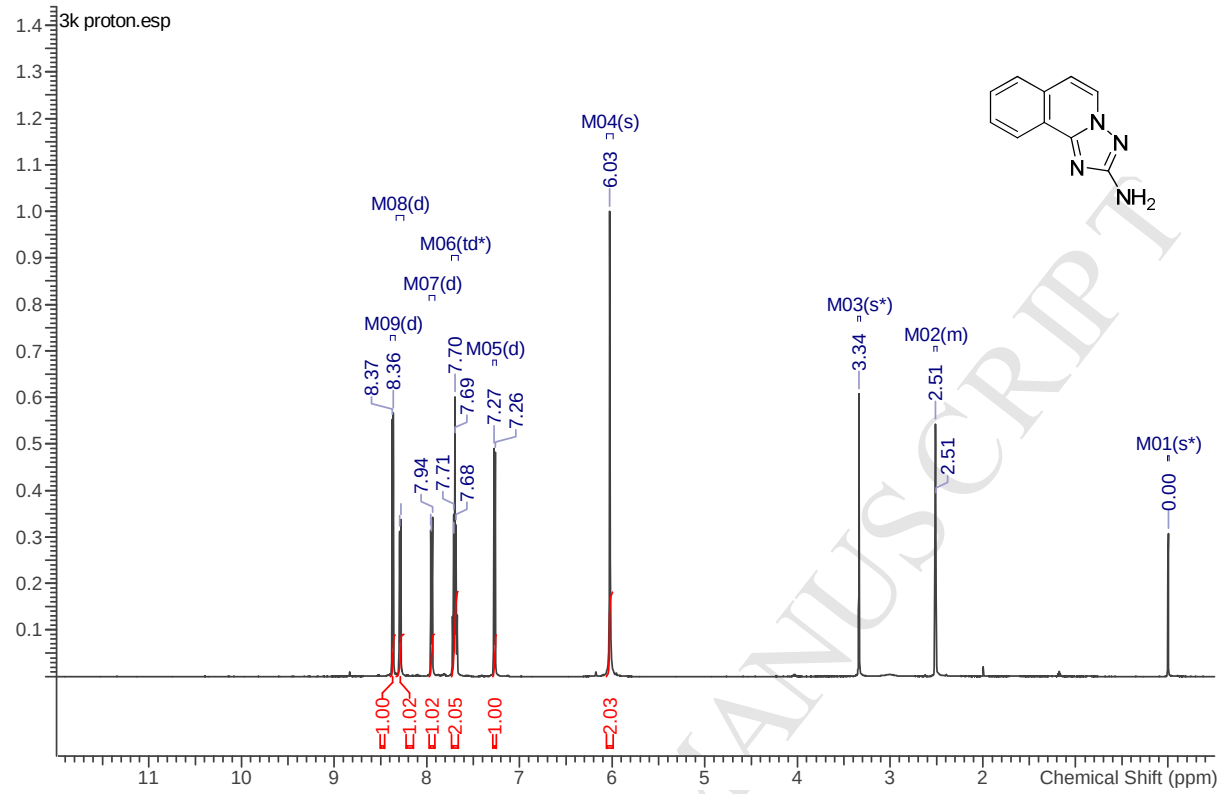


NOESY spectrum (expansion of aromatic region)

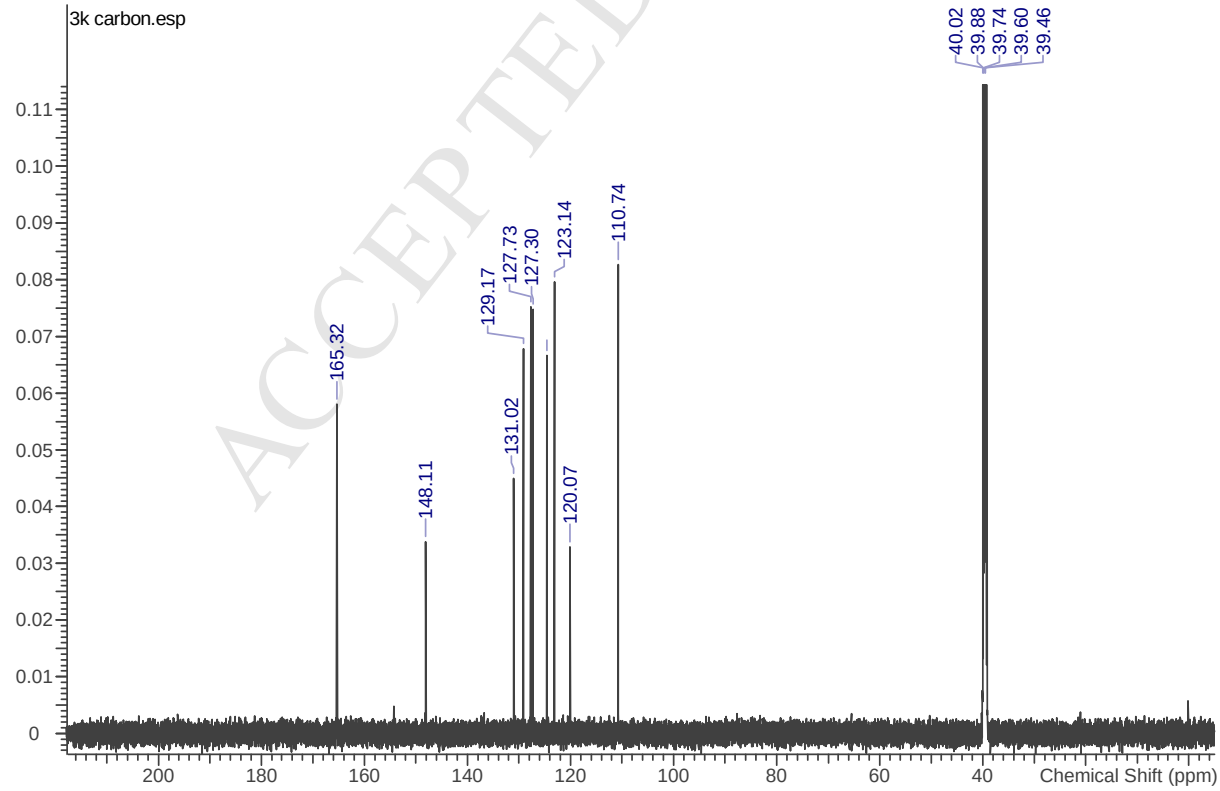


[1,2,4]triazolo[5,1-a]isoquinolin-2-amine (**3k**)

