SUPPORTING INFORMATION

Transformation of Amides into Highly Functionalized Triazolines

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Instrumentation

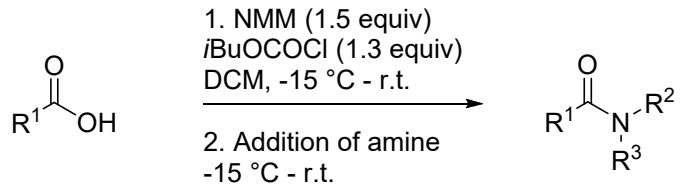
Characterizations were made by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy. NMR spectra were recorded at Bruker 400, 500 MHz (^{1}H), 100, 125 MHz (^{13}C) and 337 MHz (^{19}F) and were referenced internally with $CDCl_3$ (δH 7.26, δC 77.16 ppm) and $(CD_3)_2SO$ (δH 2.50, δC 39.52 ppm). For ^{19}F NMR monofluorobenzene was used as internal standard (-113.18 ppm). High temperature experiments were performed at Bruker 500 MHz (^{1}H) and 125 MHz (^{13}C). High resolution mass spectroscopy (HRMS) was performed on Bruker microTOF/ESI masspectrometer.

Material

Unless otherwise noted, materials were purchased from commercial suppliers and were used without purification. $Mo(CO)_6$, sublimed 99.9+% was purchased from Sigma-Aldrich and used as received.

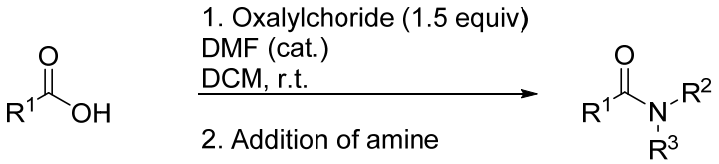
Preparation of Amides

Method A:[1]



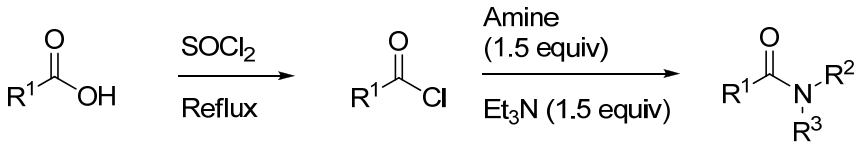
Carboxylic acid was suspended in dichloromethane in a round bottom flask fitted with rubber septa. The suspension was cooled to -15 °C and *N*-methylmorpholine (NMM) (1.5 equiv) was added which usually gave a clear solution. This was followed by slow addition of isobutyl chloroformate (1.3 equiv) and the reaction was stirred at -15 °C for 15-30 min and then at r.t. for 1 h. The reaction was again cooled to -15 °C followed by slow addition of amine (1.5 equiv). The completion of the reaction was followed by TLC. The crude reaction mixture was extracted three times with HCl (1M) and the organic phase was dried using anhydrous sodium sulphate and concentrated under reduced pressure. The amides were then purified using either manual flash column chromatography or on an ISCO Combiflash using EtOAc and pentane as eluent.

Method B:[2]



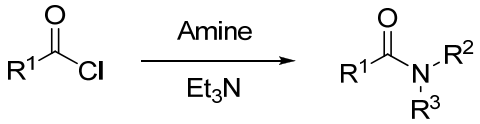
Carboxylic acid was suspended in dichloromethane and a few drops of DMF in a round bottom flask fitted with rubber septa. The reaction vessel was connected to a manifold with a flow of nitrogen and oxalylchloride (1.5 equiv) was slowly added. Upon completion of gas evolution amine (1.5 equiv) was added slowly and the reaction was stirred until completion (checked with TLC). The crude reaction mixture was extracted three times with HCl (1M) and three times with KOH (2M) and the organic phase was dried using anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the crude amide products were purified using either manual flash column chromatography or on an ISCO Combiflash using EtOAc and pentane as eluent.

Method C:[3]



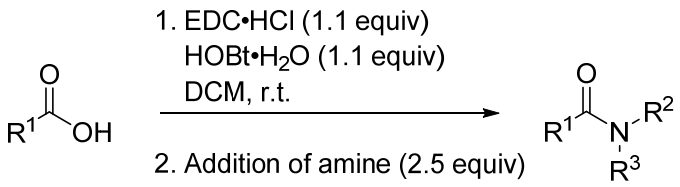
Thionyl chloride was added in excess to the carboxylic acid together with cat. amount of DMF and the reaction was refluxed for 3 h. Thionyl chloride was evaporated and the crude acid chloride was dissolved in dichloromethane and slowly added to a stirred solution of amine (1.5 equiv) and triethyl amine (1.5 equiv) at r.t. The completion of the reaction was followed by TLC and then the reaction mixture was extracted three times with HCl (1M) and three times with KOH (2M). The organic phase was dried using anhydrous sodium sulphate and concentrated under reduced pressure. The crude amide products were purified using either manual flash column chromatography or on an ISCO Combiflash using EtOAc and pentane as eluent.

Method D:[4]



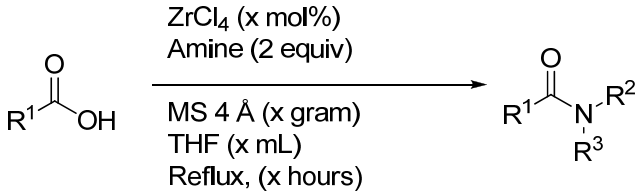
Amine and Et_3N (1.2 equiv) were dissolved in dichloromethane and commercially available acid chloride (1.2 equiv) was slowly added at r.t. The reaction was followed by TLC and upon completion extracted with HCl (1M) and KOH (2M) three times each. The organic phase was dried using sodium sulphate and concentrated under reduced pressure. The crude amide products were purified using either manual flash column chromatography or on an ISCO Combiflash using EtOAc and pentane as eluent.

Method E:[5]



Carboxylic acid was suspended in dichloromethane and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl) (1.1 equiv) was added dropwise followed by 1-hydroxybenzotriazole hydrate (HOBt·H_2O) (1.1 equiv). After 5 minutes the amine (2.5 equiv) was added dropwise and the reaction was allowed to stir overnight. An aqueous solution of citric acid (10 wt%) was added and the reaction was stirred for 30 min before the crude was filtered off. The crude reaction mixture was extracted three times with aqueous solution of citric acid (10 wt%), three times with saturated aqueous solution of $NaHCO_3$ three times with KOH (2M) and the organic phase was dried using anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the crude amide products were purified using either manual flash column chromatography or on an ISCO Combiflash using EtOAc and pentane as eluent.

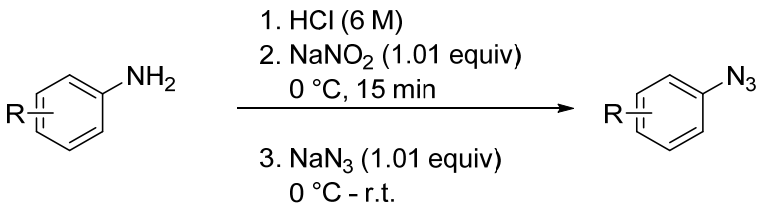
Method F:[6]



Carboxylic acid, $ZrCl_4$ and molecular sieves (4 Å) were added to a round bottom flask which was fitted with a condenser and a septa. The atmosphere was exchanged to N_2 and THF was added through the septa. The reaction was heated to 70 °C and amine was added. The reaction was stirred for 24 h and the allowed to cool to r.t. The crude reaction was filtered through a pad of silica eluted with ethyl acetate : Et_3N (200 : 1). The solvent was removed under reduced pressure and if required further purification was performed using ISCO Combiflash using EtOAc and pentane as eluent.

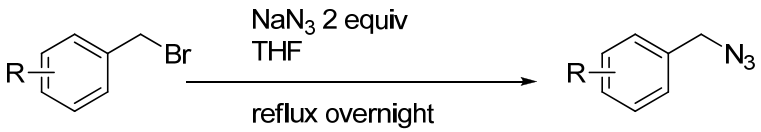
Preparation of Azides

Method A:[7]



Aniline (1 equiv) was dissolved in HCl (6M, 0.65 mL/mmol aniline) and the mixture was cooled to 0 °C. A solution of $NaNO_2$ (1.01 equiv) in water (0.35 mL/mmol aniline) was added dropwise with a dropping funnel and the reaction was allowed to stir for 10 min at 0 °C (make sure the reaction temperature does not get higher than 5 °C). At 0 °C, a solution of NaN_3 (1.01 equiv) in water (0.35 mL/mmol aniline) was added dropwise with a dropping funnel and the reaction was allowed to heat to r.t. The crude reaction mixture was extracted two times with diethyl ether and one time with water. The organic layer was dried using anhydrous sodium sulphate and concentrated under reduced pressure yielding the azide. The crude products were purified using either manual flash column chromatography or on an ISCO Combiflash using EtOAc and pentane as eluent.

Method B:[8]

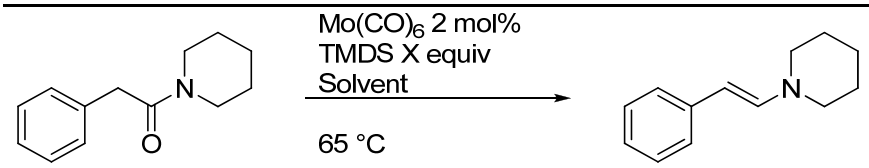


Bensyl bromide (1 equiv) was suspended in THF and a solution of NaN_3 (2 equiv) in water (0.1 M) was added dropwise. The reaction was left to reflux overnight and the crude reaction mixture was extracted three times with ethyl acetate and dried using anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the crude amide products were purified using either manual flash column chromatography or on an ISCO Combiflash using EtOAc and pentane as eluent.

CAUTION! Some azides are known to be explosive substances that can rapidly release nitrogen gas through the slightest input of external energy (for example pressure, impact, heat) these compounds should be handled with care. Also, some of the syntheses are passing through highly reactive intermediates, so be aware of the risks associated with both the products and intermediates.

Optimization of $Mo(CO)_6$-catalyzed Reduction of Amides into Enamines

We recently developed protocols for the hydrosilylation of tertiary amides based on catalytic amounts of $Mo(CO)_6$.[9] We observed that enamines were formed when employing aliphatic amides without branched substitution pattern at the α-carbon and we continued our investigation to find optimal conditions for this transformation (Table S1).



1a **2a**

Table S1. Optimization of reaction conditions.[a]

Entry	Solvent	Time [h]	Enamine [%][b]
1	THF	3	>95
2	Toluene	3	20
3	MeCN	3	3
4	DCM	3	14
5	DMF	3	0
6	Diethyl ether	3	78
7	Acetone	3	6
8	Ethyl acetate	3	83
9[c]	Ethyl acetate	3	>95
10[c,d]	Ethyl acetate	3	>95
11[c,d]	Ethyl acetate	1	>95
12[c,d]	Ethyl acetate	0.5	94
13[c,d]	Ethyl acetate	0.25	68
14[c,d,e]	Ethyl acetate	1	>95
15[c,f]	Ethyl acetate	3	20

[a] $Mo(CO)_6$ (0.02 mmol), amide **1a** (1.0 mmol), dried solvent (2.0 mL, 0.5 M), TMDS (2 equiv), reaction temperature 65 °C for 3 h. [b] Determined by ^{1}H NMR with 1,3,5-trimethoxy benzene as internal standard. [c] Ethyl acetate (0.5 mL, 2 M). [d] TMDS (1.5 equiv) was used. [e] Non-dried ethyl acetate were used. [f] PMHS (3 equiv) was used.

General Procedure for the Formation Enamines

Amide (0.5 mmol) and $Mo(CO)_6$ (0.0027 g, 0.01 mmol) were added to an oven dried 10 mL vial equipped with a magnetic stirring bar and the atmosphere was exchanged to N_2 via the septa. To the sealed vial, dry ethyl acetate (0.25 mL) was added. The reaction mixture was heated at 80 °C for 10 minutes to activate the catalyst followed by exchange of the atmosphere into N_2 again and was then allowed to reach the optimized reaction temperature (See Table S2). TMDS (0.75 mmol, 0.13 mL) was added and the reaction was run the required amount of time and the ^{1}H NMR yield were determined by using either 1,3,5-trimethoxybenzene or 1,4-dimethoxybenzene as internal standard.

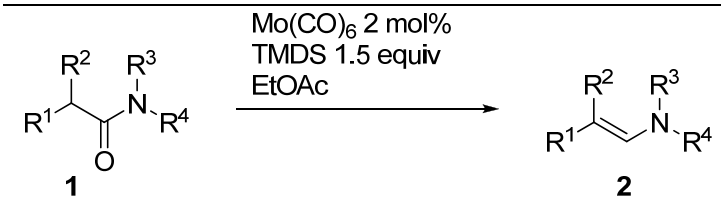
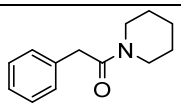
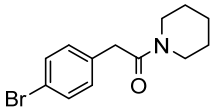
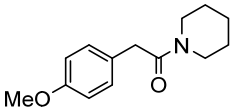
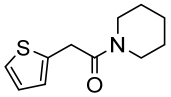
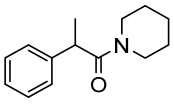
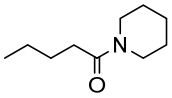
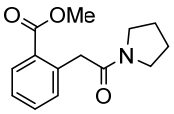
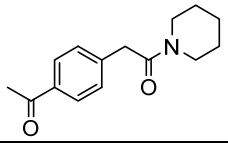
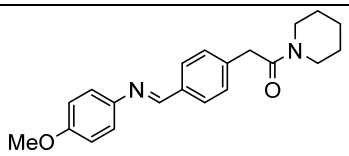
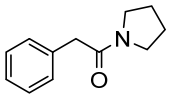
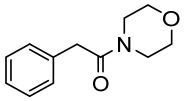
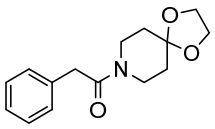
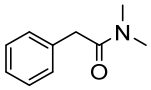
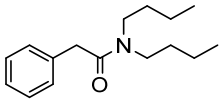
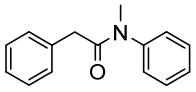
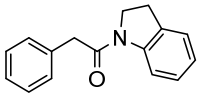
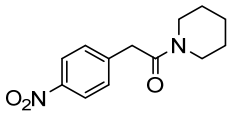
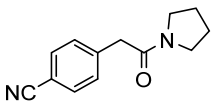


Table S2. Optimized conditions of the enamine formation for different amides.[a]

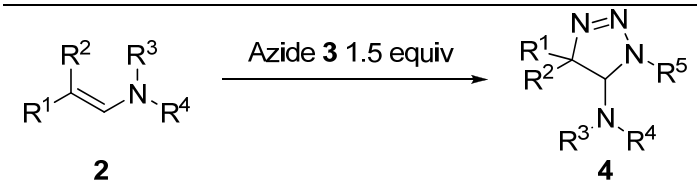
Entry		Amide	Temp [°C]	Time [h]	^{1}H NMR yield of enamine [%][b]
1	**1a**		65	1	>95
2	**1b**		65	3	>95
3	**1c**		65	1	>95
4	**1d**		65	3	>95
5[c]	**1e**		65	7	67
6	**1f**		80	2	70
7	**1g**		65	1	>95
8[d]	**1h**		40	5	89

9[e]	**1i**		65	4	>95
10	**1n**		65	0.5	>95
11	**1o**		65	3	>95
12	**1p**		65	1	>95
13	**1q**		65	1	>95
14	**1r**		65	5	>95
15[f]	**1s**		65	15	>95
16[g]	**1t**		65	9	>95
17[g]	**1u**		65	24	85
18	**1v**		75	3	>95

[a] $Mo(CO)_6$ (2 mol%), amide **1** (0.5 mmol), dried EtOAc (0.25 mL, 2 M), TMDS (1.5 equiv), reaction temperature 65 °C for 3 h. [b] Determined by ^1H NMR with 1,3,5-trimethoxy benzene as internal standard. [c] 1,4-dimethoxybenzene was used as internal standard. [d] Ethyl acetate (0.50 mL, 1 M). [e] Ethyl acetate (0.75 mL, 0.67 M). [f] Et_3N (10 mol%) was added. [g] $Mo(CO)_6$ (5 mol%).

General Procedure for the Formation of Triazolines

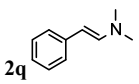
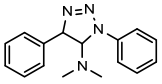
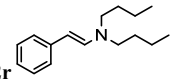
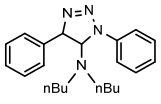
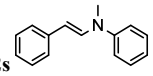
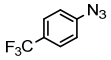
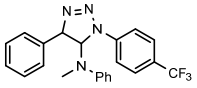
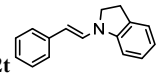
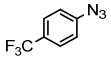
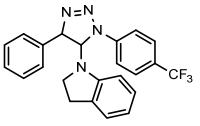
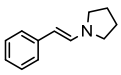
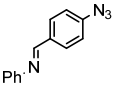
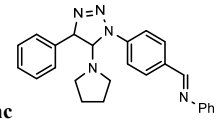
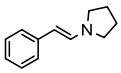
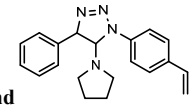
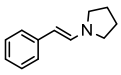
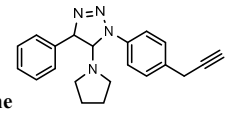
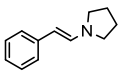
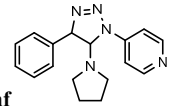
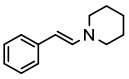
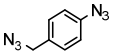
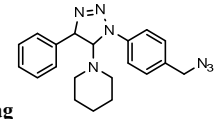
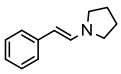
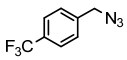
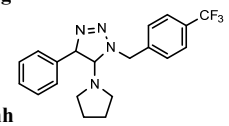
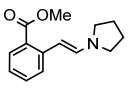
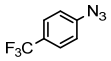
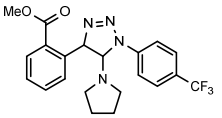
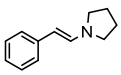
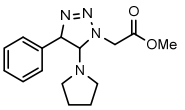
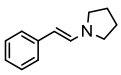
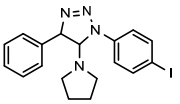
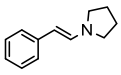
Amide (1.0 mmol) and $Mo(CO)_6$ (0.0054 g, 0.02 mmol) were added to an oven dried 10 mL vial equipped with a magnetic stirring bar and the atmosphere was exchanged to N_2 via the septa. To the sealed vial, dry ethyl acetate (0.5 mL) was added. The reaction mixture was heated at 80 °C for 10 minutes to activate the catalyst followed by exchange of the atmosphere into N_2 again and was then allowed to reach the optimized reaction temperature (See Table S3). TMDS (1.5 mmol, 0.26 mL) was added and the reaction was run the required amount of time to form the corresponding enamine. To the crude reaction azide (1.5 mmol) was added and when completion into triazoline was observed the crude reaction was transferred to a round bottom flask and evaporated in combination with celite. The triazolines were purified by column chromatography using pentane: EtOAc as eluent and then stored in freezer (-15 °C)



2 4

Table S3. Optimized conditions of the cyclization of enamines with different azides to form triazolines.[a]

Entry	Enamine	Azide	T [°C]	Time [h]	Triazoline	Isolated yield [%][b]
1	**2a**	**3a**	65	2	**4aa**	91
2	**2b**	**3a**	65	2	**4ba**	86
3	**2c**	**3a**	65	2	**4ca**	88
4	**2d**	**3a**	65	2.5	**4da**	83
5	**2e**	**3a**	65	15	**4ea**	61
6	**2f**	**3a**	65	3	**4fa**	66
7	**2g**	**3a**	65	2	**4ga**	94
8	**2h**	**3a**	60	2.5	**4ha**	84
9	**2i**	**3a**	65	3	**4ia**	88
10	**2n**	**3a**	65	3	**4na**	90
11	**2o**	**3a**	65	3	**4oa**	72
12	**2p**	**3a**	65	1	**4pa**	78

13	 **2q**	 **3a**	65	3	 **4qa**	92
14	 **2r**	 **3a**	65	5	 **4ra**	90
15	 **2s**	 **3b**	65	5	 **4sb**	82
16	 **2t**	 **3b**	65	3	 **4tb**	60
17	 **2n**	 **3c**	40	3	 **4nc**	92
18	 **2n**	 **3d**	40	3	 **4nd**	85
19	 **2n**	 **3e**	40	3	 **4ne**	93
20	 **2n**	 **3f**	40	2	 **4nf**	88
21	 **2a**	 **3g**	65	3	 **4ag**	78
22	 **2n**	 **3h**	65	15	 **4nh**	75
23	 **2g**	 **3b**	r.t.	3	 **4gb**	88
24	 **2n**	 **3i**	50	22	 **4ni**	79
25	 **2n**	 **3j**	40	3	 **4nj**	95
26	 **2n**	**3k**	40	3	**4nk**	82
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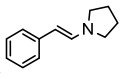
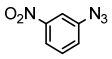
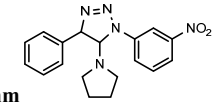
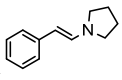
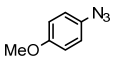
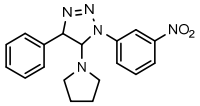
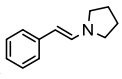
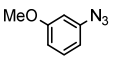
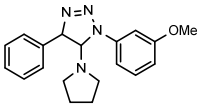
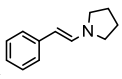
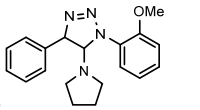
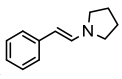
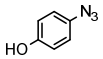
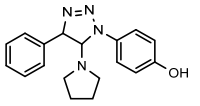
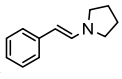
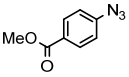
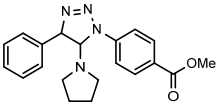
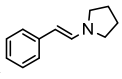
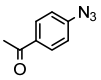
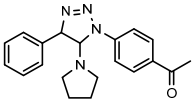
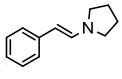
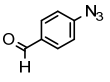
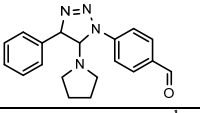
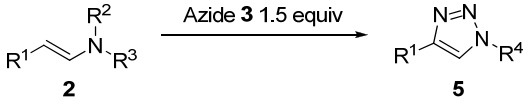
28	**2a**	**3l**	40	3	**4al**	85

29	**2n** 	**3m** 	40	2	**4nm** 	92
30	**2n** 	**3n** 	40	20	**4nn** 	89
31	**2n** 	**3o** 	40	3	**4no** 	97
32	**2n** 	**3p** 	40	7	**4np** 	85
33	**2n** 	**3q** 	40	3	**4nq** 	35
34	**2n** 	**3r** 	40	3	**4nr** 	91
35[c]	**2n** 	**3s** 	40	3	**4ns** 	90
36	**2n** 	**3t** 	40	3	**4nt** 	93

[a] Azide (1.5 equiv) was added to the *in situ* formed enamine from catalysis. [b] Isolation was performed on 1 mmol scale. [c] Also performed on large scale (5 mmol) giving the triazoline in 92% yield.

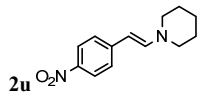
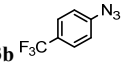
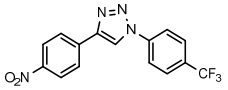
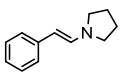
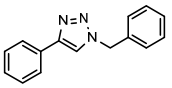
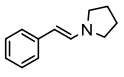
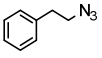
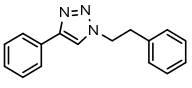
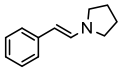
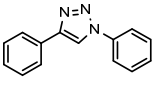
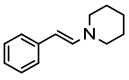
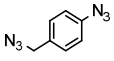
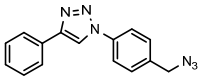
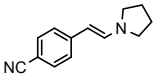
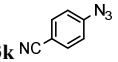
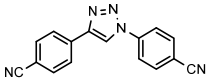
General Procedure for the Formation of Triazoles

Amide (1.0 mmol) and $Mo(CO)_6$ (0.0054 g, 0.02 mmol) were added to an oven dried 10 mL vial equipped with a magnetic stirring bar and the atmosphere was exchanged to N_2 via the septa. To the sealed vial, dry ethyl acetate (0.5 mL) was added. The reaction mixture was heated at 80 °C for 10 minutes to activate the catalyst followed by exchange of the atmosphere into N_2 again and was then allowed to reach the optimized reaction temperature (See Table S4). TMDS (1.5 mmol, 0.26 mL) was added and the reaction was run the required amount of time to form the corresponding enamine. To the crude reaction azide (1.5 mmol) was added and when completion into triazole was observed, or alternatively, after reaction with methanolic KOH (2 M, 0.15 mL, 0.25 mmol) the crude reaction was transferred to a round bottom flask and evaporated in combination with celite. The triazoles were purified by column chromatography using pentane: EtOAc as eluent.



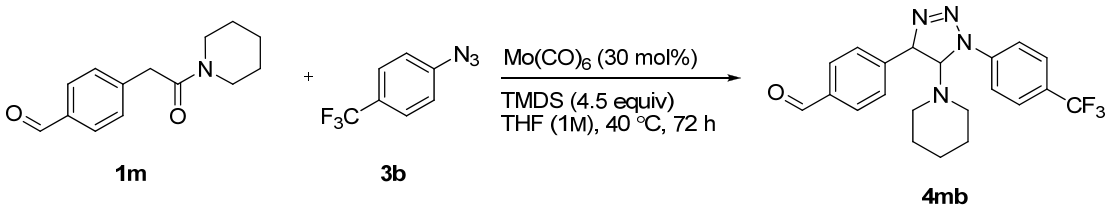
2 **5**

Table S4. Optimized conditions of the cyclization of enamines with different azides to form triazoles.[a]

Entry	Enamine	Azide	T [°C]	Time [h]	Triazole	Isolated yield [%][b]
1[c]	**2u** 	**3b** 	r.t.	15	**5ub** 	58
2[d]	**2n** 	**3u** 	80	24	**5nu** 	79
3	**2n** 	**3v** 	80	65	**5nv** 	96
4[e]	**2n** 	**3a** 	65	3	**5na** 	92
5[e]	**2a** 	**3g** 	r.t.	2	**5ag** 	78
6[f]	**2v** 	**3k** 	75	2.5	**5vk** 	88

[a] Azide (1.5 equiv) was added to the *in situ* formed enamine from catalysis. [b] Isolation was performed on 1 mmol scale. [c] $Mo(CO)_6$ (5 mol%). [d] 0.5 mmol scale. [e] KOH in methanol (2 M, 0.25 equiv) was added and reaction was left for additional 3 h at 65 °C. [f] Performed on large scale (5 mmol).

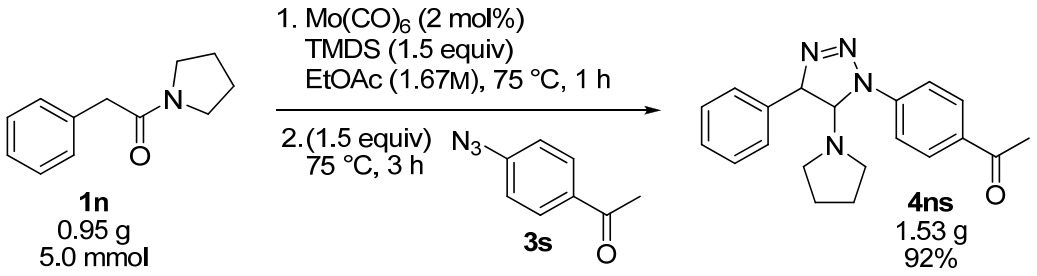
Procedure for the Tandem Reaction – Formation of Triazoline 4mb



1m **3b** **4mb**

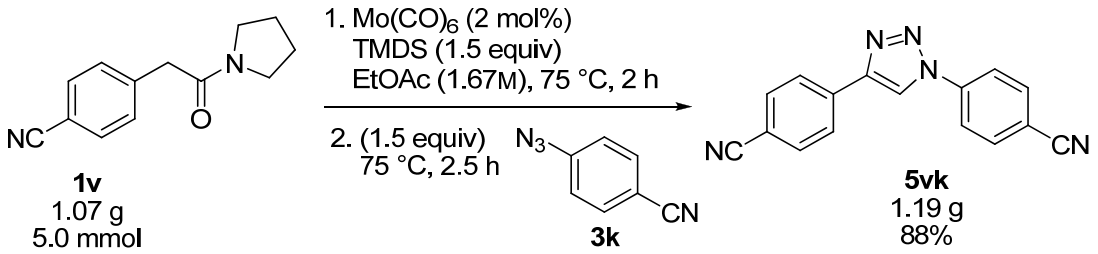
Amide **1m** (115.6 mg, 0.5 mmol) and $Mo(CO)_6$ (0.0405 g, 0.15 mmol) were added to an oven dried 10 mL vial equipped with a magnetic stirring bar and the atmosphere was exchanged to N_2 via the septa. To the sealed vial, dry THF (0.5 mL, 1M) was added. The reaction mixture was heated at 80 °C for 10 minutes to activate the catalyst followed by exchange of the atmosphere into N_2 again and was then allowed to reach 40 °C. TMDS (0.4 mL, 2.25 mmol, 4.5 equiv) and 4-trifluorophenylazide **3b** (140 mg, 0.75 mmol) were added and the reaction was run for 72 h at 40 °C. The crude reaction was transferred to a round bottom flask and evaporated with celite and purified by automatic column (petroleum ether : ethyl acetate as eluent) to give target compound **4mb** as a yellow solid (160 mg, 80% yield).

Large-Scale Transformation of Amide into Triazoline 4ns



2-phenyl-1-(pyrrolidin-1-yl)ethanone (**1n**) (5.0 mmol, 0.945 g) and $Mo(CO)_6$ (0.1 mmol, 0.027 g) was added to a 25 mL two-necked round bottom flask which was fitted with a rubber septa and condenser. The condenser was connected to a manifold with a needle through the septa and the atmosphere was exchanged to nitrogen. Dry ethyl acetate (3 mL) was added and the solution was heated to 75 °C under stirring for 10 minutes. The reaction was allowed to cool down to r.t. upon which, the atmosphere was exchanged into N_2 and TMDS (7.5 mmol, 1.3 mL) was added at 75 °C. The reaction was stirred at 75 °C for 1 h and then allowed to reach 40 °C. 1-(4-azidophenyl)ethanone (**3s**) (7.5 mmol, 1.21 g) dissolved in ethyl acetate (5 mL) was added to the reaction mixture which was left to stir at 40 °C for 3 hours. The solvent was evaporated under reduced pressure and the crude mixture was purified on ISCO Combiflash using EtOAc and pentane as eluent to give the corresponding triazoline (**4ns**) in 92% yield (4.6 mmol, 1.53 g).

Large-Scale Transformation of Amide into Triazole 5vk



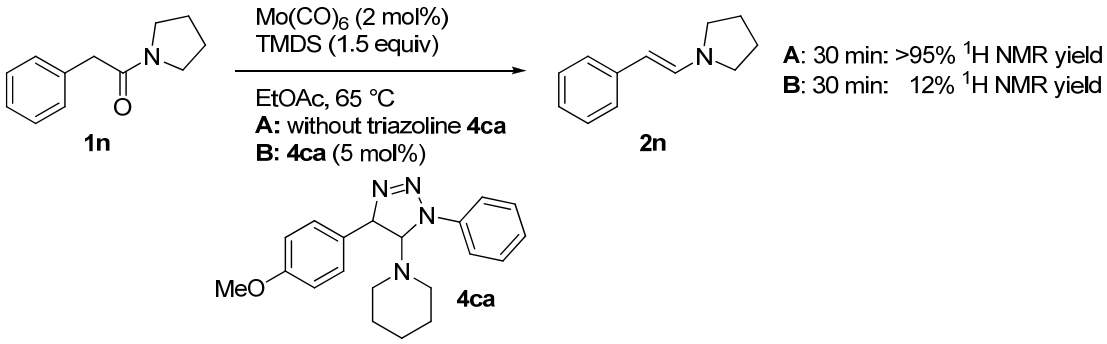
1v
1.07 g
5.0 mmol

3k

5vk
1.19 g
88%

4-(2-oxo-2-(pyrrolidin-1-yl)ethyl)benzonitrile (**1v**) (5 mmol, 1.07 g) and $Mo(CO)_6$ (26.5 mg, 0.1 mmol) was added to a 25 mL two-necked round bottom flask which was fitted with a condenser and a rubber septa. The condenser was connected to a manifold with a needle through the septa and the atmosphere was exchanged to nitrogen. EtOAc (3 mL) was added. and the reaction was heated to 75 °C and stirred for 10 minutes. TMDS (7.5 mmol, 1.3 mL) was added through the septa and the reaction was stirred for 2 h. 4-azidobenzonitrile (**3k**) (7.5 mmol, 1.08 g) was dissolved in EtOAc (2 mL) and injected slowly thereafter the reaction was kept at 75 °C for another 2.5 h. The triazole precipitated out of the reaction as an orange/brown solid, which was washed with diethyl ether (4 × 10 mL) directly in the round flask and the solvent was removed with pipette. The product **5vk** was then dried under vacuum to yield a orange/brown solid in 88% yield (1.19 g).

Product Inhibition Investigation

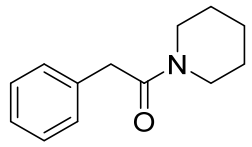


To investigate if the formed product (triazoline) inhibits the enamine formation the following set up was performed: amide **1n** (0.5 mmol), internal standard (1,3,5-trimethoxybenzene) and $Mo(CO)_6$ (0.0027 g, 0.01 mmol) were added to an oven dried 10 mL vial equipped with a magnetic stirring bar and the atmosphere was exchanged to N_2 via the septa. To the sealed vial, dry ethyl acetate (0.25 mL) was added. The reaction mixture was heated at 80 °C for 10 minutes to activate the catalyst followed by exchange of the atmosphere into N_2 again and was then allowed to reach 65 °C. Triazoline **4ca** (8.4 mg, 0.025 mmol) was dissolved in dry ethyl acetate (0.25 mL) and added to the reaction mixture together with TMDS (0.75 mmol, 0.13 mL) was added and a sample was taken after 30 min.

Compound Characterization

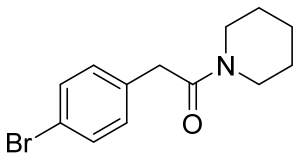
Amides:

2-phenyl-1-(piperidin-1-yl)ethan-1-one (1a)



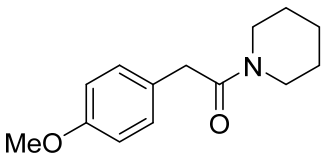
2-Phenylacetyl chloride (40 mmol, 6.4 mL) was subjected to method D (amine; piperidine, 1.15 equiv) to give the corresponding amide as an colorless oil in 83% yield (33 mmol, 6.80 g). Spectral data is in agreement with published data.[10]

2-(4-bromophenyl)-1-(piperidin-1-yl)ethan-1-one (1b)



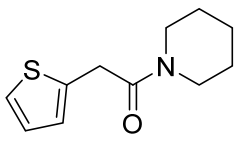
2-(4-bromophenyl)acetic acid (20 mmol, 4.3 g) was subjected to method B to give the corresponding amide as a white solid in 40% yield (8 mmol, 2.09 g). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.45 – 7.41 (m, 2H), 7.15 – 7.10 (m, 2H), 3.66 (s, 2H), 3.59 – 3.54 (m, 2H), 3.39 – 3.33 (m, 2H), 1.63 – 1.56 (m, 2H), 1.55 – 1.48 (m, 2H), 1.42 – 1.35 (m, 2H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 168.8, 134.6, 131.9, 130.6, 120.7, 47.4, 43.1, 40.5, 26.4, 25.6, 24.5; **HRMS** (ESI, m/z) calcd. for $C_{13}H_{16}BrNONa^+$ $[M + Na]^+$ 304.0307, found 304.0323.

2-(4-methoxyphenyl)-1-(piperidin-1-yl)ethan-1-one (1c)



2-(4-methoxyphenyl)acetic acid (40 mmol, 6.65 g) was subjected to method B (amine; piperidine 1.5 equiv) to give the corresponding amide as an pale yellow oil in 69% yield (27.6 mmol, 9.57 g). Spectral data is in agreement with published data.[11]

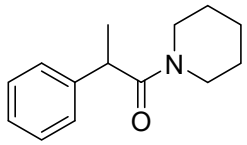
1-(piperidin-1-yl)-2-(thiophen-2-yl)ethan-1-one (1d)



2-(thiophen-2-yl)acetic acid (10 mmol, 1.42 g) was subjected to method F ($ZrCl_4$ (20 mol%, 0.467 g), THF (80 mL), MS 4Å (5.0 g), piperidine 2.0 equiv) to give the corresponding amide as an off white solid in 78% yield (7.8 mmol, 1.64 g). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ =

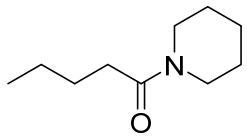
7.17 – 7.15 (dd, *J* = 5.17, 1.20 Hz, 1H), 6.93 – 6.91 (m, 1H), 6.88 – 6.86 (m, 1H), 3.88 (s, 2H), 3.55 (m, 2H), 3.42 (m, 2H), 1.62 – 1.39 (m, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 168.1, 136.9, 126.8, 125.9, 124.7, 47.4, 43.0, 35.3, 26.2, 25.4, 24.4; **HRMS** (ESI, m/z) calcd. for $C_{11}H_{15}NOSNa^+$ $[M + Na]^+$ 232.0767, found 232.0765.

2-phenyl-1-(piperidin-1-yl)propan-1-one (1e)



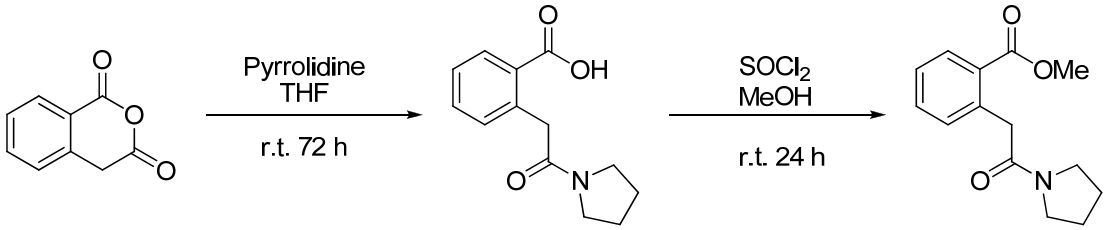
2-phenylpropanoic acid (18 mmol, 2.5 mL) was subjected to method E (amine; piperidine 2 equiv) to give the corresponding amide as an yellow oil in 83% yield (15 mmol, 3.3 g). Spectral data is in agreement with published data.[12]

1-(piperidin-1-yl)pentan-1-one (1f)



Valeroyl chloride (20 mmol, 2.4 mL) was subjected to method D (amine; piperidine 1.1 equiv) to give the corresponding amide as an pale yellow oil in 80% yield (16 mmol, 2.7 g). Spectral data is in agreement with published data.[13]

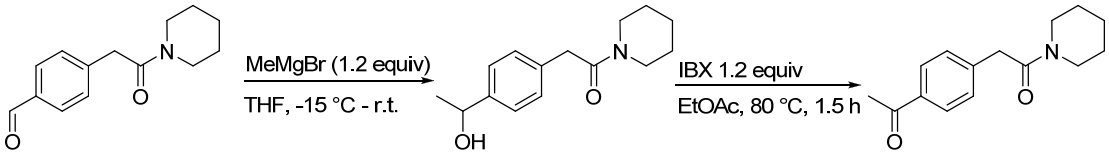
methyl 2-(2-oxo-2-(pyrrolidin-1-yl)ethyl)benzoate (1g)



Isochromane-1,3-dione (13 mmol, 2.15 g) was dissolved in THF (20 mL) and pyrrolidine (1 equiv, 1.06 mL) was added. The reaction was stirred at r.t. for 72 h and then extracted with DCM and HCl (2M). The organic layer was dried over Na_2SO_4 and concentrated under vacuum to give the carboxylic acid as an orange solid (2.96 g). The crude product, 2-(2-oxo-2-(pyrrolidin-1-yl)ethyl)benzoic acid (2.33 g, 9.4 mmol), was reacted with $SOCl_2$ (1.75 equiv) in MeOH (20 mL) at r.t. for 24 h. The crude reaction was concentrated under reduced pressure. The residue was dissolved in DCM and extracted with KOH (2M, checked that the water phase was basic). The organic phase was dried over Na_2SO_4 and concentrated under vacuum and then

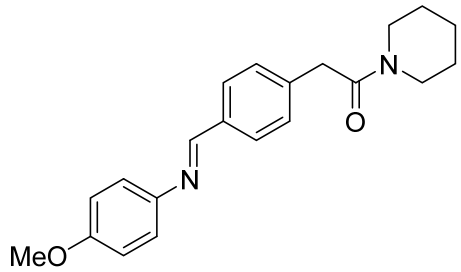
purified by column chromatography to yield **1g** as pale brown solid in 68% yield (1.6 g). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.98 (dd, *J* = 7.79, 1.33 Hz, 1H), 7.46 (dt, *J* = 7.54, 1.41 Hz, 1H), 7.32 (dt, *J* = 7.62, 1.23 Hz, 1H), 7.25 (d, *J* = 7.40 Hz, 1H), 4.02 (s, 2H), 3.82 (s, 3H), 3.53 (t, *J* = 6.81 Hz, 2H), 3.48 (t, J = 6.86 Hz, 2 H), 1.98 (qv, *J* = 6.70 Hz, 2H), 1.86 (qv, *J* = 6.70 Hz, 2H); **^{13}C-NMR** (100 MHz, CDCl3): δ = 169.3, 167.7, 137.4, 132.2, 132.0, 130.8, 130.0, 126.8, 52.0, 46.6, 45.8, 40.6, 26.2, 24.5; **HRMS** (ESI, m/z) calcd. for $C_{14}H_{17}NO_3Na^+$ $[M + Na]^+$ 270.1101, found 270.1089.

2-(4-acetylphenyl)-1-(piperidin-1-yl)ethan-1-one (1h)



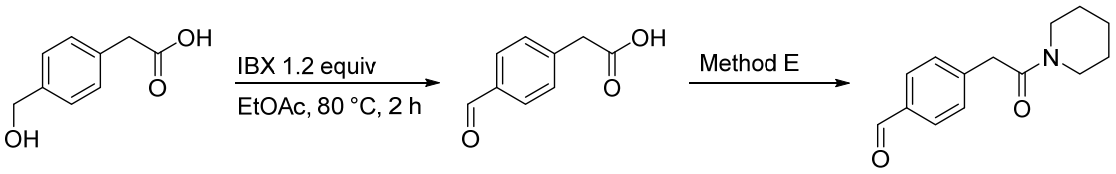
Amide **1m** (10 mmol, 2.3 g) was dissolved in dry THF (80 mL) and the reaction was cooled to -15 °C while stirring. A solution of MeMgBr (3M in Et_2O, 4 mL) was added dropwise to a stirring solution of the amide at -15 °C. After the addition the reaction mixture was allowed to warm to r.t. and stirred for 1 h. Saturated solution of NH_4Cl was added to the reaction mixture and allowed to stir for 15 min. The alcohol product was extracted with DCM (3 × 50 mL) and dried with Na_2SO_4. The solvent was removed under reduced pressure to give the corresponding alcohol containing compound in quantitative yield as a white solid. The compound was used in the oxidation step without purification. To a stirred solution of alcohol substituted amide (10 mmol, 2.46 g) in dry ethyl acetate (50 mL) at 80 °C, 2-iodoxybenzoic acid (IBX, 12 mmol, 3.36 g) was added portion wise. The reaction was allowed to stir for 2 h at 80 °C. The reaction mixture was cooled to r.t. and the precipitate was filtered off using a glass filter funnel and washed with ethyl acetate (3 × 30 mL). Ethyl acetate solution was concentrated under reduced pressure and was purified by column chromatography to give target amide **1h** as a pale brown solid in 76% yield (1.86 g). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.93 – 7.88 (m, 2H), 7.37 – 7.33 (m, 2H), 3.77 (s, 2H), 3.59 – 3.54 (m, 2H), 3.39 – 3.34 (m, 2H), 2.58 (s, 3H), 1.62 – 1.49 (m, 4H), 1.41 – 1.34 (m, 2H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 197.9, 168.5, 141.1, 135.8, 129.1, 128.8, 47.3, 43.1, 41.1, 26.7, 26.4, 25.6, 24.5; **HRMS** (ESI, m/z) calcd. for $C_{15}H_{19}NO_2Na^+$ $[M + Na]^+$ 268.1308, found 268.1303.