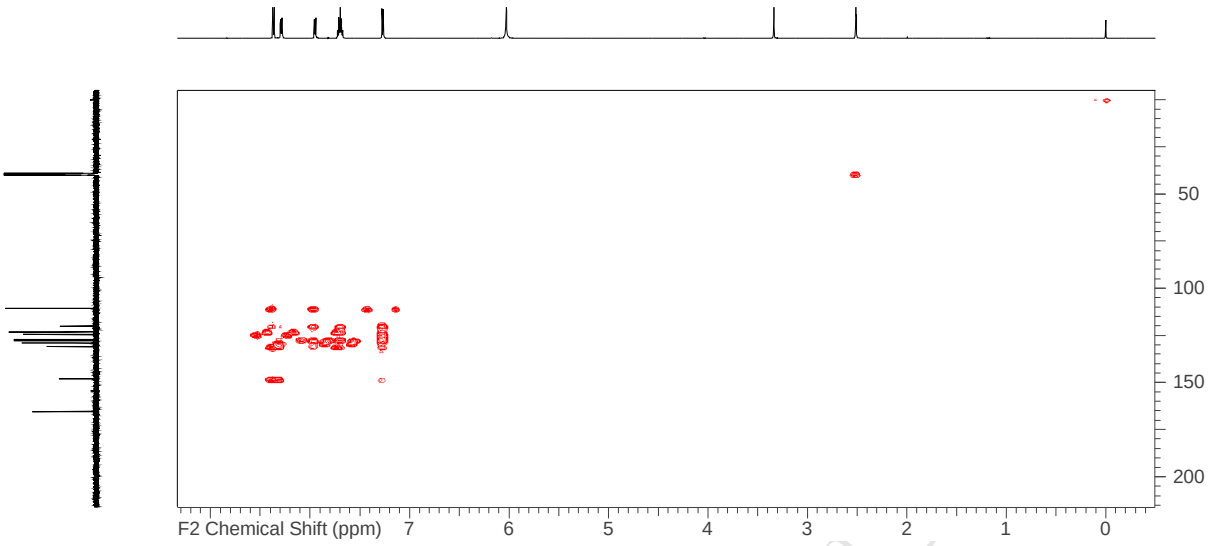
^{1}H NMR spectrum



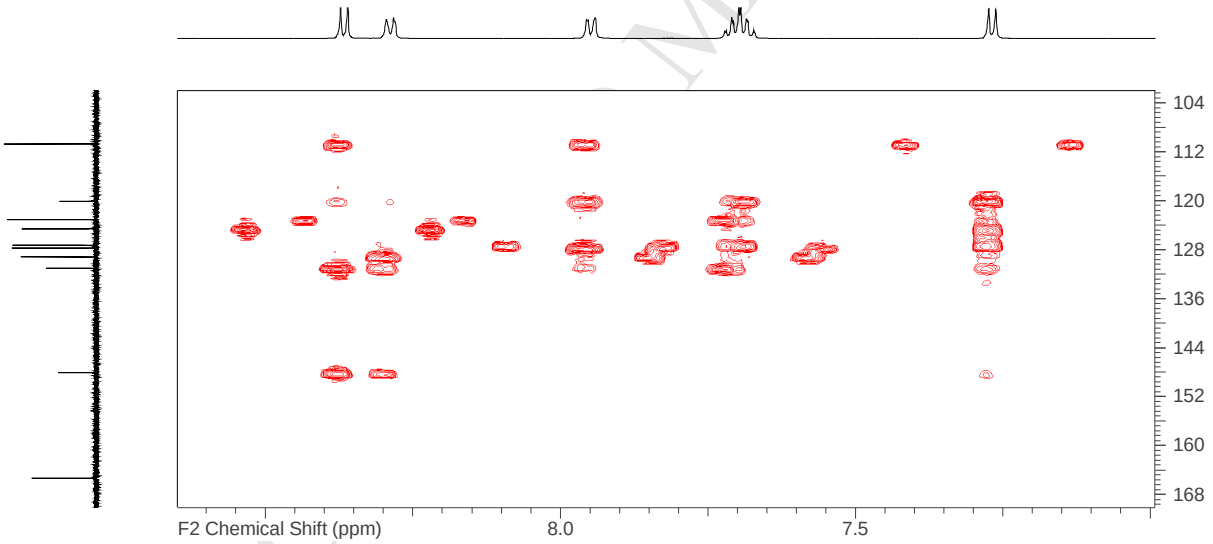
^{13}C NMR spectrum



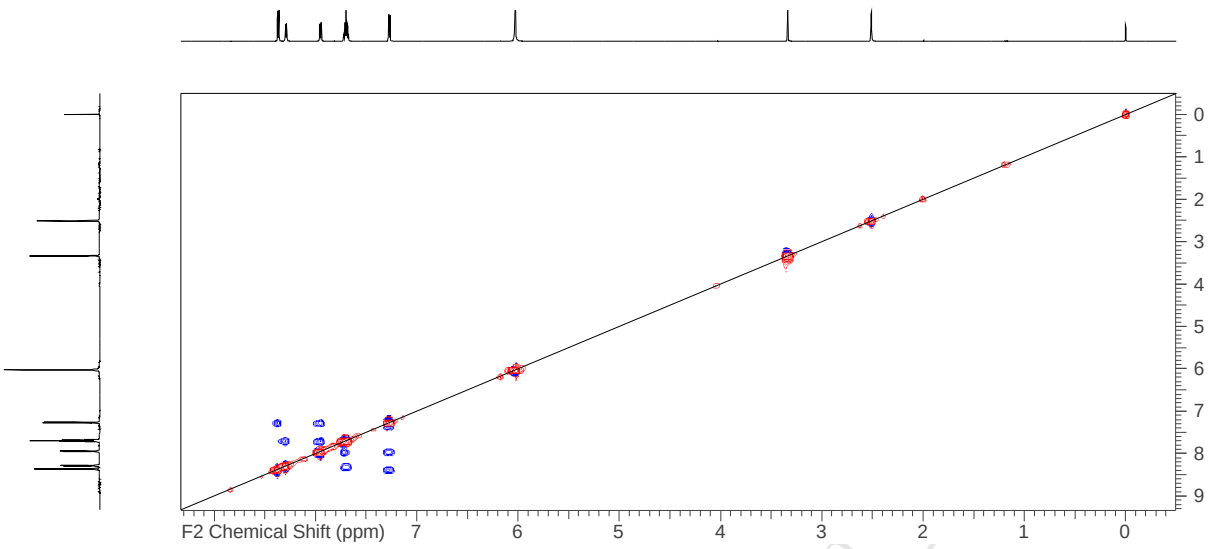
HMBC spectrum



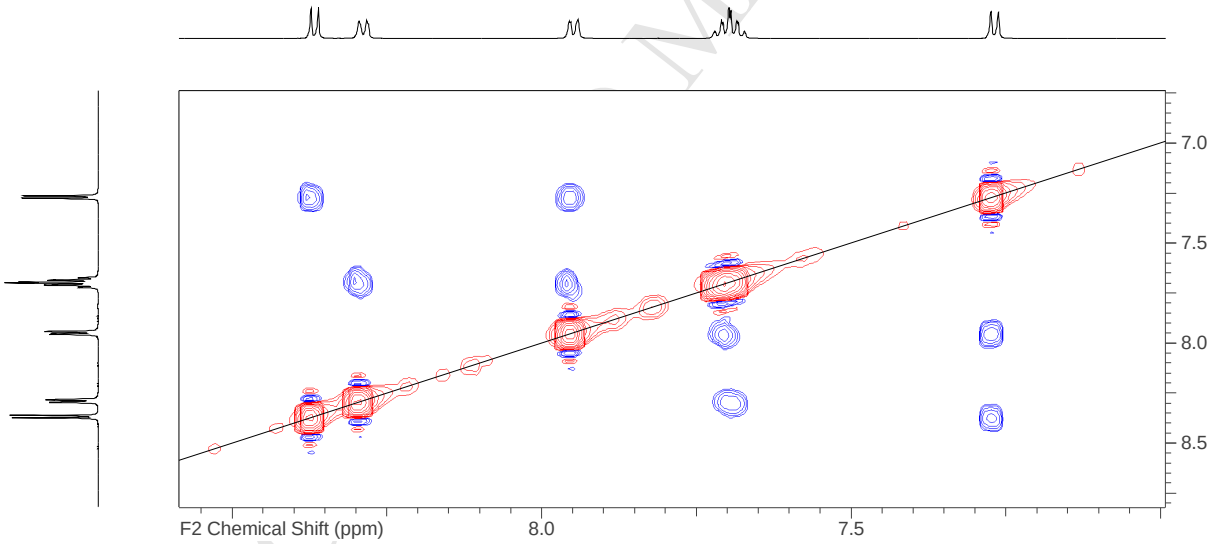
HMBC spectrum (expansion of aromatic region)



NOESY spectrum

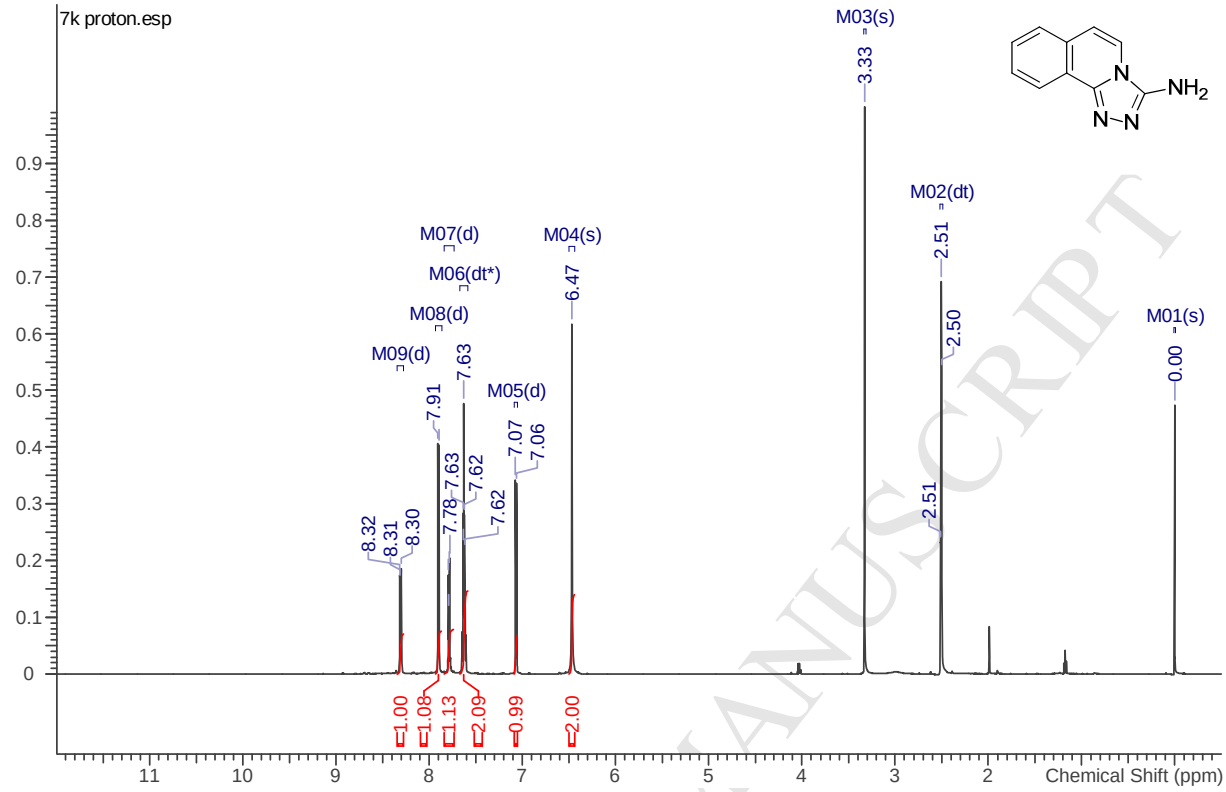


NOESY spectrum (expansion of aromatic region)

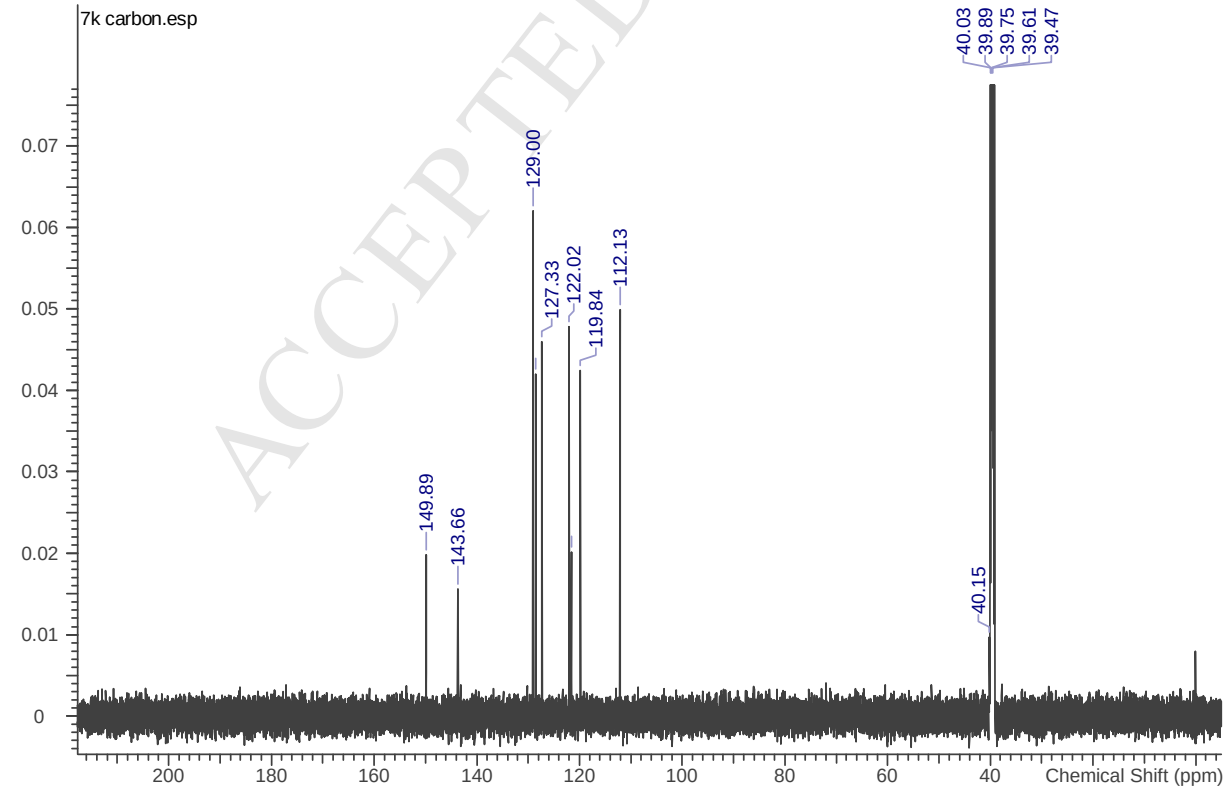


[1,2,4]triazolo[3,4-a]isoquinolin-3-amine (**7k**)