(*E*)-2-(4-(((4-methoxyphenyl)imino)methyl)phenyl)-1-(piperidin-1-yl)ethan-1-one (1i)



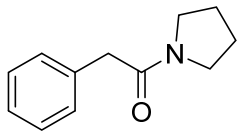
Amide **1m** (4.3 mmol, 1.0 g) and *p*-anisidine (4.3 mmol, 0.57 g) were stirred in ethanol (15 mL) for 16 h at r.t. The solvent was removed under reduced pressure to yield **1i** as an off-white solid in quantitative yield (4.3 mmol, 1.45 g). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.46 (s, 1H), 7.86 – 7.82 (m, 2H), 7.37 – 7.34 (m, 2H), 7.25 – 7.20 (m, 2H), 6.95 – 6.90 (m, 2H), 3.83 (s, 3H), 3.78 (s, 2H), 3.60 – 3.55 (m, 2H), 3.39 – 3.35 (m, 2H), 1.62 – 1.49 (m, 4H), 1.39 – 1.32 (m, 2H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 168.9, 158.4, 158.2, 145.0, 138.8, 135.2, 129.2, 129.1, 122.3, 114.5, 55.7, 47.4, 43.1, 41.4, 26.4, 25.6, 24.5; **HRMS** (ESI, m/z) calcd. for $C_{21}H_{24}N_2O_2Na^+$ $[M + Na]^+$ 359.1730, found 359.1736.

4-(2-oxo-2-(piperidin-1-yl)ethyl)benzaldehyde (1m)



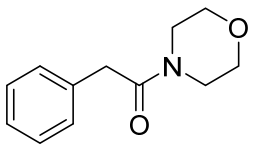
To a stirred solution of 4-(hydroxymethyl)phenylacetic acid (18 mmol, 3.0 g) in dry ethyl acetate (50 mL) at 80 °C 2-iodoxybenzoic acid (IBX, 21.4 mmol, 6.0 g) was added portion wise. The reaction was allowed to stir for 2 h at 80 °C. The reaction mixture was cooled to r.t. and the precipitate was filtered off using a glass filter funnel and washed with ethyl acetate (3×30 mL). The ethyl acetate solution was concentrated under reduced pressure yielding target (4-formyl-phenyl)-acetic acid as a white solid. (4-formyl-phenyl)-acetic acid (18 mmol, 3.0 g) was subjected to method E (amine; piperidine, 2 equiv) without additional purification to give the corresponding amide **1m** as off-white solid in 77% yield (13.8 mmol, 2.9 g). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 9.97 (s, 1H), 7.84 – 7.97 (m, 2H), 7.43 – 7.38 (m, 2H), 3.78 (s, 2H), 3.58 – 3.53 (m, 2H), 3.40 – 3.34 (m, 2H), 1.62 – 1.47 (m, 4H), 1.41 – 1.34 (m, 2H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 191.9, 168.2, 142.7, 135.2, 130.2, 129.6, 47.3, 43.1, 41.1, 26.4, 25.5, 24.4; **HRMS** (ESI, m/z) calcd. for $C_{14}H_{17}NO_2Na^+$ $[M + Na]^+$ 254.1151, found 254.1164.

2-phenyl-1-(pyrrolidin-1-yl)ethan-1-one (1n)



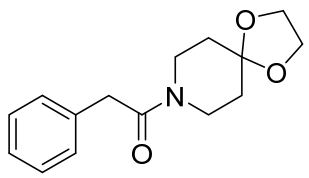
2-Phenylacetyl chloride (40 mmol, 5.3 mL) was subjected to method D (amine; pyrrolidine, 1.2 equiv) to give the corresponding amide as a yellow solid in 92% yield (36.9 mmol, 6.97 g). Spectral data is in agreement with published data.[10]

1-morpholino-2-phenylethan-1-one (1o)



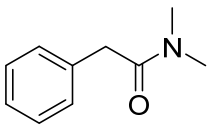
2-Phenylacetyl chloride (48 mmol, 6.4 mL, 1.2 equiv) was subjected to method D (amine; morpholine, 1 equiv) to give the corresponding amide as a yellow solid in 60% yield (24 mmol, 4.92 g). Spectral data is in agreement with published data.[10]

2-phenyl-1-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)ethan-1-one (1p)



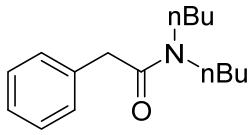
2-Phenylacetyl chloride (20 mmol, 2.7 mL) was subjected to method D (amine; 4-piperidone ethylene acetal, 1.1 equiv) to give the corresponding amide as an pale yellow oil in 96% yield (19 mmol, 5.01 g). Spectral data is in agreement with published data.[14]

***N*,*N*-dimethyl-2-phenylacetamide (1q)**



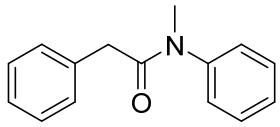
2-Phenylacetyl chloride (40 mmol, 5.3 mL) was subjected to method D (amine; dimethylamine hydrochloride, 5 equiv) to give the corresponding amide as a yellow solid in 80% yield (32 mmol, 5.19 g). Spectral data is in agreement with published data.[15]

***N*,*N*-dibutyl-2-phenylacetamide (1r)**



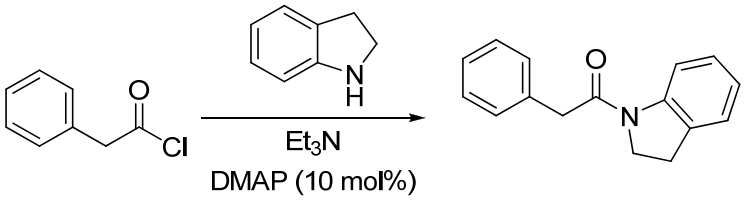
2-Phenylacetyl chloride (40 mmol, 5.3 mL) was subjected to method D (amine; dibutylamine, 1.5 equiv) to give the corresponding amide as an pale yellow oil in 97% yield (38.7 mmol, 9.57 g). Spectral data is in agreement with published data.[16]

_N_-methyl-_N_,2-diphenylacetamide (1s)



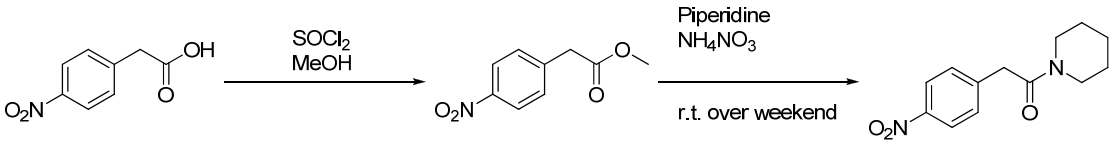
2-Phenylacetyl chloride (20 mmol, 2.7 mL) was subjected to method D (amine; *N*-methylaniline, 1.5 equiv) to give the corresponding amide as an brown liquid in 95% yield (19 mmol, 4.30 g). Spectral data is in agreement with published data.[17]

1-(indolin-1-yl)-2-phenylethanone (1t)



Phenyl acid chloride (27.2 mmol, 3.6 mL) was added dropwise to a solution of indoline (23.2 mmol, 2.73 g), DMAP (10 mol%, 245 mg) and Et_3N (1.5 equiv) in anhydrous dichloromethane (40 mL) at 0 °C. The solution was stirred overnight at room temperature. After the completion of the reaction (monitored by TLC), the mixture was extracted with H_2O (3 × 30 mL). The organic phase was dried using sodium sulphate and concentrated under reduced pressure. The crude amide product was purified by column chromatography (EtOAc : petroleum ether as eluent) to give the amide as a yellow solid in 98% yield (22.7 mmol, 5.38 g). Spectral data is in agreement with published data.[18]

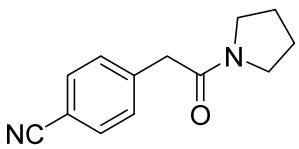
2-(4-nitrophenyl)-1-(piperidin-1-yl)ethan-1-one (1u)



To a stirred solution of 2-(4-nitrophenyl)acetic acid (30 mmol, 5.4 g) in methanol (60 mL) thionyl chloride (60 mmol, 3.6 mL, 2 equiv) was added dropwise at 0 °C over 10 min and the mixture was then refluxed for 2 hours. Excess of $SOCl_2$ was removed under reduced pressure. The formed white solid was dissolved in ethyl acetate (20 mL). The mixture was washed with water (10 mL) and saturated aqueous $NaHCO_3$ solution (10 mL), the organic phase was then dried using anhydrous sodium sulphate and the solvent was evaporated yielding the ester as an yellow solid in 93% yield (28

mmol, 5.56 g) with no need of further purification, spectral data is in agreement with published data. The ester was dissolved in piperidine (84 mmol, 8.4 mL, 3 equiv) and NH_4NO_3 (14 mmol, 1.13 g, 0.5 equiv) was added to the mixture, which was stirred at r.t. for 72 hours. The reaction mixture was extracted three times with diethyl ether (3 × 50 mL) and dried using anhydrous sodium sulphate. The solvent was evaporated yielding the desired product as an colorless oil, which was further purified by automatic column (petroleum ether : ethyl acetate as eluent) and the desired product was obtained as on orange solid in 50% yield (14 mmol, 3.45 g). Spectral data is in agreement with published data.[19,20,21]

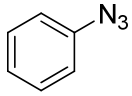
4-(2-oxo-2-(pyrrolidin-1-yl)ethyl)benzonitrile (1v)



2-(4-cyanophenyl)acetic acid (27 mmol, 4.35g) was subjected to method E (amide; pyrrolidine 2.5 equiv) to give the corresponding amide as an off-white solid in 79% yield (21.3 mmol, 4.56 g). Spectral data is in agreement with published data.[22]

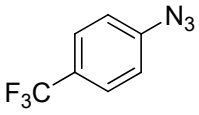
Azides:

azidobenzene (3a)



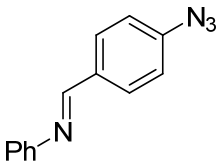
Aniline (20 mmol, 1.8 mL) was subjected to method A to give the corresponding azide as an yellow oil in 70% yield (14 mmol, 1.68 g). Spectral data is in agreement with published data.[23]

1-azido-4-(trifluoromethyl)benzene (3b)



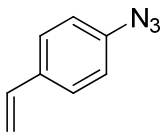
4-(trifluoromethyl)aniline (30 mmol, 3.76 mL) was subjected to method A to give the corresponding azide as an yellow oil in 80% yield (24 mmol, 4.49 g). Spectral data is in agreement with published data.[24]

(*E*)-*N*-(4-azidobenzylidene)aniline (3c)



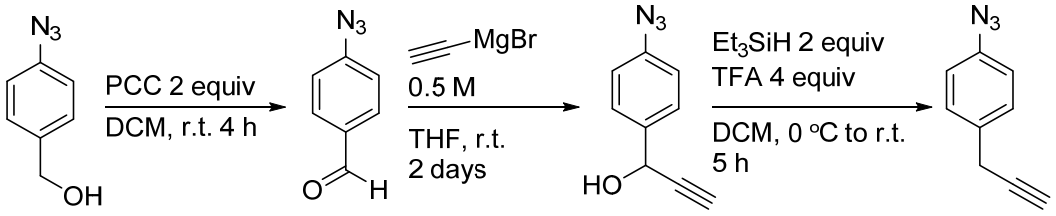
To a solution of aniline (1.1 equiv) dissolved in EtOH (2 mL) a solution of 4-azidobenzaldehyde (**3s**, 4 mmol, 588 mg) in EtOH (1 mL) was added portion wise at room temperature. A white precipitate was formed immediately and the reaction mixture was allowed to stir for an additional hour. The solid was collected by vacuum filtration and the crude product was purified by silica gel column chromatography (petroleum ether : ethyl acetate as eluent) to give the azide as a white solid in 85% yield (3.4 mmol, 756 mg). Spectral data is in agreement with published data.[25]

1-azido-4-vinylbenzene (3d)



4-Vinylaniline (20 mmol, 1.2 g) was subjected to method A to give the corresponding azide as a brown solid in 80% yield (16 mmol, 2.32 g). Spectral data is in agreement with published data.[26]

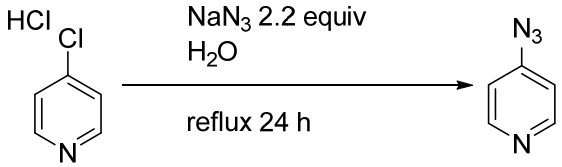
1-azido-4-(prop-2-ynyl)benzene (3e)



To a stirred solution of pyridinium chlorochromate (PCC, 2 equiv) in anhydrous DCM (68 mL) a solution of (4-azidophenyl) methanol (prepared with method A, 28.98 mmol, 4.31 g, 1 equiv) in anhydrous DCM (30 mL) was added. $MgSO_4$ (1 equiv) was added and the reaction was stirred at r.t. for 4 hours. Upon completion, the reaction was poured onto diethyl ether and the solution was then filtered through a pad of silica and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether : ethyl acetate as eluent) and the azido aldehyde was obtained in 90% yield (24.5 mmol, 3.61 g). The aldehyde (1 equiv) was dissolved in dry THF (40 mL) and ethynylmagnesium bromide (0.5M solution in THF, 1.05 equiv) was added dropwise at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to reach room temperature and was then stirred for 2 days at the same temperature. After completion of the reaction (checked by TLC) the reaction mixture was quenched with saturated NH_4Cl solution at 0 °C. The solvent was removed under reduced pressure and the resulting residue was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether : ethyl acetate as eluent) to afford the acetylenic carbinol in 43% yield (8.5 mmol, 1.47 g). The acetylenic carbinol (1 equiv) was dissolved in dry DCM (15 mL) and triethylsilane (2 equiv) and trifluoroacetic acid (4 equiv) was added simultaneously at 0 °C under nitrogen atmosphere. The reaction was allowed to stir at room temperature and the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure and the resulting residue was dissolved in EtOAc (50 mL). The pH of the solution was adjusted to 7 by dropwise addition of aqueous $NaHCO_3$ solution. The mixture was then washed with H_2O (30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether : ethyl acetate as eluent) and the azide was obtained

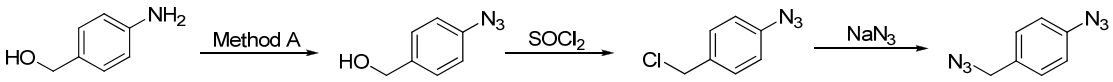
as a yellow oil in 20% yield (1.62 mmol, 255 mg). Spectral data is in agreement with published data.[27,28]

4-azidopyridine (3f)



To a 100 mL round bottom flask equipped with a stirring bar sodium azide (2.2 equiv) was added together with water (50 mL). To the stirred solution 4-chloropyridine hydrochloride (1 equiv) was slowly added and a condenser was subsequently attached. The reaction mixture was refluxed open to atmosphere and in the dark placed in a well-ventilated hood for 24 hours (**CAUTION:** this procedure can generate hydrazoic acid (HN_3)). The reaction mixture was cooled to r.t. and extracted with EtOAc (3 × 15 mL). After extraction, the pH of the aqueous layer should be checked to ensure that the solution is slightly basic (pH 8-10). If not, it should be adjusted with the addition of sat. $NaHCO_3$ (aq) prior to its disposal to a separate azide waste container. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the azide as an red oil in 60% yield (21 mmol, 2.5 g). Spectral data is in agreement with published data.[29]

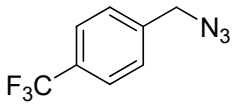
1-azido-4-(azidomethyl)benzene (3g)



(4-aminophenyl)methanol (30 mmol, 3.2 g) was subjected to method A to give hydroxyl azide in 74% yield (22.4 mmol, 3.33 g). This compound was dissolved in DCM (20 mL) and $SOCl_2$ (44 mmol, 3.2 mL) was added dropwise at 0 °C. The reaction was allowed to reach r.t. and left to stir for 16 h. The reaction was cooled to 0 °C and quenched with water, follwed by extraction with diethylether (3 x 50 mL). The organic phase was dried with Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography (pentane : ethyl acetate) to give the chloro azide as a yellow solid in 88% yield (19.7 mmol, 3.3 g). This compound (8.7 mmol, 1.46 g) was dissolved in water/acetone 1:3 (35 mL) and NaN_3 (17.4 mmol,

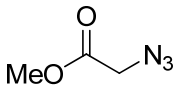
1.13 g) was added in portions. The reaction was stirred at r.t. for 24 h and DCM was added (100 mL). The organic phase was extracted, washed with water and then dried over Na_2SO_4. The drying agent was filtered off and the DCM was removed under vacuum to give pure product **3g** in 95% yield (8.27 mmol, 1.44 g). Spectral data is in agreement with published data.[30]

1-(azidomethyl)-4-(trifluoromethyl)benzene (3h)



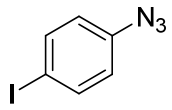
1-(Bromomethyl)-4-(trifluoromethyl)benzene (8.1 mmol, 1.92 g) was subjected to method B to give the corresponding azide as an colorless oil in 95% yield (7.7 mmol, 1.54 g). Spectral data is in agreement with published data.[31]

methyl 2-azidoacetate (3i)



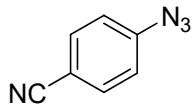
The azide was purchased from Sigma Aldrich and used directly in the reaction.

1-azido-4-iodobenzene (3j)



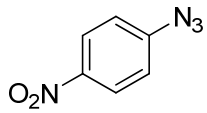
4-Iodoaniline (30 mmol, 6.57 g) was subjected to method A to give the corresponding azide as a brown-orange solid in 84% yield (25 mmol, 6.15 g). Spectral data is in agreement with published data.[32]

4-azidobenzonitrile (3k)



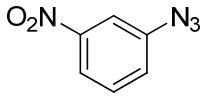
4-Aminobenzonitrile (30 mmol, 3.54 g) was subjected to method A to give the corresponding azide as a yellow solid in 96% yield (29 mmol, 4.15 g). Spectral data is in agreement with published data.[32]

1-azido-4-nitrobenzene (3l)



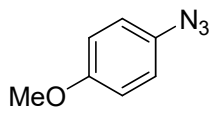
4-Nitroaniline (30 mmol, 4.14 g) was subjected to method A to give the corresponding azide as a yellow solid 83% yield (25 mmol, 4.08 g). Spectral data is in agreement with published data.[33]

1-azido-3-nitrobenzene (3m)



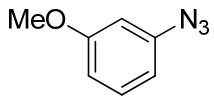
3-Nitroaniline (20 mmol, 2.76 g) was subjected to method A to give the corresponding azide as an orange solid in 94% yield (18.8 mmol, 3.07 g). Spectral data is in agreement with published data.[34]

1-azido-4-methoxybenzene (3n)



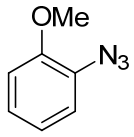
3-Methoxyaniline (20 mmol, 2.46 g) was subjected to method A to give the corresponding azide in 64% yield (12.74 mmol, 1.9 g). Spectral data is in agreement with published data.[32]

1-azido-3-methoxybenzene (3o)



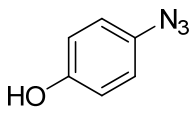
3-Methoxyaniline (20 mmol, 2.3 mL) was subjected to method A to give the corresponding azide as an yellow oil in 35% yield (7.0 mmol, 1.06 g). Spectral data is in agreement with published data.[35]

1-azido-2-methoxybenzene (3p)



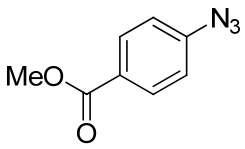
2-Methoxyaniline (20 mmol, 2.3 mL) was subjected to method A to give the corresponding azide as an yellow oil in 41% yield (8.2 mmol, 1.22 g). Spectral data is in agreement with published data.[36]

4-azidophenol (3q)



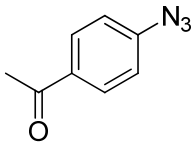
4-Aminophenol (20 mmol, 2.2 g) was subjected to method A to give the corresponding azide as an dark purple solid in 75% yield (15 mmol, 2.04 g). Spectral data is in agreement with published data.[36]

methyl 4-azidobenzoate (3r)



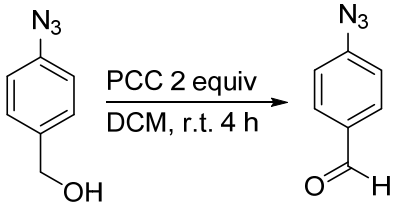
Methyl 4-aminobenzoate (20 mmol, 3.0 g) was subjected to method A to give the corresponding azide as an yellow oil in 92% yield (18.4 mmol, 3.3 g). Spectral data is in agreement with published data.[37]

1-(4-azidophenyl)ethanone (3s)



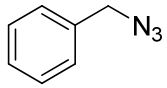
4-Aminoacetophenone (30 mmol, 4.05 g) was subjected to method A to give the corresponding azide as an orange solid in 95% yield (28.5 mmol, 4.6 g). Spectral data is in agreement with published data.[32]

4-azidobenzaldehyde (3t)



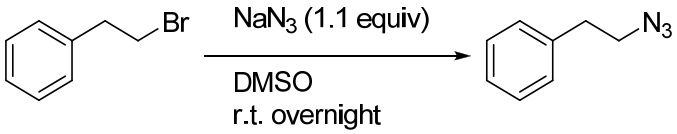
(4-Azidophenyl) methanol (prepared by method A, 27.3 mmol, 4.06 g) in anhydrous DCM (30 mL) was subjected to a stirred solution of pyridinium chlorochromate (PCC, 2 equiv) in anhydrous DCM (68 mL). $MgSO_4$ (1 equiv) was added and the reaction was stirred at r.t. for 4 hours. Upon completion, the reaction was poured onto diethyl ether and the solution was then filtered through a pad of silica and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether : ethyl acetate as eluent) and the azide was obtained as an yellow oil in 90% yield (24.5 mmol, 3.61 g). Spectral data is in agreement with published data.[27]

(azidomethyl)benzene (3u)



Benzylbromide (20 mmol, 2.38 mL) was subjected to method B to give the corresponding azide as colorless liquid in 98% yield (19.6 mmol, 2.61g). Spectral data is in agreement with published data.[38]

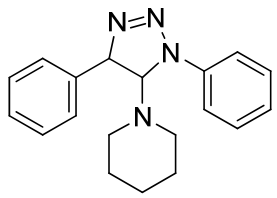
(2-azidoethyl)benzene (3v)



NaN_3 (22 mmol, 1.43 g) was dissolved in DMSO (44 mL) and allowed to stir overnight at r.t. (2-Bromoethyl)benzene (20 mmol, 2.0 mL) was dropwise added to the solution and the mixture was allowed to stir for 2 hours before the reaction was quenched by H_2O (100 mL). When the reaction mixture cooled down to r.t. the mixture was extracted three times with diethyl ether (3 × 60 mL), H_2O (2 × 100 mL) and brine (100 mL). The organic layer was dried using anhydrous sodium sulphate and the solvent was evaporated yielding the desired product an colorless oil in 73% yield (14.5 mmol, 2.13 g) with no need of further purification. Spectral data is in agreement with published data.[39,40]

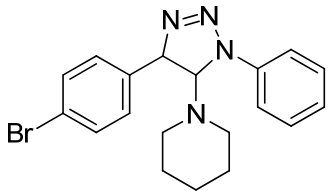
Triazolines:

1-(1,4-diphenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)piperidine (4aa)



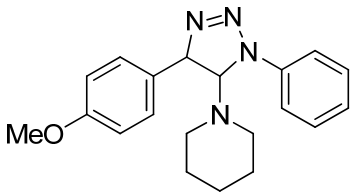
Cyclization of enamine with azide for 2 h at 65 °C yielded the triazoline after purification by automatic column (pentane : ethyl acetate) as an off white solid (282 mg, 91% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.56 (m, 2H), 7.39 – 7.27 (m, 5H), 7.10 – 7.05 (m, 3H), 5.44 (d, *J* = 3.48 Hz, 1H), 4.73 (d, *J* = 3.64 Hz, 1H), 2.47 – 2.36 (m, 4H), 1.58 – 1.41 (m, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 140.5, 138.3, 129.2, 128.1, 126.8, 123.0, 116.1, 82.3, 78.1, 47.2, 25.8, 24.6; **HRMS** (ESI, m/z) calcd. for $C_{19}H_{22}N_4Na^+$ $[M + Na]^+$ 329.1737, found 329.1731.

1-(4-(4-bromophenyl)-1-phenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)piperidine (4ba)



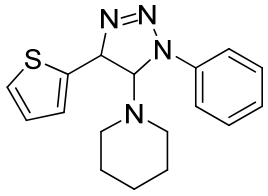
Cyclization of enamine with azide for 2 h at 65 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as an offwhite solid (331 mg, 86% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.56 – 7.51 (m, 2H), 7.49 – 7.44 (m, 2H), 7.39 – 7.32 (m, 2H), 7.11 – 7.06 (m, 1H), 6.98 – 6.93 (m, 2H), 5.38 (d, *J* = 3.60 Hz, 1H), 4.69 (d, *J* = 3.60 Hz, 1H), 2.46 – 2.32 (m, 4H), 1.58 – 1.39 (m, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 140.3, 137.3, 132.3, 129.3, 128.5, 123.2, 122.1, 116.2, 82.3, 77.5, 47.3, 25.8, 24.5; **HRMS** (ESI, m/z) calcd. for $C_{19}H_{21}BrN_4Na^+$ $[M + Na]^+$ 407.0853, found 407.0847.

1-(4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)piperidine (4ca)

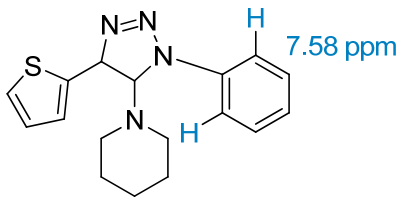


Cyclization of enamine with azide for 2 h at 65 °C yielded the triazoline after purification by automatic column (pentane : ethyl acetate as eluent) as a pale yellow solid (296 mg, 88% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.56 – 7.53 (m, 2H), 7.37 – 7.33 (m, 2H), 7.09 – 7.05 (m, 1H), 7.00 – 6.97 (m, 2H), 6.88 – 6.84 (m, 2H), 5.38 (d, *J* = 3.58 Hz, 1H), 4.69 (d, *J* = 3.58 Hz, 1H), 3.78 (s, 3H), 2.46 – 2.34 (m, 4H), 1.58 – 1.41 (m, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 159.4, 140.6, 130.4, 129.2, 128.0, 122.9, 116.0, 114.6, 82.3, 77.6, 55.4, 47.2, 25.8, 24.6; **HRMS** (ESI, m/z) calcd. for $C_{20}H_{24}N_4ONa^+$ $[M + Na]^+$ 359.1842, found 359.1832.

1-(1-phenyl-4-(thiophen-2-yl)-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)piperidine (4da)

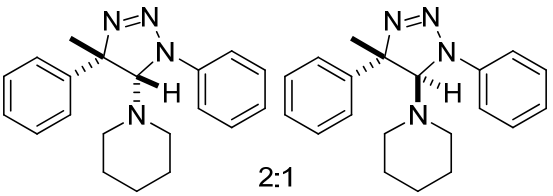


Cyclization of enamine with azide for 2.5 h at 40 °C yielded the triazoline after purification by automatic column (pentane : ethyl acetate as eluent) as an yellow solid (259 mg, 83% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.57 (m, 2H), 7.38 (m, 2H), 7.27 (m, 1H), 7.12 (m, 1H), 7.00 (m, 1H), 6.94 (m, 1H), 5.71 (d, *J* = 3.55 Hz, 1H), 4.89 (d, *J* = 3.55 Hz, 1H), 2.45 (m, 4H), 1.64 – 1.42 (m, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 140.6, 140.5, 129.2, 127.3, 125.3, 124.8, 123.2, 116.2, 82.5, 73.2, 47.3, 25.8, 24.5; **HRMS** (ESI, m/z) calcd. for $C_{17}H_{20}N_4SNa^+$ $[M + Na]^+$ 335.1301, found 335.1289.

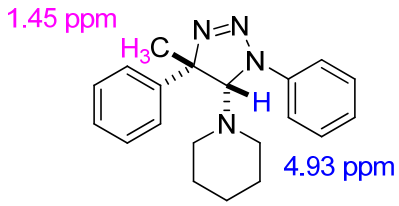


The regiochemistry of the product was investigated using ^{1}H NMR NOE experiment. By irradiating the signal of the aromatic protons (7.57 ppm) an increase in intensity of the piperidine protons (2.45 ppm (m, 4H) and 1.64 – 1.42 ppm (m, 6H)) was observed, indicating that these functional groups are close in space and situated on the 1 and 5 positions of the triazoline ring.

1-(4-methyl-1,4-diphenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)piperidine (4ea)

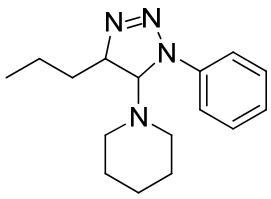


Cyclization of enamine with azide for 15 h at 65 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as an yellow solid (190 mg, 61% yield). The triazoline was obtained in an 2:1 mixture of the diasteromers and the major diastereomer could be separated from the minor for the characterization. **^{1}H-NMR** of the major diastereomer (500 MHz, -5°C, $CDCl_3$): δ = 7.66 – 7.61 (m, 2H), 7.50 – 7.45 (m, 2H), 7.40 – 7.34 (m, 4H), 7.30 – 7.27 (m, 1H), 7.12 – 7.07 (m, 1H), 4.93 (s, 1H), 2.93 (br s, 1H), 2.57 (br s, 1H), 1.61 (br s, 2H), 1.46 (s, 3H), 1.29 (br s, 1H), 1.15 (br s, 2H), 0.79 (br s, 2H), 0.08 (br s, 1H); **^{13}C-NMR** of the major diastereomer (125 MHz, -5°C, $CDCl_3$): δ = 141.9, 139.9, 129.2, 127.7, 127.5, 126.8, 123.3, 117.4, 84.8, 82.8, 55.3, 44.4, 28.2, 26.6, 24.3, 23.7. **HRMS** (ESI, m/z) calcd. for $C_{20}H_{24}N_4Na^+$ $[M + Na]^+$ 343.1893, found 343.1890.



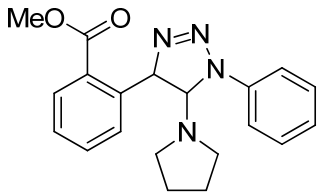
The relative stereochemistry of the major diastereomer was confirmed using ^{1}H NMR NOE experiment. By irradiating the signal of the CH_3 group (1.45 ppm) an increase in intensity of the adjacent proton (4.93 ppm) was observed, indicating cis relationship between the triazoline proton and the methyl group.

1-(1-phenyl-4-propyl-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)piperidine (4fa)



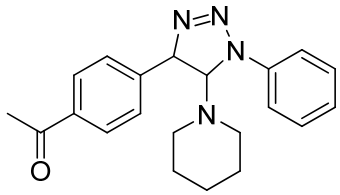
Cyclization of enamine with azide for 3 h at 65 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as a white solid (179 mg, 66% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.30 – 7.34 (m, 2H) 7.48 – 7.50 (m, 2H), 7.02 – 7.05 (m, 1H), 4.46 (d, *J* = 3.50 Hz, 1H), 4.39 – 4.35 (m, 1H), 2.29 – 2.26 (m, 4H), 1.65 – 1.58 (m, 1H), 1.50 – 1.36 (m, 9H), 0.97 (t, *J* = 7.20 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 140.8, 128.9, 122.4, 115.6, 79.2, 74.5, 47.1, 34.8, 25.7, 24.4, 18.7, 13.9; **HRMS** (ESI, m/z) calcd. for $C_{16}H_{25}N_4^+$ $[M + H]^+$ 273.2074, found 273.2070.

methyl 2-(1-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-4-yl)benzoate (4ga)



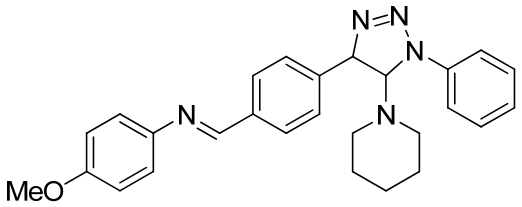
Cyclization of enamine with azide for 2 h at 65 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as an plae brown solid (165 mg, 94% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.00 – 7.95 (m, 1H), 7.53 – 7.47 (m, 2H), 7.44 – 7.38 (m, 1H), 7.37 – 7.30 (m, 3H), 7.09 – 7.03 (m, 1H), 6.80 – 6.75 (m, 1H), 6.52 – 6.48 (m, 1H), 5.13 – 5.08 (m, 1H), 3.94 (s, 3H), 2.70 – 2.57 (m, 4H), 1.78 – 1.68 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 167.7, 140.5, 138.2, 132.9, 130.9, 129.1, 128.8, 127.7, 127.4, 122.9, 116.2, 78.2, 75.9, 52.3, 46.7, 24.3; **HRMS** (ESI, m/z) calcd. for $C_{20}H_{22}N_4O_2Na^+$ $[M + Na]^+$ 373.1635, found 373.1634.

1-(4-(1-phenyl-5-(piperidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-4-yl)phenyl)ethanone (4ha)



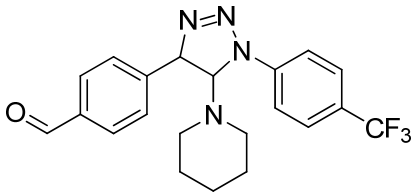
Cyclization of enamine with azide for 2.5 h at 60 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as a pale brown solid (292 mg, 84% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.94 – 7.90 (m, 2H), 7.55 – 7.51 (m, 2H), 7.37 – 7.32 (m, 2H), 7.19 – 7.15 (m, 2H), 7.10 – 7.05 (m, 1H), 5.47 (d, *J* = 3.64 Hz, 1H), 4.71 (d, *J* = 3.64 Hz, 1H), 2.56 (*s*, 3H), 2.46 – 2.40 (m, 2H), 2.40 – 2.34 (m, 2H), 1.57 – 1.47 (m, 4H), 1.46 – 1.39 (m, 2H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 197.5, 143.3, 140.2, 136.7, 129.2, 129.2, 127.0, 123.3, 116.2, 82.3, 77.7, 47.2, 26.7, 25.7, 24.4; **HRMS** (ESI, m/z) calcd. for $C_{21}H_{24}N_4ONa^+$ $[M + Na]^+$ 371.1842, found 371.1857.

(*E*)-4-methoxy-*N*-(4-(1-phenyl-5-(piperidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-4-yl)benzylidene)aniline (4ia)



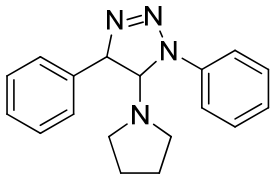
Cyclization of enamine with azide for 3 h at 65 °C yielded the triazoline after washing of the reaction mixture with pentane (3×2 mL) and drying under reduced pressure as a pale solid (385 mg, 88% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.94 – 7.90 (m, 2H), 7.55 – 7.51 (m, 2H), 7.37 – 7.32 (m, 2H), 7.19 – 7.15 (m, 2H), 7.10 – 7.05 (m, 1H), 5.47 (d, *J* = 3.64 Hz, 1H), 4.71 (d, *J* = 3.64 Hz, 1H), 2.56 (s, 3H), 2.46 – 2.40 (m, 2H), 2.40 – 2.34 (m, 2H), 1.57 – 1.47 (m, 4H), 1.46 – 1.39 (m, 2H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 158.5, 157.6, 144.9, 141.1, 140.4, 136.4, 129.4, 129.3, 127.3, 123.2, 122.4, 116.2, 114.5, 82.5, 77.9, 55.6, 47.3, 25.8, 24.6; **HRMS** (ESI, m/z) calcd. for $C_{27}H_{29}N_5ONa^+$ $[M + Na]^+$ 462.2264, found 462.2261.

4-(5-(piperidin-1-yl)-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-1,2,3-triazol-4-yl)benzaldehyde (4mb)



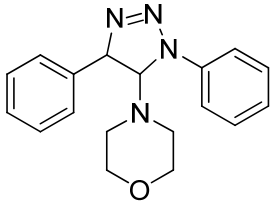
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.99 (s, 1H), 7.90-7.84 (m, 2H), 7.64 – 7.58 (m, 4H), 7.25 – 7.21 (m, 2H), 5.58 (d, *J* = 3.63 Hz, 1H), 4.73 (d, *J* = 3.63 Hz, 1H), 2.45 – 2.36 (m, 4H), 1.60 – 1.43 (m, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 191.6, 144.1, 142.6, 136.3, 130.7, 128.5, 127.5, 126.7, 126.6, 126.6, 126.6, 125.8, 125.5, 125.2, 124.8, 124.5, 123.1, 120.4, 115.6, 81.9, 77.9, 47.1, 25.7, 24.4; **HRMS** (ESI, m/z) calcd. for $C_{21}H_{21}N_4F_3ONa^+$ $[M + Na]^+$ 425.1560, found 425.1557.

1,4-diphenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazole (4na)



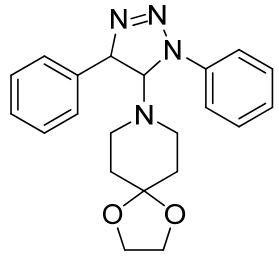
Cyclization of enamine with azide for 3 h at 65 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as an white solid (262 mg, 90% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.55 – 7.50 (m, 2H), 7.40 – 7.30 (m, 5H), 7.15 – 7.06 (m, 3H), 5.36 (d, *J* = 3.21 Hz, 1H), 5.12 (d, *J* = 3.21 Hz, 1H), 2.64 – 2.57 (m, 4H), 1.79 – 1.72 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 104.6, 137.7, 129.2, 129.1, 128.0, 126.7, 123.0, 116.2, 80.0, 77.4, 46.6, 23.8; **HRMS** (ESI, m/z) calcd. for $C_{18}H_{20}N_4Na^+$ $[M + Na]^+$ 315.1580, found 315.1580.

4-(1,4-diphenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)morpholine (4oa)



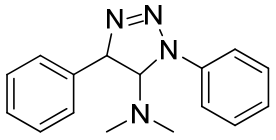
Cyclization of enamine with azide for 4 h at 65 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as an yellow solid (222 mg, 72% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.59 – 7.53 (m, 2H), 7.42 – 7.30 (m, 5H), 7.15 – 7.07 (m, 3H), 5.51 (d, *J* = 3.55 Hz, 1H), 4.78 (d, *J* = 3.55 Hz, 1H), 3.74 – 3.63 (m, 4H), 2.58 – 2.45 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 140.1, 137.5, 129.3, 129.2, 128.3, 126.7, 123.2, 115.9, 81.4, 78.3, 66.7, 46.2; **HRMS** (ESI, m/z) calcd. for $C_{18}H_{20}N_4ONa^+$ $[M + Na]^+$ 331.1529, found 331.1543.

8-(1,4-diphenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)-1,4-dioxa-8-azaspiro[4.5]decane (4pa)



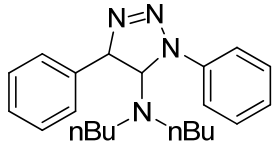
Cyclization of enamine with azide for 3 h at 65 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as an yellow solid (286 mg, 78% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.61 – 7.57 (m, 2H), 7.42 – 7.28 (m, 5H), 7.14 – 7.07 (m, 3H), 5.51 (d, *J* = 3.78 Hz, 1H), 4.80 (d, *J* = 3.78 Hz, 1H), 3.97 (s, 4H), 2.64 – 2.50 (m, 4H), 1.79 – 1.65 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 140.0, 137.9, 129.3, 129.2, 128.2, 126.8, 123.0, 115.7, 107.0, 81.4, 77.6, 64.4, 43.8, 34.7; **HRMS** (ESI, m/z) calcd. for $C_{21}H_{24}N_4O_2Na^+$ $[M + Na]^+$ 387.1791, found 387.1794.

***N*,*N*-dimethyl-1,4-diphenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-amine (4qa)**



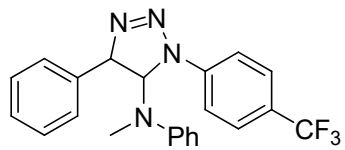
Cyclization of enamine with azide for 3 h at 65 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as an pale yellow solid (245 mg, 92% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.59 – 7.54 (m, 2H), 7.43 – 7.33 (m, 5H), 7.15 – 7.09 (m, 3H), 5.44 (d, *J* = 3.47 Hz, 1H), 4.83 (d, *J* = 3.47 Hz, 1H), 2.26 (s, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ =140.1, 137.9, 129.3, 129.2, 128.1, 126.7, 123.1, 116.0, 81.5, 77.5, 38.1; **HRMS** (ESI, m/z) calcd. for $C_{16}H_{18}N_4Na^+$ $[M + Na]^+$ 289.1422, found 289.1424.

***N*,*N*-dibutyl-1,4-diphenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-amine (4ra)**



Cyclization of enamine with azide for 3 h at 65 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as an colorless oil (326 mg, 90% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.60 – 7.56 (m, 2H), 7.43 – 7.31 (m, 5H), 7.14 – 7.08 (m, 3H), 5.44 (d, *J* = 3.78 Hz, 1H), 4.95 (d, *J* = 3.78 Hz, 1H), 2.58 – 2.39 (m, 4H), 1.50 – 1.35 (m, 4H), 1.35 – 1.17 (m, 4H), 0.87 (t, *J* = 7.29 Hz, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 140.1, 138.3, 129.2, 129.0, 128.0, 126.7, 122.8, 115.9, 80.2, 80.0, 48.3, 30.2, 20.4, 13.9; **HRMS** (ESI, m/z) calcd. for $C_{22}H_{30}N_4Na^+$ $[M + Na]^+$ 373.2363, found 373.2380.

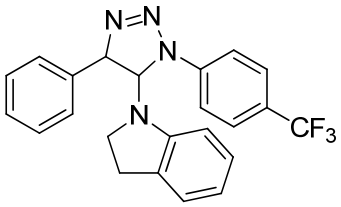
***N*-methyl-*N*,4-diphenyl-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,3-triazol-5-amine (4sb)**



Cyclization of enamine with azide for 5 h at 65 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as an light yellow solid (325 mg, 82% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.58 – 7.52 (m, 2H), 7.48 – 7.41 (m, 3H), 7.37 – 7.29 (m, 4H), 7.18 – 7.14 (m, 2H), 6.99 – 6.93 (m, 1H), 6.86 – 6.81 (m, 2H), 5.77 (d, *J* = 3.67 Hz, 1H), 5.51 (d, *J* = 3.67 Hz, 1H), 2.58 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 147.7, 142.0, 136.1, 129.8, 129.5, 128.8, 126.8 (q, *J* = 3.65 Hz), 126.7, 124.7 (q, *J* = 33.12 Hz), 124.2 (q, *J* = 271.41 Hz), 120.0, 114.9, 114.8, 85.2, 76.6, 30.6; **^{19}F-NMR** (337 MHz, $CDCl_3$): δ = -61.96

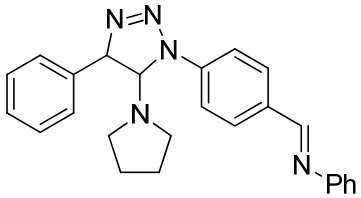
(monofluorobenzene as IS; -113.15 ppm); **HRMS** (ESI, m/z) calcd. for $C_{22}H_{19}N_4F_3Na^+$ $[M + Na]^+$ 419.1456, found 419.1456.