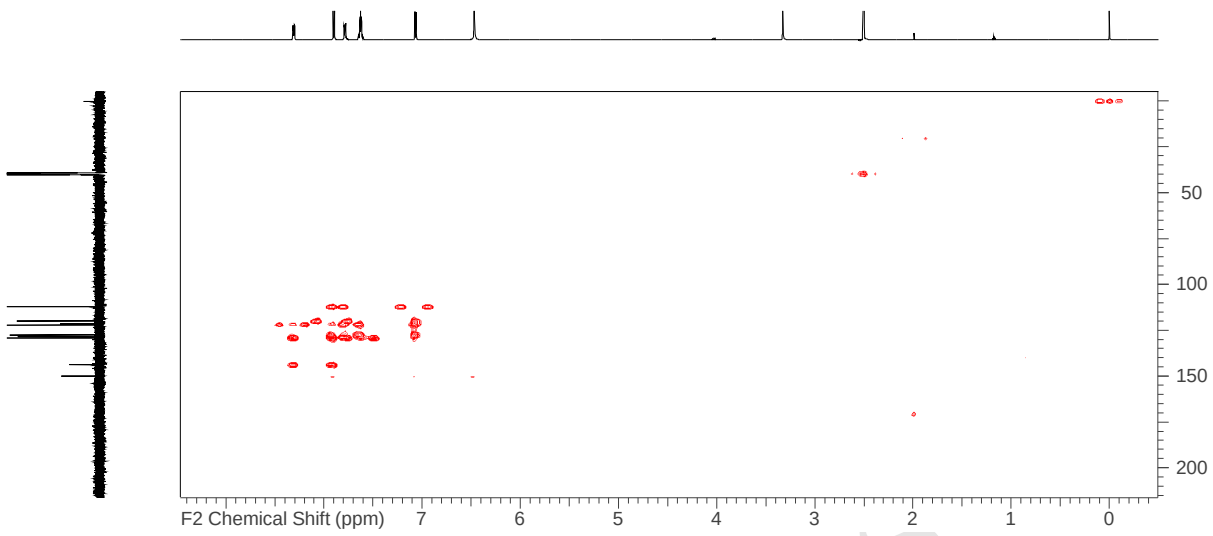
^{1}H NMR spectrum



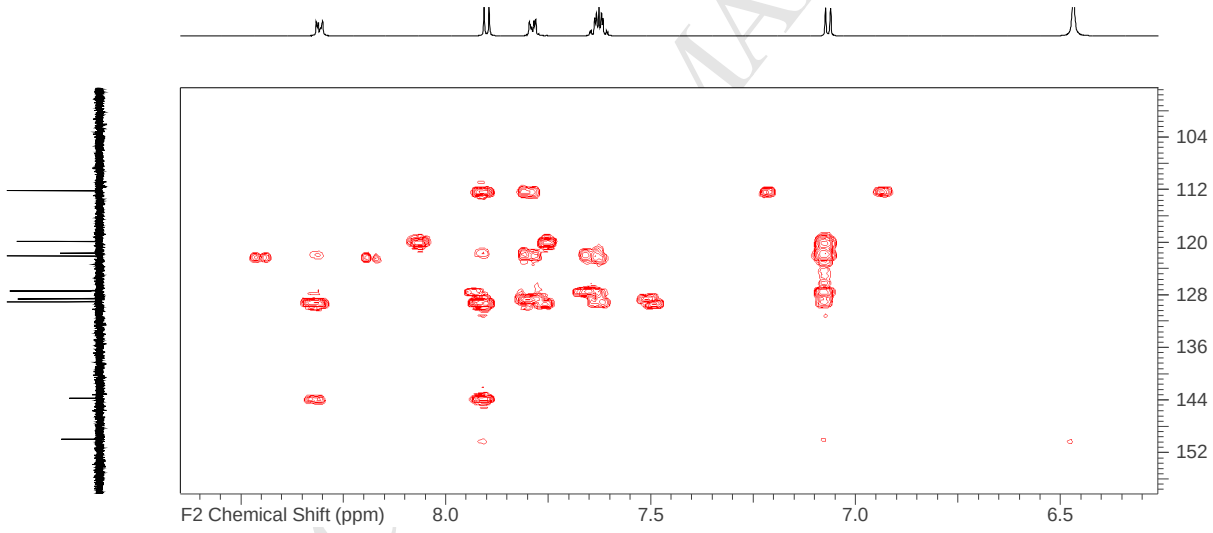
^{13}C NMR spectrum



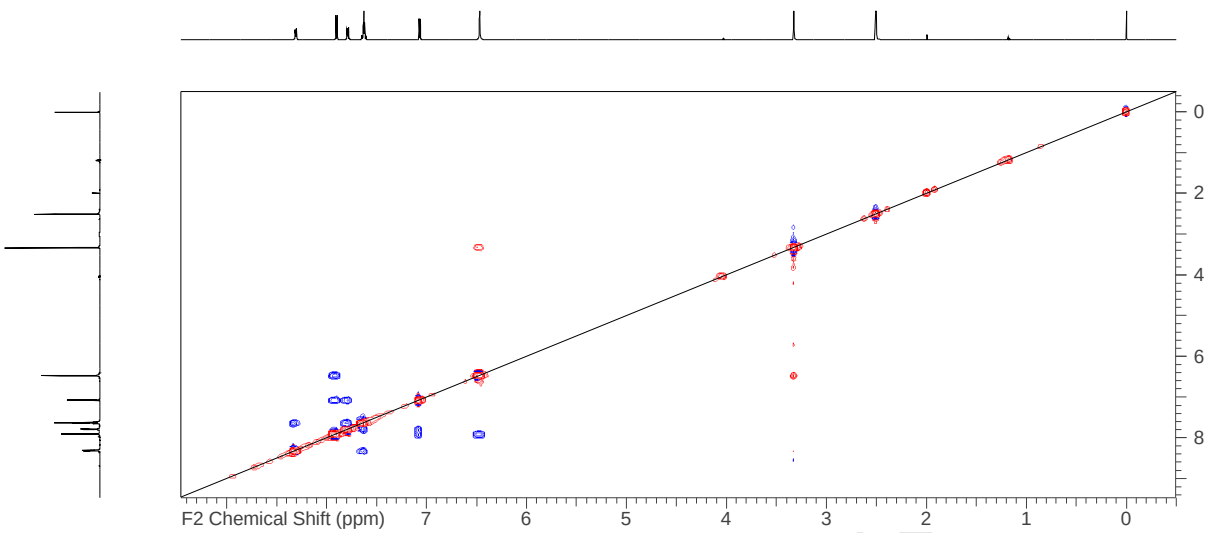
HMBC spectrum



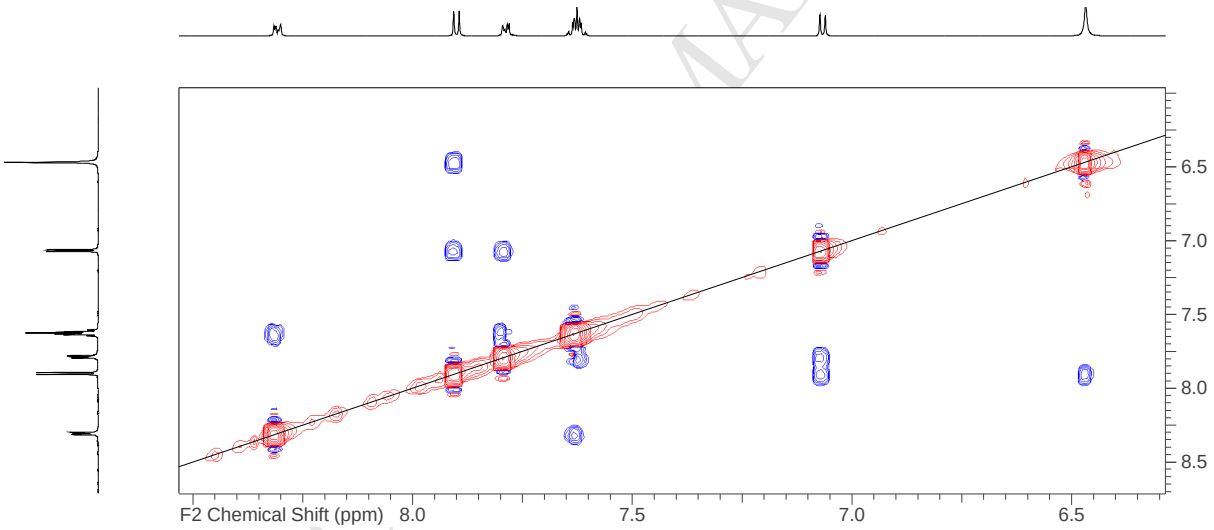
HMBC spectrum (expansion of aromatic region)



NOESY spectrum

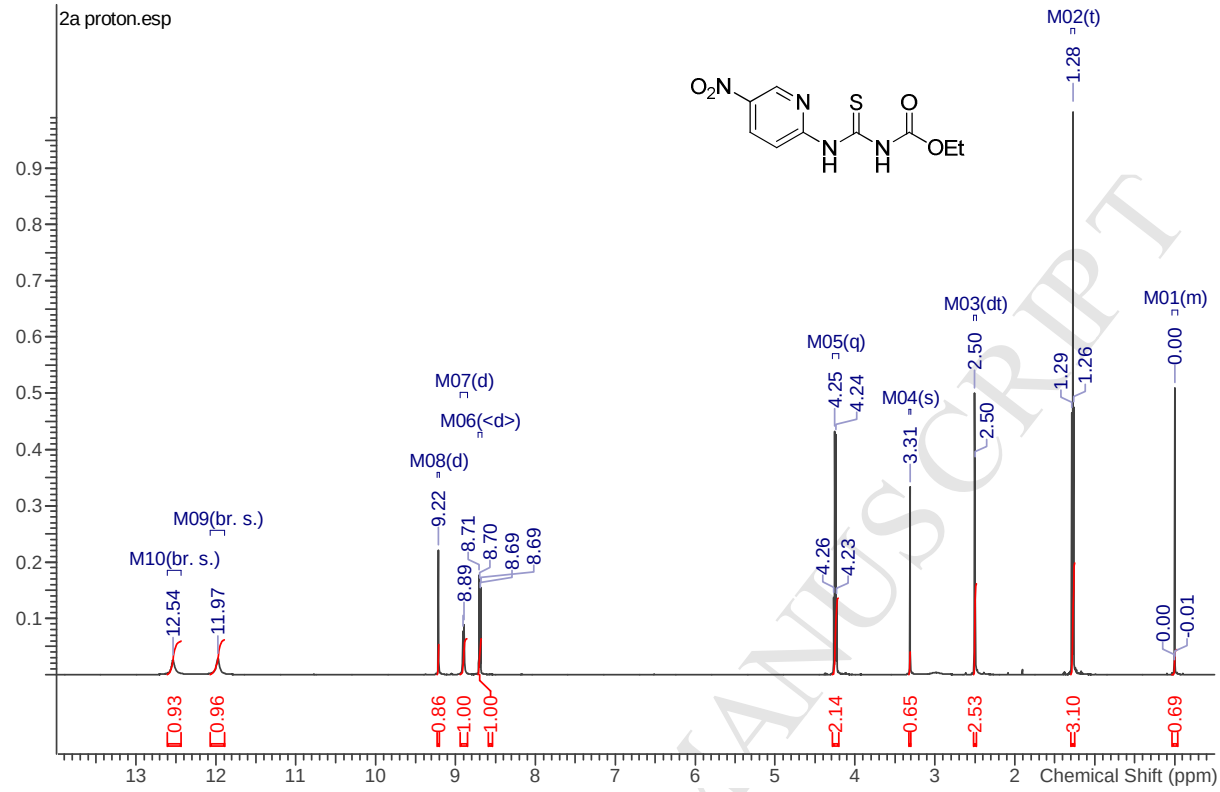


NOESY spectrum (expansion of aromatic region)