1-(4-phenyl-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-1,2,3-triazol-5-yl)indoline (4tb)



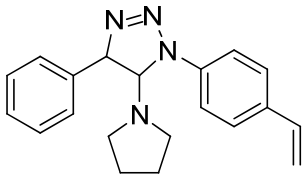
Cyclization of enamine with azide for 3 h at 65 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as an yellow oil (245 mg, 60% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.58 – 7.50 (m, 4H), 7.40 – 7.35 (m, 3H), 7.13 – 7.07 (m, 4H), 6.76 (t, *J* = 7.50 Hz, 1H), 6.50 (d, *J* = 7.94 Hz, 1H), 5.66 (d, *J* = 3.31 Hz, 1H), 5.47 (d, *J* = 3.31 Hz, 1H), 3.12 – 2.89 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 141.9, 136.2, 130.2, 129.3, 128.6, 127.5, 126.7 (q, *J* = 3.76 Hz), 126.7, 125.4, 124.9 (q, *J* = 34.6 Hz), 124.2 (q, *J* = 273.45 Hz), 119.3, 115.0, 107.1, 83.2, 72.8, 46.3, 27.8; **HRMS** (ESI, m/z) calcd. for $C_{23}H_{19}F_3N_4Na^+$ $[M + Na]^+$ 431.1369, found 431.1367.

(*E*)-*N*-(4-(4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)benzylidene)aniline (4nc)



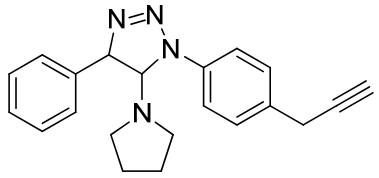
Cyclization of enamine with azide for 3 h at 40 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as a pale yellow solid (295 mg, 92% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8,41 (s, 1H), 7.89 (d, *J* = 8.70 Hz, 2H), 7.59 (d, *J* = 8.70 Hz, 2H), 7.30 – 7.41 (m, 5H), 7.24 – 7.20 (m, 3H), 7.10 (dd, *J* = 1.80, 8.20 Hz, 2H), 5.40 (d, *J* = 3.10 Hz, 1H), 5.14 (d, *J* = 3.10 Hz, 1H), 2.59 – 2.56 (m, 4H), 1.77 – 1.74 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 159.5, 152.2, 142.9, 137.2, 130.9, 130.0, 129.2, 129.1, 128.2, 126.6, 125.7, 120.8, 115.9, 80.2, 77.1, 46.5, 23.8; **HRMS** (ESI, m/z) calcd. for $C_{25}H_{25}N_5Na^+$ $[M + Na]^+$ 418.2002, found 418.2002.

4-phenyl-5-(pyrrolidin-1-yl)-1-(4-vinylphenyl)-4,5-dihydro-1*H*-1,2,3-triazole (4nd)



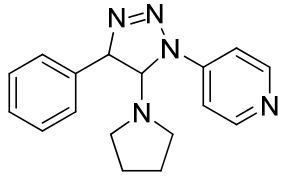
Cyclization of enamine with azide for 3 h at 40 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as a yellow oil (269 mg, 85% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.52 – 7.33 (m, 7H), 7.13 (d, *J* = 7.60 Hz, 2H), 6.72 (dd, *J* = 11.70, 17.60 Hz, 1H), 5.72 (d, *J* = 17.60 Hz, 1H), 5.38 (d, *J* = 3.10 Hz, 1H), 5.22 (d, *J* = 11.70 Hz, 1H), 5.41 (d, *J* = 3.10 Hz, 1H), 2.60 (br s, 4H), 1.77 – 1.74 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 139.9, 137.5, 136.1, 132.4, 129.1, 128.0, 127.0, 126.6, 116.1, 112.4, 79.9, 77.3, 46.6, 23.7; **HRMS** (ESI, m/z) calcd. for $C_{20}H_{22}N_4Na^+$ $[M + Na]^+$ 341.1737, found 341.1752.

4-phenyl-1-(4-(prop-2-ynyl)phenyl)-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazole (4ne)



Cyclization of enamine with azide for 3 h at 40 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as a white solid (154 mg, 93% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.40 Hz, 2H), 7.35 – 7.29 (m, 5H), 7.08 (d, *J* = 8.40 Hz, 2H), 5.33 (d, *J* = 3.02 Hz, 1H), 5.09 (d, *J* = 3.02 Hz, 1H), 3.59 (d, *J* = 2.90 Hz, 2H), 2.58 – 2.56 (m, 4H), 2.20 (t, *J* = 2.90 Hz, 1H), 1.74 – 1.72 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 139.3, 137.6, 130.5, 129.0, 128.5, 127.9, 126.6, 119.0, 116.3, 82.0, 79.8, 77.4, 70.4, 46.5, 23.7; **HRMS** (ESI, m/z) calcd. for $C_{21}H_{22}N_4Na^+$ $[M + Na]^+$ 353.1737, found 353.1754.

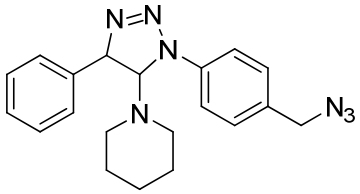
4-(4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)pyridine (4nf)



Cyclization of enamine with azide for 2 h at 40 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as an red oil (259 mg, 88% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 8.40 Hz, 2H), 7.36 – 7.28 (m, 5H), 7.05 – 7.03 (m, 2H), 5.44 (d, *J* = 3.06 Hz, 1H), 5.04 (d, *J* =

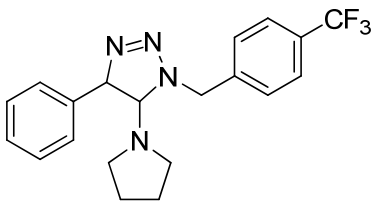
3.06 Hz, 1H), 2.57 – 2.52 (m, 4H), 1.77 – 1.74 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 150.4, 146.2, 136.6, 129.1, 128.2, 126.4, 109.8, 80.3, 76.1, 46.2, 23.6; **HRMS** (ESI, m/z) calcd. for $C_{17}H_{19}N_5Na^+$ $[M + Na]^+$ 316.1538, found 316.1535.

1-(1-(4-(azidomethyl)phenyl)-4-phenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)piperidine (4ag)



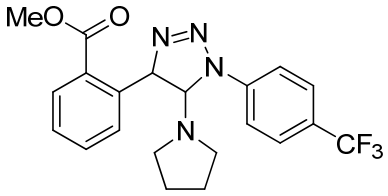
Cyclization of enamine with azide for 3 h at 65 °C yielded the triazoline after purification by automatic column (pentane : ethyl acetate) as an yellow solid (282 mg, 78% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.51 Hz, 2H), 7.37 – 7.27 (m, 5H), 7.06 (m, 2H), 5.45 (d, *J* = 3.63 Hz, 1H), 4.72 (d, *J* = 3.63 Hz, 1H), 4.32 (s, 2H) 2.46 – 2.34 (m, 4H), 1.58 – 1.41 (m, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 140.5, 138.1, 129.7, 129.4, 129.3, 128.2, 126.8, 116.2, 82.3, 78.1, 54.6, 47.1, 25.8, 24.6; **HRMS** (ESI, m/z) calcd. for $C_{20}H_{23}N_7Na^+$ $[M + Na]^+$ 384.1907, found 384.1918.

4-phenyl-5-(pyrrolidin-1-yl)-1-(4-(trifluoromethyl)benzyl)-4,5-dihydro-1*H*-1,2,3-triazole (4nh)



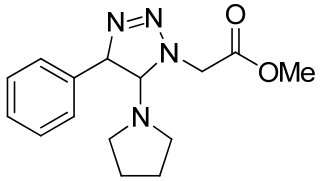
Cyclization of enamine with azide overnight at 65 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as an white solid (281 mg, 75% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.64 – 7.59 (m, 2H), 7.48 – 7.44 (m, 2H), 7.36 – 7.25 (m, 3H), 7.07 – 7.02 (m, 2H), 5.27 (d, *J* = 15.29 Hz, 1H), 5.23 (d, *J* = 3.57 Hz, 1H), 4.68 (d, *J* = 15.29 Hz, 1H), 4.39 (d, *J* = 3.57 Hz, 1H) 2.63 – 2.51 (m, 4H), 1.88 – 1.77 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 141.2, 137.9, 129.9 (q, *J* = 32.59 Hz), 128.9, 128.4, 127.8, 126.6, 125.6 (q, *J* = 3.75 Hz), 124.1 (q, *J* = 272.63 Hz), 79.1, 78.6, 49.9, 47.1, 24.1; **^{19}F-NMR** (337 MHz, $CDCl_3$): δ = -62.59 (monofluorobenzene as IS; -113.15 ppm); the signals at 5.27 and 4.68 ppm in ^{1}H NMR spectrum belong to benzylic CH_2 group which was confirmed by HSQC NMR experiment; **HRMS** (ESI, m/z) calcd. for $C_{20}H_{22}N_4F_3^+$ $[M + H]^+$ 375.1791, found 375.1789.

methyl 2-(5-(pyrrolidin-1-yl)-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,3-triazol-4-yl)benzoate (4gb)



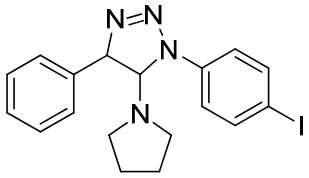
Cyclization of enamine with azide for 3 h at r.t. yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as an plae brown solid (185 mg, 88% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.03 – 7.98 (m, 1H), 7.62 – 7.54 (m, 4H), 7.45 – 7.39 (m, 1H), 7.38 – 7.32 (m, 1H), 6.75 – 6.70 (m, 1H), 6.62 (d, *J* = 3.26 Hz, 1H), 5.10 (d, *J* = 3.26 Hz, 1H), 3.95 (s, 3H), 2.67 – 2.58 (m, 4H), 1.81 – 1.70 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 167.6, 143.1, 137.8, 133.0, 131.2, 128.8, 128.5, 128.0, 127.4, 126.5, 126.5, 126.5, 126.4, 125.8, 124.9, 124.6, 124.2, 123.9, 123.1, 120.4, 115.6, 77.9, 76.2, 52.4, 46.6, 24.3; **HRMS** (ESI, m/z) calcd. for $C_{21}H_{21}F_3N_4O_2Na^+$ $[M + Na]^+$ 441.1509, found 441.1561.

methyl 2-(4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1H-1,2,3-triazol-1-yl)acetate (4ni)



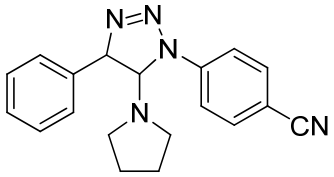
Cyclization of enamine with azide for 22 h at 50 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as a pale yellow solid (240 mg, 79% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.38 – 7.22 (m, 5H), 5.18 (d, *J* = 4.28 Hz, 1H), 4.87 (d, *J* = 18.00 Hz, 1H), 4.76 (d, *J* = 4.28 Hz, 1H), 4.31 (d, *J* = 18.00 Hz, 1H), 3.76 (s, 3H), 2.51 (m, 4H), 1.78 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 170.0, 138.1, 129.0, 128.0, 127.2, 79.3, 78.7, 52.4, 47.3, 46.9, 23.8; **HRMS** (ESI, m/z) calcd. for $C_{15}H_{20}N_4O_2Na^+$ $[M + Na]^+$ 311.1478, found 311.1478.

1-(4-iodophenyl)-4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazole (4nj)



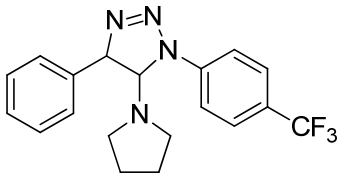
Cyclization of enamine with azide for 3 h at 40 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as a white solid (395 mg, 95% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.90 Hz, 2H), 7.25 – 7.34 (m, 5H), 7.05 (d, *J* = 8.90 Hz, 2H), 5.34 (d, *J* = 3.10 Hz, 1H), 5.04 (d, *J* = 3.10 Hz, 1H), 2.51 – 2.55 (m, 4H), 1.72 – 1.75 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 140.0, 137.9, 137.2, 129.1, 128.1, 126.6, 117.9, 85.6, 79.7, 46.4, 23.7; **HRMS** (ESI, m/z) calcd. for $C_{18}H_{19}IN_4Na^+$ $[M + Na]^+$ 441.0547, found 441.0550.

4-(4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)benzonitrile (4nk)



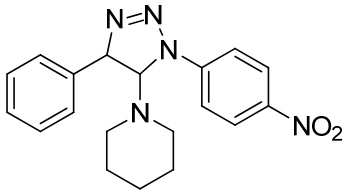
Cyclization of enamine with azide for 3 h at 40 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as a white solid (257 mg, 82% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 9.00 Hz, 2H), 7.58 (d, *J* = 9.00 Hz, 2H), 7.40 – 7.34 (m, 3H), 7.07 (dd, *J* = 8.20, 1.70 Hz, 2H), 5.46 (d, *J* = 3.10 Hz, 1H), 5.07 (d, *J* = 3.10 Hz, 1H), 2.59 – 2.55 (m, 4H), 1.81 – 1.78 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 143.5, 136.7, 133.4, 129.2, 128.4, 126.5, 119.2, 115.6, 105.3, 79.9, 46.2, 23.7; **HRMS** (ESI, m/z) calcd. for $C_{19}H_{19}N_5Na^+$ $[M + Na]^+$ 340.1533, found 340.1528.

4-phenyl-5-(pyrrolidin-1-yl)-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,3-triazole (4nb)



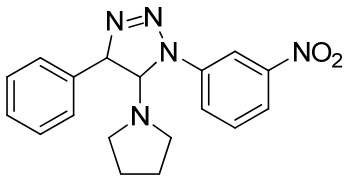
Cyclization of enamine with azide for 3 h at 40 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as a yellow solid (290 mg, 80% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.62 (m, 4H), 7.40 – 7.31 (m, 3H), 7.12 – 7.09 (m, 2H), 5.44 (d, *J* = 3.00 Hz, 1H), 5.12 (d, *J* = 3.00 Hz, 1H), 2.61 – 2.58 (m, 4H), 1.81 – 1.77 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 142.9, 137.0, 129.1, 128.2, 126.5, 126.4 (q, *J* = 3.90 Hz), 124.3 (q, *J* = 32.91 Hz), 124.3 (q, *J* = 271.42 Hz), 115.3, 79.8, 76.9, 46.3, 23.7; **HRMS** (ESI, m/z) calcd. for $C_{19}H_{19}F_3N_4Na^+$ $[M + Na]^+$ 383.1454, found 383.1454.

1-(1-(4-nitrophenyl)-4-phenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)piperidine (4al)



Cyclization of enamine with azide for 3 h at 40 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as a yellow solid (298 mg, 85% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 9.30 Hz, 2H), 7.64 (d, *J* = 9.30 Hz, 2H), 7.08 – 7.06 (m, 2H), 7.41 – 7.32 (m, 3H), 5.60 (d, *J* = 3.50 Hz, 1H), 4.76 (d, *J* = 3.50 Hz, 1H), 2.42 – 2.40 (m, 4H), 1.58 – 1.49 (m, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 145.1, 142.4, 136.9, 129.3, 128.4, 126.6, 125.4, 114.9, 81.3, 78.5, 46.7, 25.5, 24.3; **HRMS** (ESI, m/z) calcd. for $C_{19}H_{21}N_5O_2Na^+$ $[M + Na]^+$ 374.1587, found 374.1596.

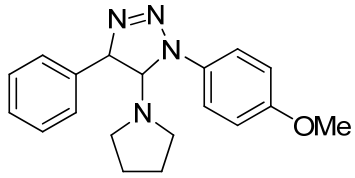
1-(3-nitrophenyl)-4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazole (4nm)



Cyclization of enamine with azide for 2 h at 40 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as an yellow solid (311 mg, 92% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.33 – 8.29 (m, 1H), 7.92 – 7.85 (m, 2H), 7.54 – 7.48 (m, 1H), 7.40 – 7.29 (m, 3H), 7.13 – 7.07 (m, 2H), 5.48 (d, *J* = 3.08 Hz, 1H), 5.14 (d, *J* = 3.08 Hz,

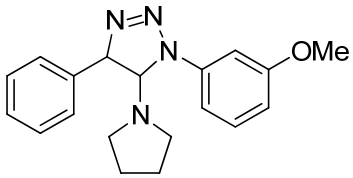
1H), 2.65 – 2.54 (m, 4H), 1.85 – 1.72 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 149.0, 141.3, 136.9, 130.0, 129.3, 128.3, 126.6, 121.4, 117.2, 110.4, 80.1, 77.2, 46.4, 23.8; **HRMS** (ESI, m/z) calcd. for $C_{18}H_{19}N_5O_2Na^+$ $[M + Na]^+$ 360.1431, found 360.1429.

1-(4-methoxyphenyl)-4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazole (4nn)



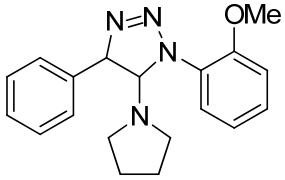
Cyclization of enamine with azide for 20 h at 40 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as a yellow solid (286 mg, 89% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 9.00 Hz, 2H), 7.29 – 7.36 (m, 3H), 7.10 – 7.11 (m, 2H), 6.9 (d, *J* = 8.80 Hz, 2H), 5.3 (d, *J* = 3.20 Hz, 1H), 5.1 (d, *J* = 3.20 Hz, 1H), 3.80 (s, 3H), 2.58 – 2.55 (m, 4H), 1.73 – 1.69 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 155.9, 137.9, 134.4, 128.9, 127.9, 126.6, 118.1, 114.4, 79.9, 78.2, 55.5, 46.7, 23.8; **HRMS** (ESI, m/z) calcd. for $C_{19}H_{22}N_4ONa^+$ $[M + Na]^+$ 345.1686, found 345.1683.

1-(3-methoxyphenyl)-4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazole (4no)



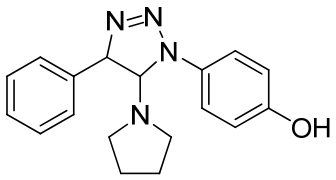
Cyclization of enamine with azide for 3 h at 40 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as an yellow solid (311 mg, 97% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.39 – 7.32 (m, 3H), 7.26 – 7.22 (m, 1H), 7.19 – 7.16 (m, 1H), 7.13 – 7.08 (m, 2H), 7.07 – 7.04 (m, 1H), 6.67 – 6.63 (m, 1H), 5.34 (d, *J* = 3.05 Hz, 1H), 5.08 (d, *J* = 3.05 Hz, 1H), 3.86 (s, 3H), 2.63 – 2.57 (m, 4H), 1.78 – 1.73 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 160.4, 141.8, 137.7, 130.0, 129.1, 128.1, 126.7, 108.6, 102.1, 80.1, 77.4, 55.3, 46.7, 23.8; **HRMS** (ESI, m/z) calcd. for $C_{19}H_{22}N_4ONa^+$ $[M + Na]^+$ 345.1686, found 345.1689.

1-(2-methoxyphenyl)-4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazole (4np)



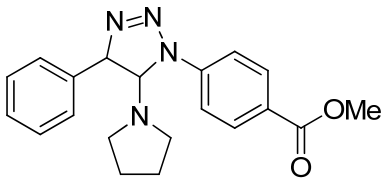
Cyclization of enamine with azide for 7 h at 40 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as an yellow solid (282 mg, 85% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$). δ = 7.77 – 7.73 (m, 1H), 7.40 – 7.30 (m, 5H), 7.25 – 7.19 (m, 1H), 7.06 – 7.00 (m, 1H), 6.97 – 6.92 (m, 1H), 5.58 (d, *J* = 2.76 Hz, 1H), 5.22 (d, *J* = 2.76 Hz, 1H), 3.86 (s, 3H), 2.56 – 2.51 (m, 4H), 1.65 – 1.51 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 150.9, 138.1, 130.8, 128.9, 127.9, 127.0, 126.5, 123.5, 121.3, 111.8, 83.5, 78.2, 55.6, 47.2, 24.2; **HRMS** (ESI, m/z) calcd. for $C_{19}H_{22}N_4ONa^+$ $[M + Na]^+$ 345.1686, found 345.1688.

4-(4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)phenol (4nq)



Cyclization of enamine with azide for 3 h at 40 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as an brown solid (107 mg, 35% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.38 – 7.31 (m, 5H), 7.15 – 7.10 (m, 2H), 6.89 – 6.84 (m, 2H), 5.31 (d, *J* = 2.96 Hz, 1H), 5.13 (d, *J* = 2.96 Hz, 1H), 2.64 – 2.55 (m, 4H), 1.76 – 1.69 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 153.2, 137.7, 133.5, 129.1, 128.1, 126.6, 119.0, 116.2, 79.5, 78.9, 46.9, 23.9; **HRMS** (ESI, m/z) calcd. for $C_{18}H_{20}N_4ONa^+$ $[M + Na]^+$ 331.1529, found 331.1531.

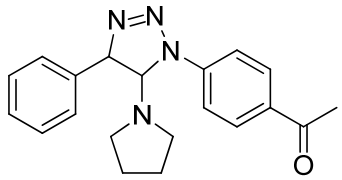
methyl 4-(4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)benzoate (4nr)



Cyclization of enamine with azide for 3 h at 40 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as a white solid (319 mg, 91% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 9.20 Hz, 2H), 7.52 (d, *J* = 8.80 Hz, 2H), 7.37 – 7.30 (m, 3H), 7.08 – 7.06 (m, 2H), 5.39 (d, *J* = 3.10 HZ, 1H), 5.10 (d, *J* = 3.10 Hz, 1H), 3.90 (s, 3H), 2.58 – 2.54 (m, 4H), 1.76 – 1.73 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$):

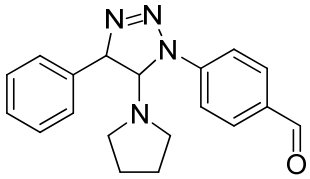
δ = 167.7, 144.0, 137.0, 131.0, 129.2, 128.2, 126.6, 124.1, 115.0, 80.1, 76.8, 51.9, 46.4, 23.7; **HRMS** (ESI, m/z) calcd. for $C_{20}H_{22}N_4O_2Na^+$ $[M + Na]^+$ 373.1635, found 373.1649.

1-(4-(4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)phenyl)ethanone (4ns)



Cyclization of enamine with azide for 3 h at 40 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as pale yellow solid (303 mg, 90% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.97 – 7.95 (m, 2H), 7.56 – 7.53 (m, 2H), 7.37 – 7.30 (m, 3H), 7.07 – 7.05 (m, 2H), 5.40 (d, *J* = 3.04 Hz, 1H), 5.10 (d, *J* = 3.04 Hz, 1H), 2.55 – 2.53 (m, 7H), 1.76 – 1.73 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 196.7, 144.1, 137.0, 131.6, 130.0, 129.2, 128.2, 126.6, 115.1, 80.2, 46.4, 26.3, 23.7; **HRMS** (ESI, m/z) calcd. for $C_{20}H_{22}N_4ONa^+$ $[M + Na]^+$ 357.1686, found 357.1690.

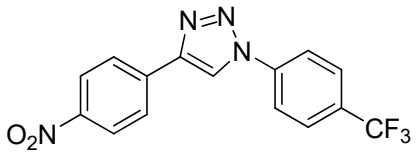
4-(4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)benzaldehyde (4nt)



Cyclization of enamine with azide for 3 h at 40 °C yielded the triazoline after purification by automatic column (petroleum ether : ethyl acetate as eluent) as a yellow oil (296 mg, 93% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 9.89 (s, 1H), 7.86 (d, *J* = 8.70 Hz, 2H), 7.61 (d, *J* = 8.70 Hz, 2H), 7.37 – 7.30 (m, 3H), 7.08 – 7.05 (m, 2H), 5.43 (d, *J* = 3.10 Hz, 1H), 5.11 (d, *J* = 3.10 Hz, 1H), 2.58 – 2.54 (m, 4H), 1.77 – 1.74 (m, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ =190.7, 145.1, 136.8, 131.4, 131.0, 129.1, 128.3, 126.5, 115.4, 80.1, 76.7, 46.3, 23.6; **HRMS** (ESI, m/z) calcd. for $C_{19}H_{20}N_4ONa^+$ $[M + Na]^+$ 343.1529, found 343.1529.

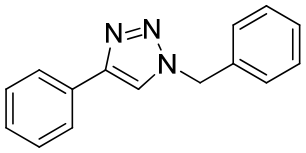
Triazoles:

4-(4-nitrophenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (5ub)



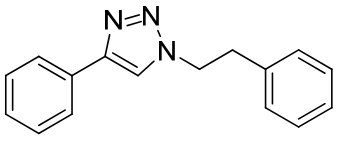
Cyclization of enamine with azide overnight at r.t. yielded the triazole as a brown solid (195 mg, 58% yield) after filtration and no further purification was needed. **^{1}H-NMR** (400 MHz, $SO(CD_3)_2$): δ = 9.72 (s, 1H), 8.41 – 8.36 (m, 2H), 8.25 – 8.18 (m, 4H), 8.08 – 8.02 (m, 2H); **^{13}C-NMR** (125 MHz, 60 °C, $SO(CD_3)_2$): δ = 146.8, 145.4, 138.9, 136.1, 128.8 (q, *J* = 32.20 Hz), 126.9 (br s), 125.9, 124.0, 123.5 (q, *J* = 268.76 Hz), 122.4, 121.5, 120.3; **^{19}F-NMR** (337 MHz, $SO(CD_3)_2$): δ = -61.16 (monofluorobenzene as IS; -113.15 ppm); **HRMS** (ESI, m/z) calcd. for $C_{15}H_9F_3N_4O_2Na^+$ $[M + Na]^+$ 357.0570, found 357.0561.

1-benzyl-4-phenyl-1*H*-1,2,3-triazole (5nu)



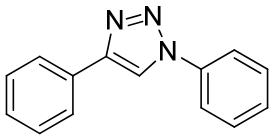
Cyclization of enamine (0.5 mmol) with azide for 24 h at 80 °C yielded the triazole as a brown solid (93 mg, 79% yield) after filtration and no further purification was needed. **^{1}H-NMR** (400 MHz, $SO(CD_3)_2$): δ = 8.64 (s, 1H), 7.87 – 7.83 (m, 2H), 7.48 – 7.31 (m, 8H), 5.65 (s, 2H); **^{13}C-NMR** (125 MHz, 50°C, $SO(CD_3)_2$): δ = 146.4, 135.6, 130.4, 128.5, 128.4, 127.8, 127.5, 127.4, 124.9, 121.1, 52.8; Spectral data is in agreement with published data.[41]

1-phenethyl-4-phenyl-1*H*-1,2,3-triazole (5nv)



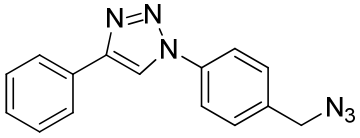
Cyclization of enamine with azide for 65 h at 80 °C yielded the triazole as a sandcolored solid (239 mg, 96% yield) after filtration and no further purification was needed. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.82 – 7.80 (m, 2H), 7.49 (s, 1H), 7.46 – 7.40 (m, 2H), 7.37 – 7.25 (m, 4H), 7.18 – 7.14 (m, 2H), 4.66 (t, *J* = 7.24 Hz, 2H), 3.28 (t, *J* = 7.24 Hz, 2H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 147.6, 137.2, 130.8, 129.0, 128.9, 128.8, 128.2, 127.3, 125.8, 120.0, 51.9, 36.9. Spectral data is in agreement with published data.[42]

1,4-diphenyl-1H-1,2,3-triazole (5na)



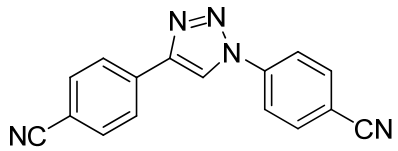
Cyclization of enamine with azide for 3 h at 65 °C, followed by treatment with metanolic KOH (2 M, 0.25 equiv) and additional 3 hours at 65 °C yielded the triazole as a beige solid (202 mg, 92% yield) after filtration and no further purification was needed. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.22 (s, 1H), 7.97 – 7.93 (m, 2H), 7.85 – 7.80 (m, 2H), 7.61 – 7.55 (m, 2H), 7.52 – 7.46 (m, 3H), 7.42 – 7.37 (m, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 148.6, 137.2, 130.4, 129.9, 129.1, 128.9, 128.6, 126.0, 120.7, 117.7. Spectral data is in agreement with published data.[43]

1-(4-(azidomethyl)phenyl)-4-phenyl-1*H*-1,2,3-triazole (5ag)



Cyclization of enamine with azide for 3 h at 65 °C, followed by treatment with metanolic KOH (2 M, 0.25 equiv) and additional 2.5 hours at r.t. yielded the triazole as a pale yellow solid (215 mg, 78% yield) after precipitation with pentane and filtration. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.20 (s, 1H), 7.92 (m, 2H), 7.83 (m, 2H), 7.53 – 7.45 (m, 4H), 7.40 – 7.36 (m, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 148.5, 136.9, 136.2, 130.1, 129.7, 129.1, 128.7, 125.9, 120.9, 117.6, 54.1; **HRMS** (ESI, m/z) calcd. for $C_{15}H_{12}N_6Na^+$ $[M + Na]^+$ 299.1016, found 299.1023.

4,4'-(1*H*-1,2,3-triazole-1,4-diyl)dibenzonitrile (5vk)



^{1}H-NMR (400 MHz, $SO(CD_3)_2$): δ = 9.65 (s, 1H), 8.20 – 8.14 (m, 4H), 8.12 (d, *J* = 8.55 Hz, 2H), 8.00 (d, *J* = 8.55 Hz, 2H); **^{13}C-NMR** (125 MHz, 50°C, $SO(CD_3)_2$): δ = 145.8, 139.1, 134.1, 134.0, 132.8, 125.7, 121.2, 120.3, 118.3, 117.6, 111.1, 110.5.

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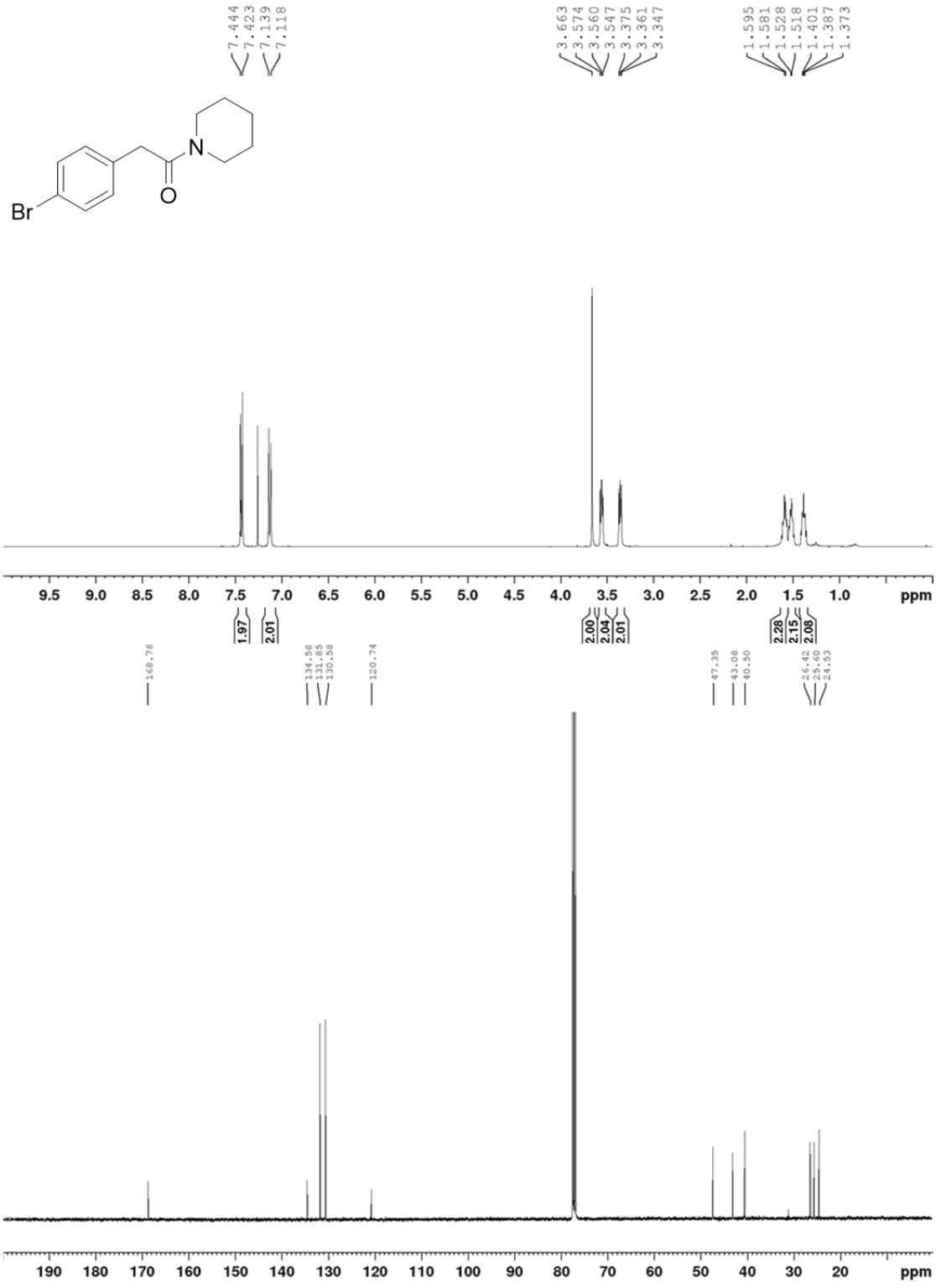
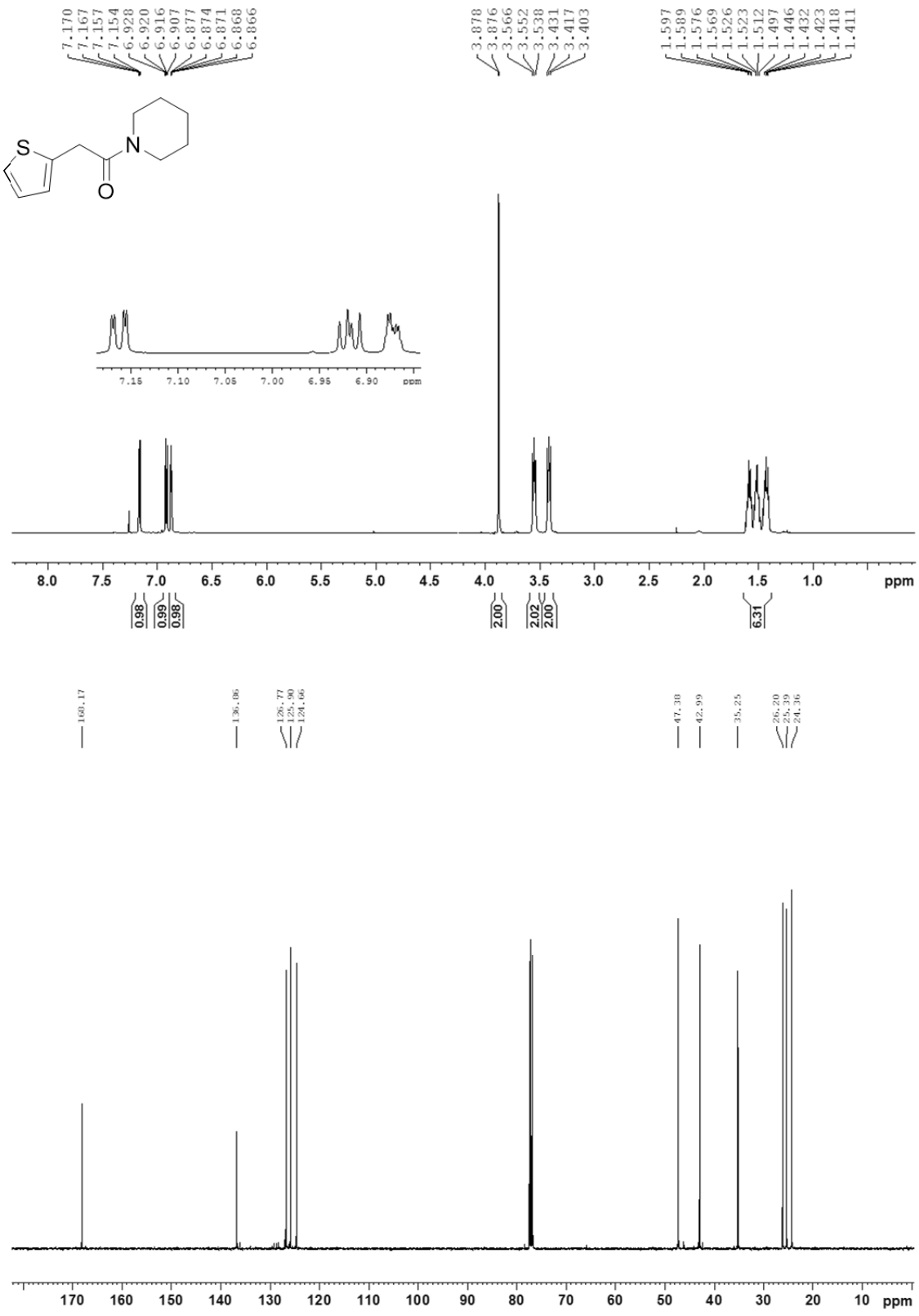
Spectroscopic Data

Amides

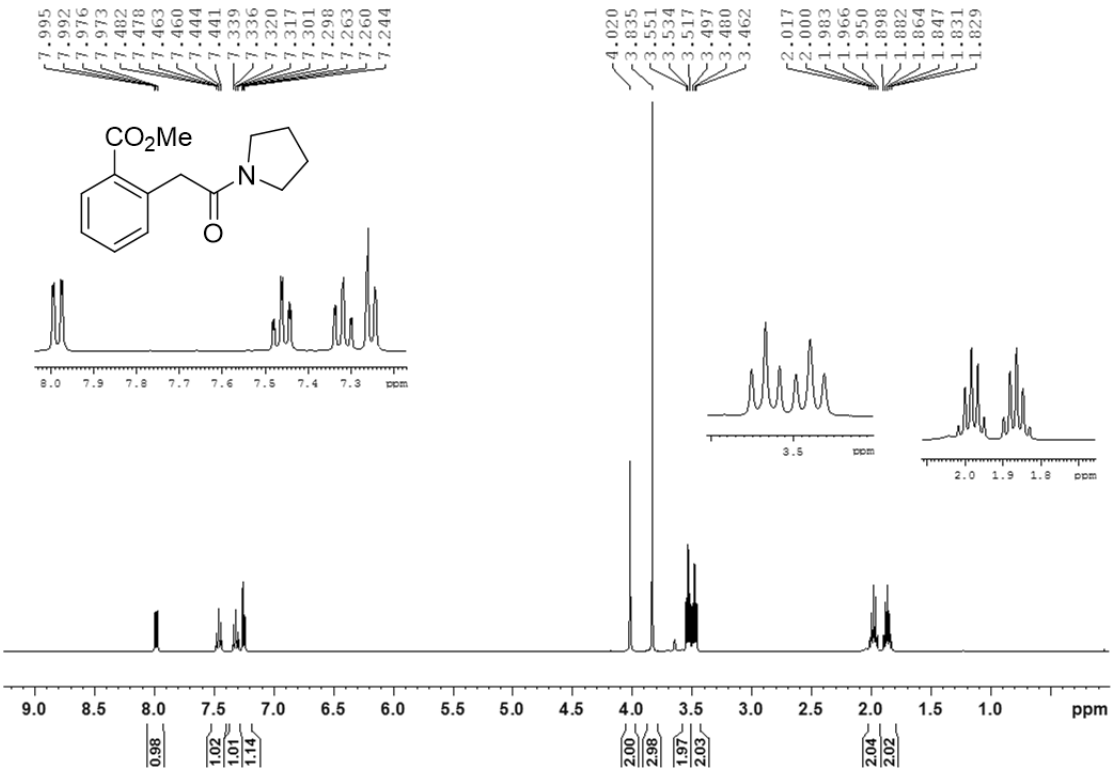
2-(4-bromophenyl)-1-(piperidin-1-yl)ethan-1-one (1b)

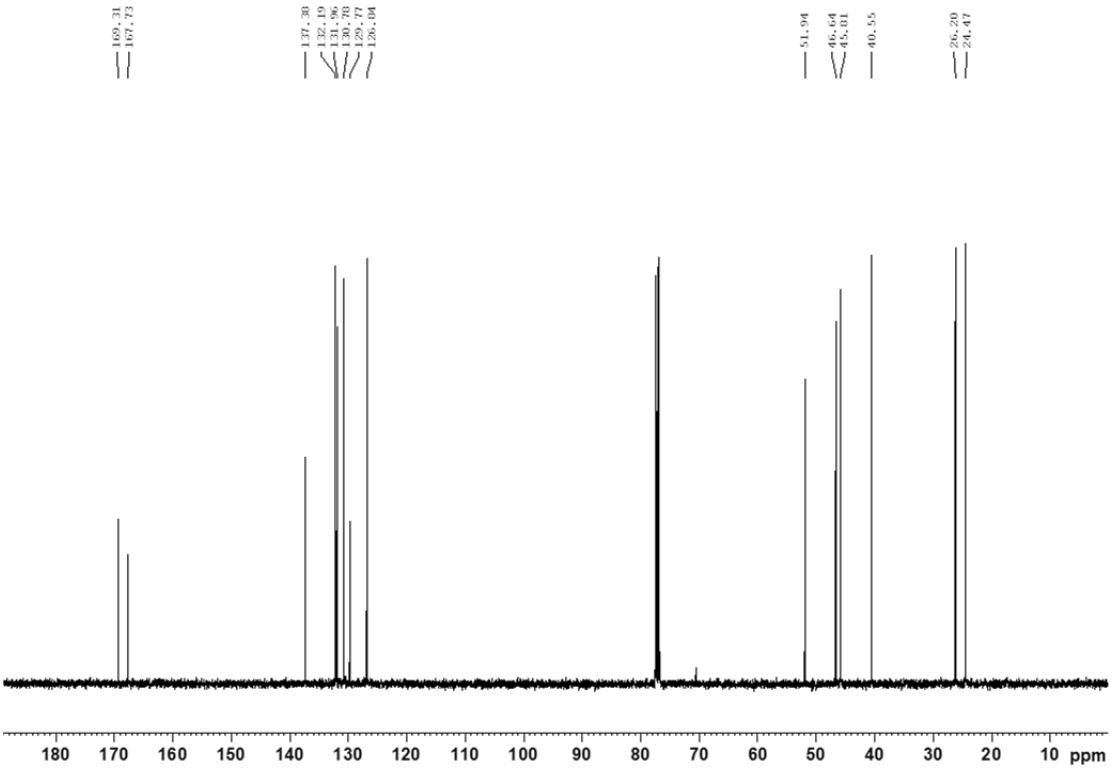


1-(piperidin-1-yl)-2-(thiophen-2-yl)ethan-1-one (1d)

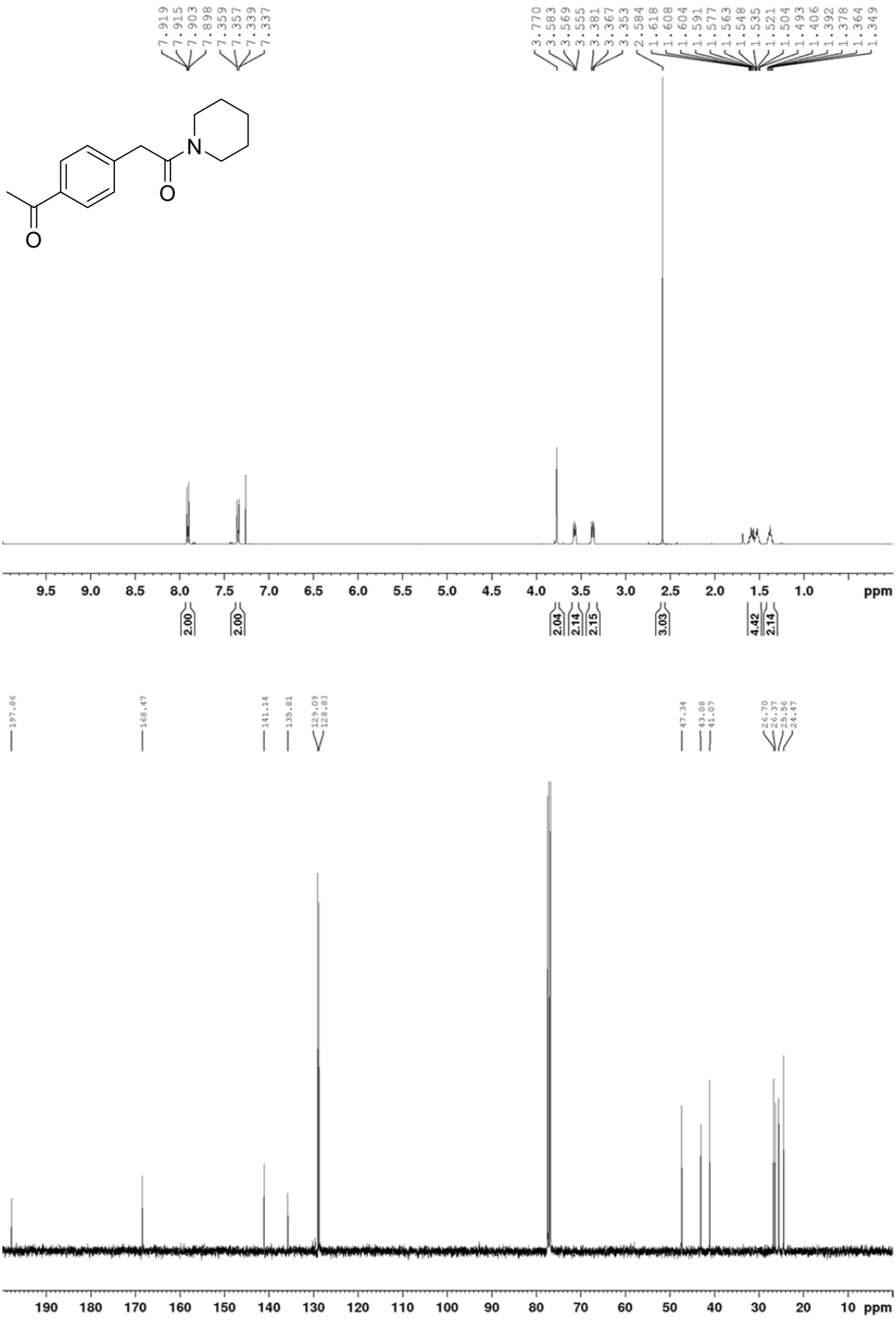


methyl 2-(2-oxo-2-(pyrrolidin-1-yl)ethyl)benzoate (1g)

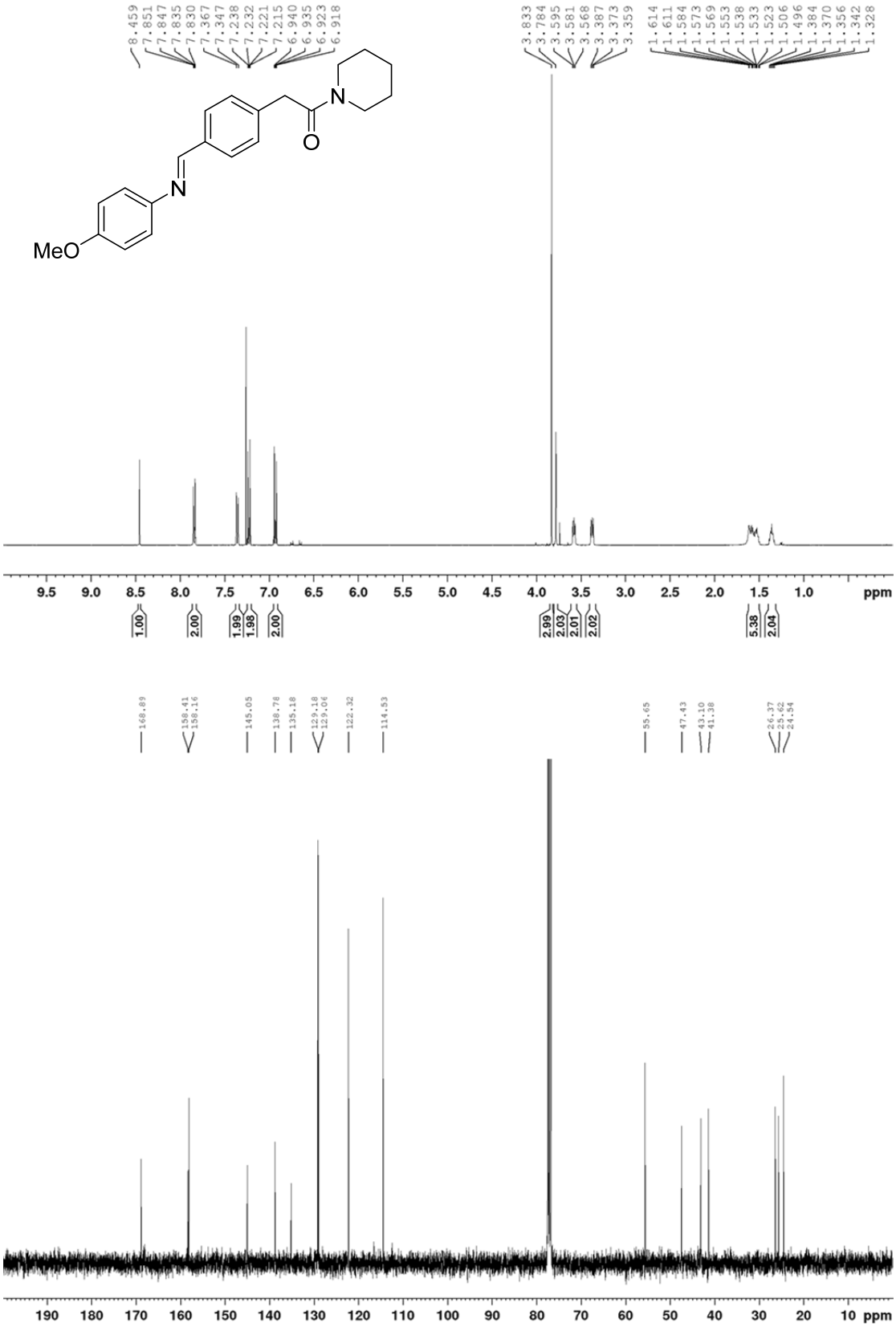




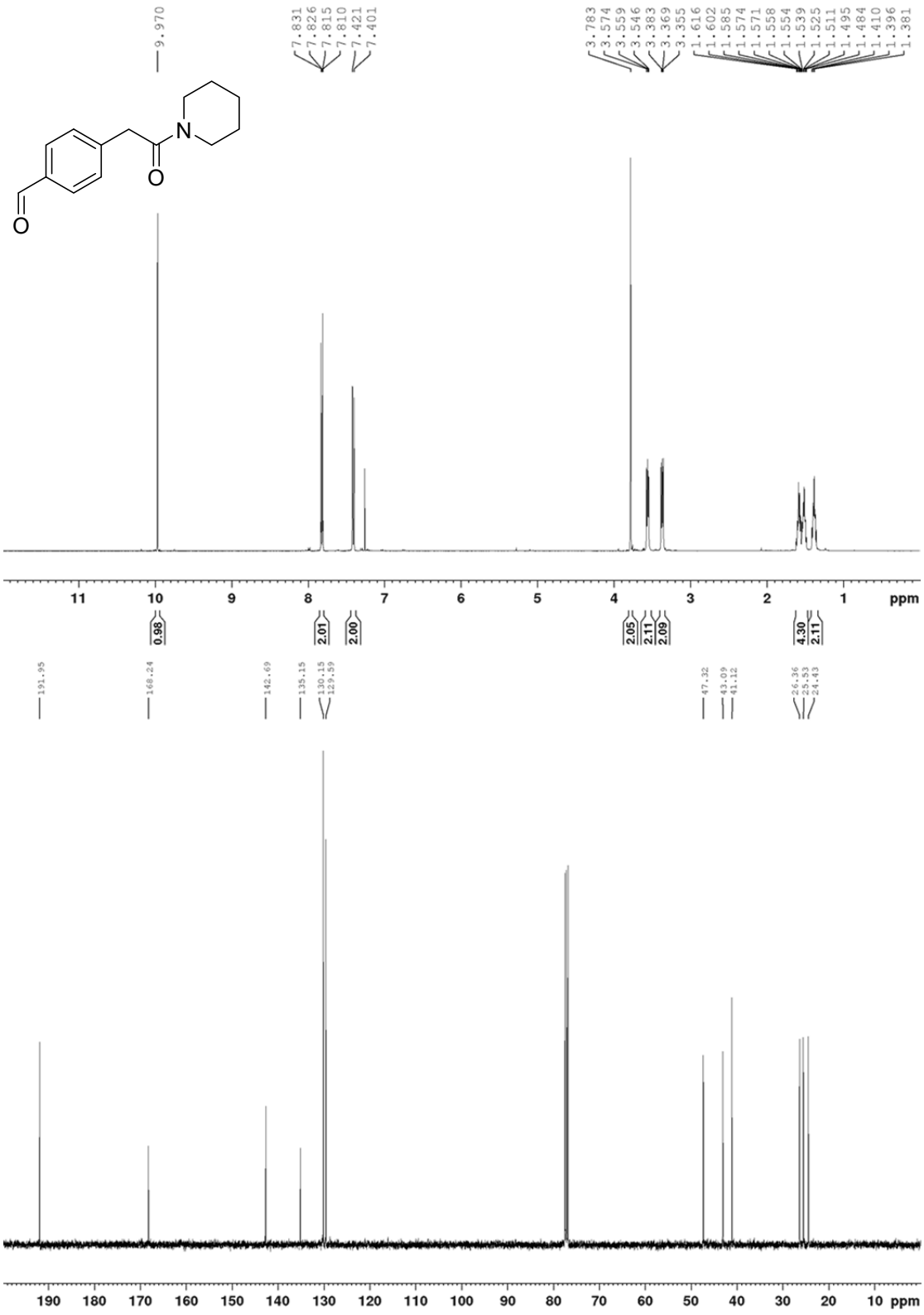
2-(4-acetylphenyl)-1-(piperidin-1-yl)ethan-1-one (1h)



(*E*)-2-(4-(((4-methoxyphenyl)imino)methyl)phenyl)-1-(piperidin-1-yl)ethan-1-one (1i)



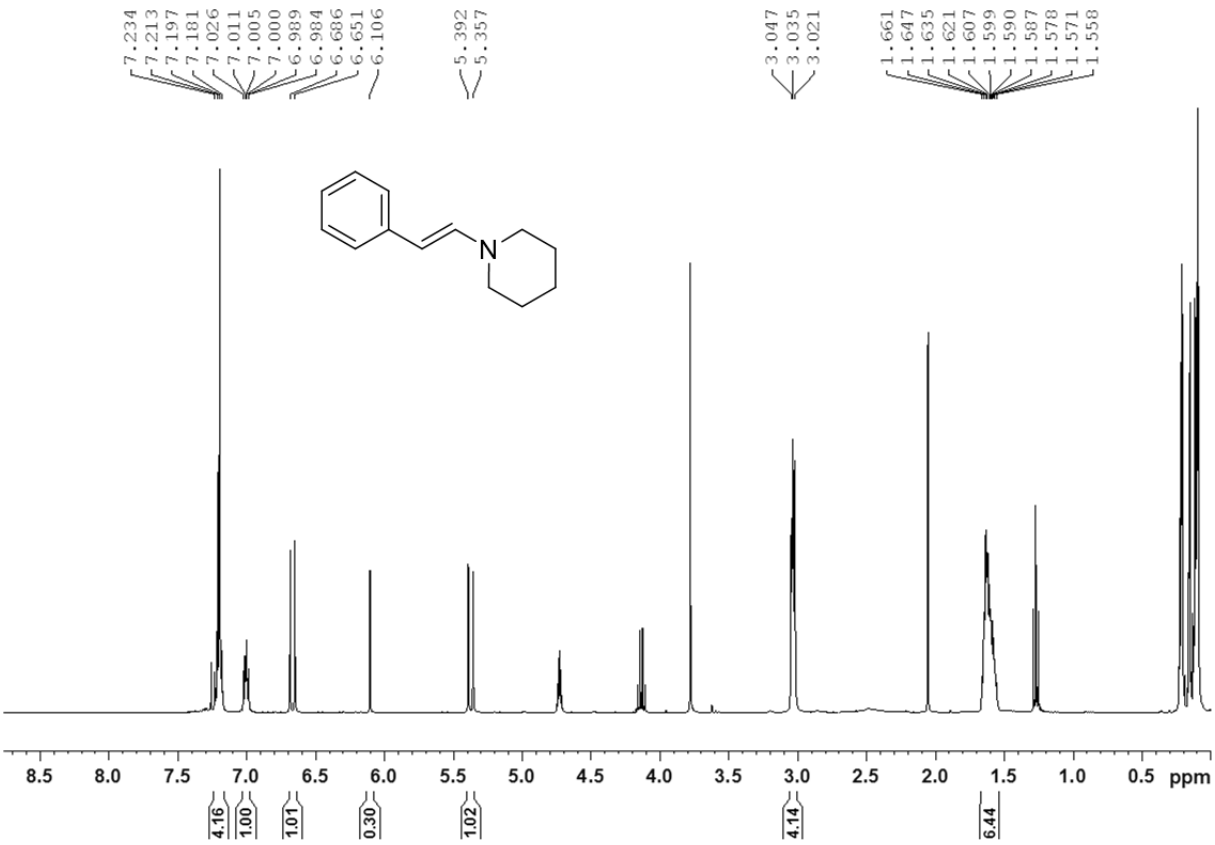
4-(2-oxo-2-(piperidin-1-yl)ethyl)benzaldehyde (1m)



Enamines

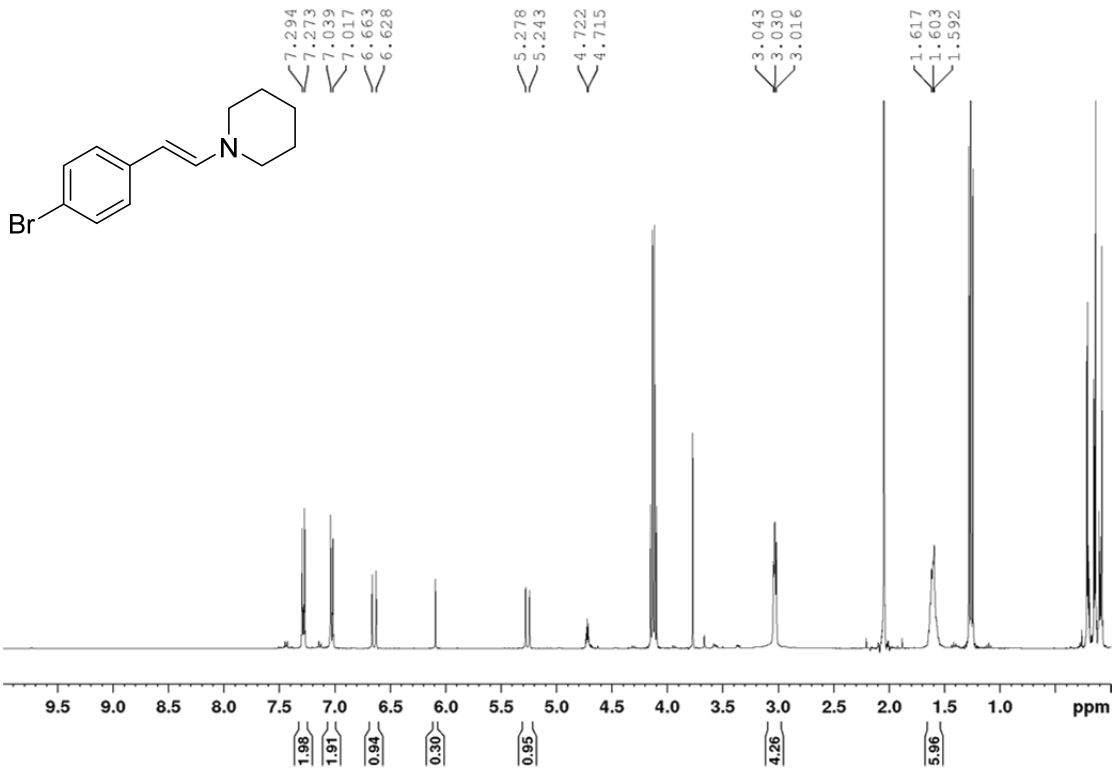
(*E*)-1-styrylpiperidine (2a)

Enamine formation; 2 h at 65 °C, 1,3,5-trimethoxybenzene (0.1 mmol / 6.11 ppm) was used as internal standard to determine the ^{1}H-NMR yield of the formed enamine to >95%. (400 MHz, $CDCl_3$)



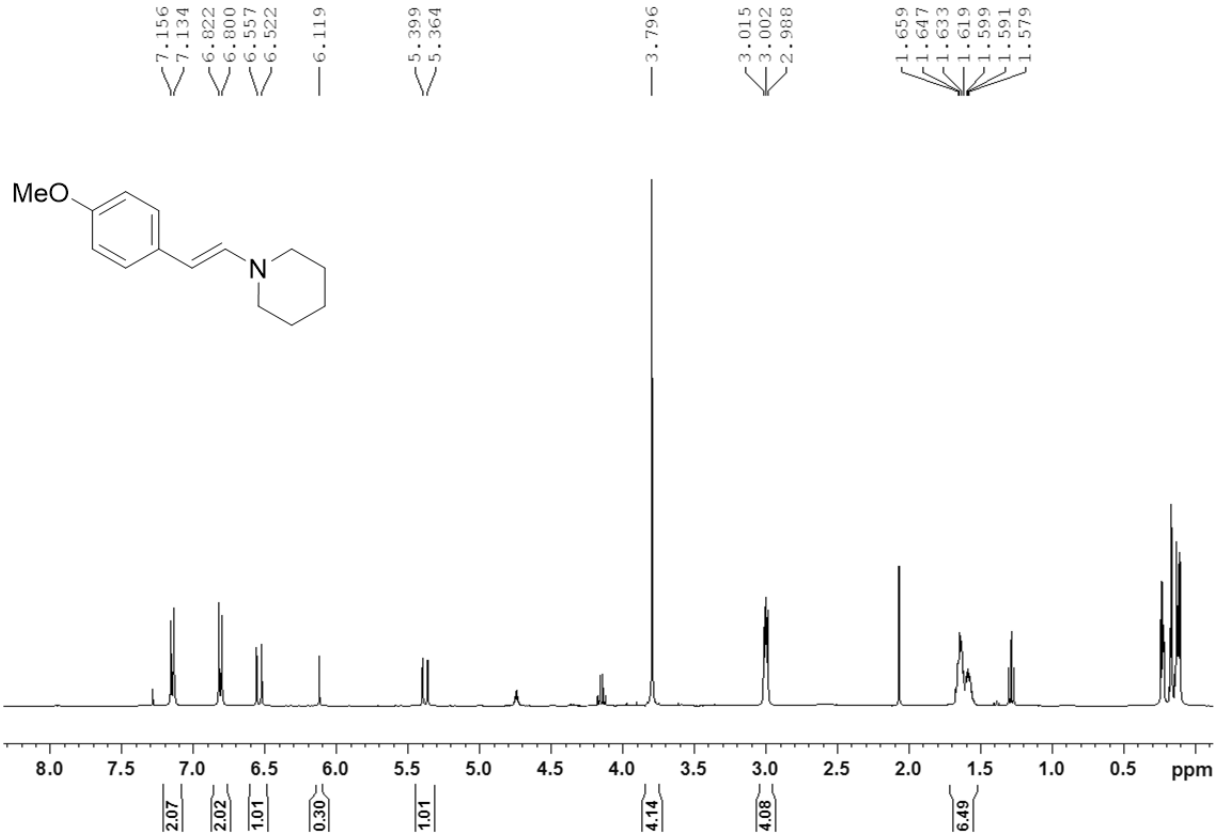
(*E*)-1-(4-bromostyryl)piperidine (2b)

Enamine formation; 3 h at 65 °C, 1,3,5-trimethoxybenzene (0.1 mmol / 6.11 ppm) was used as internal standard to determine the ^{1}H-NMR yield of the formed enamine to >95%. (400 MHz, $CDCl_3$)



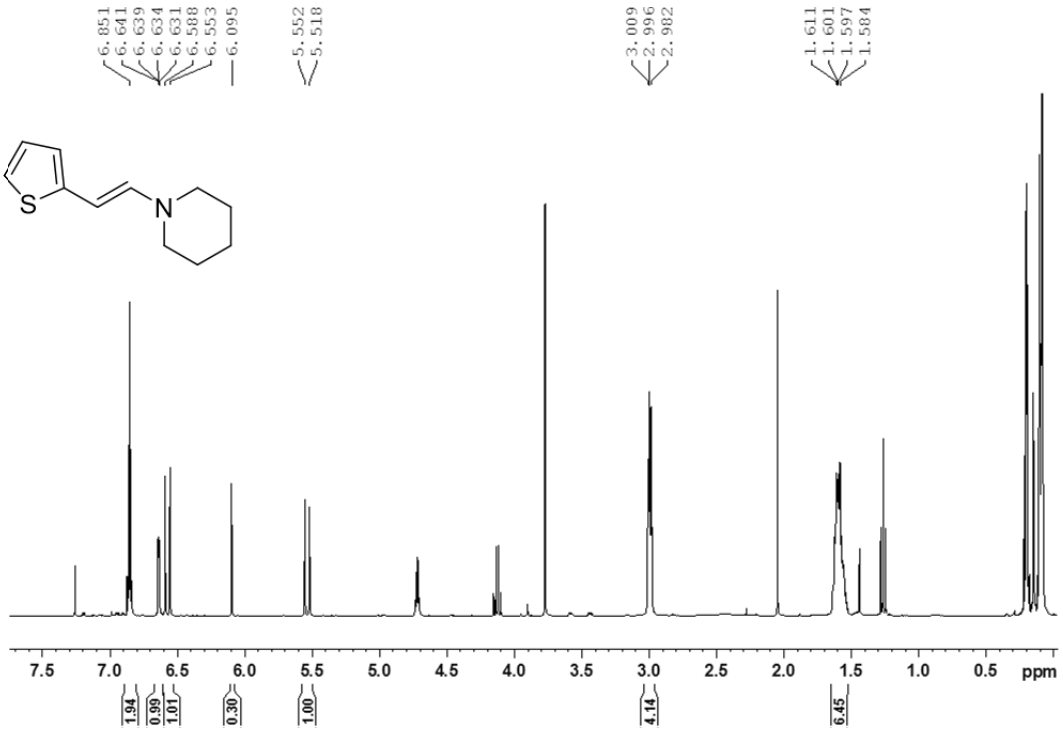
(*E*)-1-(4-methoxystyryl)piperidine (2c)

Enamine formation; 2 h at 65 °C, 1,3,5-trimethoxybenzene (0.1 mmol / 6.12 ppm) was used as internal standard to determine the ^{1}H-NMR yield of the formed enamine to >95%. (400 MHz, $CDCl_3$)



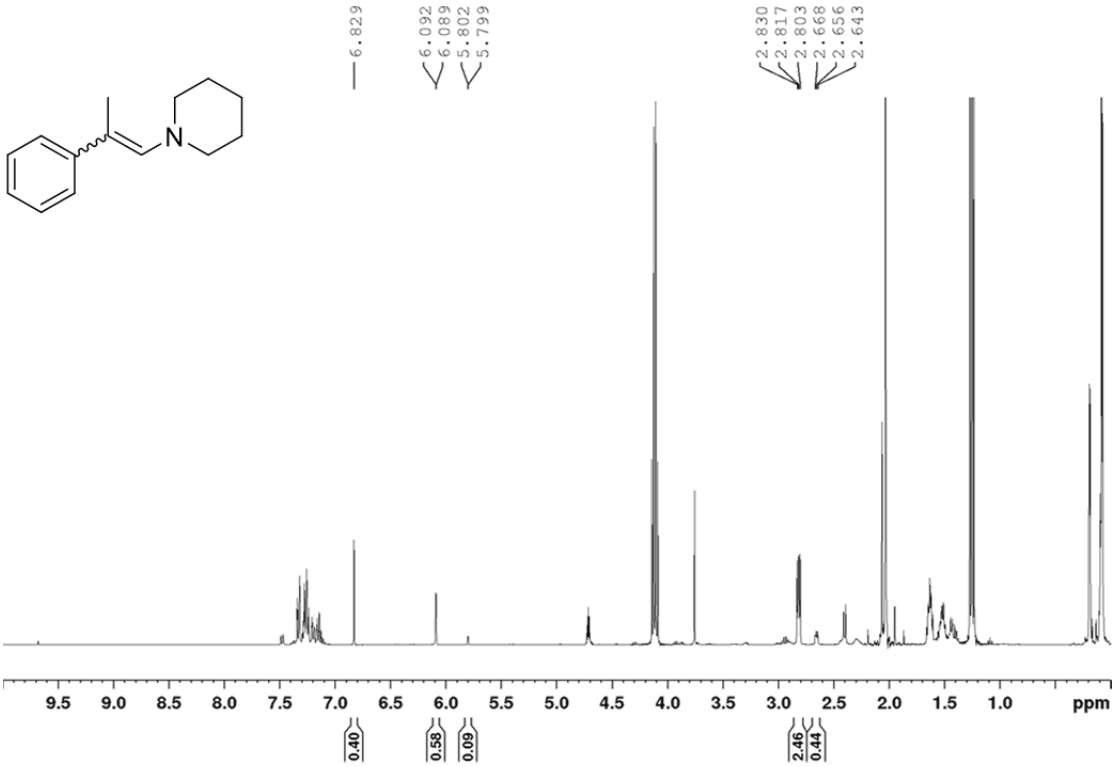
(*E*)-1-(2-(thiophen-2-yl)vinyl)piperidine (2d)

Enamine formation; 2.5 h at 65 °C, 1,3,5-trimethoxybenzene (0.1 mmol / 6.10 ppm) was used as internal standard to determine the ^{1}H-NMR yield of the formed enamine to >95%. (400 MHz, $CDCl_3$)



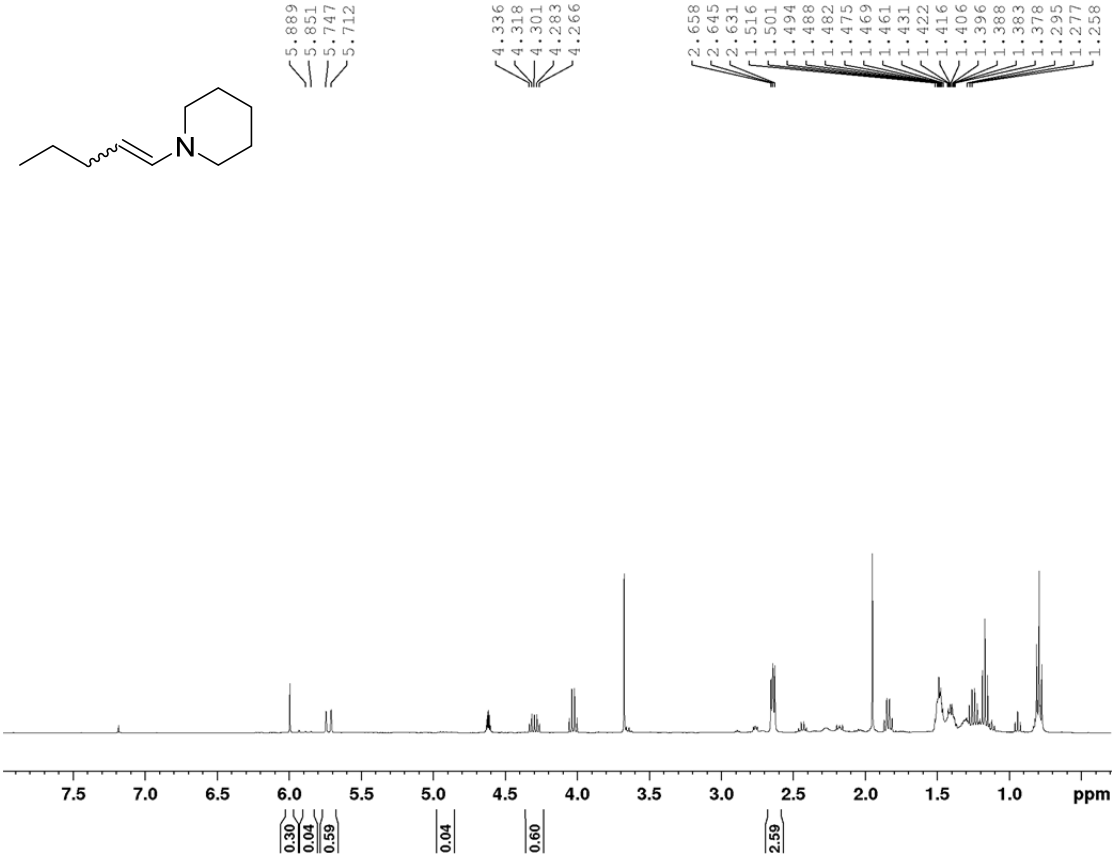
1-(2-phenylprop-1-en-1-yl)piperidine (2e)

Enamine formation; 7 h at 65 °C, 1,4-dimethoxybenzene (0.1 mmol / 6.83 ppm) was used as internal standard to determine the ^{1}H-NMR yield of the formed enamine to 67%. (400 MHz, $CDCl_3$)



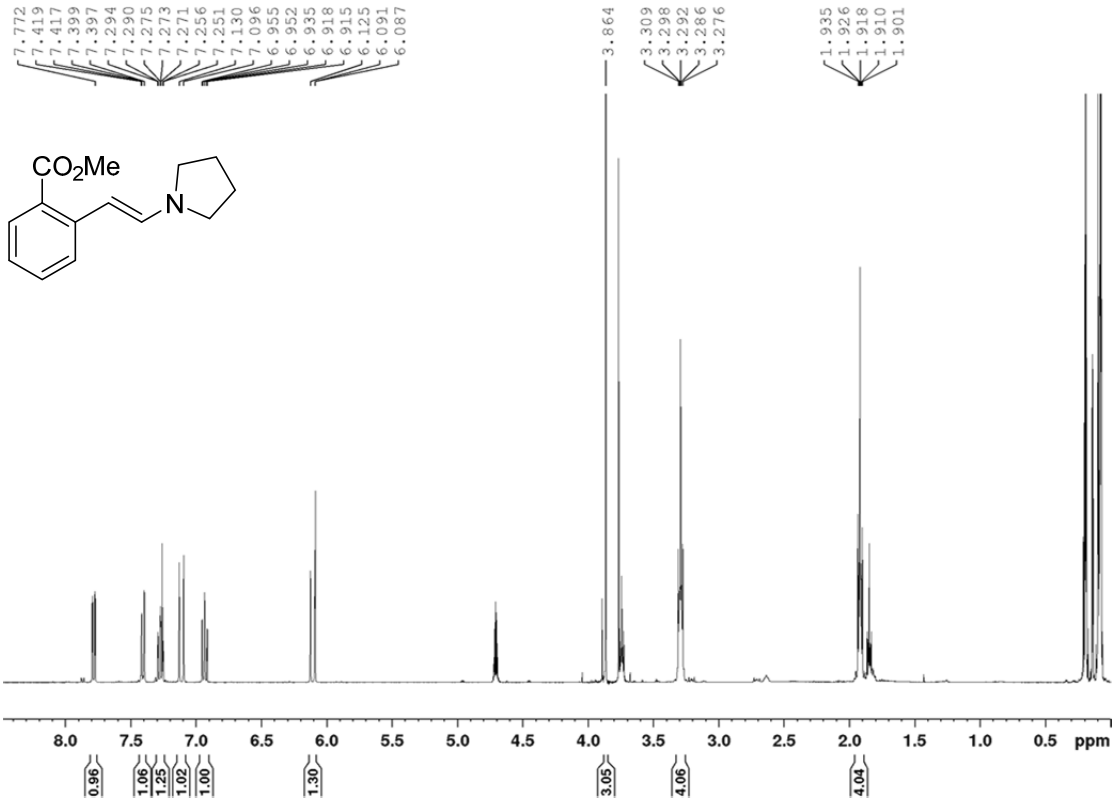
1-(pent-1-en-1-yl)piperidine (2f)

Enamine formation; 2 h at 80 °C, 1,3,5-trimethoxybenzene (0.1 mmol / 6.10 ppm) was used as internal standard to determine the ^{1}H-NMR yield of the formed enamine to 60%. (400 MHz, $CDCl_3$)



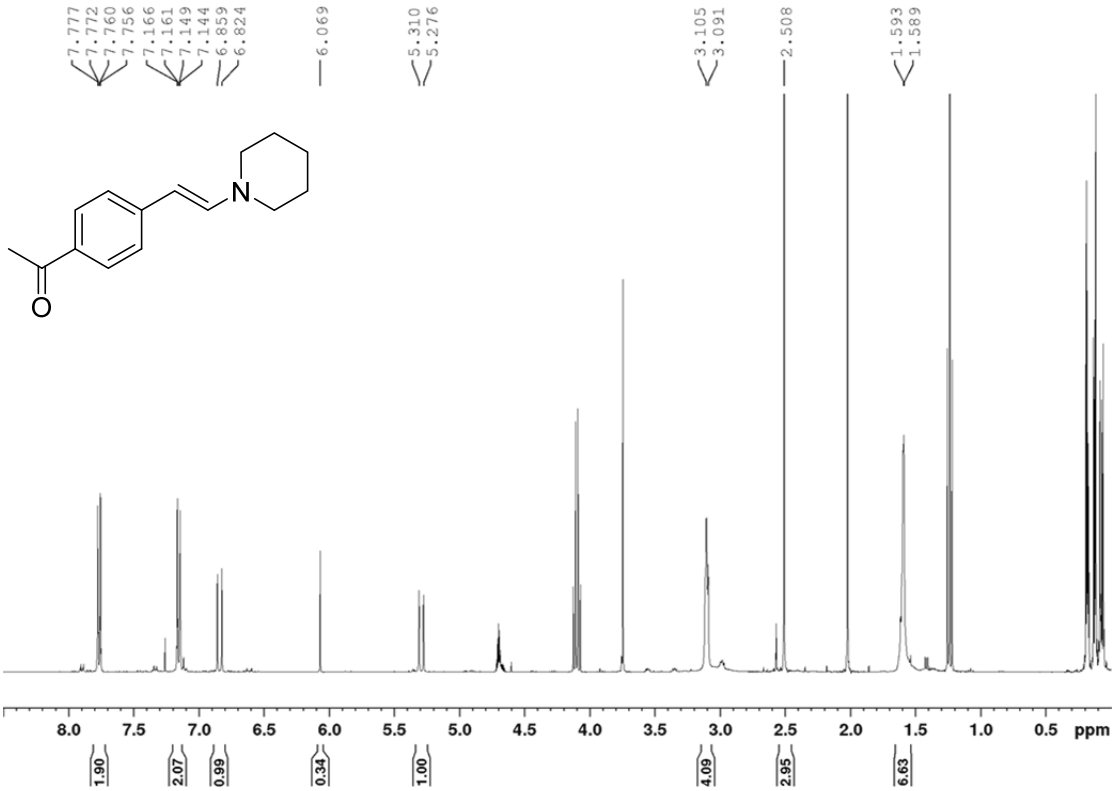
methyl (*E*)-2-(2-(pyrrolidin-1-yl)vinyl)benzoate (2g)

Enamine formation; 1 h at 65 °C, 1,3,5-trimethoxybenzene (0.1 mmol / 6.09 ppm) was used as internal standard to determine the ^{1}H-NMR yield of the formed enamine to >89%. (400 MHz, $CDCl_3$).



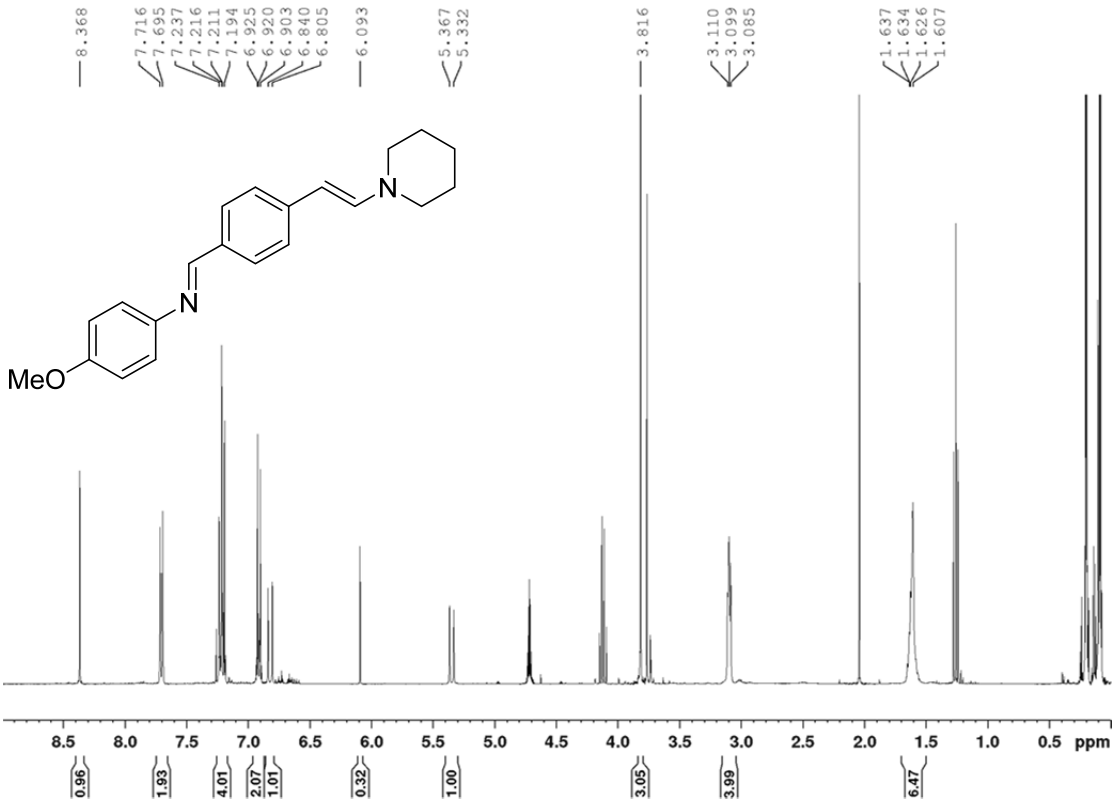
(*E*)-1-(4-(2-(piperidin-1-yl)vinyl)phenyl)ethan-1-one (2h)

Enamine formation; 5 h at 40 °C, 1,3,5-trimethoxybenzene (0.1 mmol / 6.07 ppm) was used as internal standard to determine the ^{1}H-NMR yield of the formed enamine to 89%. (400 MHz, $CDCl_3$)



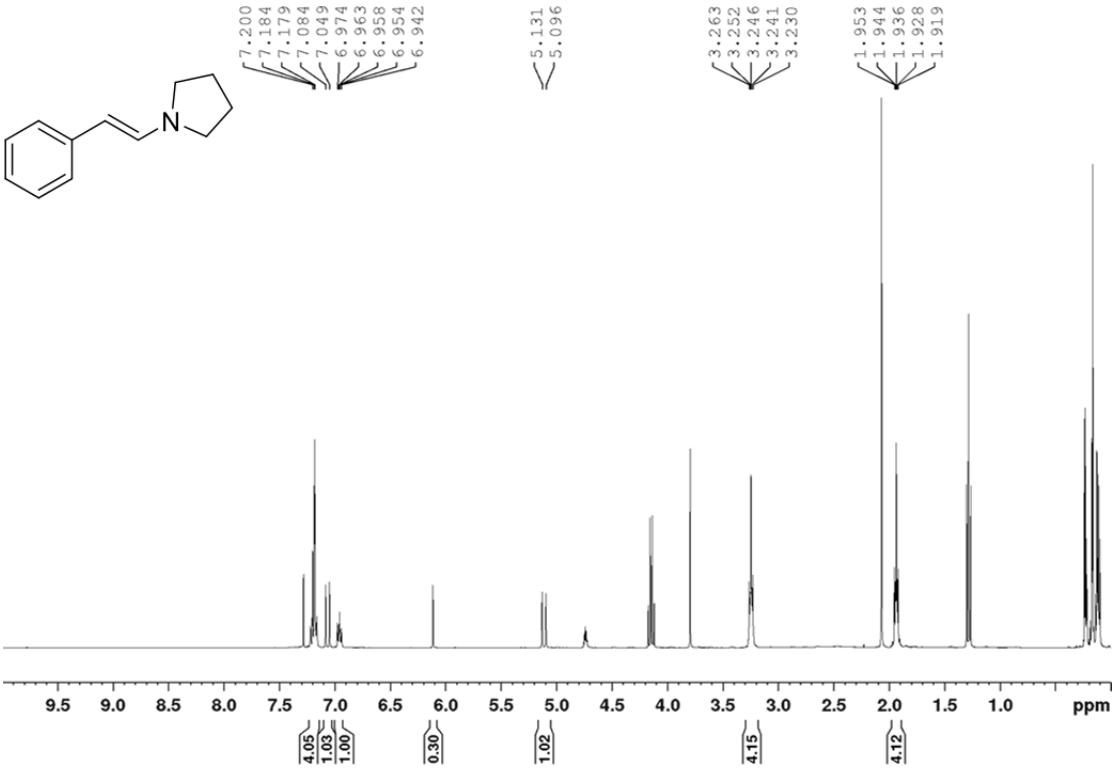
(*E*)-*N*-(4-methoxyphenyl)-1-(4-((*E*)-2-(piperidin-1-yl)vinyl)phenyl)methanimine (2i)

Enamine formation; 4 h at 65 °C, 1,3,5-trimethoxybenzene (0.1 mmol / 6.09 ppm) was used as internal standard to determine the ^{1}H-NMR yield of the formed enamine to 94%. (400 MHz, $CDCl_3$)