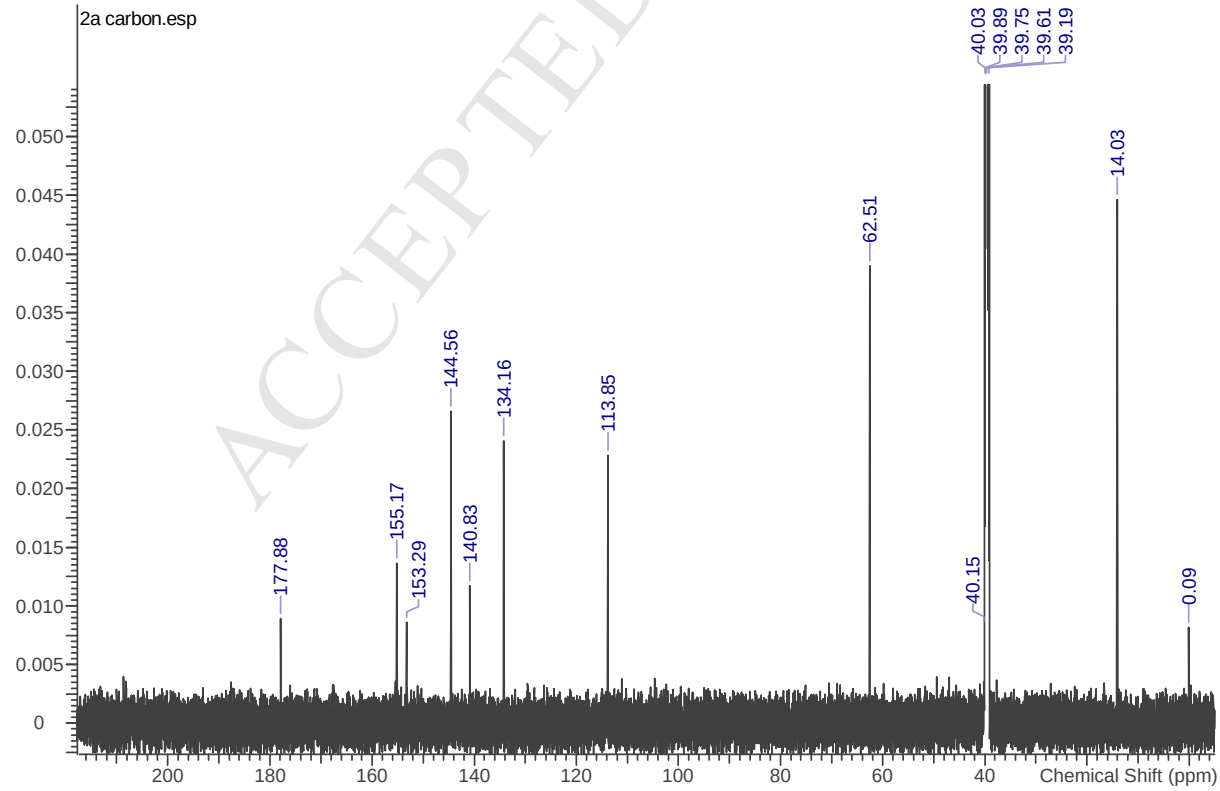


Ethyl [(5-Nitropyridin-2-yl)carbamothioyl]carbamate

^{1}H NMR spectrum

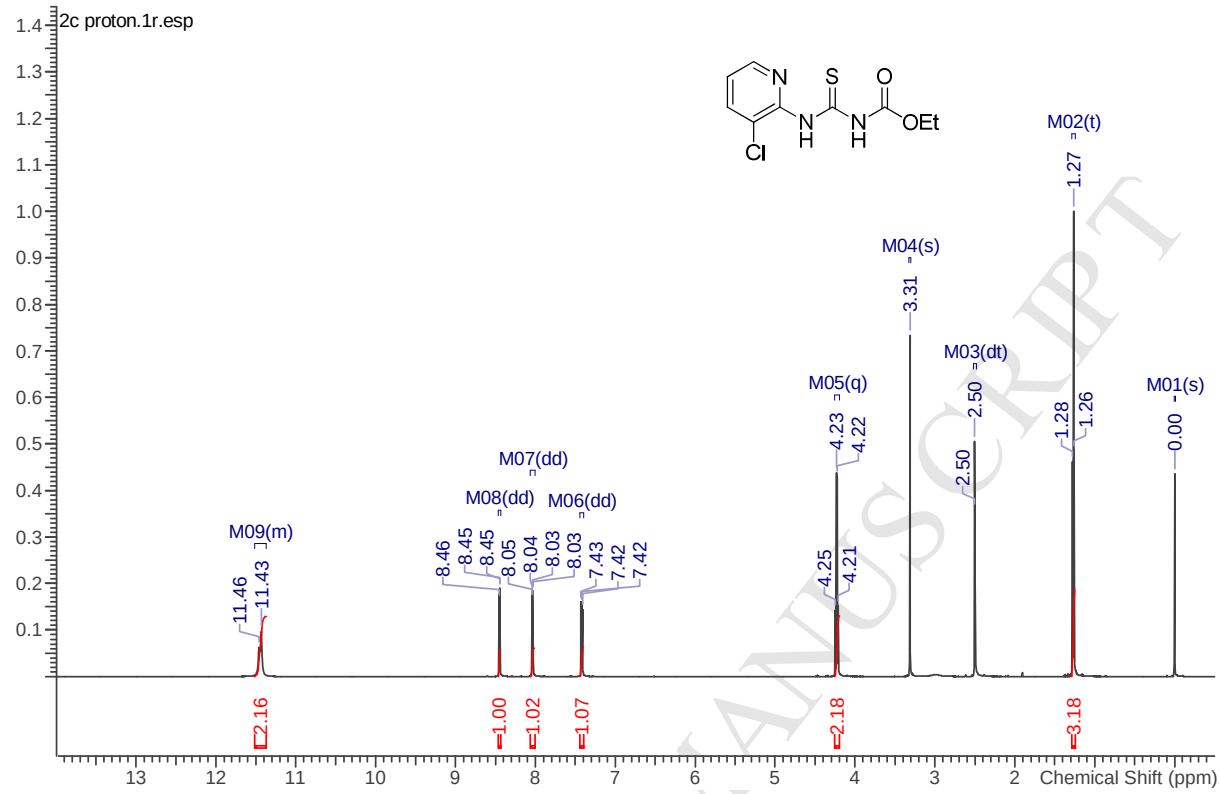


^{13}C NMR spectrum

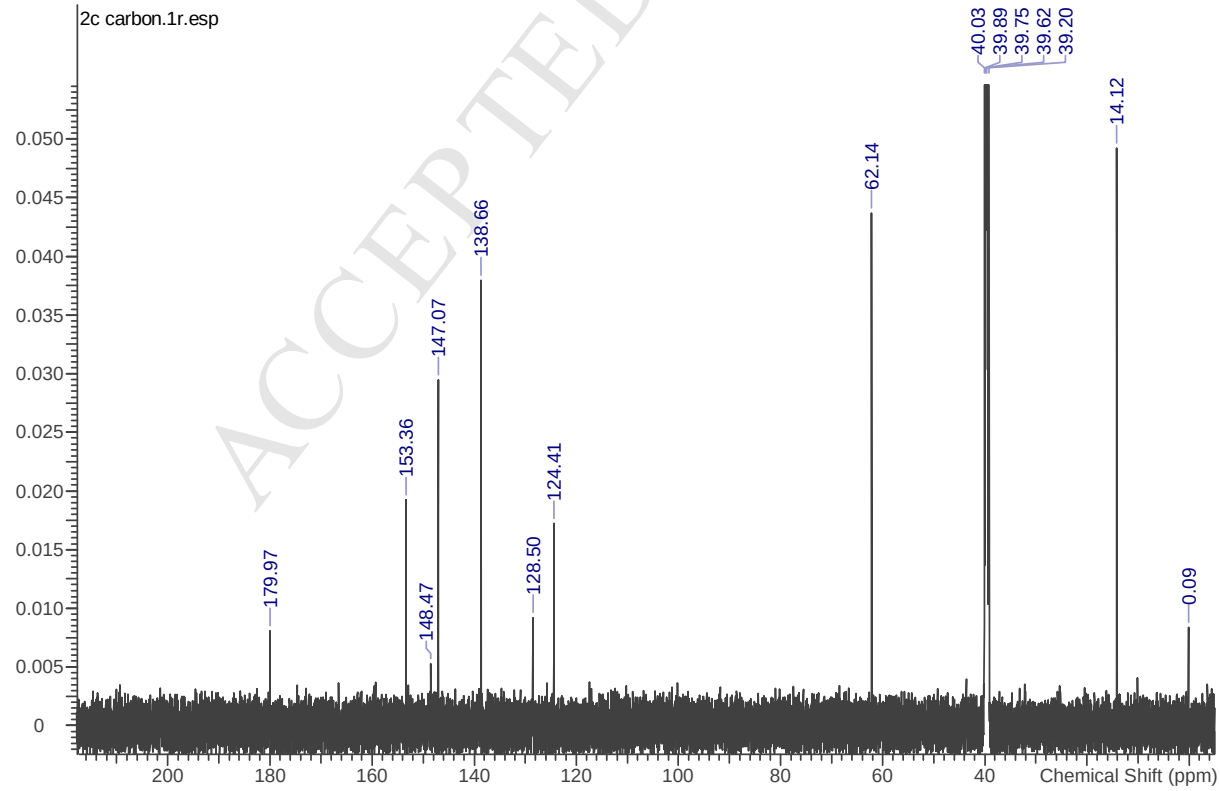


Ethyl [(3-Chloropyridin-2-yl)carbamothioyl]carbamate (**2c**)