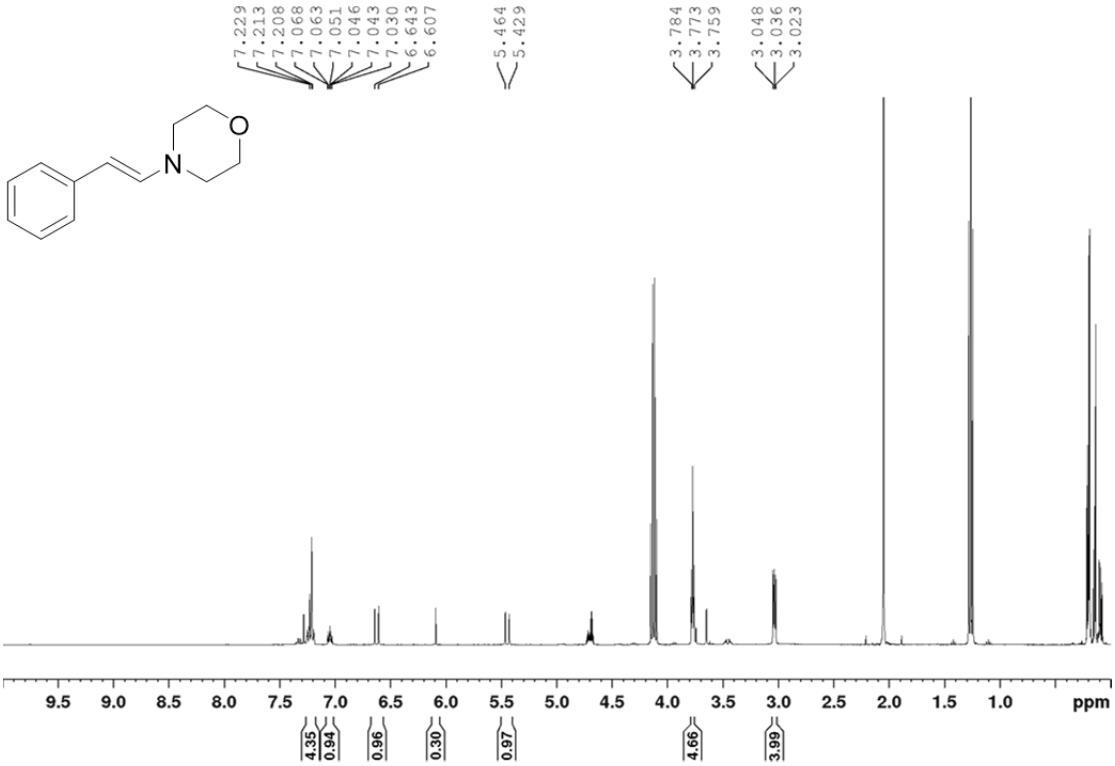
(*E*)-1-styrylpyrrolidine (2n)

Enamine formation; 30 min at 65 °C, 1,3,5-trimethoxybenzene (0.1 mmol / 6.10 ppm) was used as internal standard to determine the ^{1}H-NMR yield of the formed enamine to >95%. (400 MHz, $CDCl_3$)



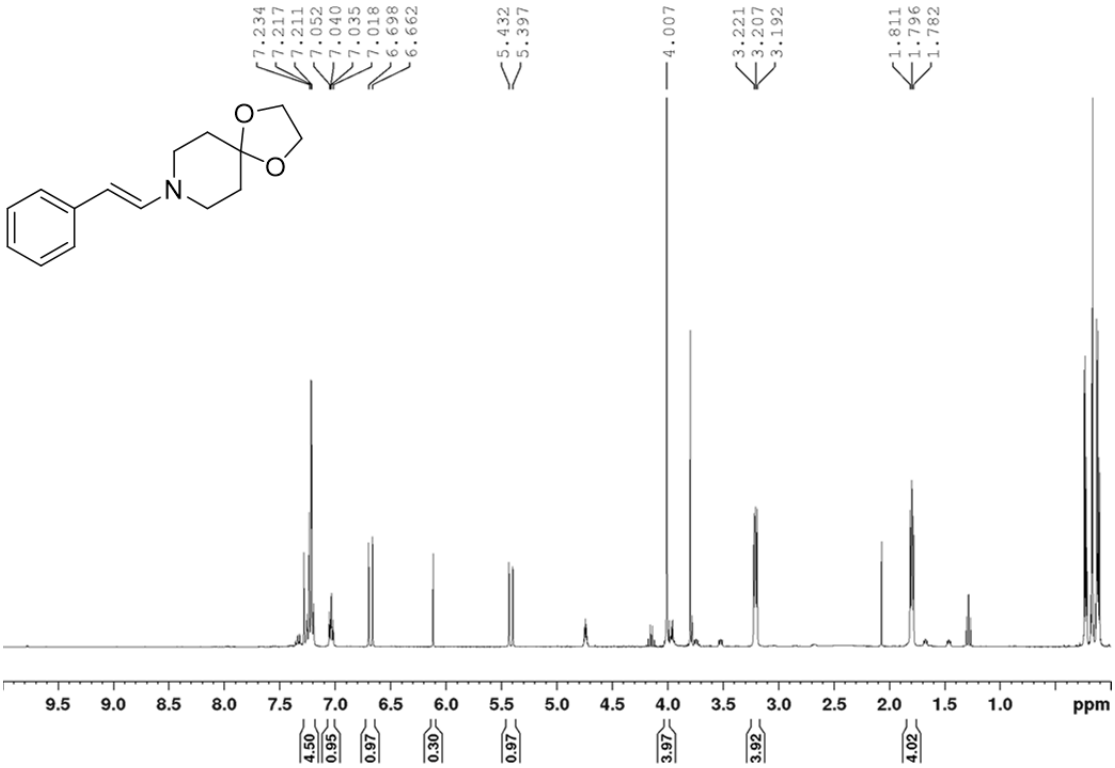
(*E*)-4-styrylmorpholine (2o)

Enamine formation; 3 h at 65 °C, 1,3,5-trimethoxybenzene (0.1 mmol / 6.10 ppm) was used as internal standard to determine the ^{1}H-NMR yield of the formed enamine to >95%. (400 MHz, $CDCl_3$)



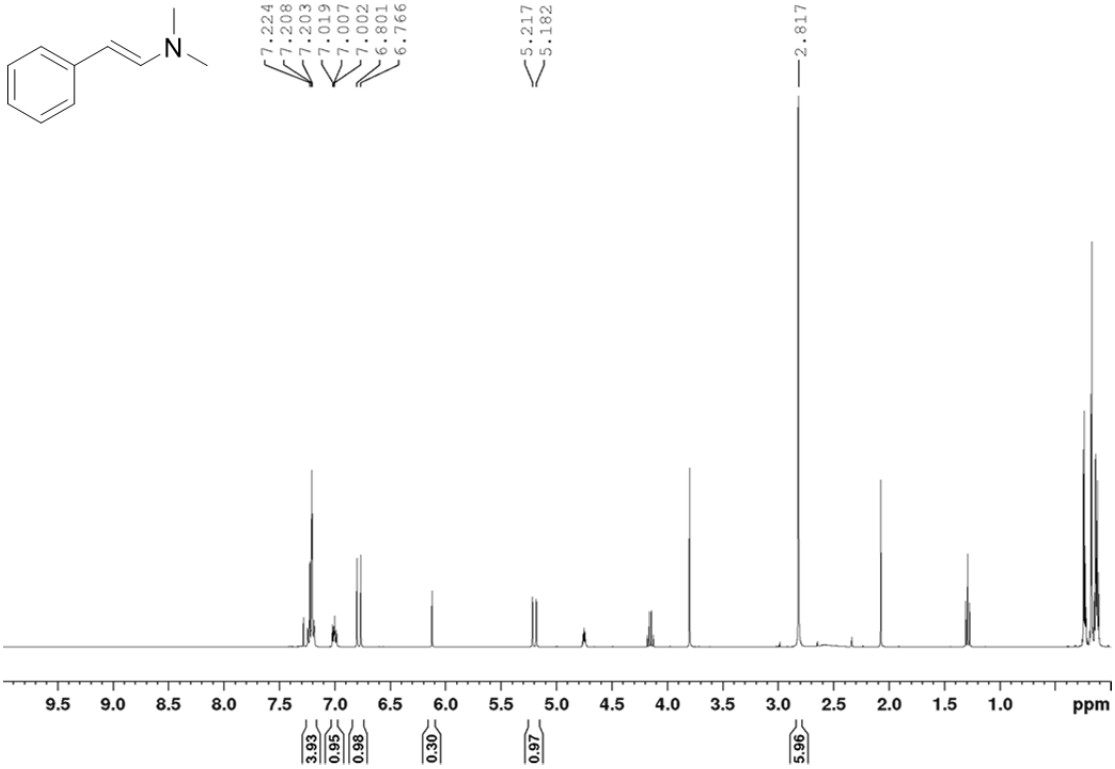
(*E*)-8-styryl-1,4-dioxa-8-azaspiro[4.5]decane (2p)

Enamine formation; 1 h at 65 °C, 1,3,5-trimethoxybenzene (0.1 mmol / 6.10 ppm) was used as internal standard to determine the ^{1}H-NMR yield of the formed enamine to >95%. (400 MHz, $CDCl_3$)



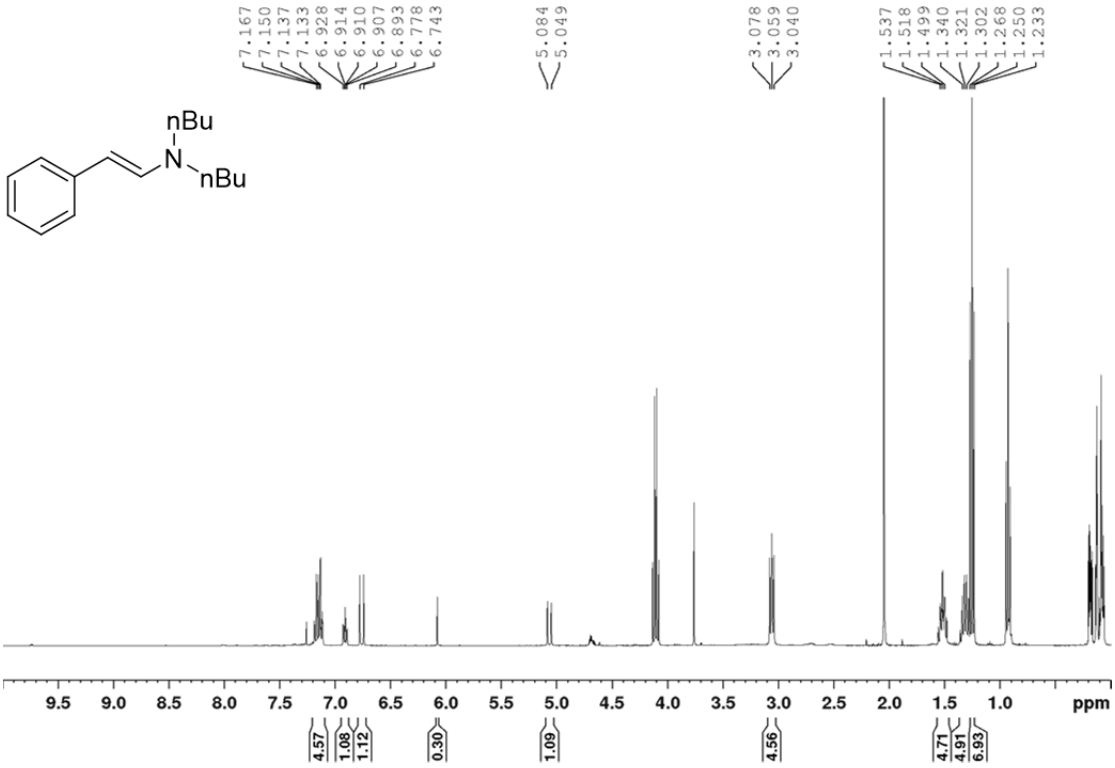
(*E*)-*N*,*N*-dimethyl-2-phenylethen-1-amine (2q)

Enamine formation; 1 h at 65 °C, 1,3,5-trimethoxybenzene (0.1 mmol / 6.10 ppm) was used as internal standard to determine the ^{1}H-NMR yield of the formed enamine to >95%. (400 MHz, $CDCl_3$)



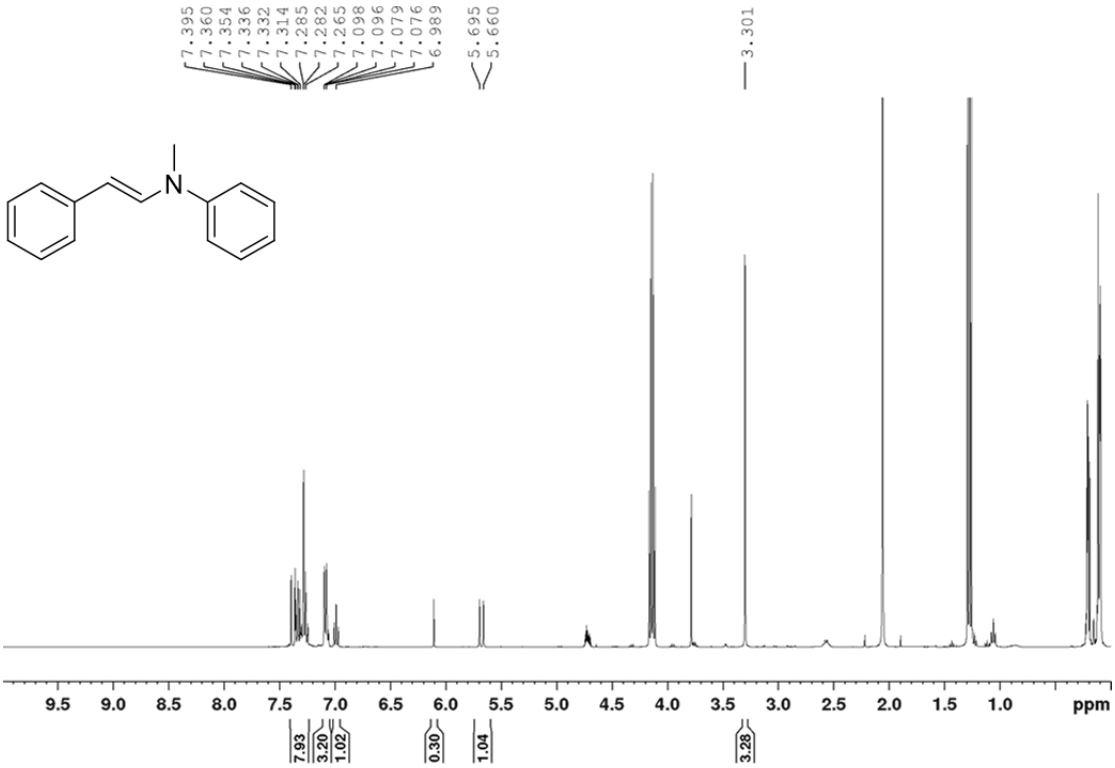
(*E*)-*N*-butyl-*N*-styrylbutan-1-amine (2r)

Enamine formation; 5 h at 65 °C, 1,3,5-trimethoxybenzene (0.1 mmol / 6.10 ppm) was used as internal standard to determine the ^{1}H-NMR yield of the formed enamine to >95%. (400 MHz, $CDCl_3$)



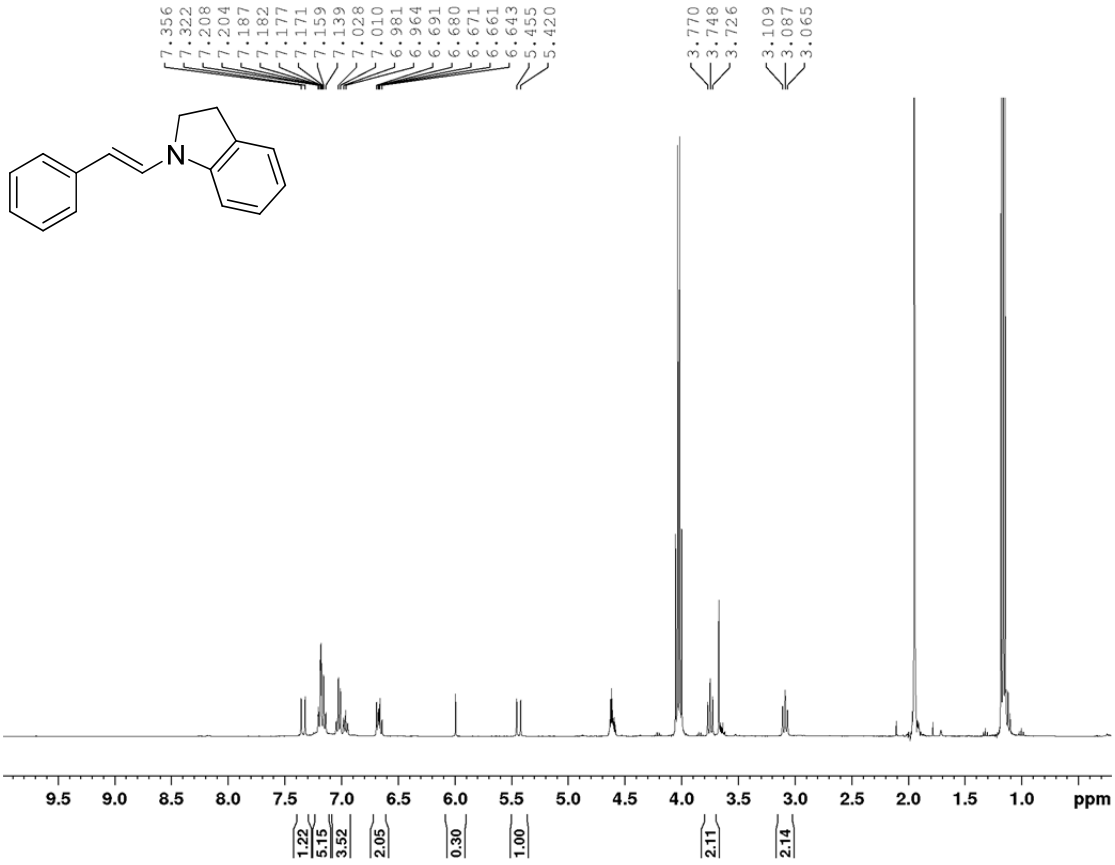
(*E*)-*N*-methyl-*N*-styrylaniline (2s)

Enamine formation; 55 h at 65 °C with Et_3N (10 mol%) as additive, 1,3,5-trimethoxybenzene (0.1 mmol / 6.10 ppm) was used as internal standard to determine the ^{1}H-NMR yield of the formed enamine to >95%. (400 MHz, $CDCl_3$)



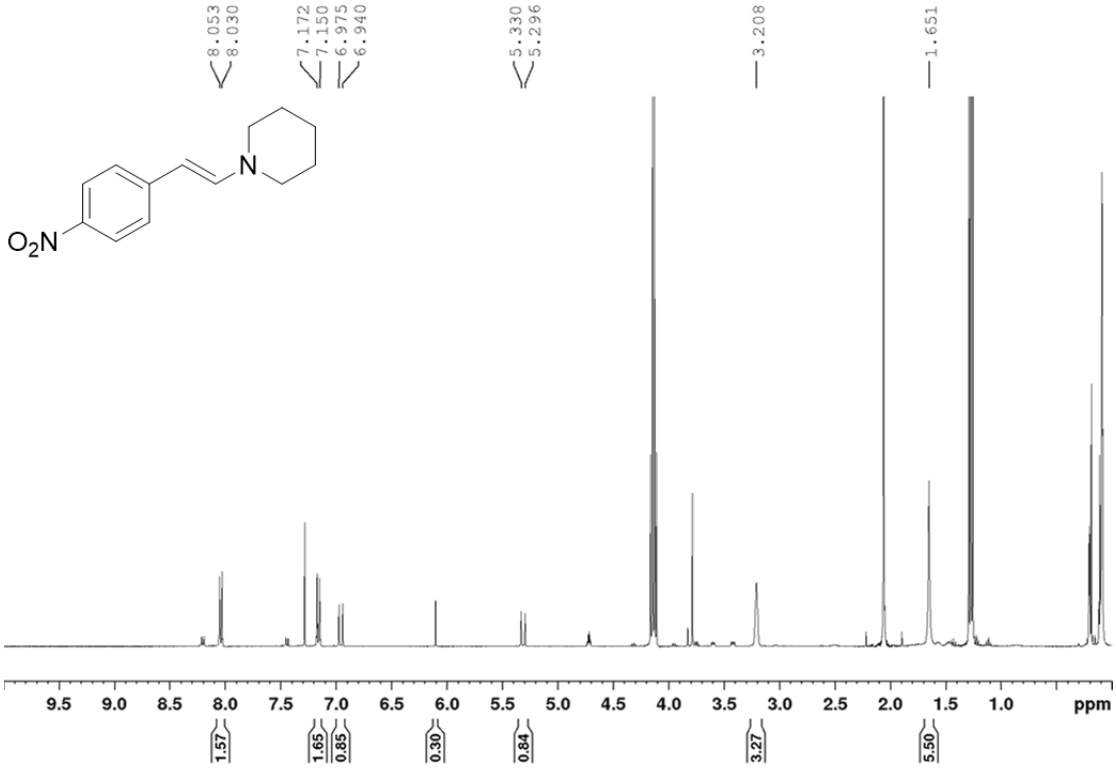
(*E*)-1-styrylindoline (2t)

Enamine formation; 9 h at 65 °C, 1,3,5-trimethoxybenzene (0.1 mmol / 6.10 ppm) was used as internal standard to determine the ^{1}H-NMR yield of the formed enamine to >95%. (400 MHz, $CDCl_3$)



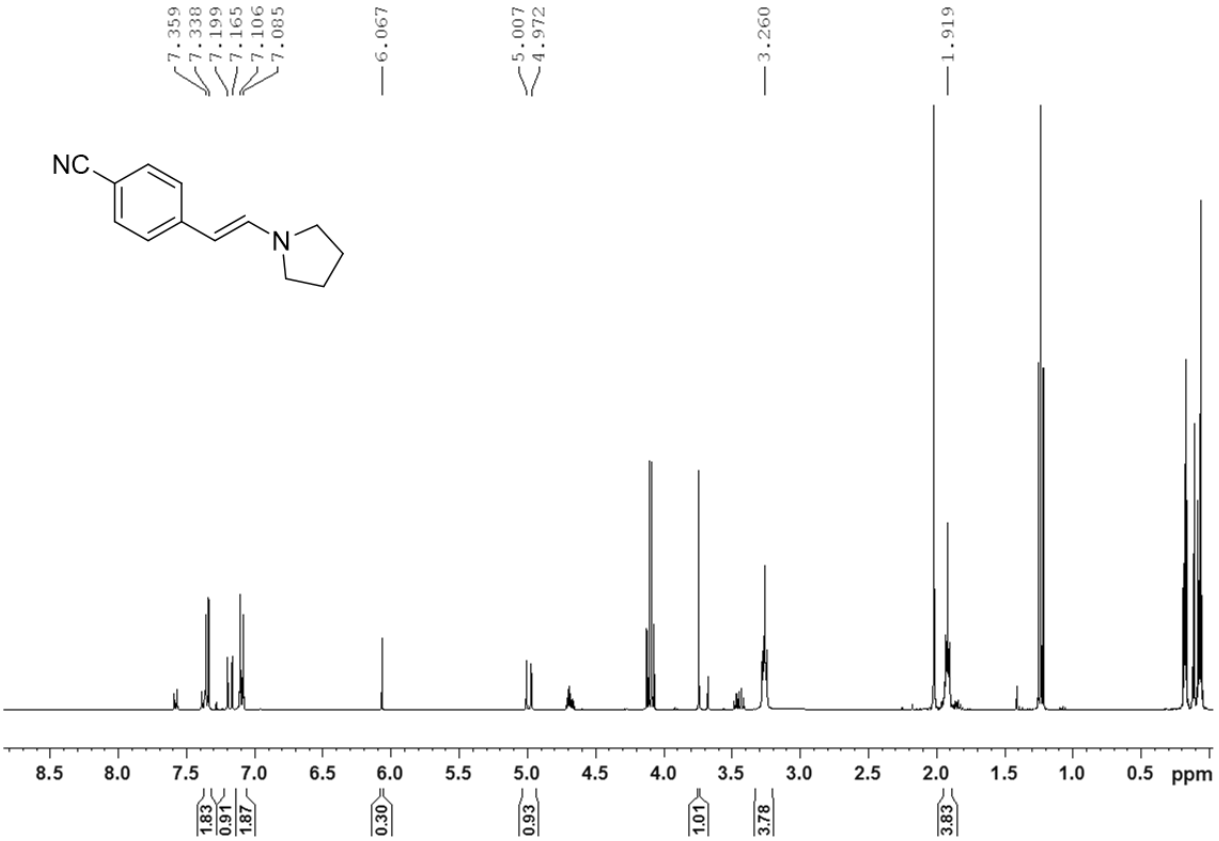
(*E*)-1-(4-nitrostyryl)piperidine (2u)

Enamine formation; 24 h at 65 °C with $Mo(CO)_6$ (5 mol%) and ethyl acetate (2 mL, 0.05 M), 1,3,5-trimethoxybenzene (0.1 mmol / 6.10 ppm) was used as internal standard to determine the ^{1}H-NMR yield of the formed enamine to 85%. (400 MHz, $CDCl_3$)



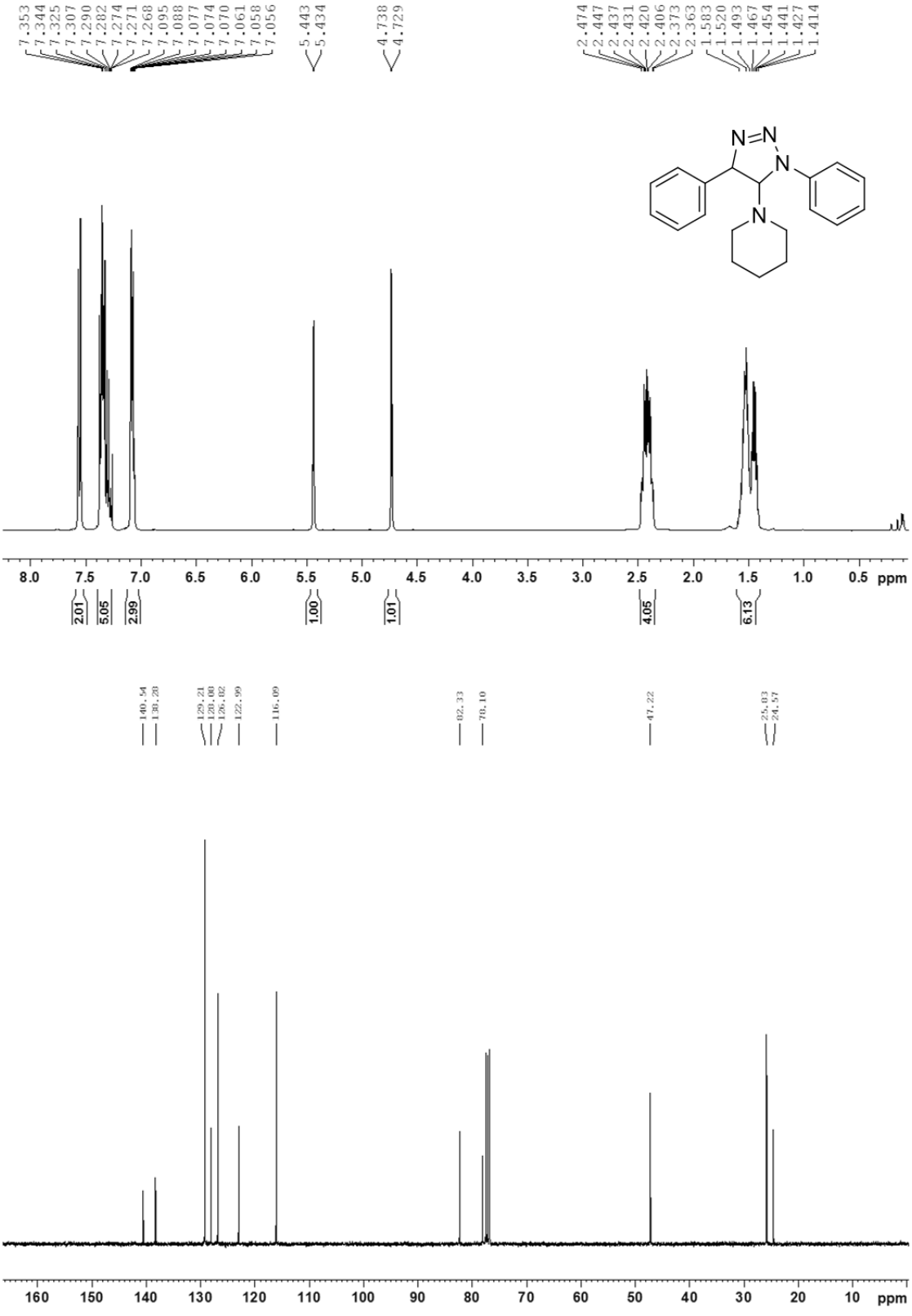
(*E*)-4-(2-(pyrrolidin-1-yl)vinyl)benzonitrile (2v)

Enamine formation; 2.5 h at 65 °C, 1,3,5-trimethoxybenzene (0.1 mmol / 6.07 ppm) was used as internal standard to determine the ^{1}H-NMR yield of the formed enamine to >95%. (400 MHz, $CDCl_3$)

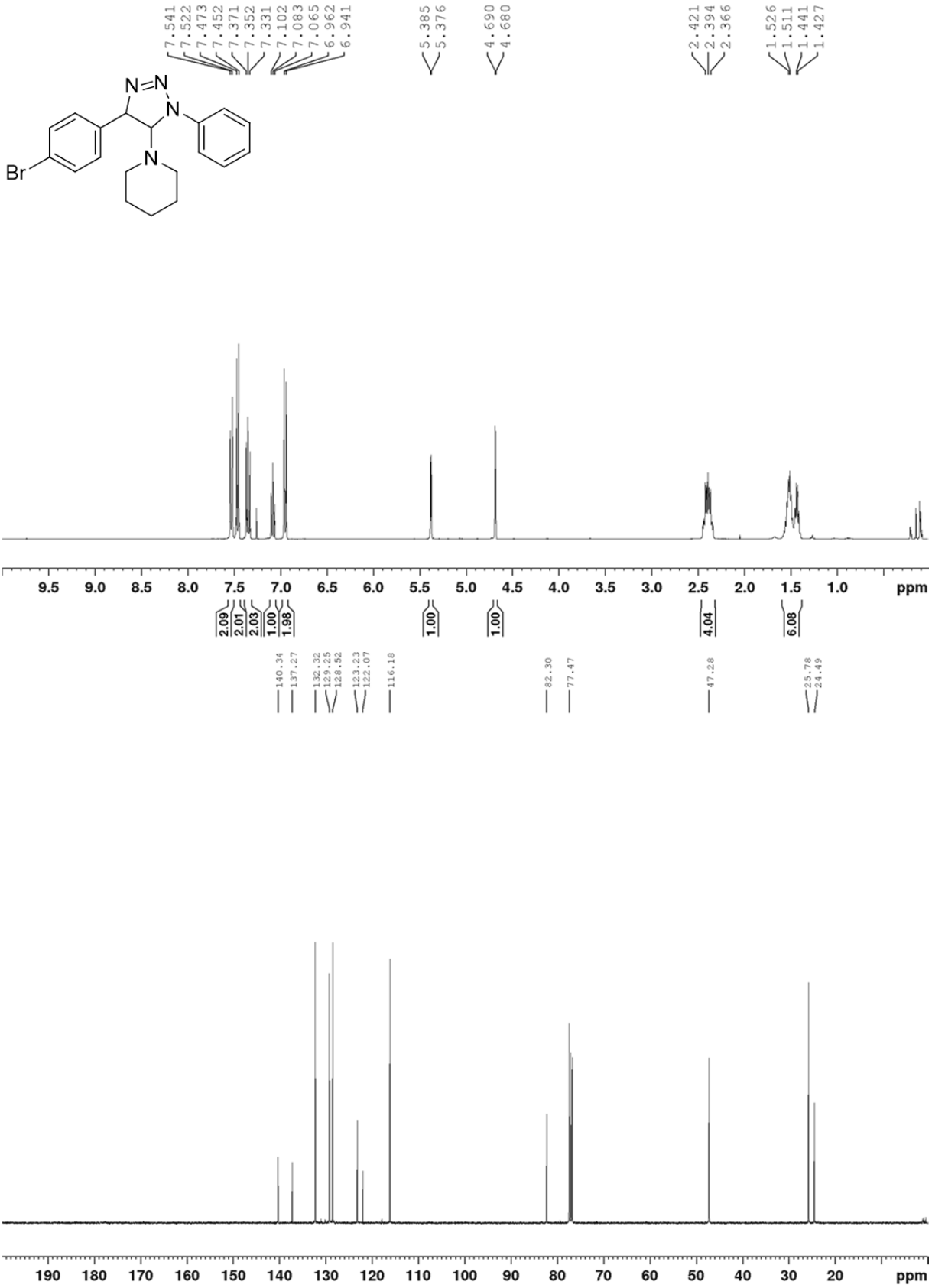


Triazolines

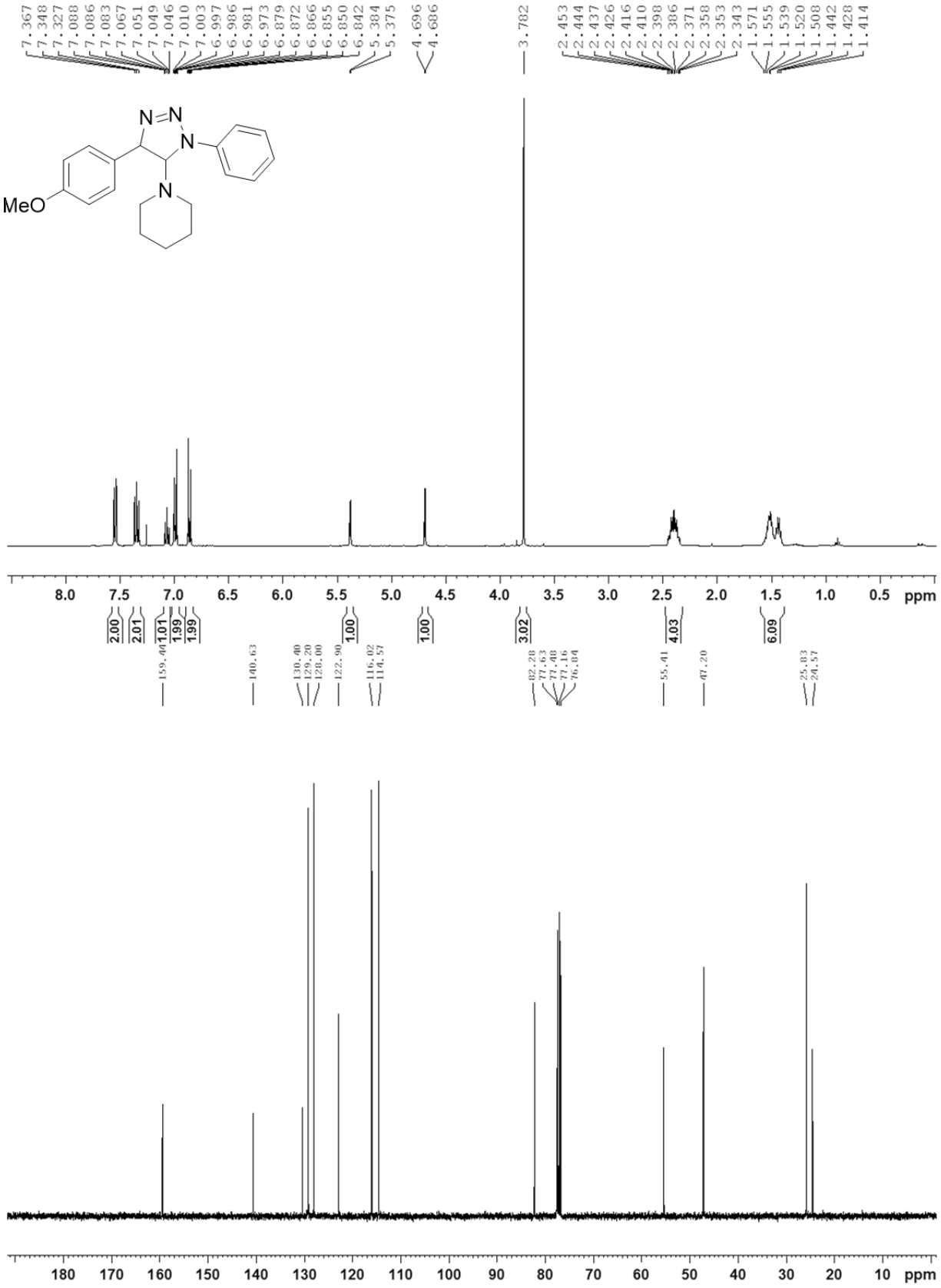
1-(1,4-diphenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)piperidine (4aa)



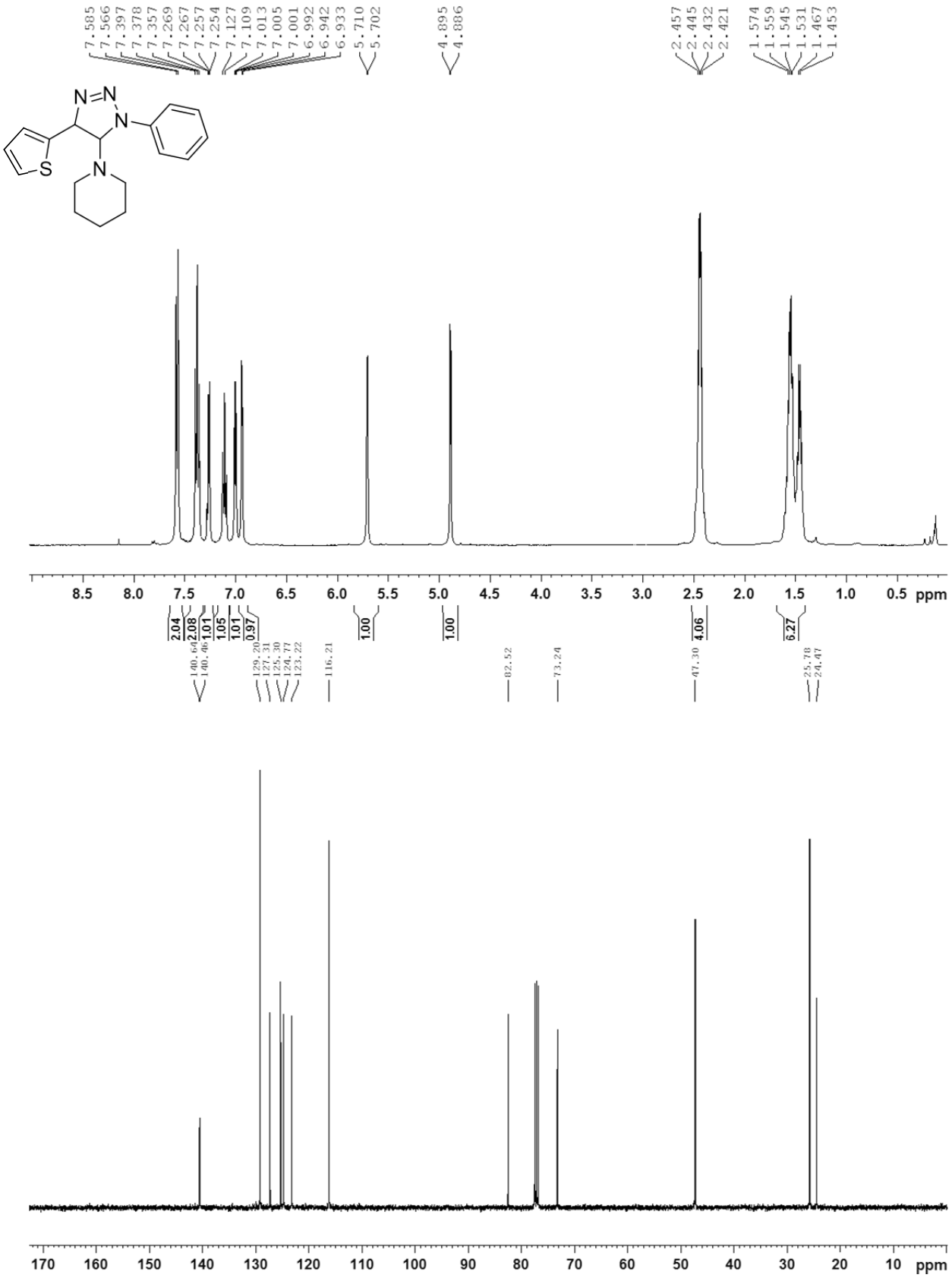
1-(4-(4-bromophenyl)-1-phenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)piperidine (4ba)

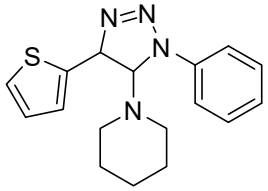


1-(4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)piperidine (4ca)

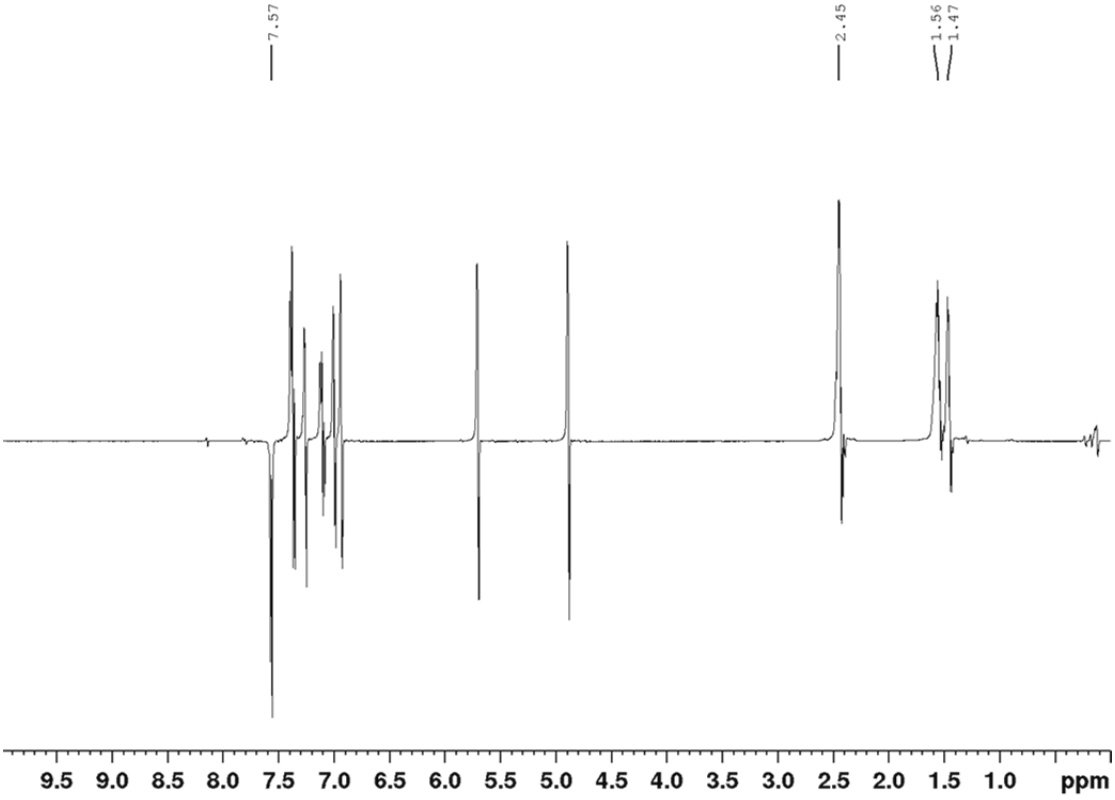


1-(1-phenyl-4-(thiophen-2-yl)-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)piperidine (4da)

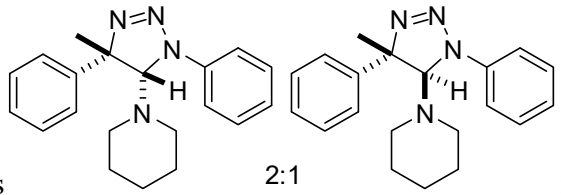




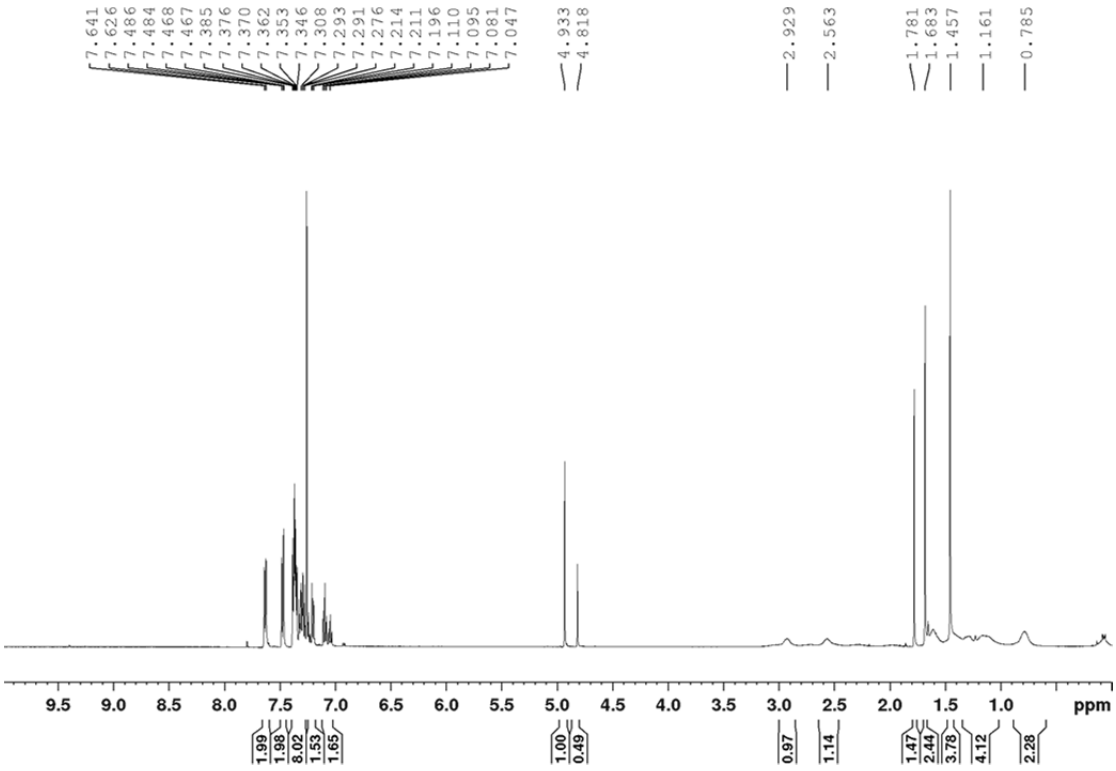
The regiochemistry of the product was investigated using ^{1}H NMR NOE experiment. By irradiating the signal of the aromatic protons (7.57 ppm) an increase in intensity of the piperidine protons (2.45 ppm (m, 4H) and 1.64 – 1.42 ppm (m, 6H)) was observed, indicating that these functional groups are close in space and situated on the 1 and 5 positions of the triazoline ring.

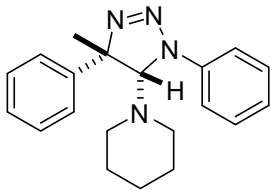


1-(4-methyl-1,4-diphenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)piperidine (4ea)

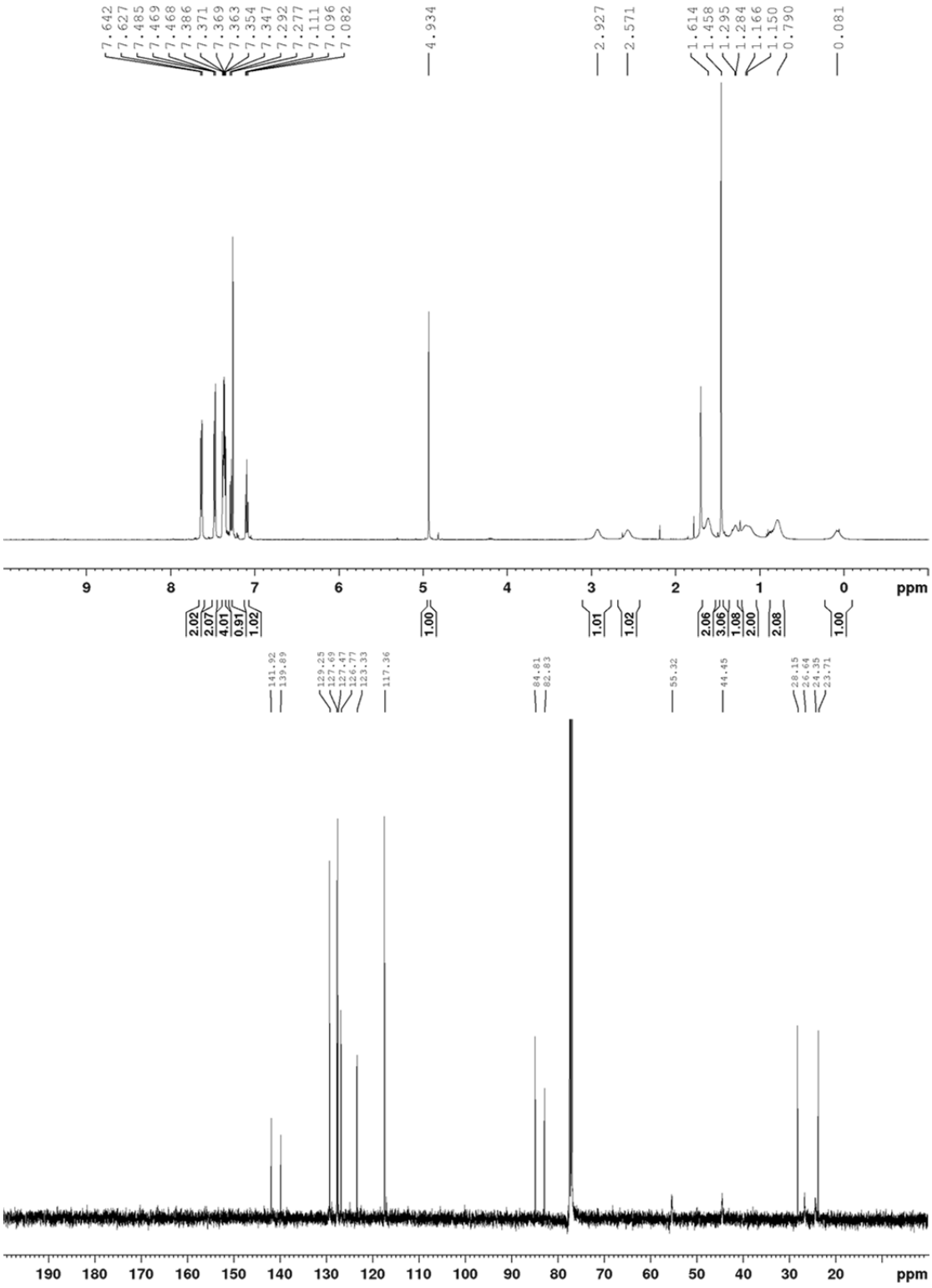


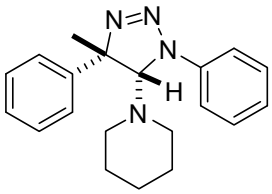
Mixture of diastereomers 2:1 :



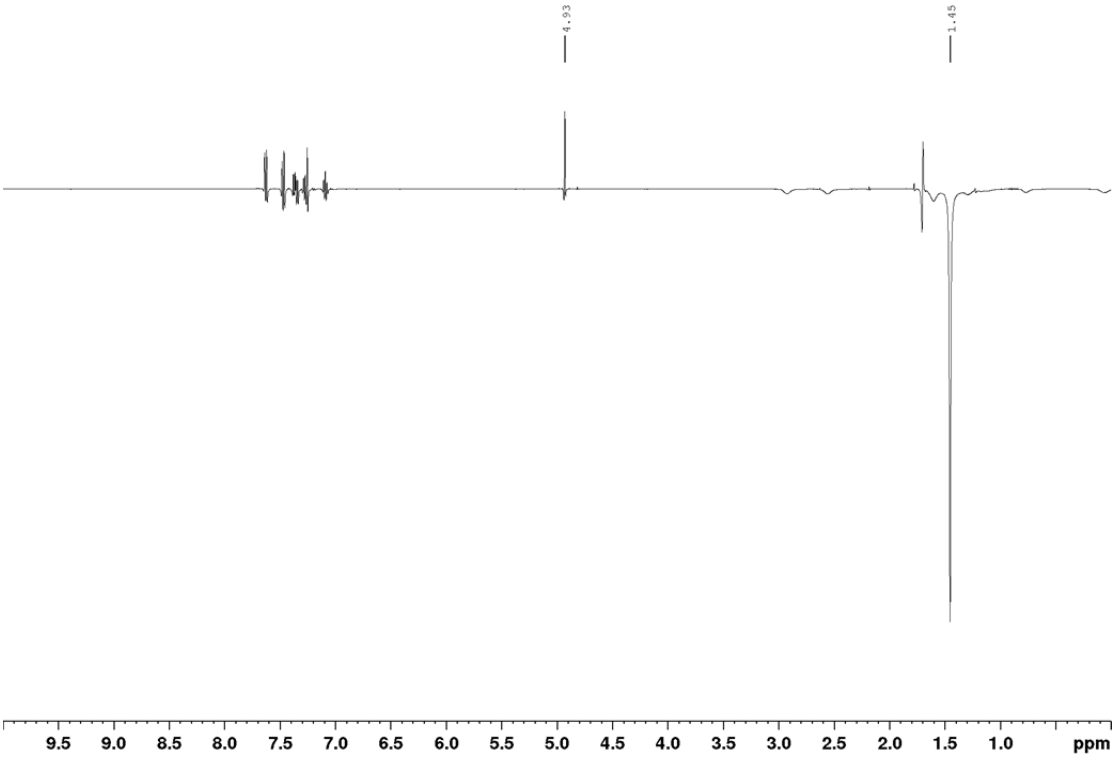


Major diastereomer:

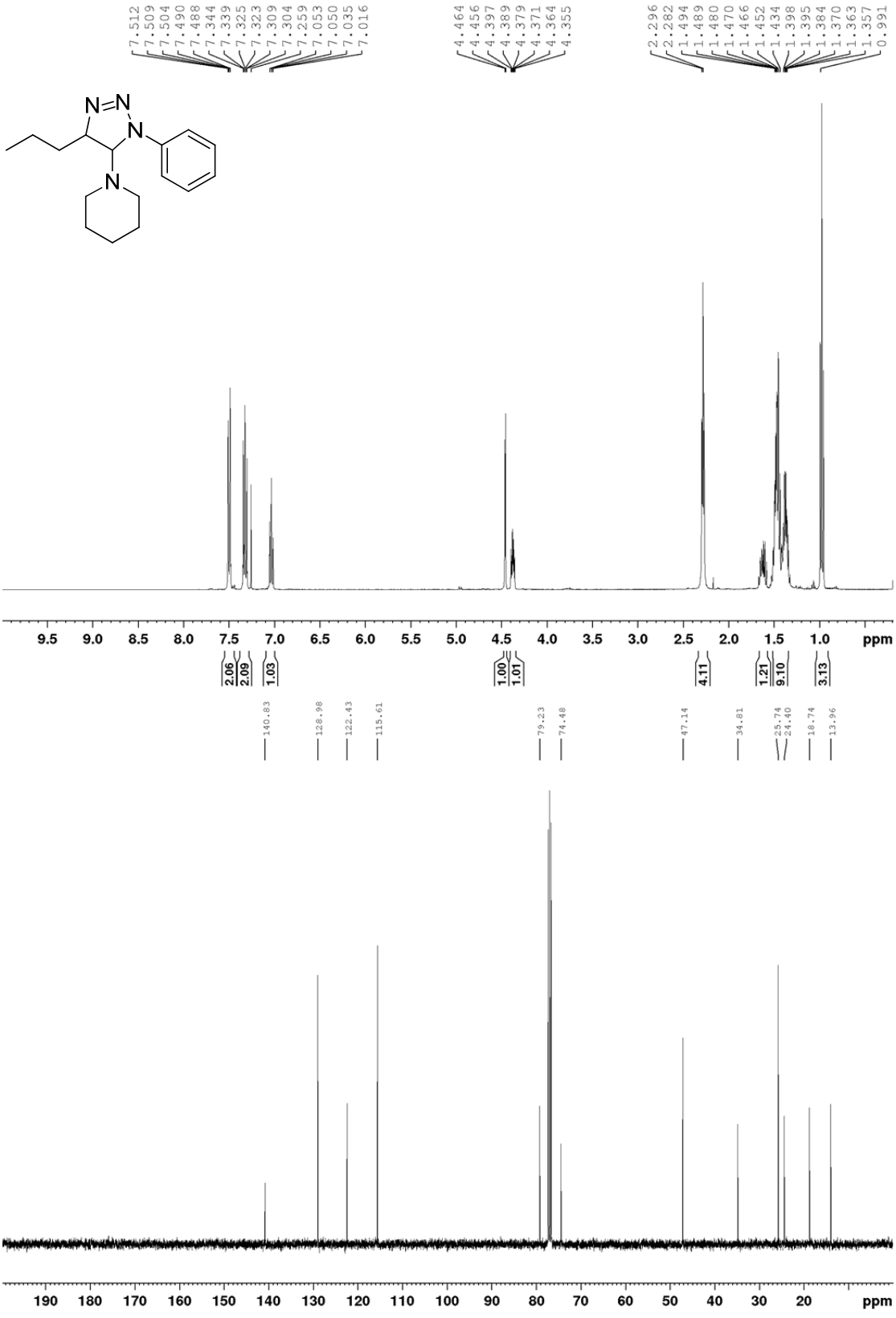




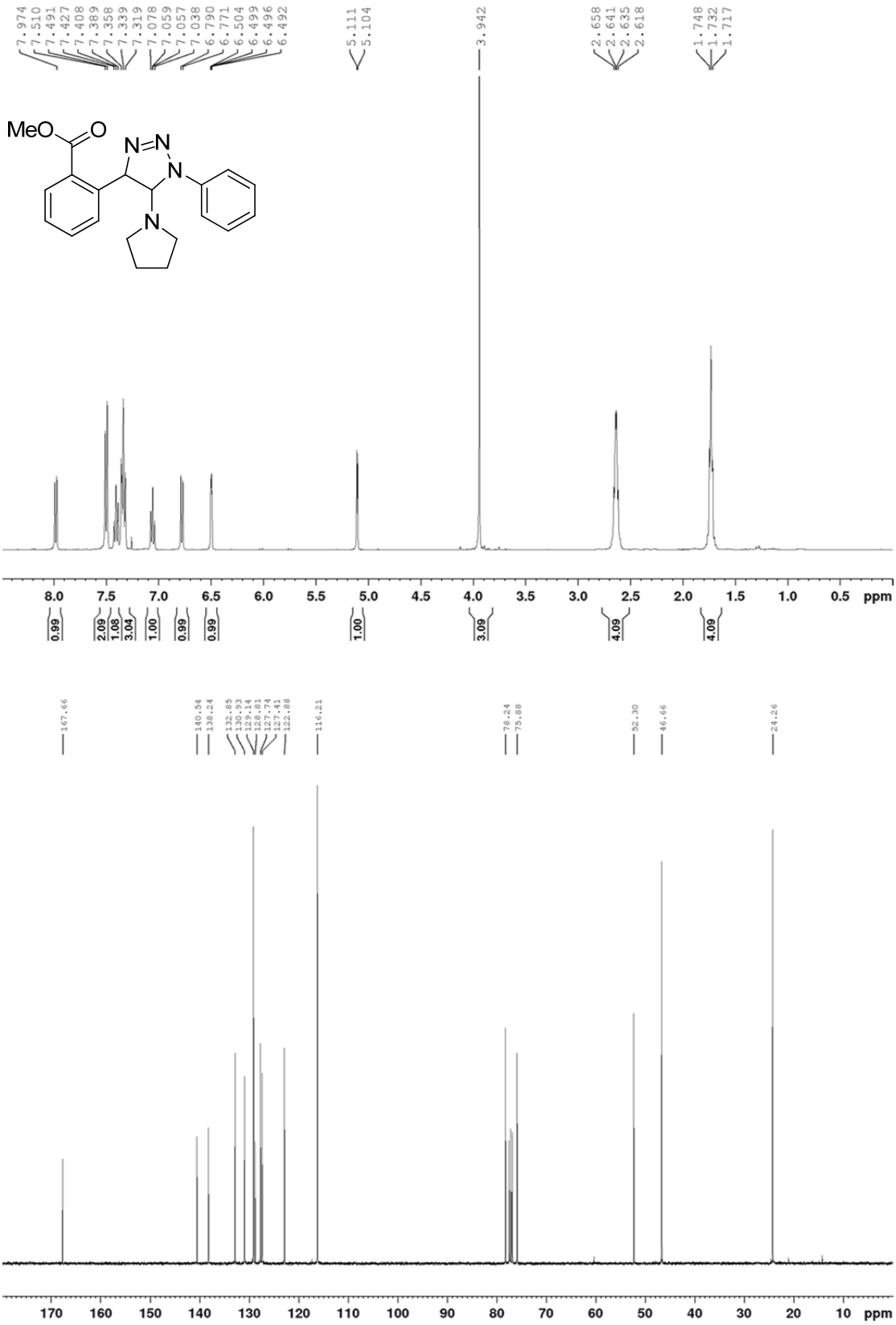
The relative stereochemistry of the major diastereomer was confirmed using ^{1}H NMR NOE experiment. By irradiating the signal of the CH_3 group (1.45 ppm) an increase in intensity of the signal of triazoline (4.93 ppm) was observed, indicating cis relationship between these two groups.



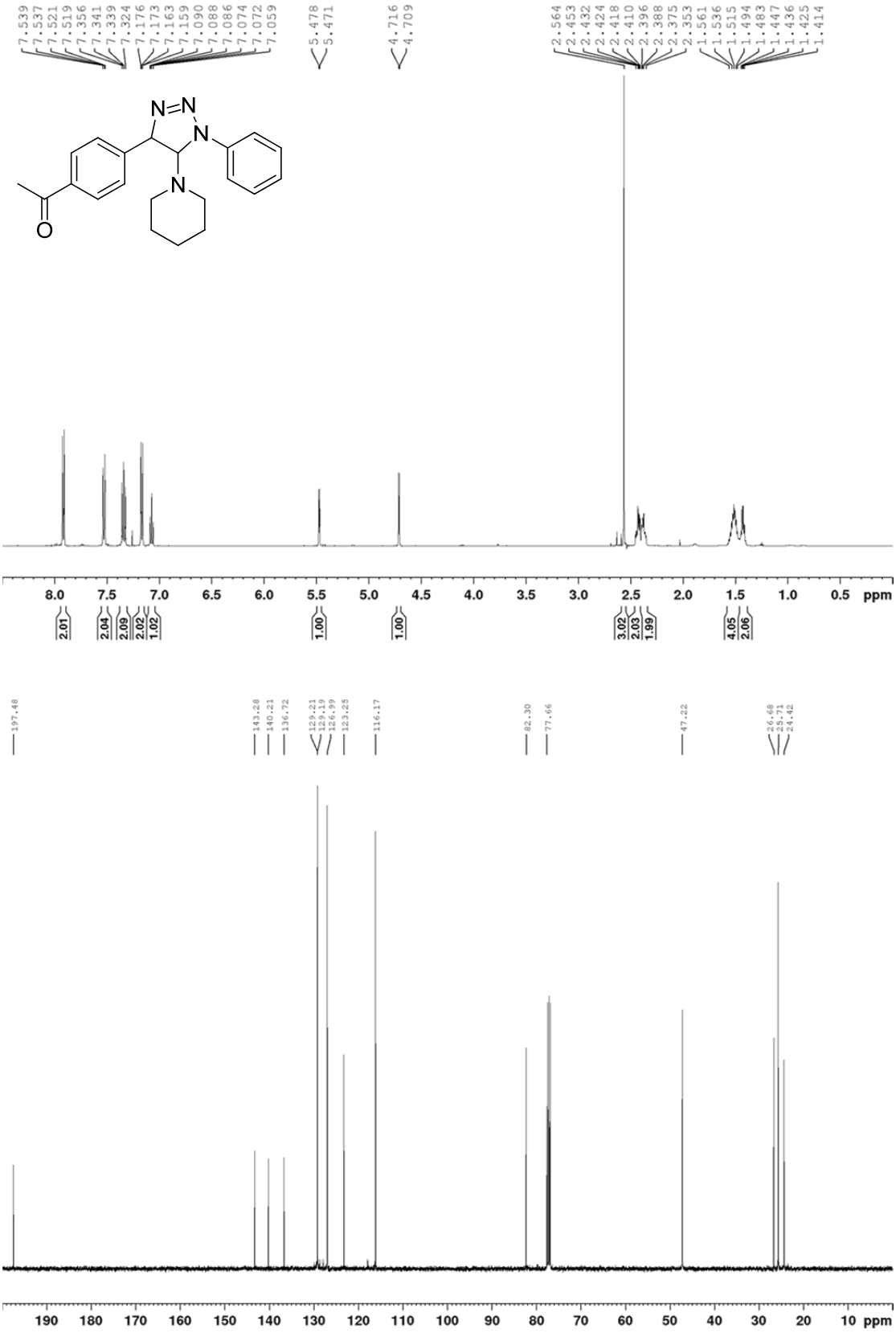
1-(1-phenyl-4-propyl-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)piperidine (4fa)



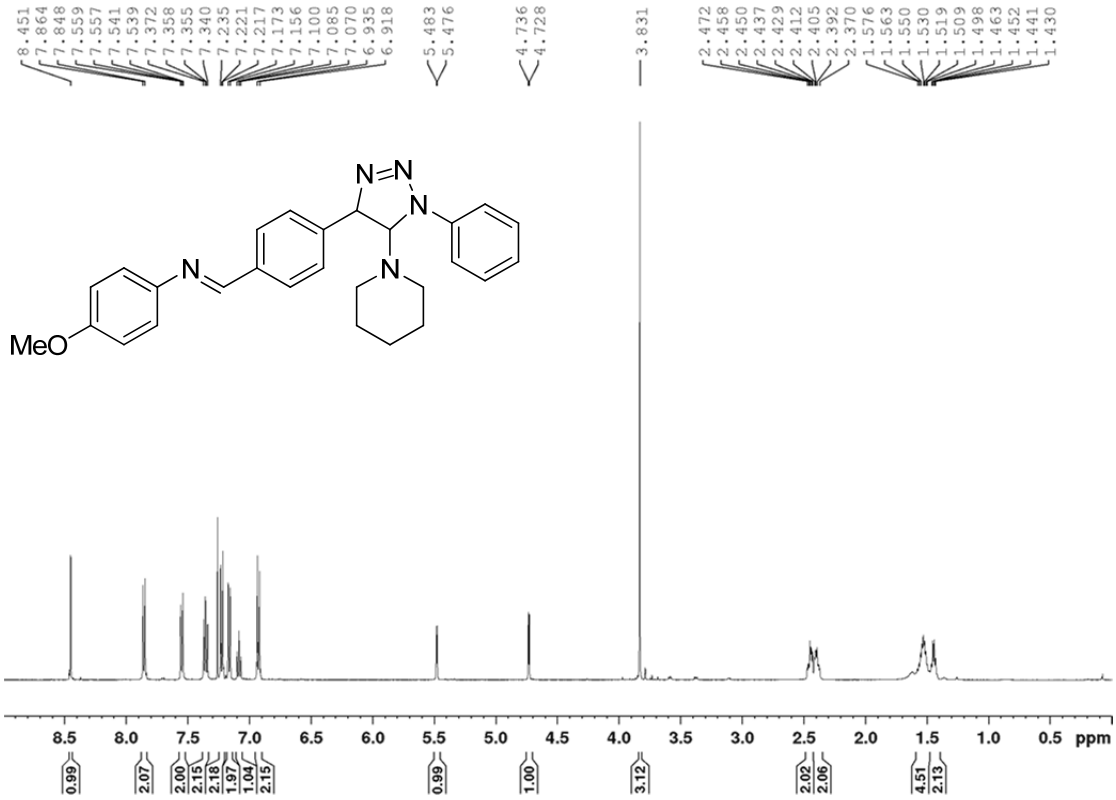
methyl 2-(1-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-4-yl)benzoate (4ga)

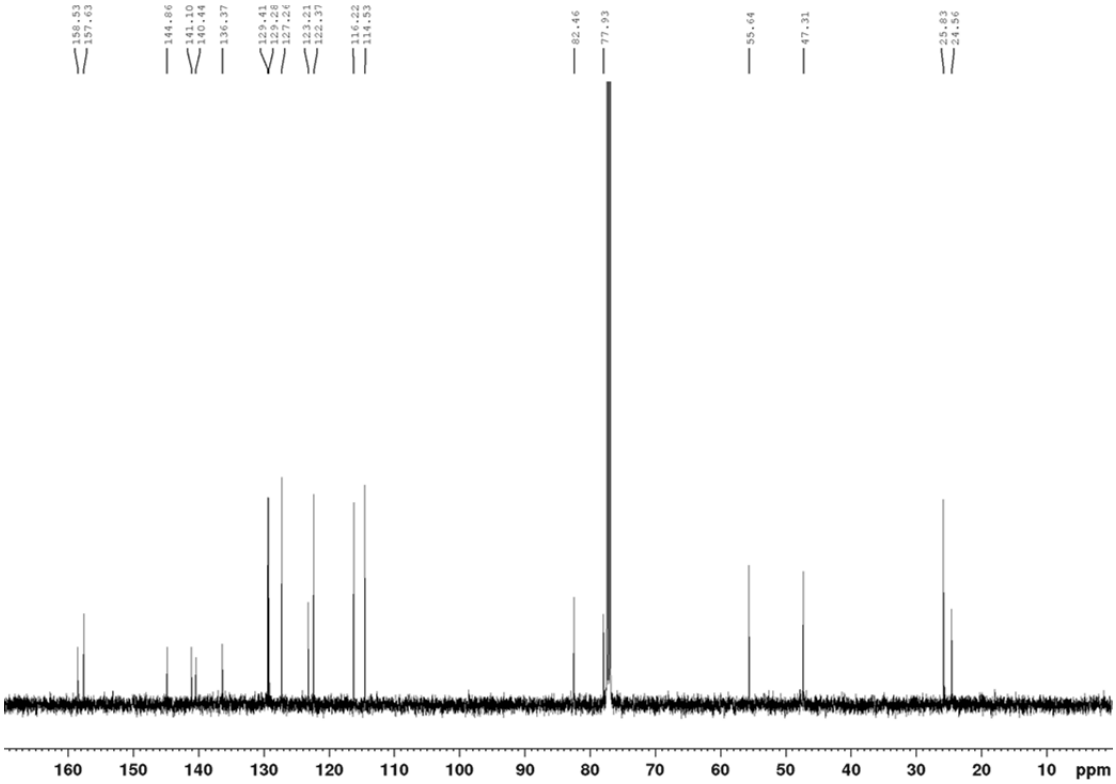


1-(4-(1-phenyl-5-(piperidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-4-yl)phenyl)ethanone (4ha)

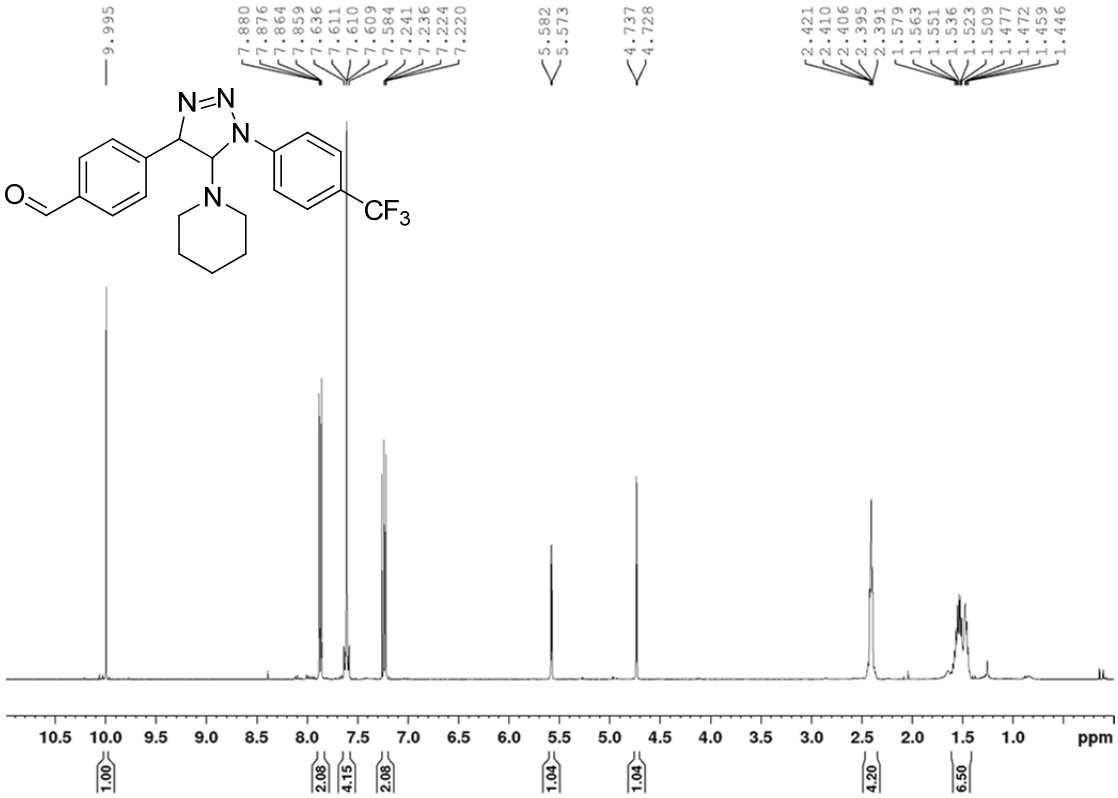


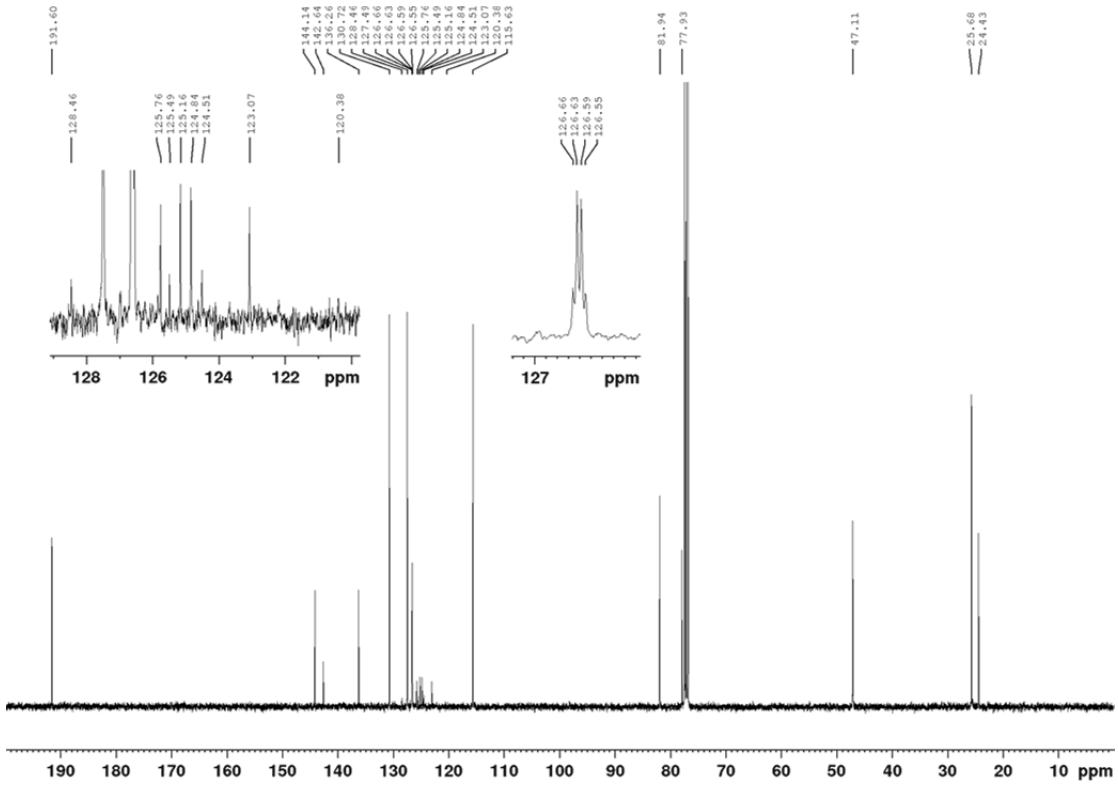
(*E*)-4-methoxy-*N*-(4-(1-phenyl-5-(piperidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-4-yl)benzylidene)aniline (4ia)



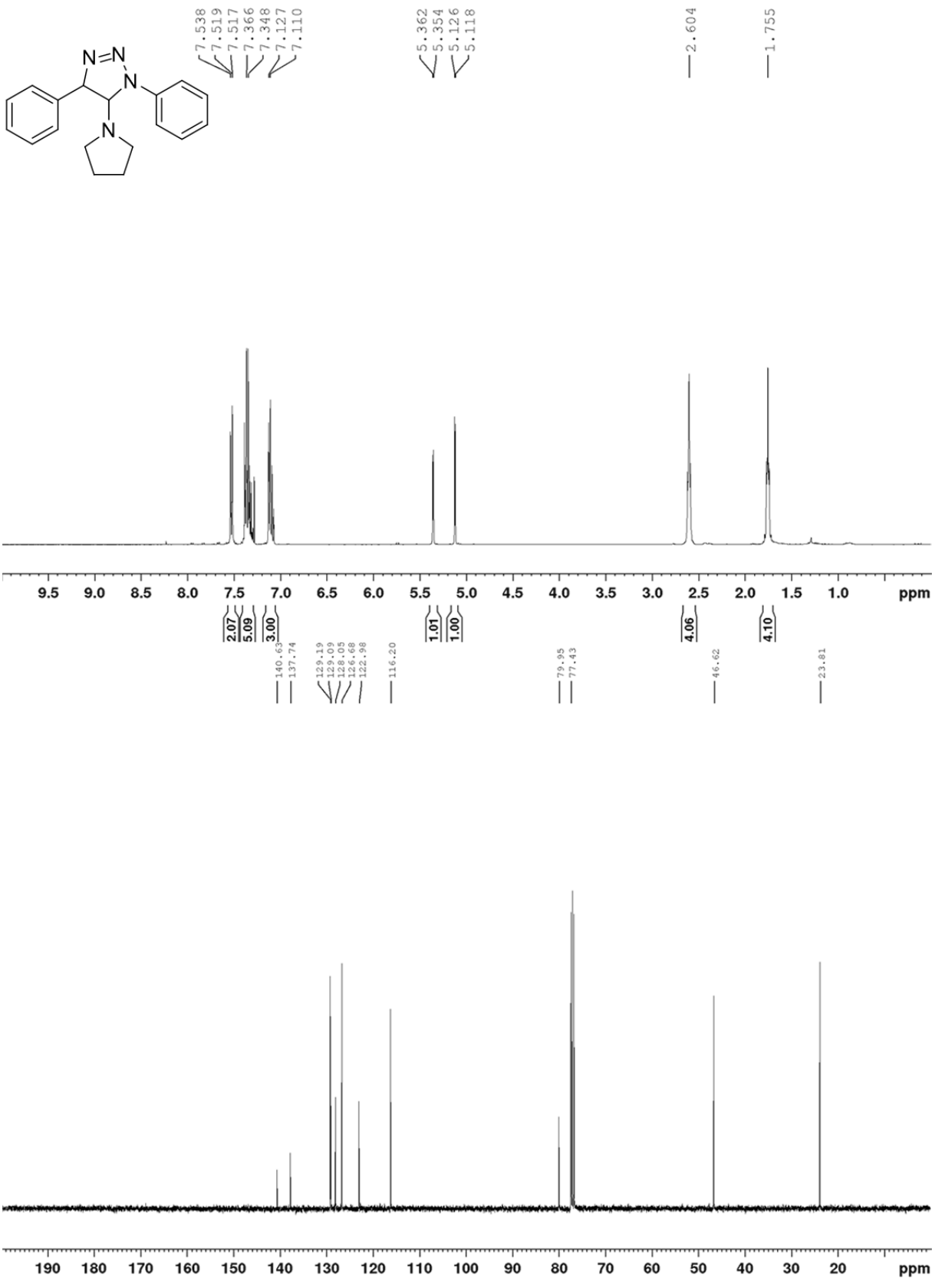


4-(5-(piperidin-1-yl)-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-1,2,3-triazol-4-yl)benzaldehyde (4mb)

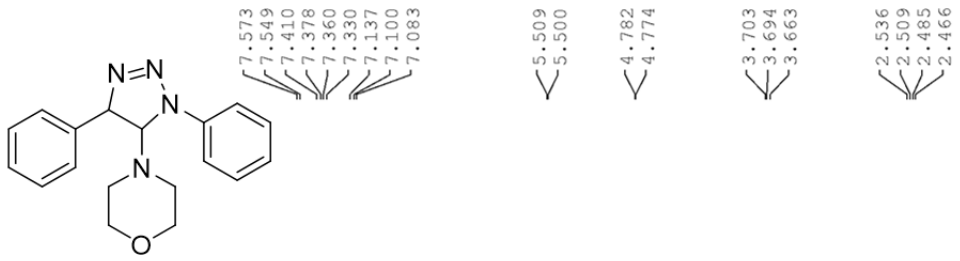


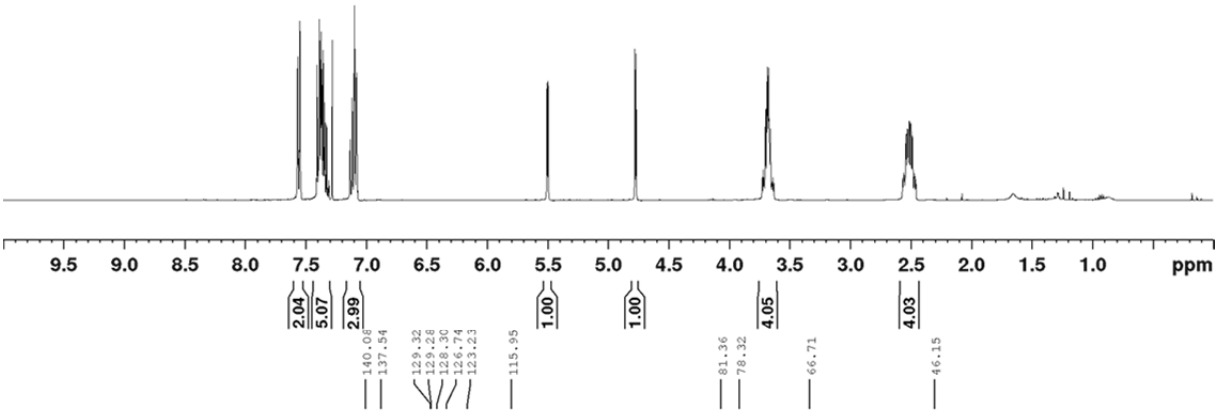


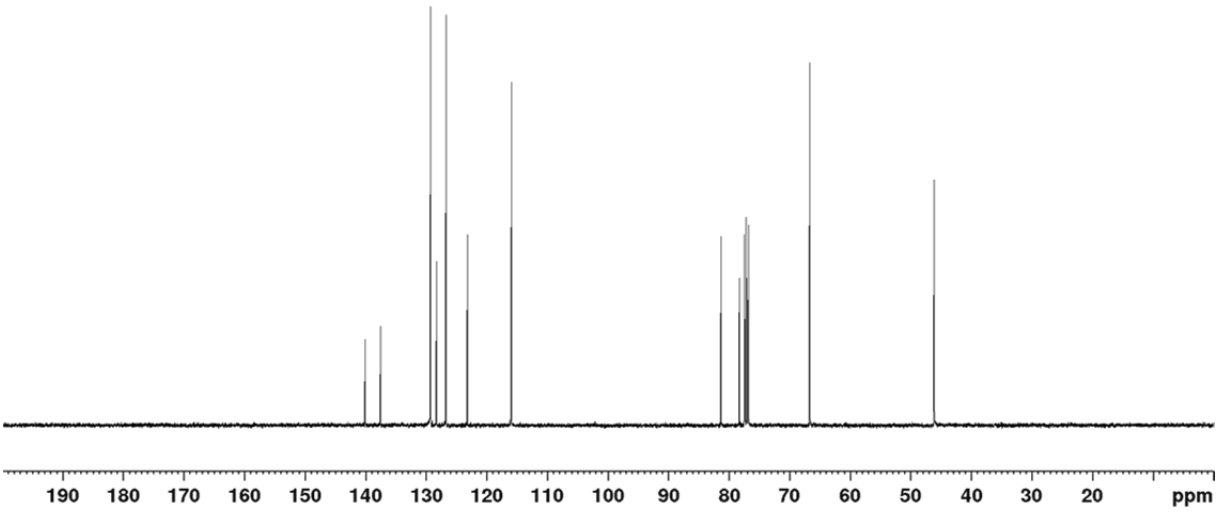
1,4-diphenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazole (4na)



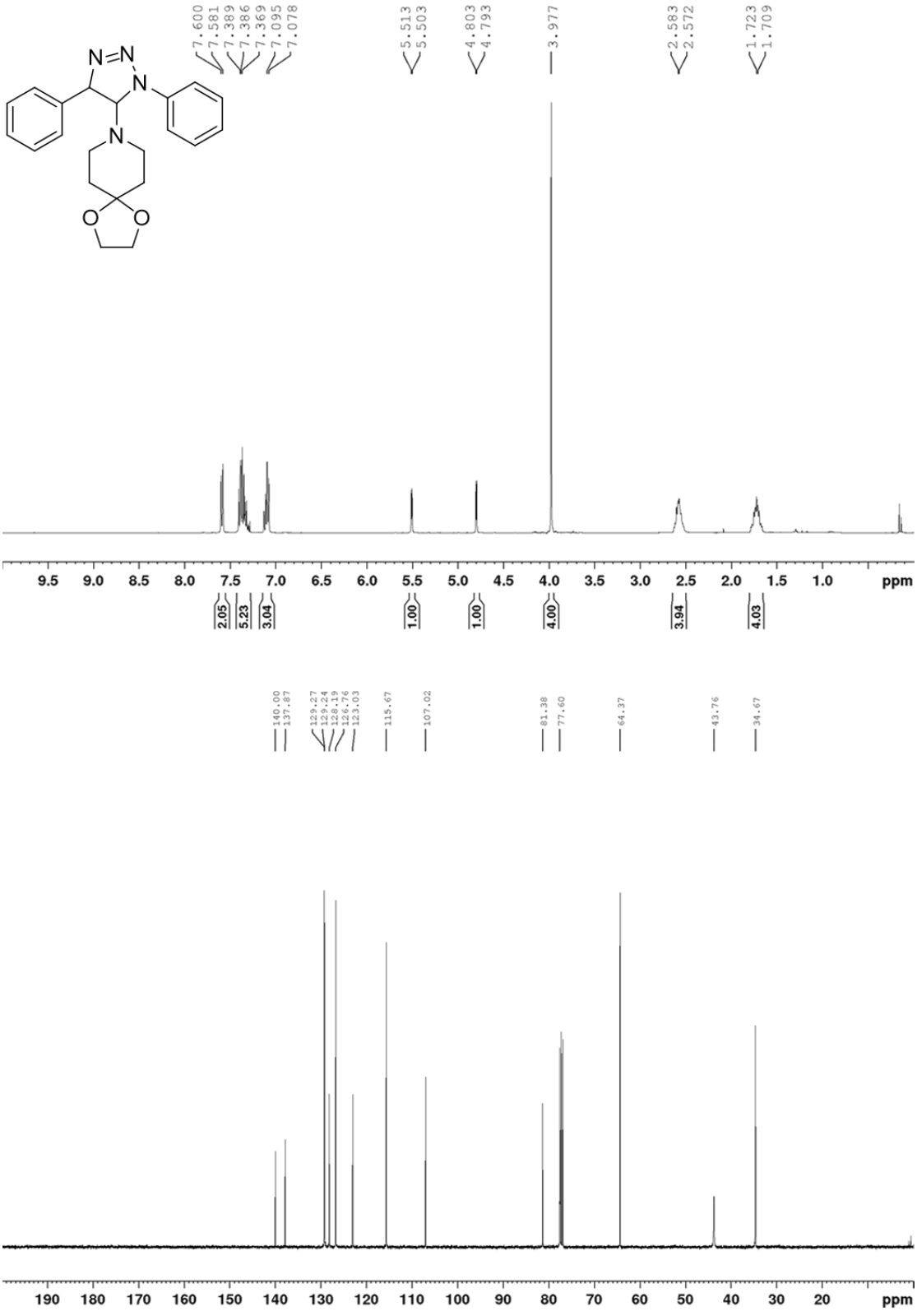
4-(1,4-diphenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)morpholine (4oa)