^{1}H NMR spectrum

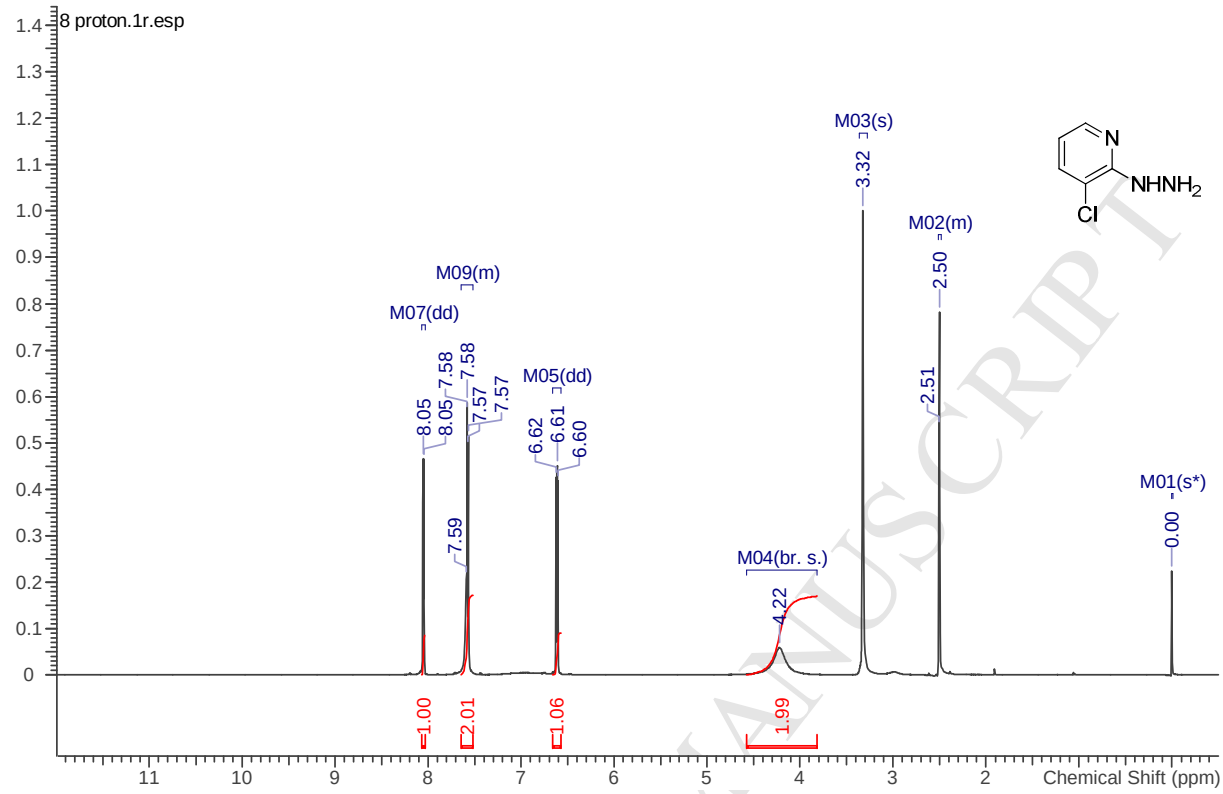


^{13}C NMR spectrum

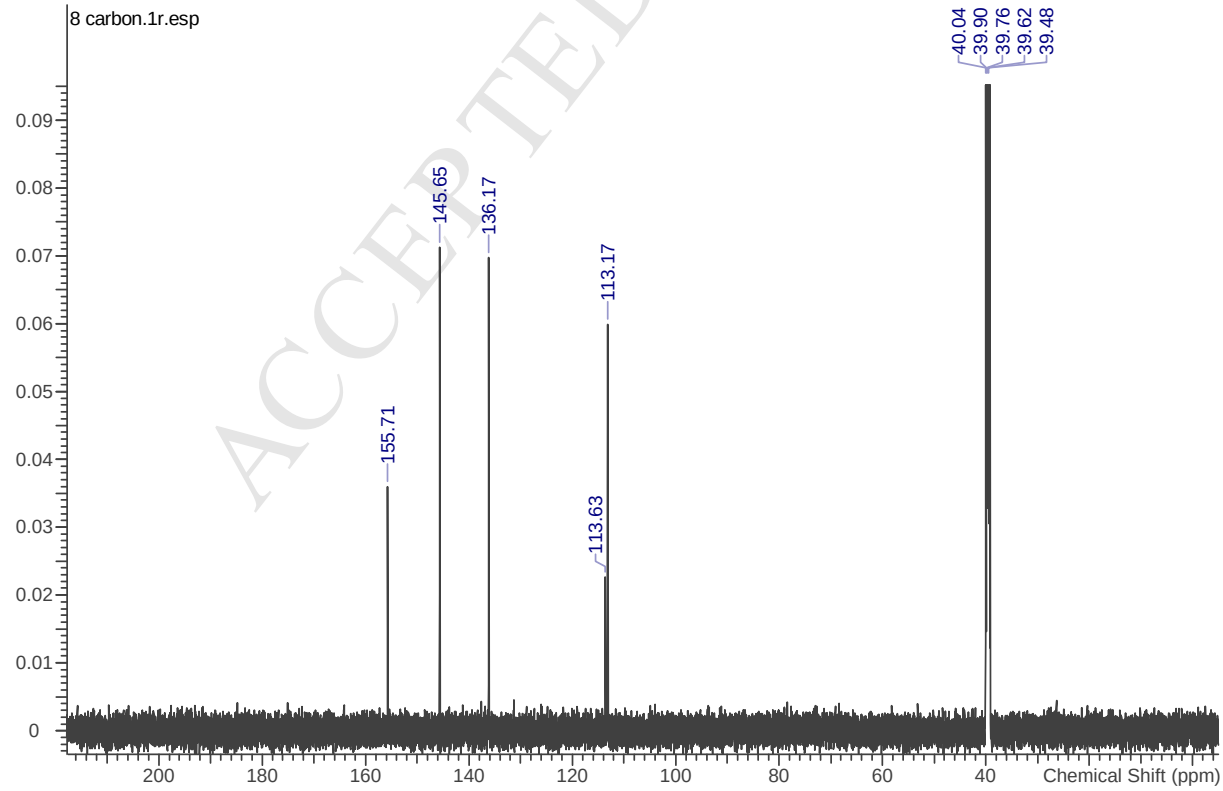


3-Chloro-2-hydrazinylpyridine (**8**)