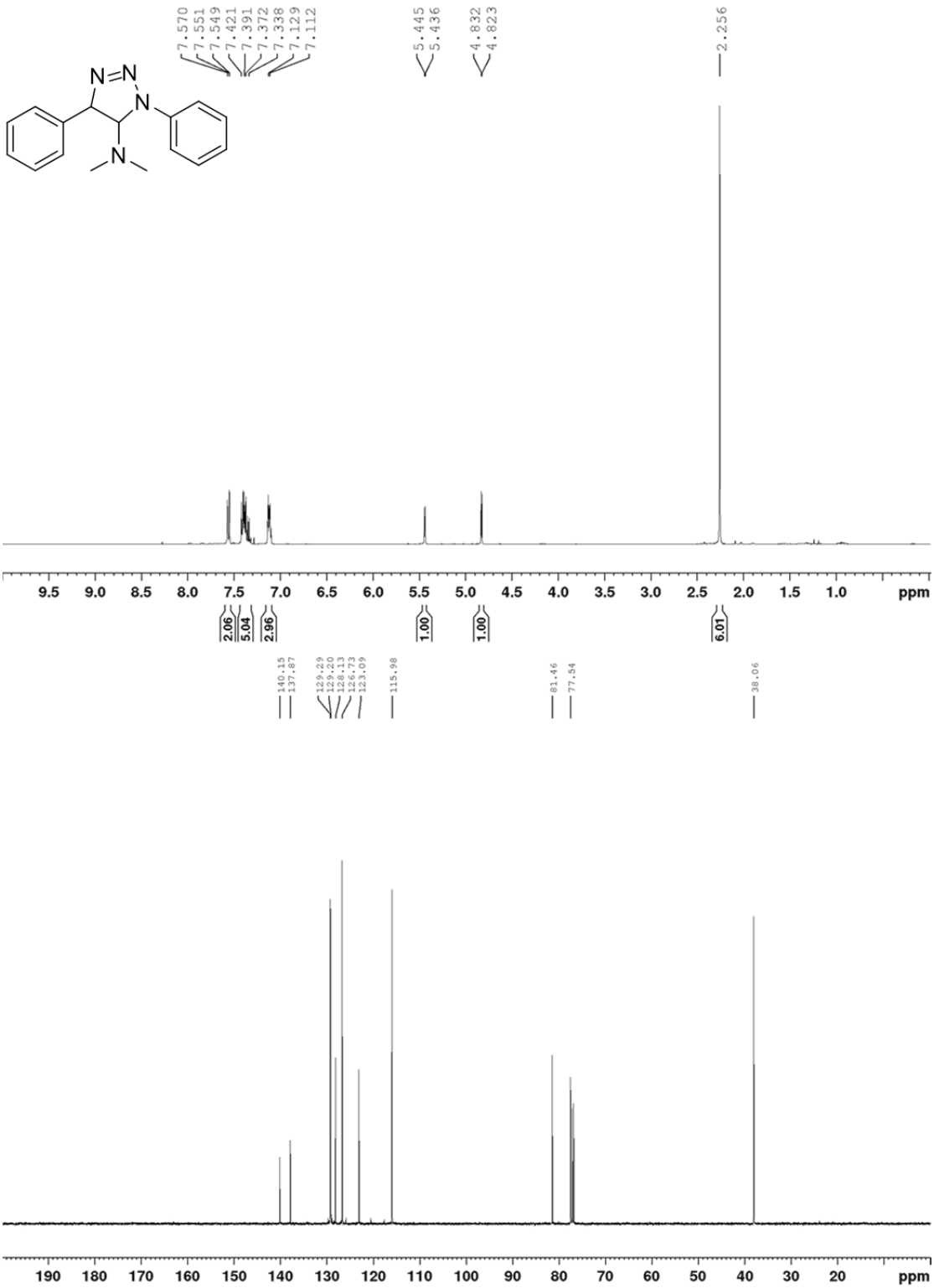




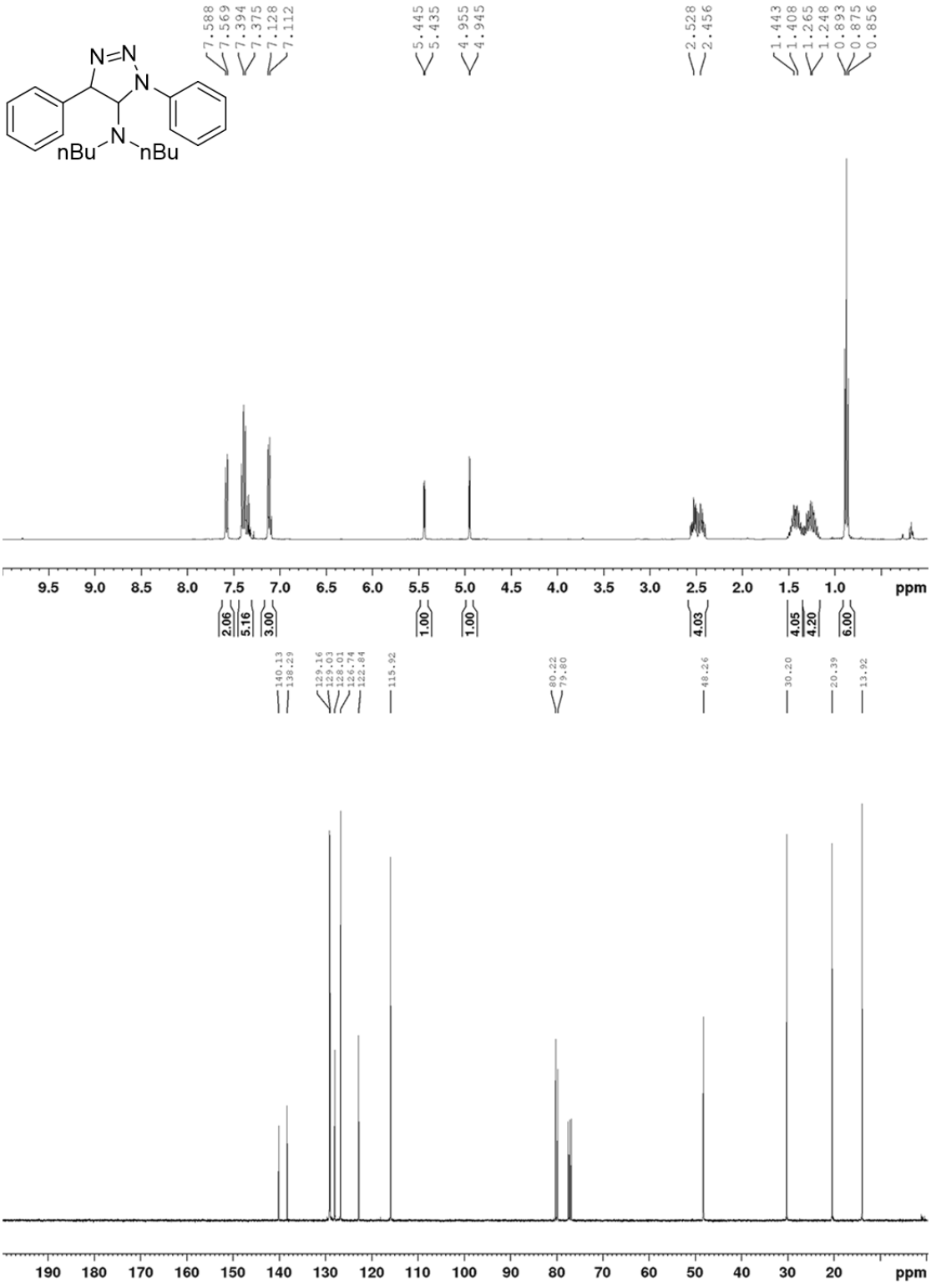
8-(1,4-diphenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)-1,4-dioxa-8-azaspiro[4.5]decane (4pa)



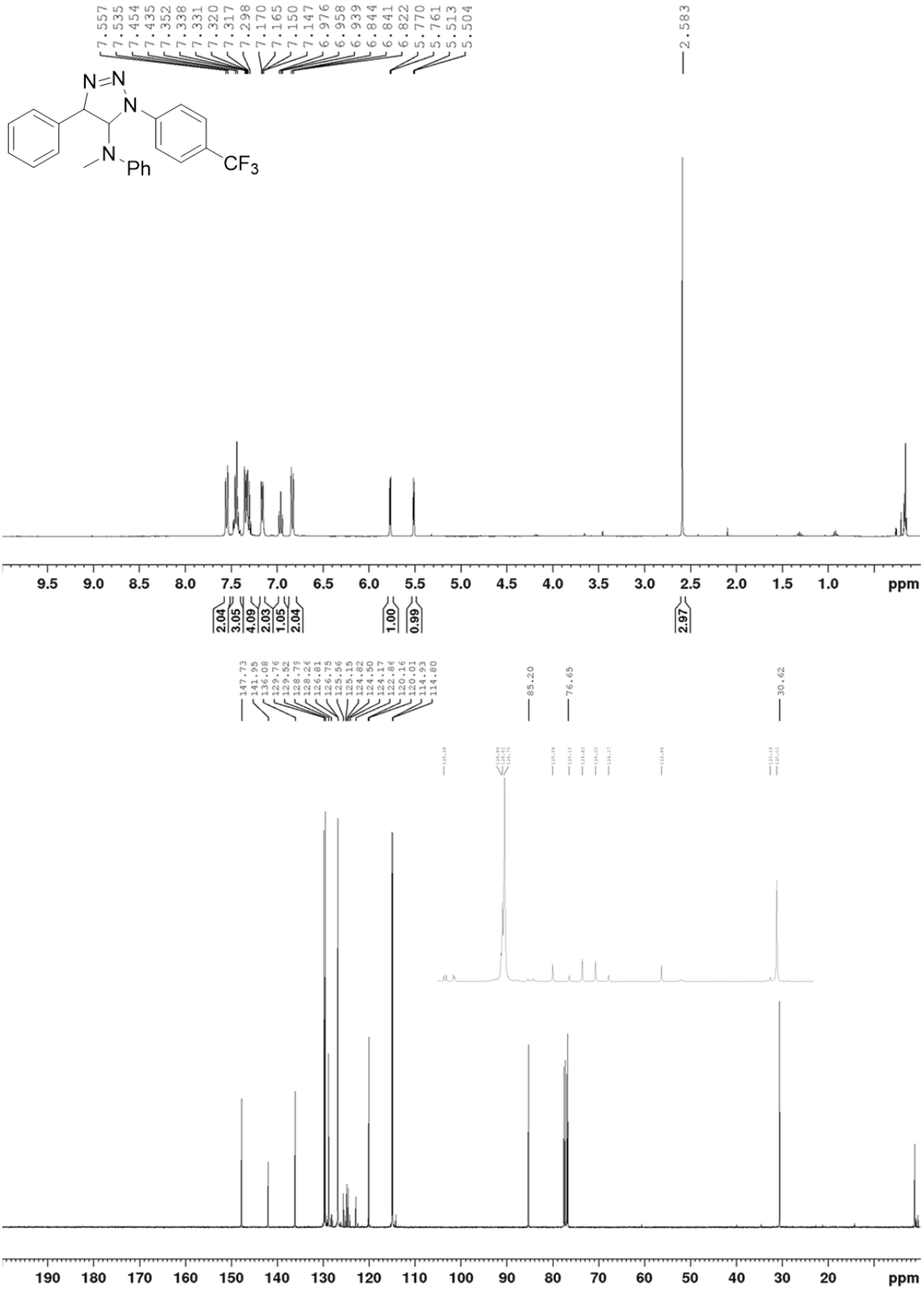
***N*,*N*-dimethyl-1,4-diphenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-amine (4qa)**

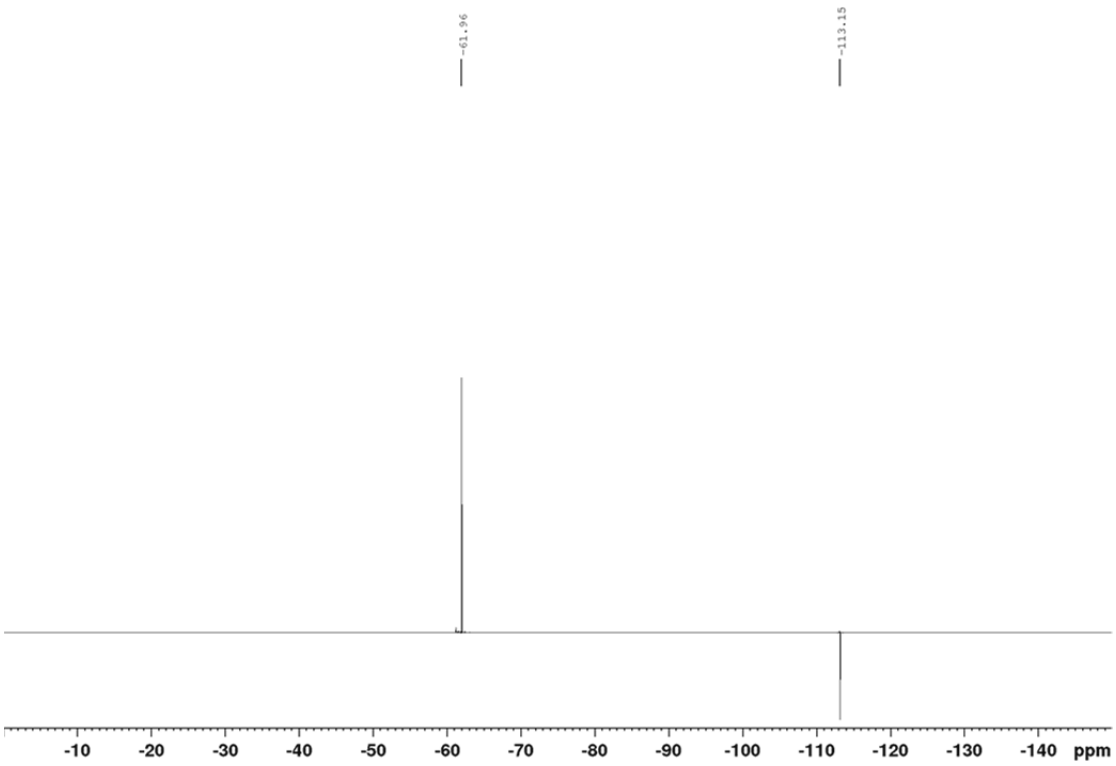


***N*,*N*-dibutyl-1,4-diphenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-amine (4ra)**

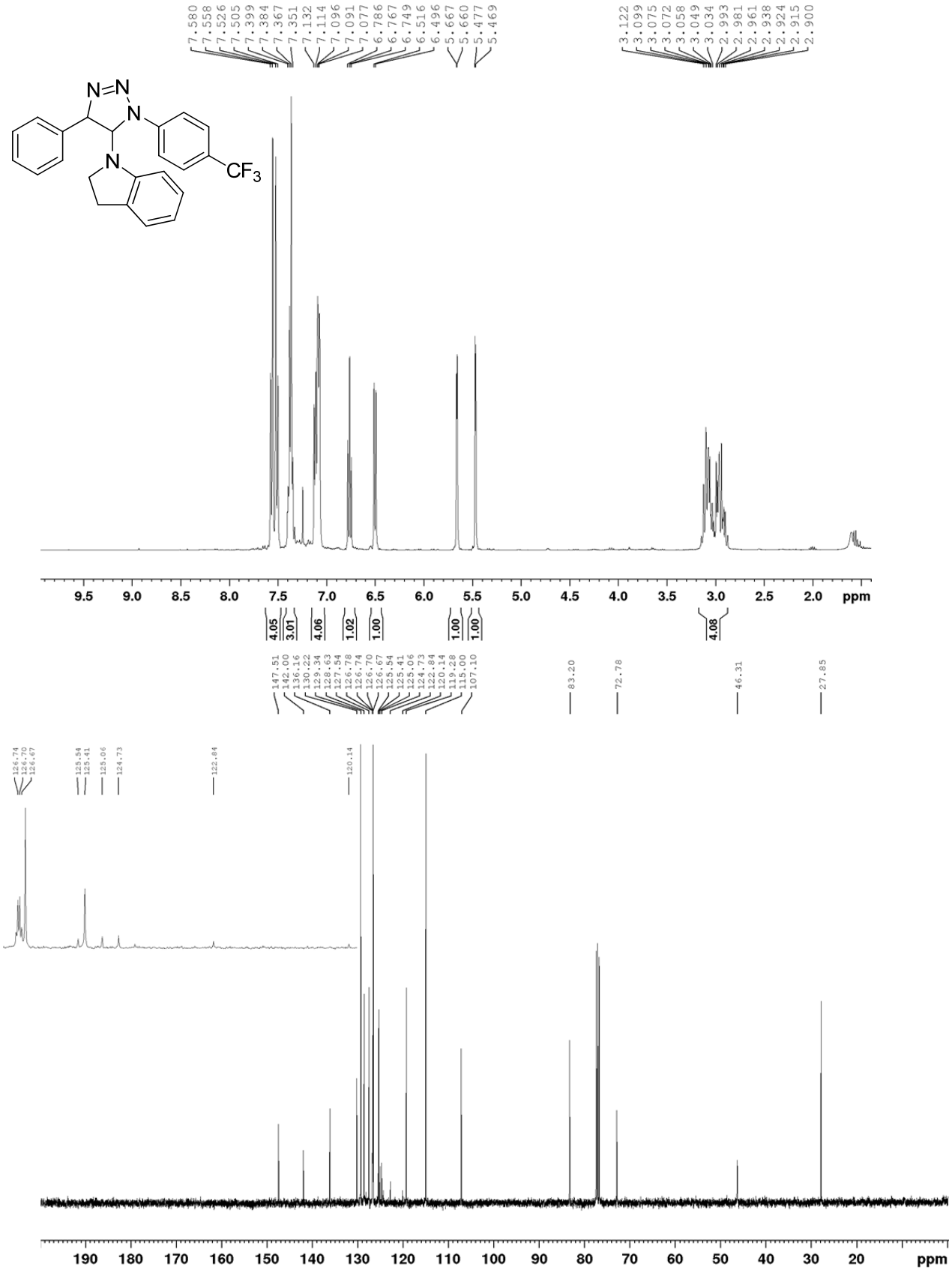


***N*-methyl-*N*,4-diphenyl-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,3-triazol-5-amine (4sb)**

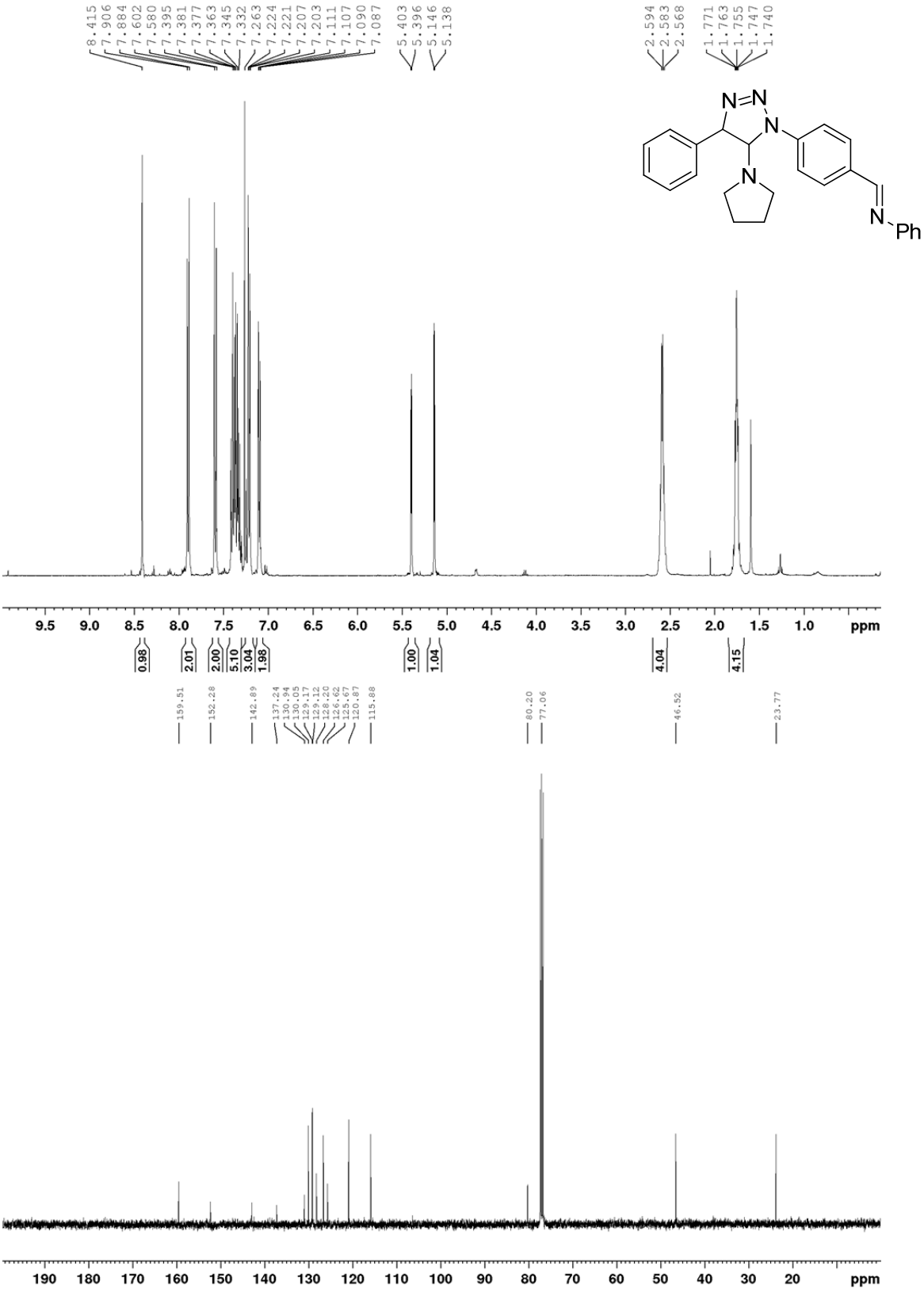



-61.96
-113.15
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
ppm

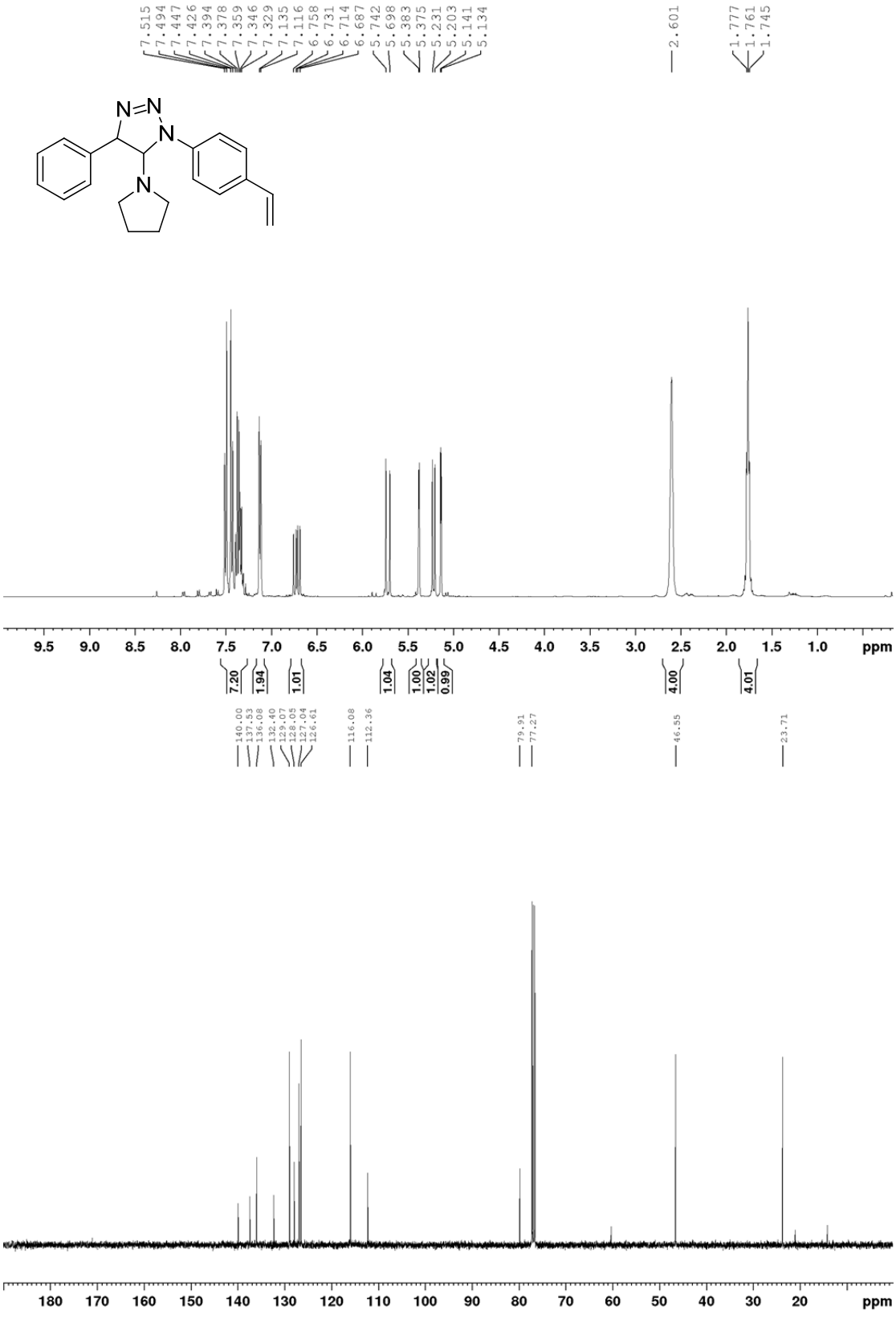
1-(4-phenyl-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)indoline (4tb)



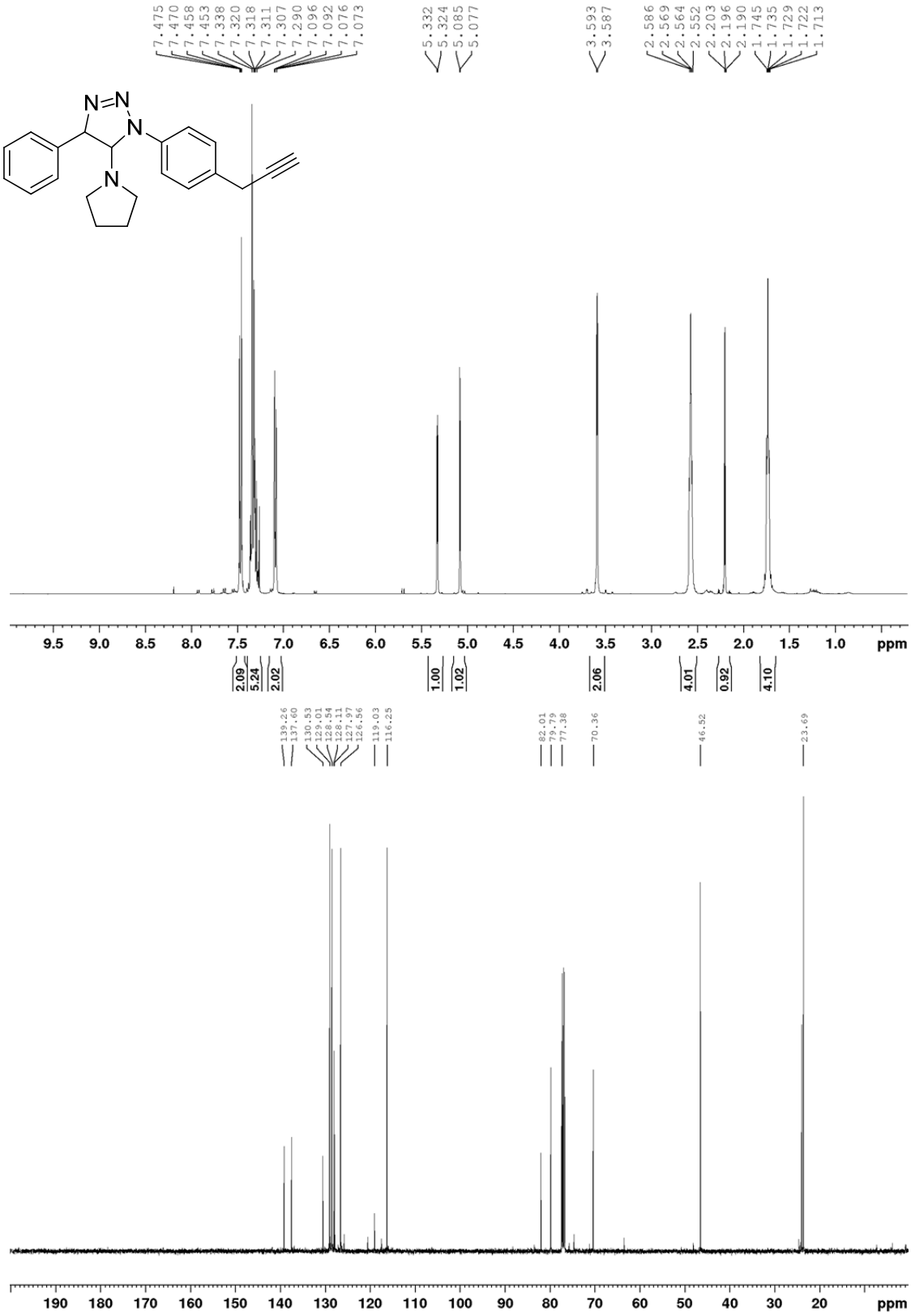
(*E*)-*N*-(4-(4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)benzylidene)aniline (4nc)



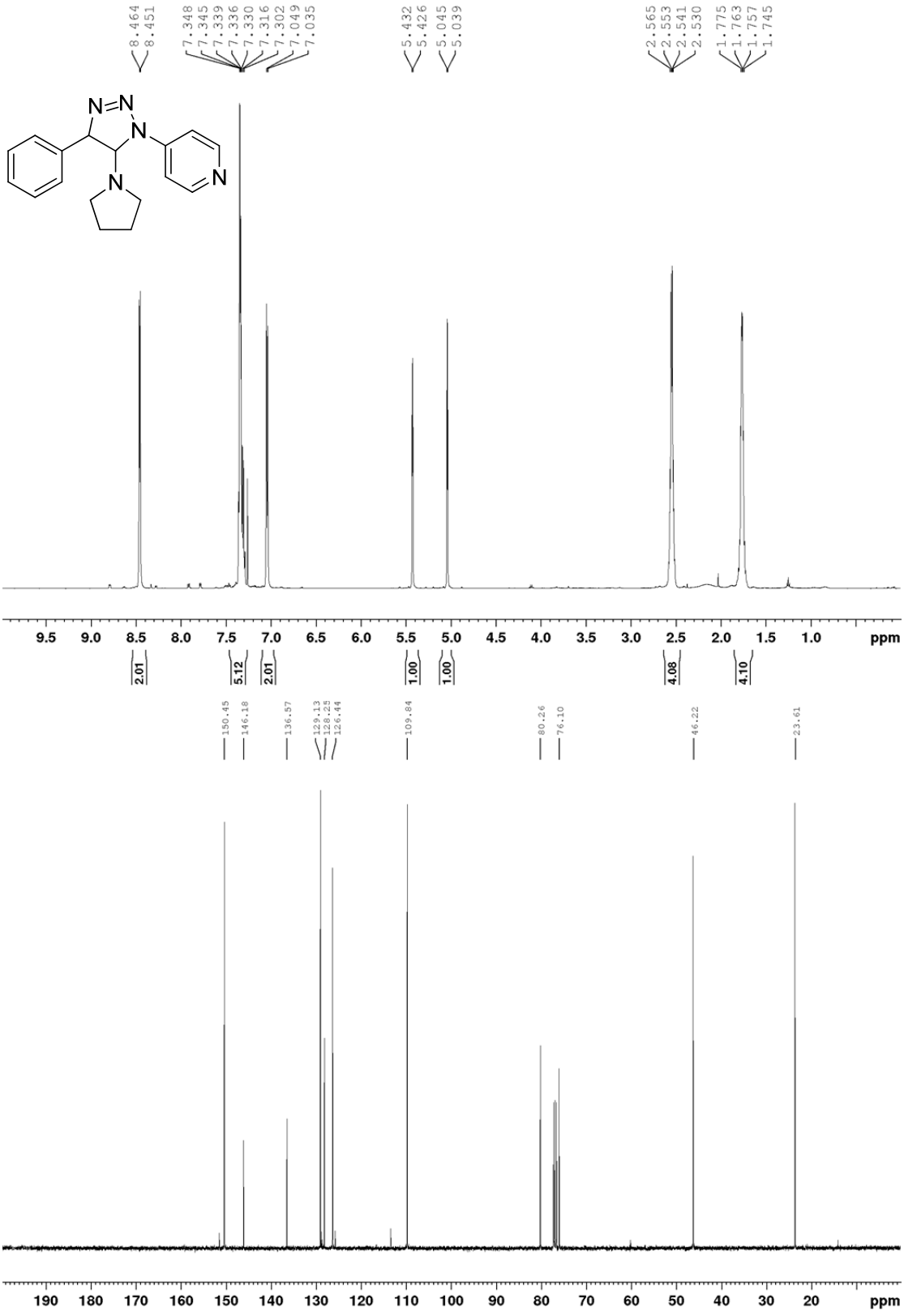
4-phenyl-5-(pyrrolidin-1-yl)-1-(4-vinylphenyl)-4,5-dihydro-1*H*-1,2,3-triazole (4nd)



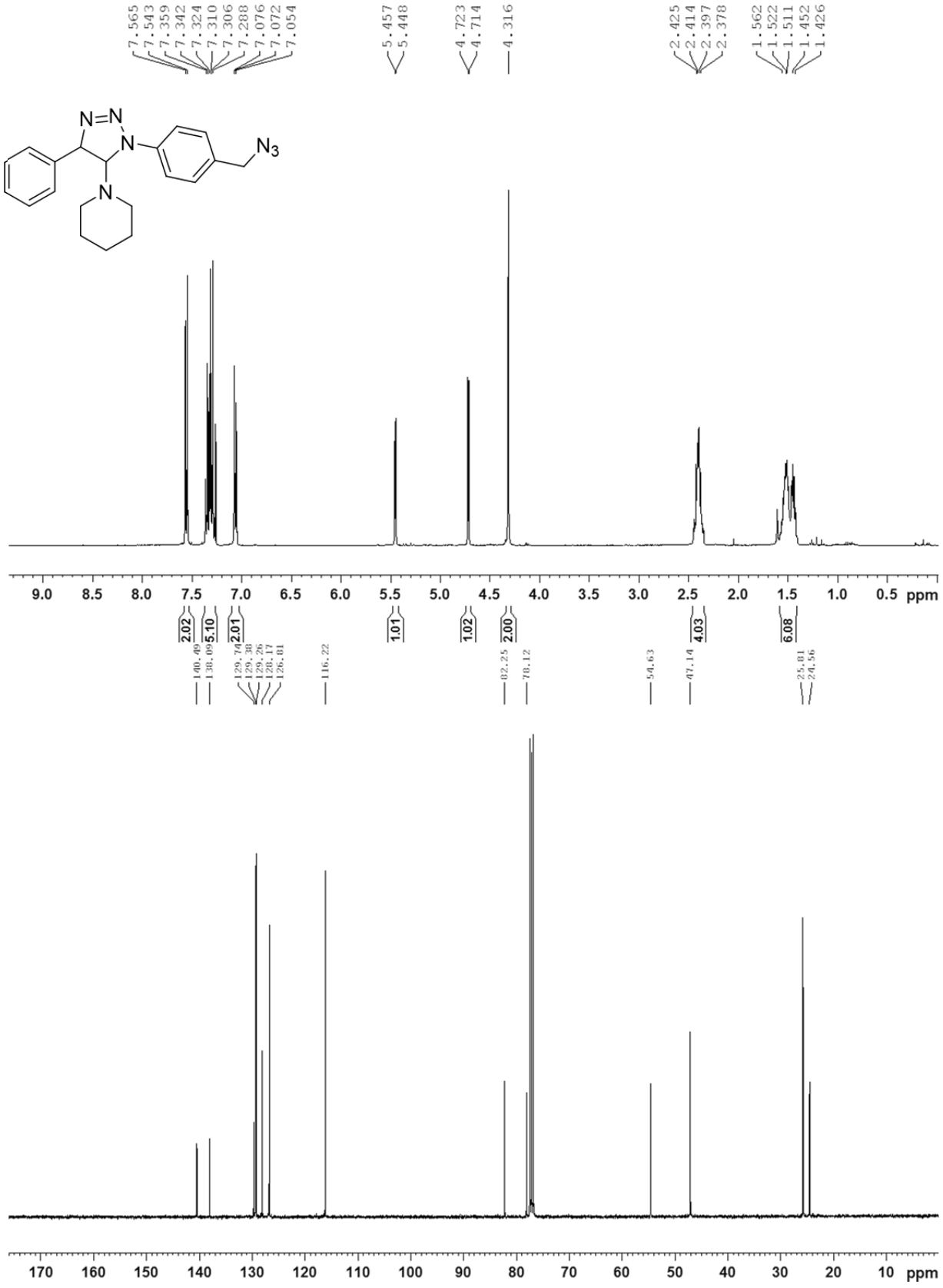
4-phenyl-1-(4-(prop-2-ynyl)phenyl)-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazole (4ne)



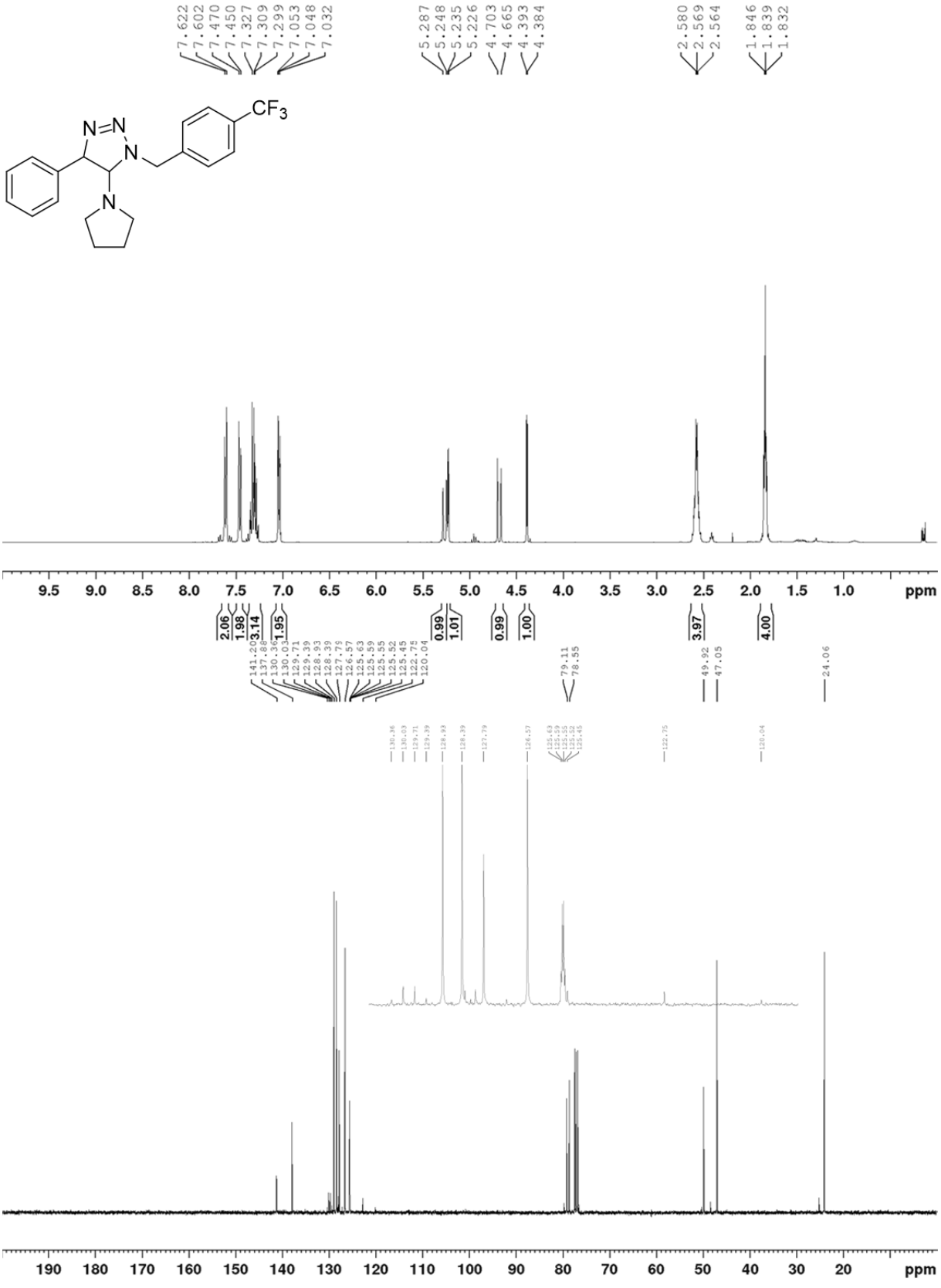
4-(4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)pyridine (4nf)

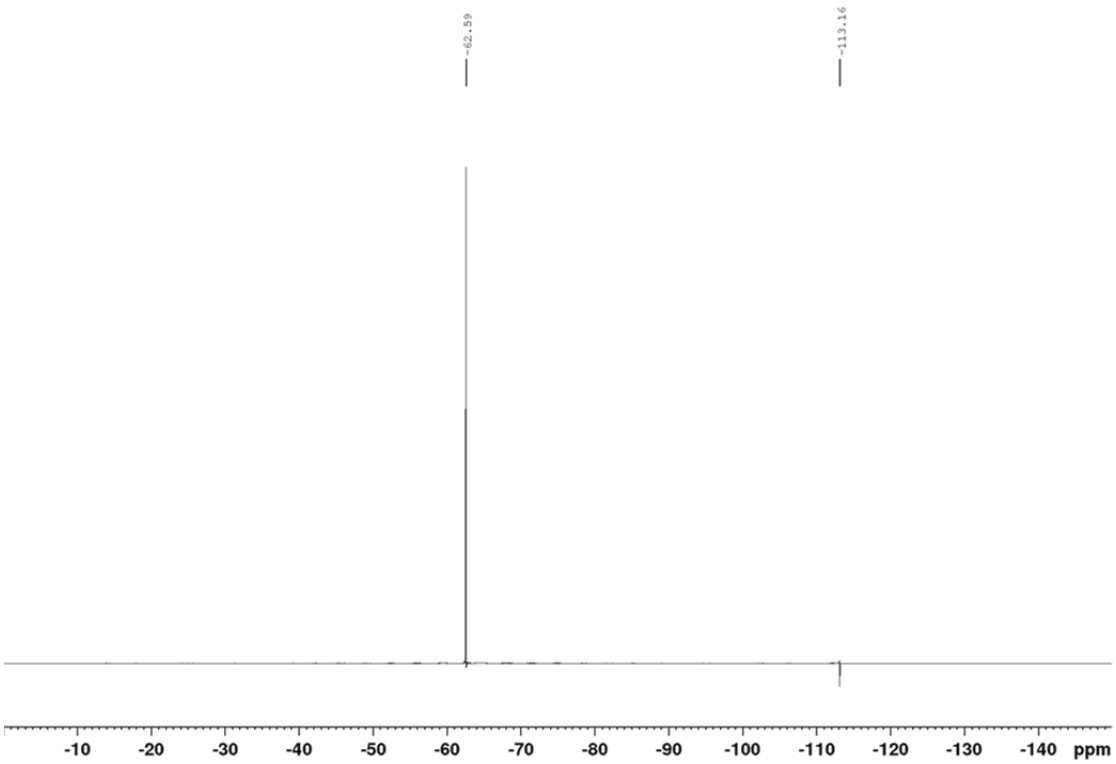


1-(1-(4-(azidomethyl)phenyl)-4-phenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)piperidine (4ag)