^{1}H NMR spectrum

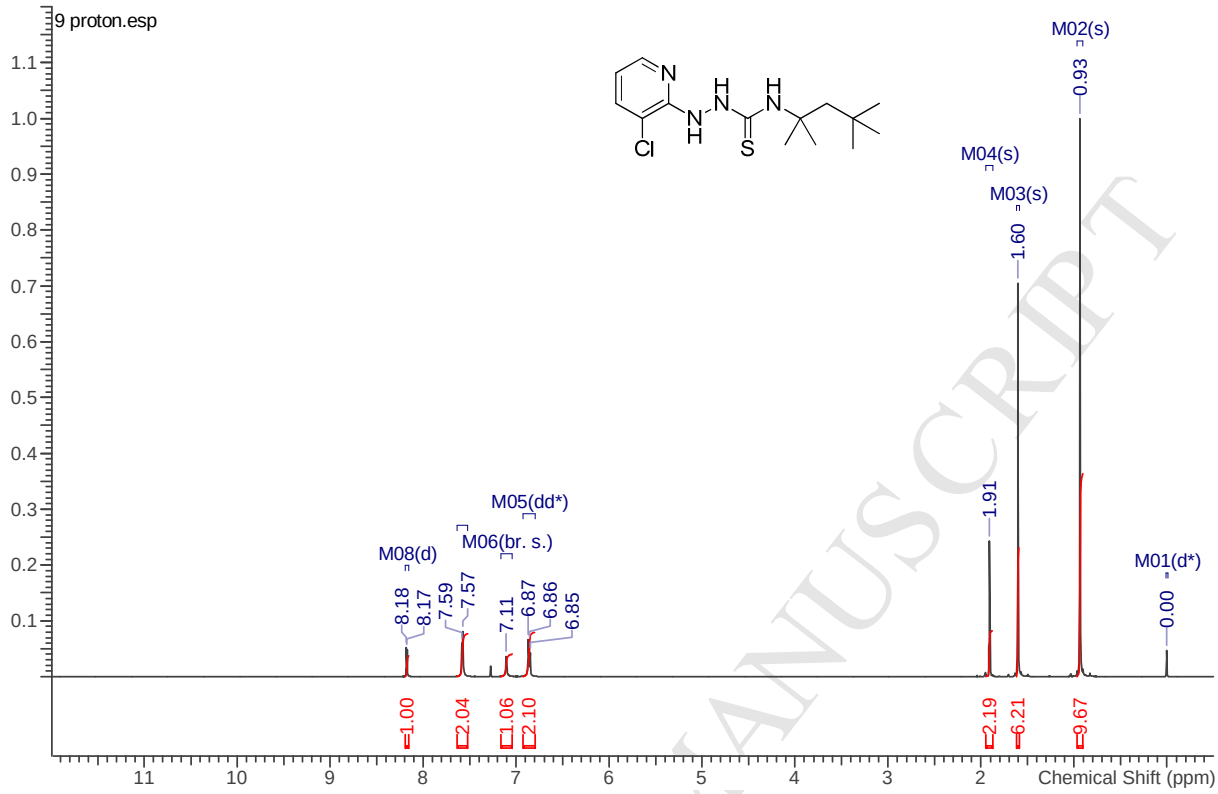


^{13}C NMR spectrum

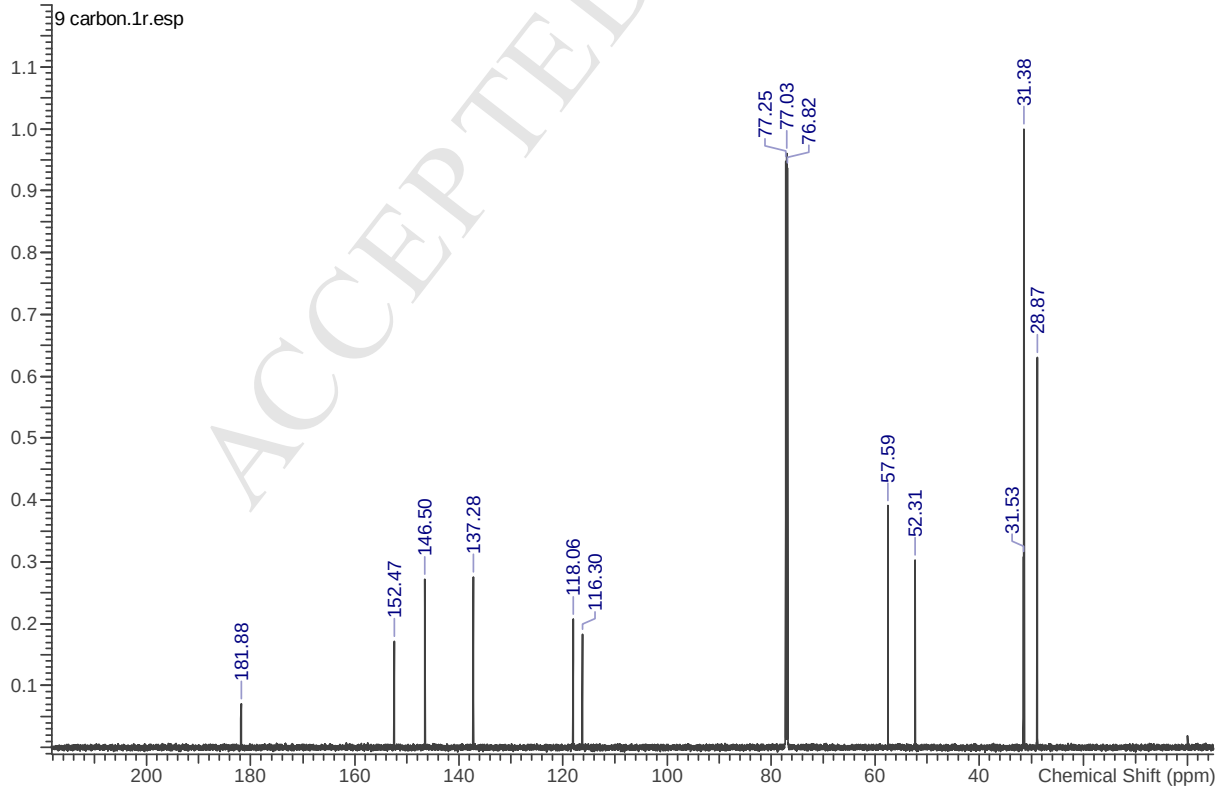


2-(3-Chloropyridin-2-yl)-N-(2,4,4-trimethylpentan-2-yl)hydrazinecarbothioamide (**9**)

^{1}H NMR spectrum

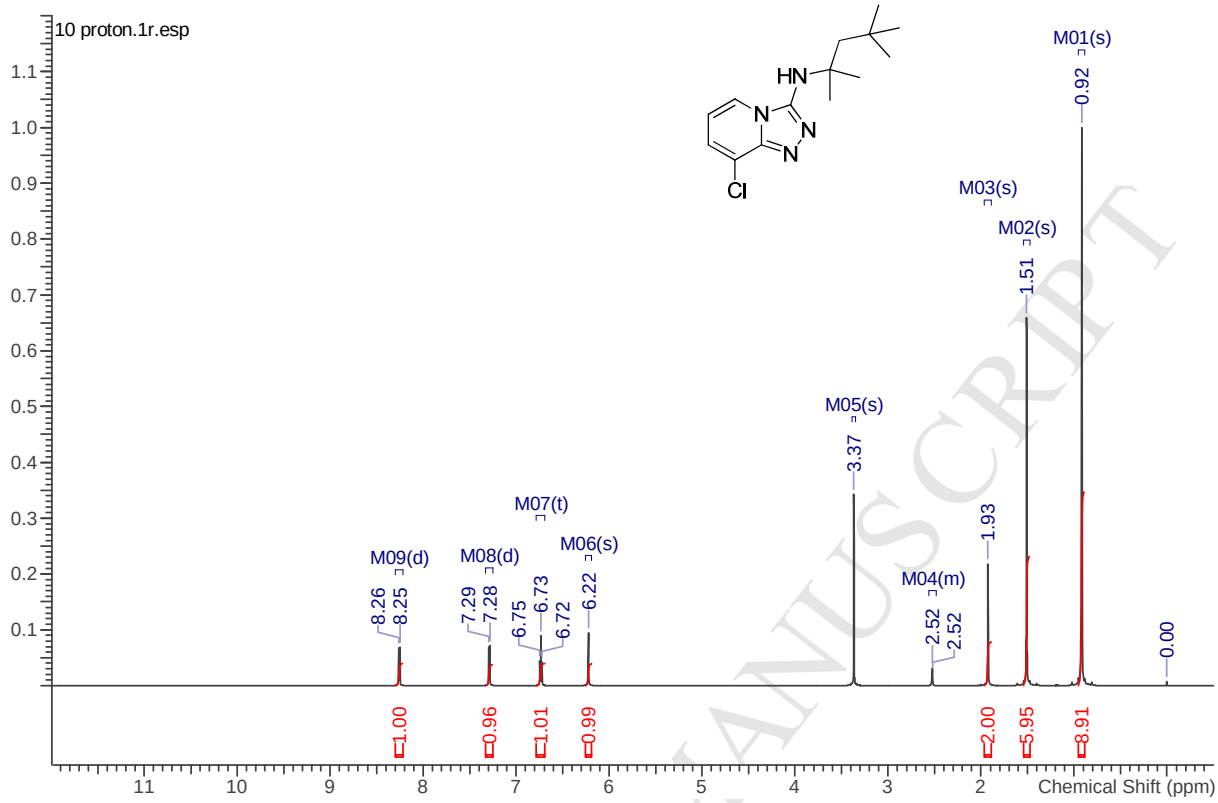


^{13}C NMR spectrum



8-Chloro-N-(2,4,4-trimethylpentan-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-amine (**10**)

^{1}H NMR spectrum



^{13}C NMR spectrum