4-phenyl-5-(pyrrolidin-1-yl)-1-(4-(trifluoromethyl)benzyl)-4,5-dihydro-1*H*-1,2,3-triazole (4nh)

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-90
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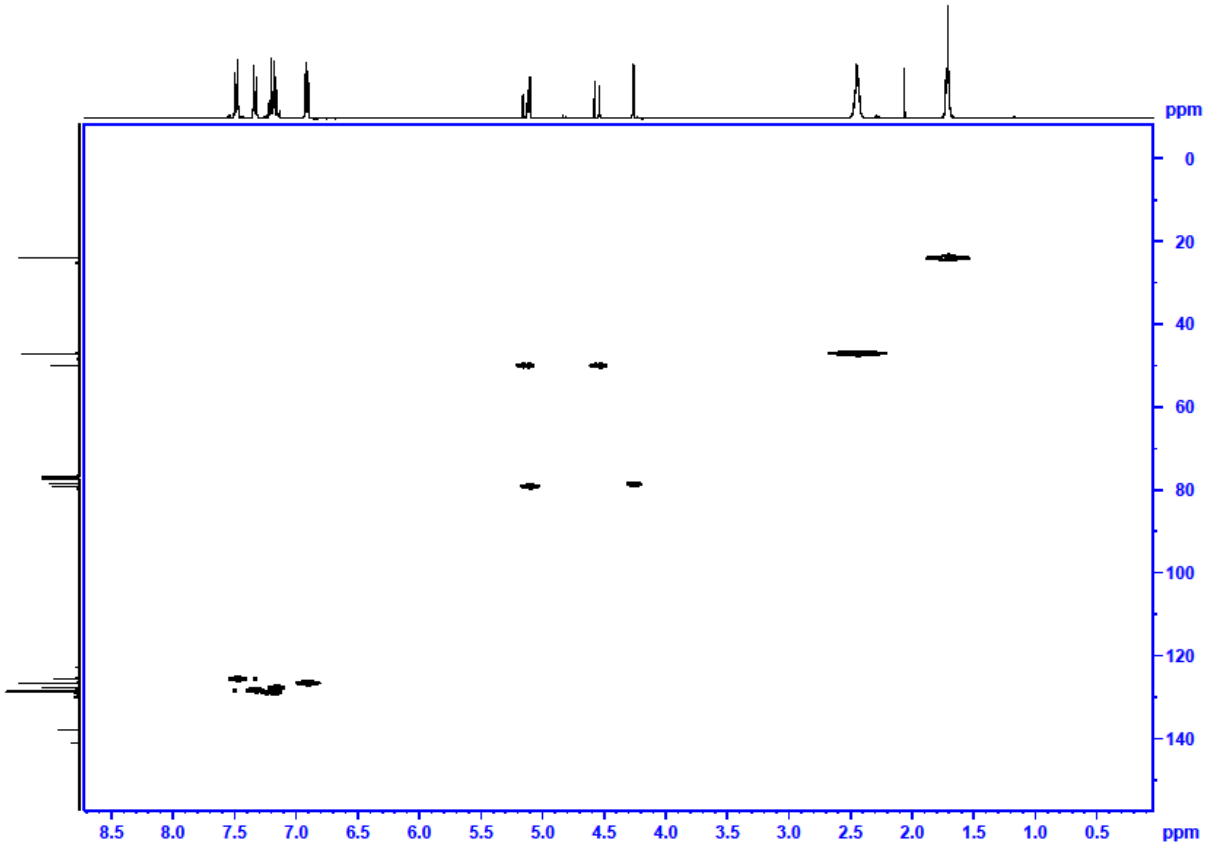
-110
-120
-130
-140
ppm

HSQC: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60
80
100
120
140
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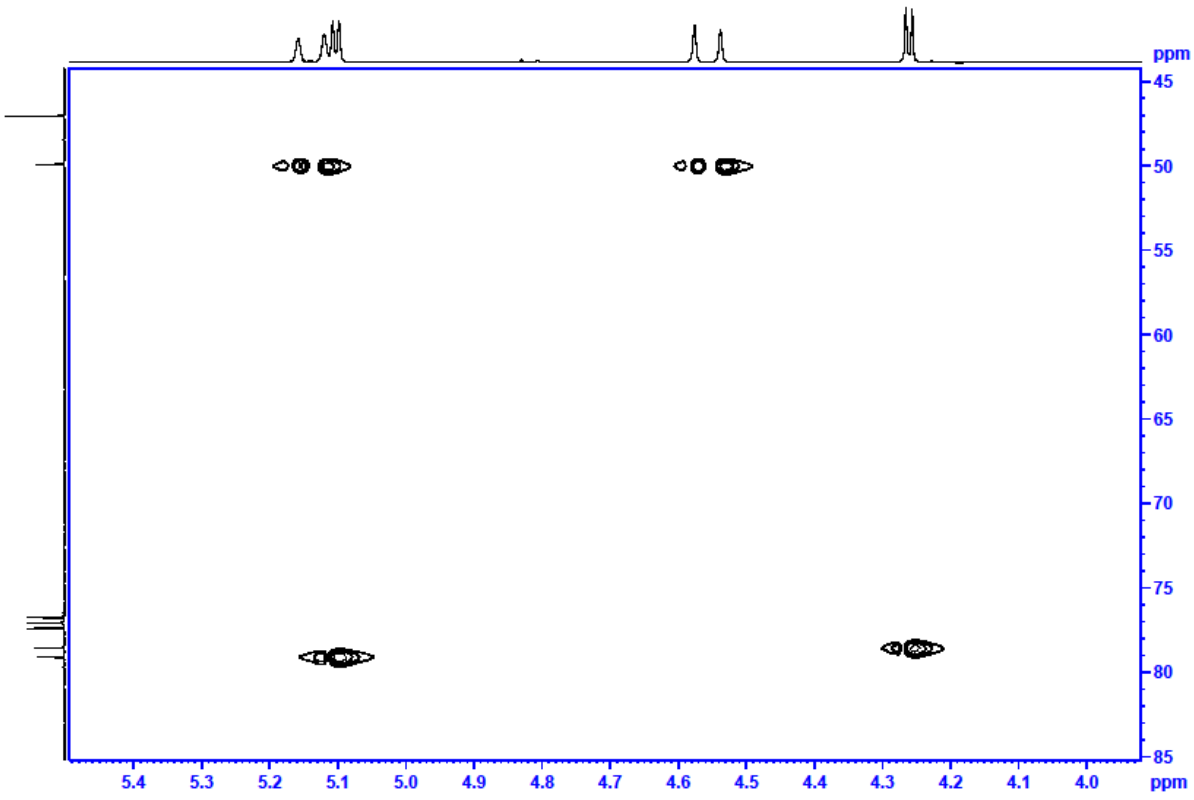
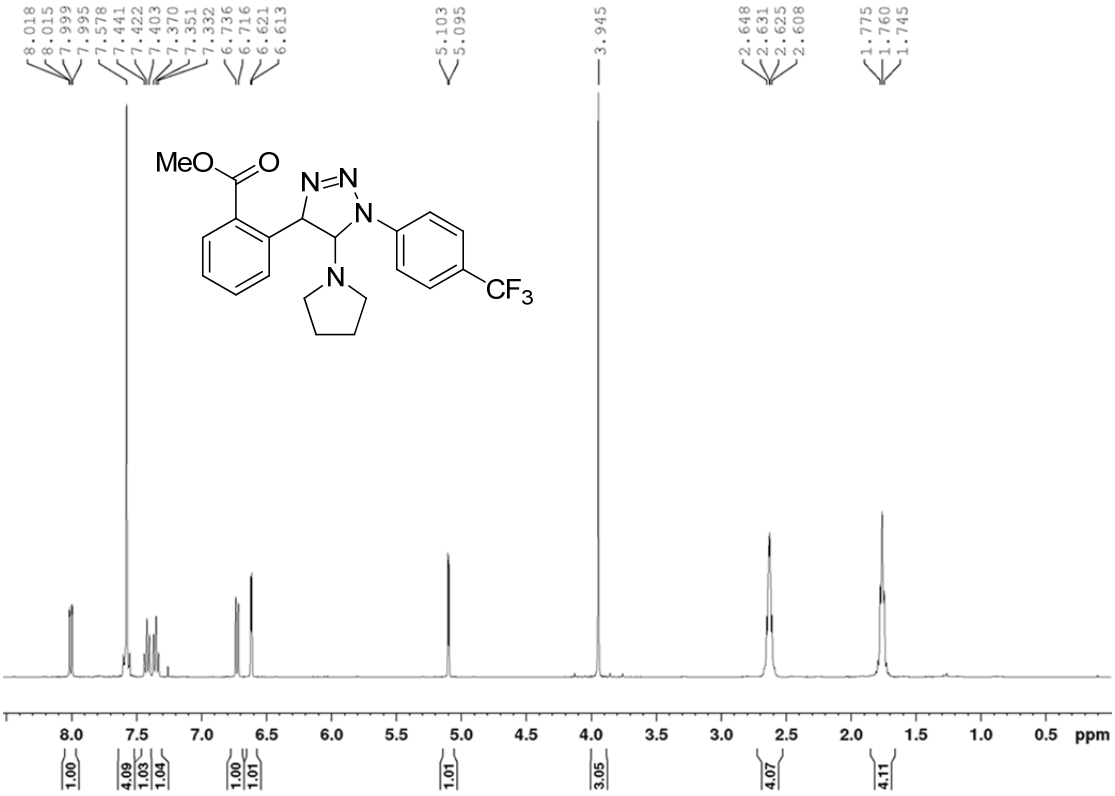
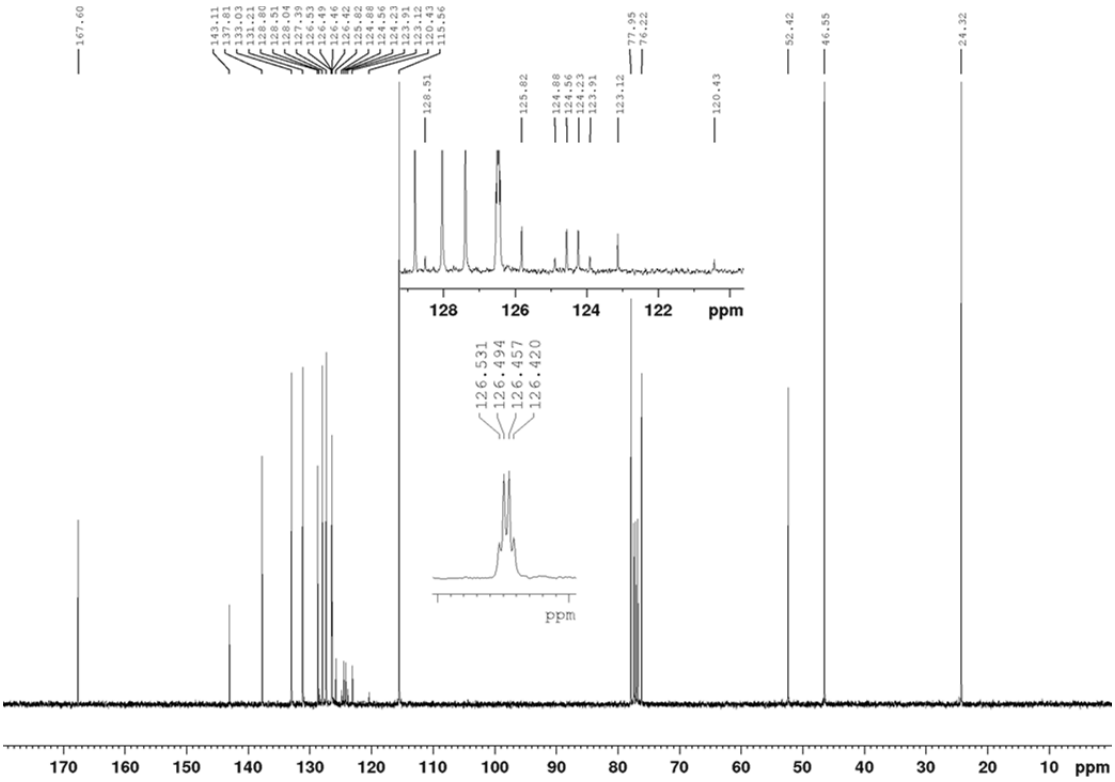
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

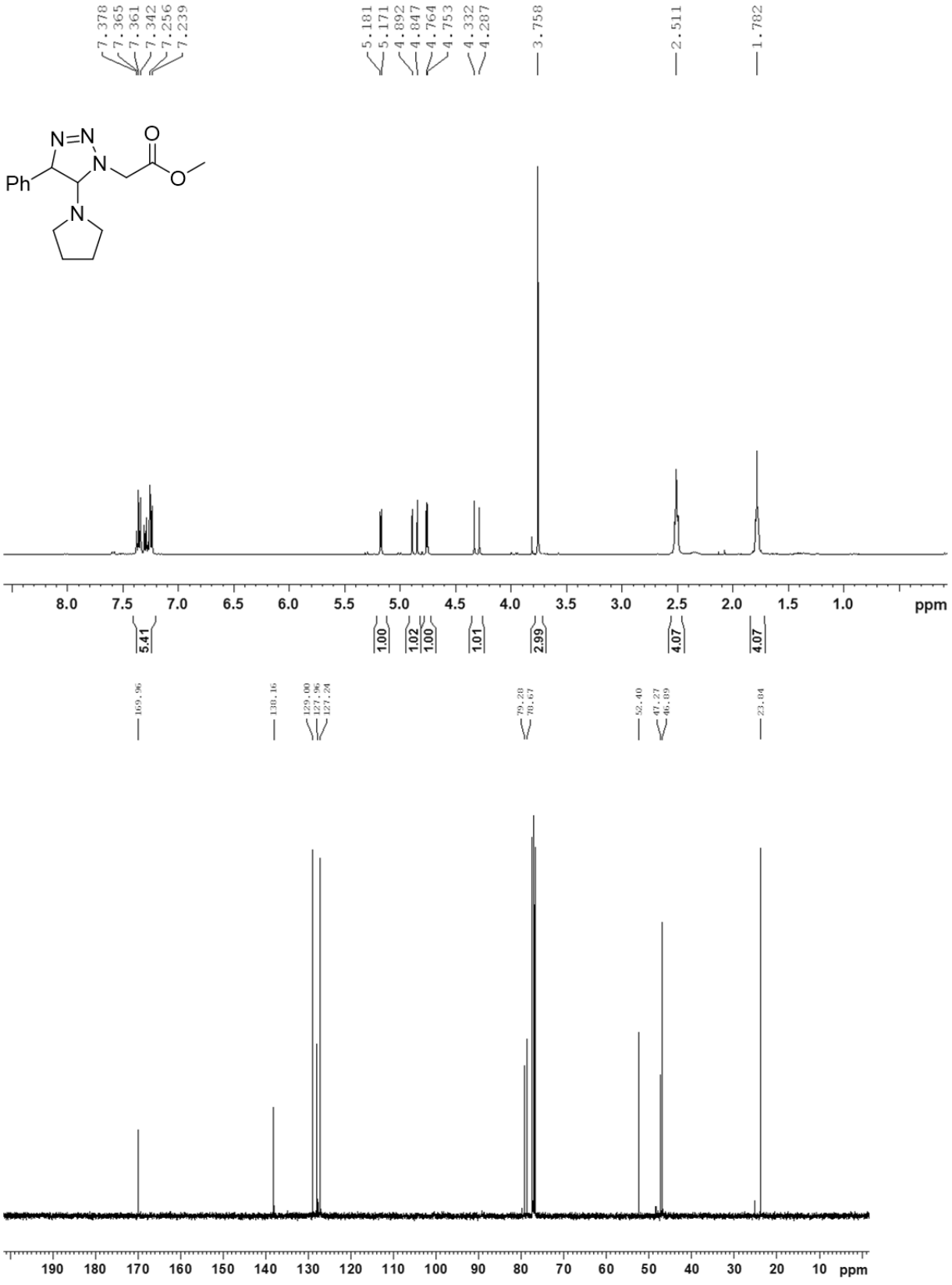

ppm
45
50
55
60
65
70
75
80
85
5.4
5.3
5.2
5.1
5.0
4.9
4.8
4.7
4.6
4.5
4.4
4.3
4.2
4.1
4.0
ppm

methyl 2-(5-(pyrrolidin-1-yl)-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,3-triazol-4-yl)benzoate (4gb)

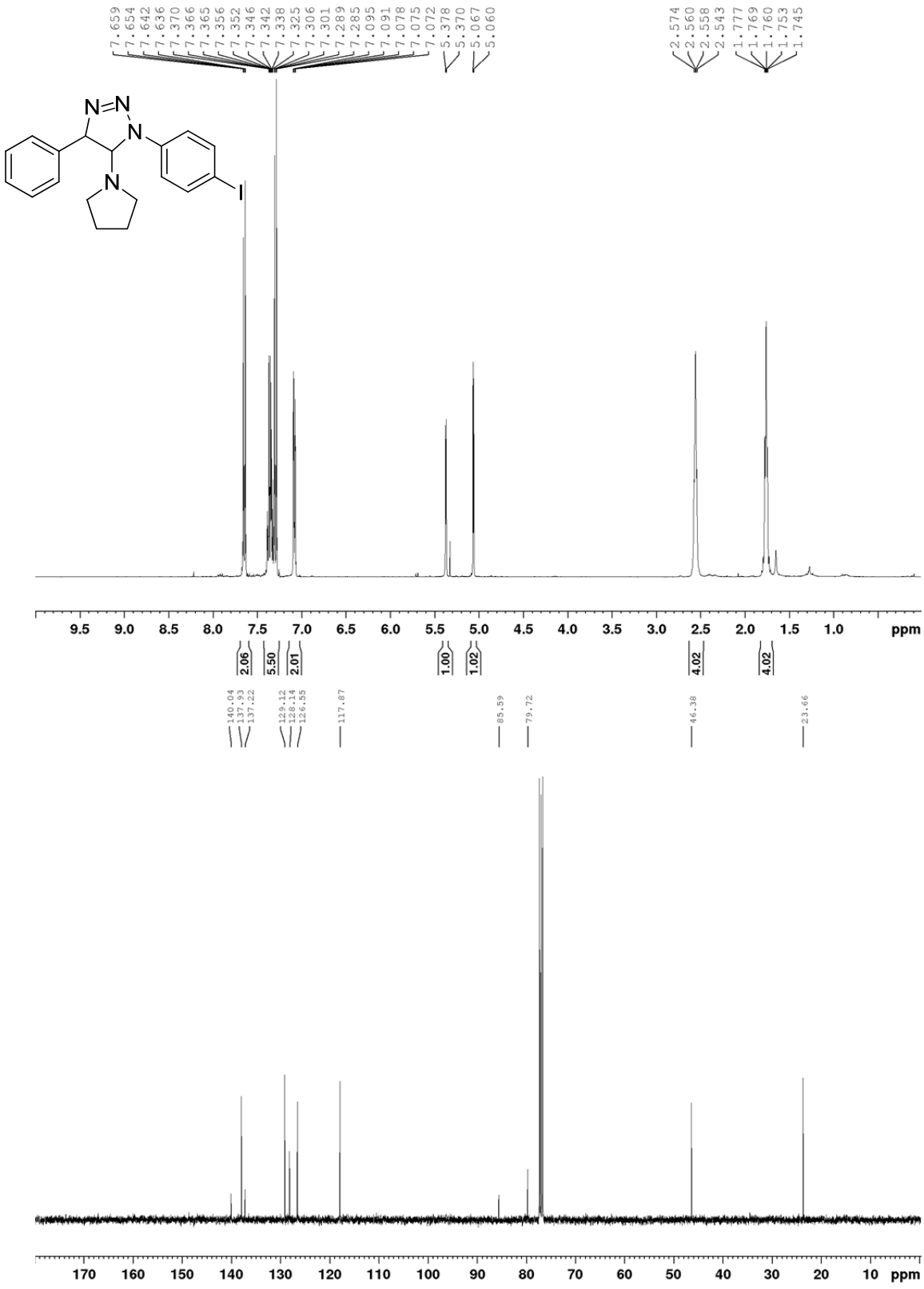




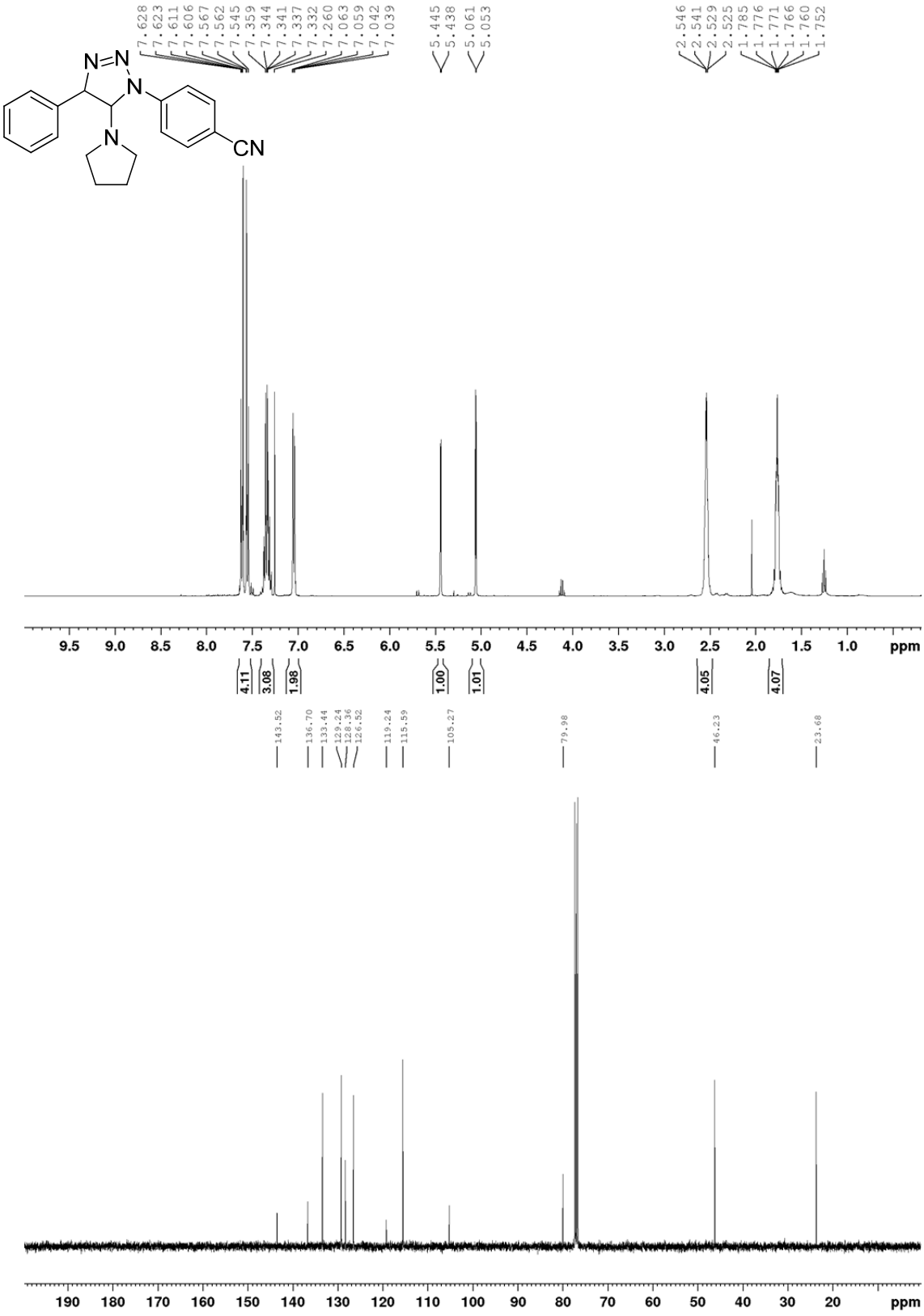
methyl 2-(4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1H-1,2,3-triazol-1-yl)acetate (4ni)



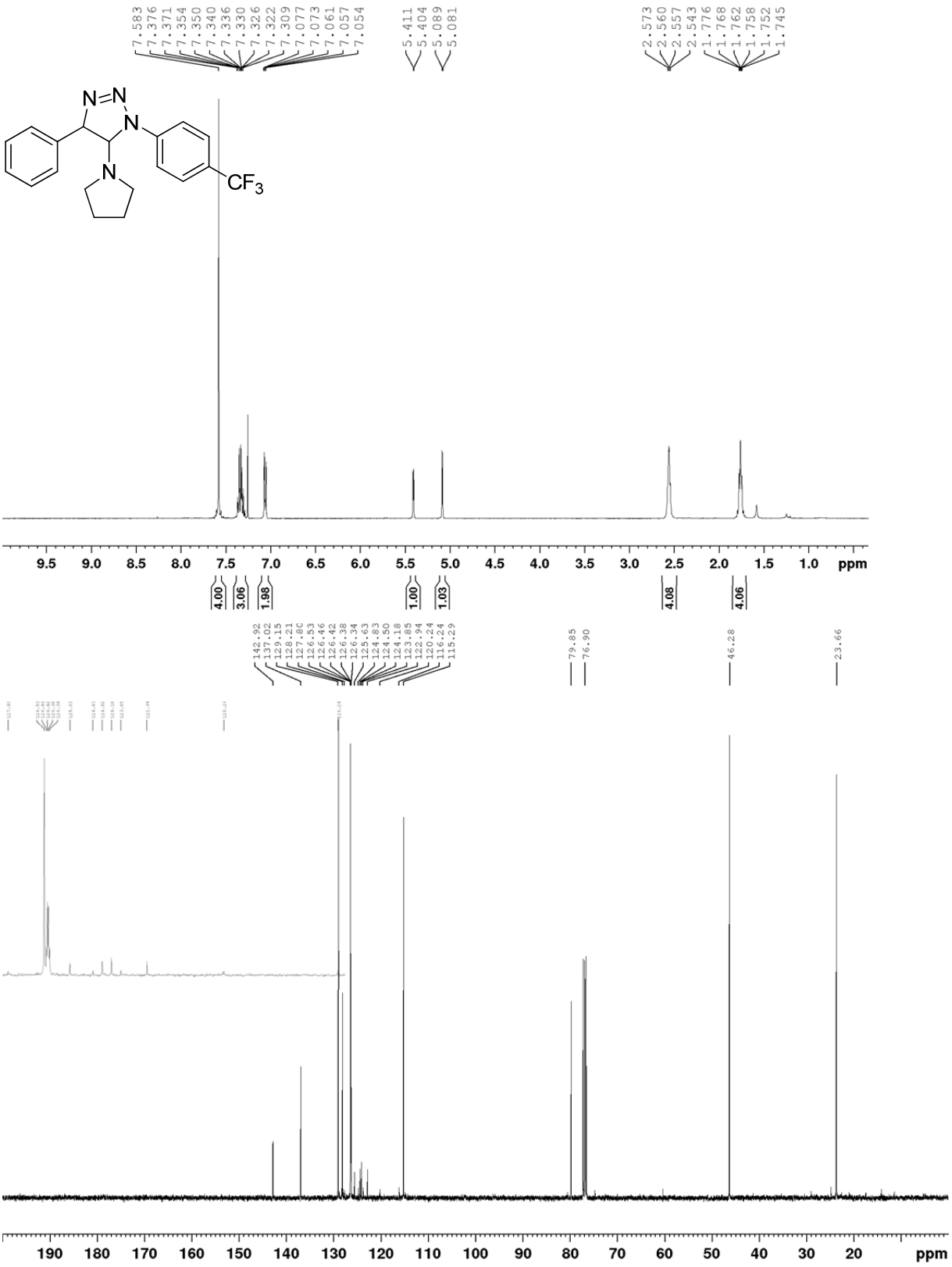
1-(4-iodophenyl)-4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazole (4nj)



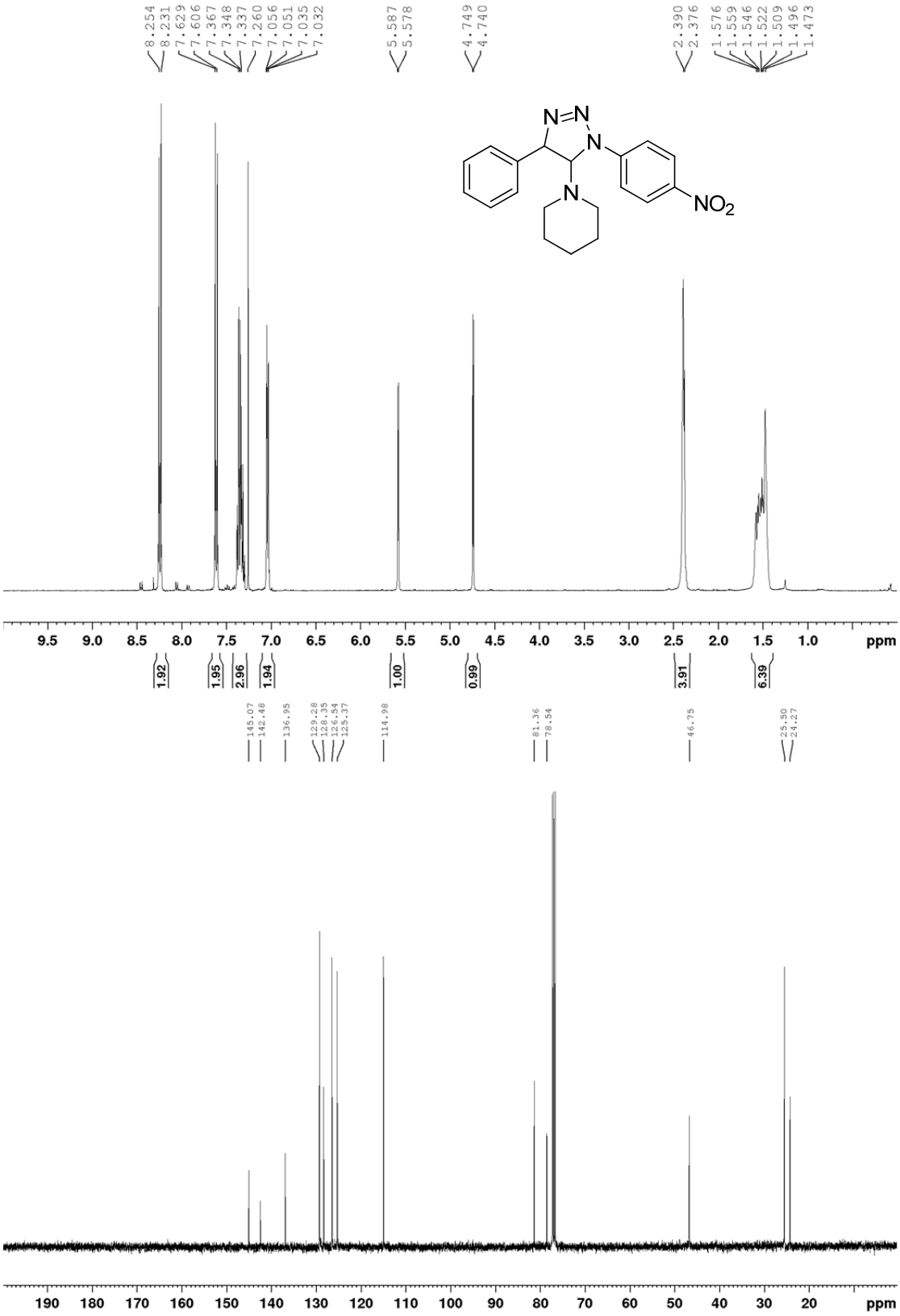
4-(4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)benzonitrile (4nk)



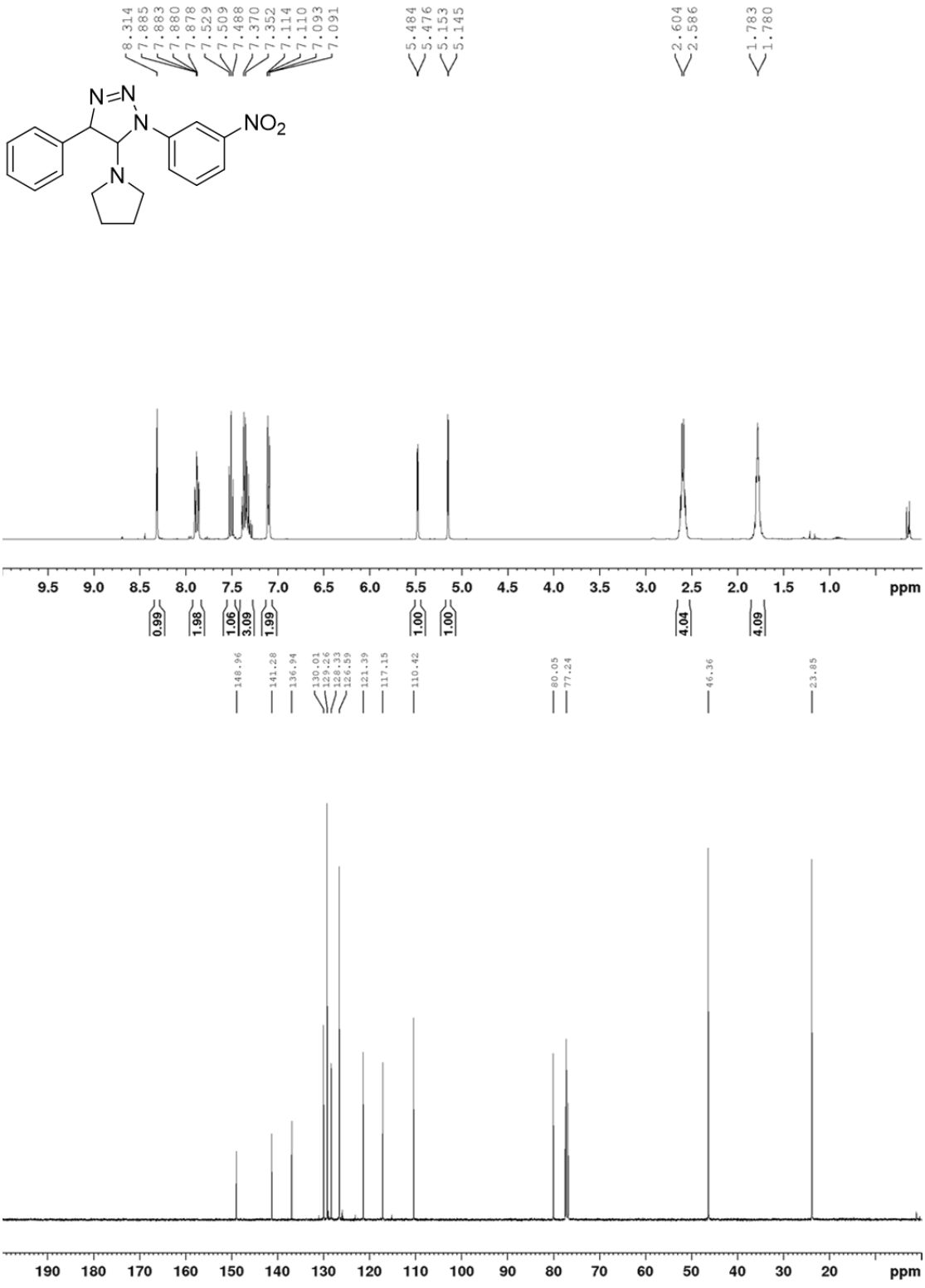
4-phenyl-5-(pyrrolidin-1-yl)-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-1,2,3-triazole (4nb)



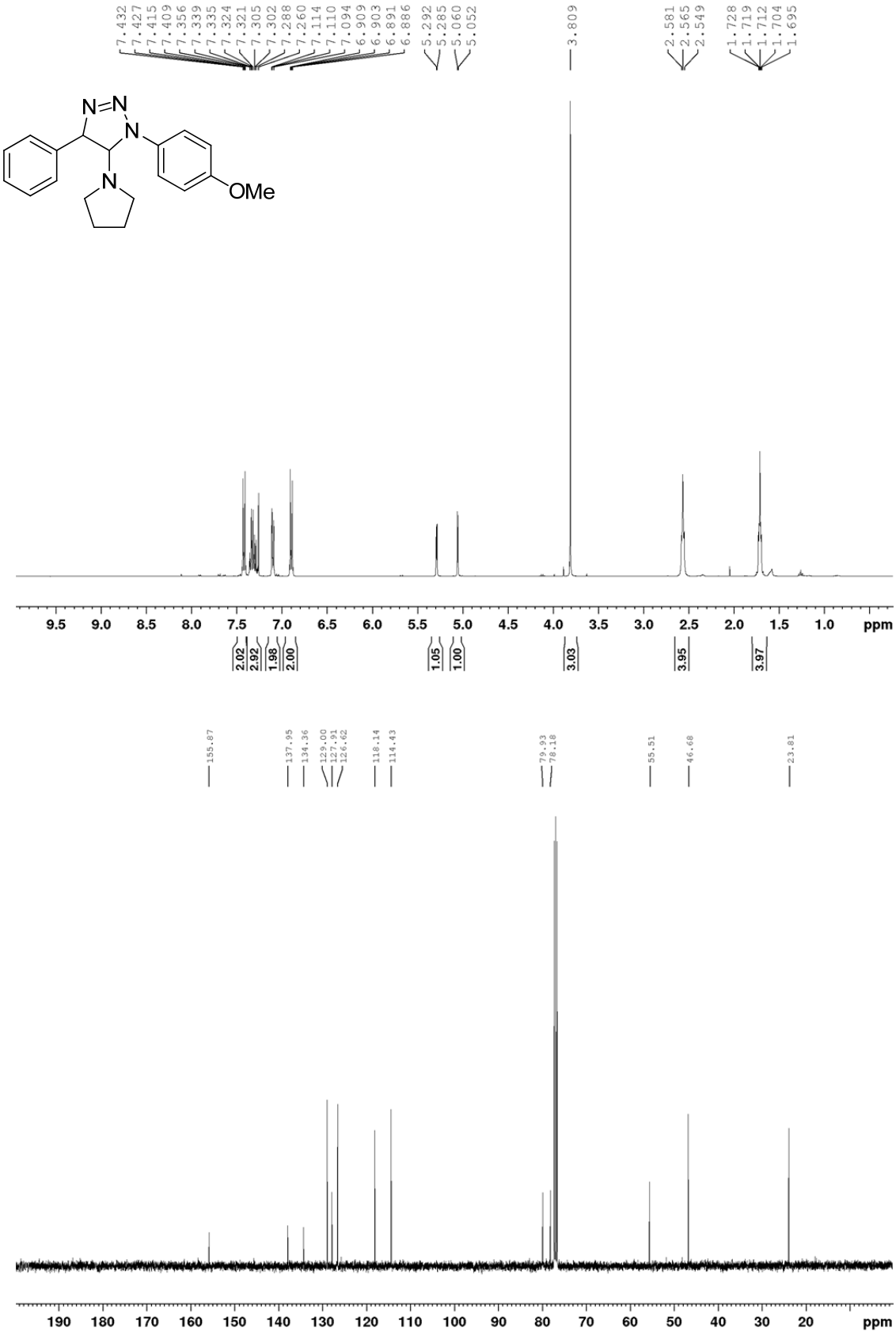
1-(1-(4-nitrophenyl)-4-phenyl-4,5-dihydro-1*H*-1,2,3-triazol-5-yl)piperidine (4al)



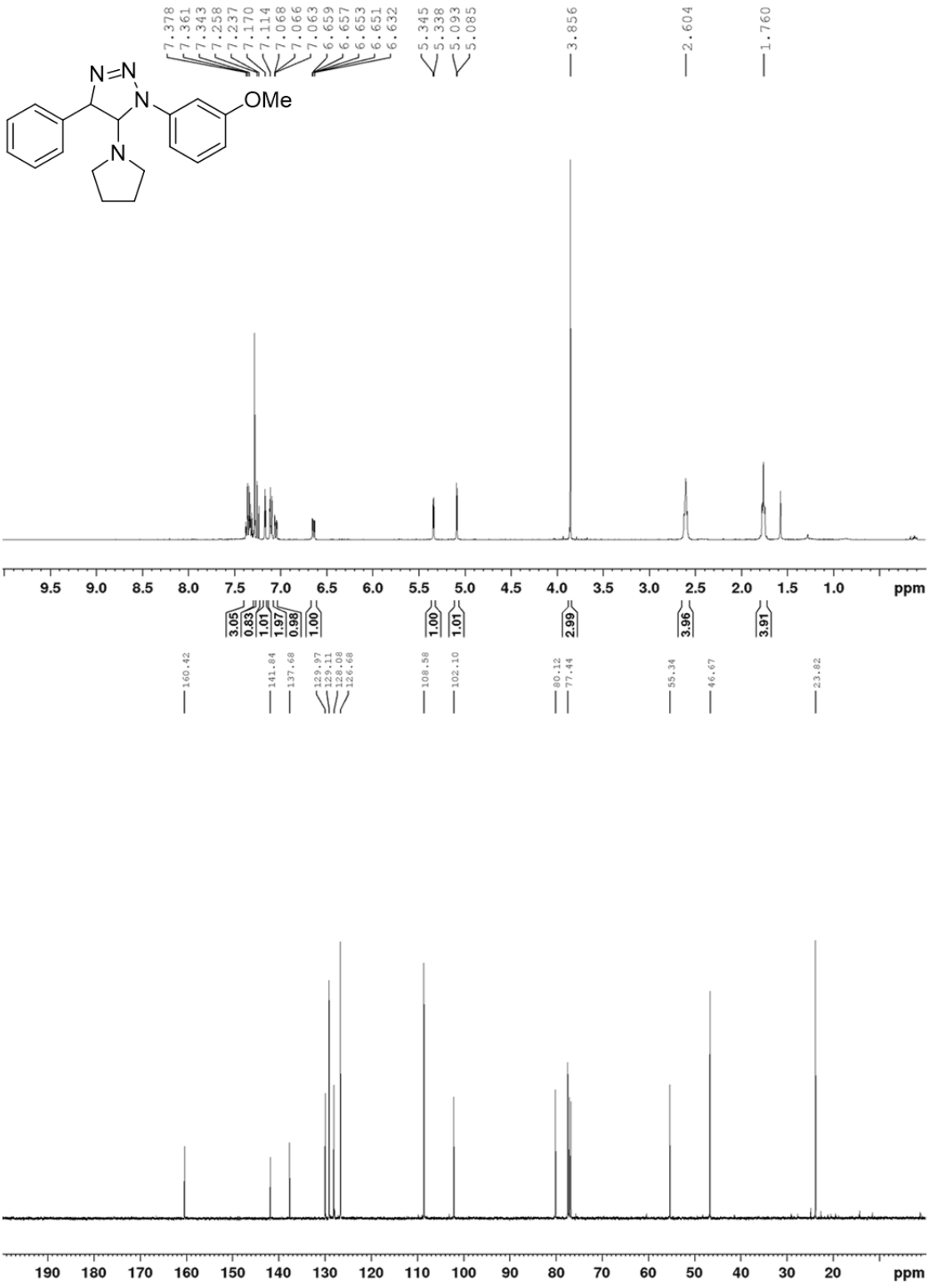
1-(3-nitrophenyl)-4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazole (4nm)



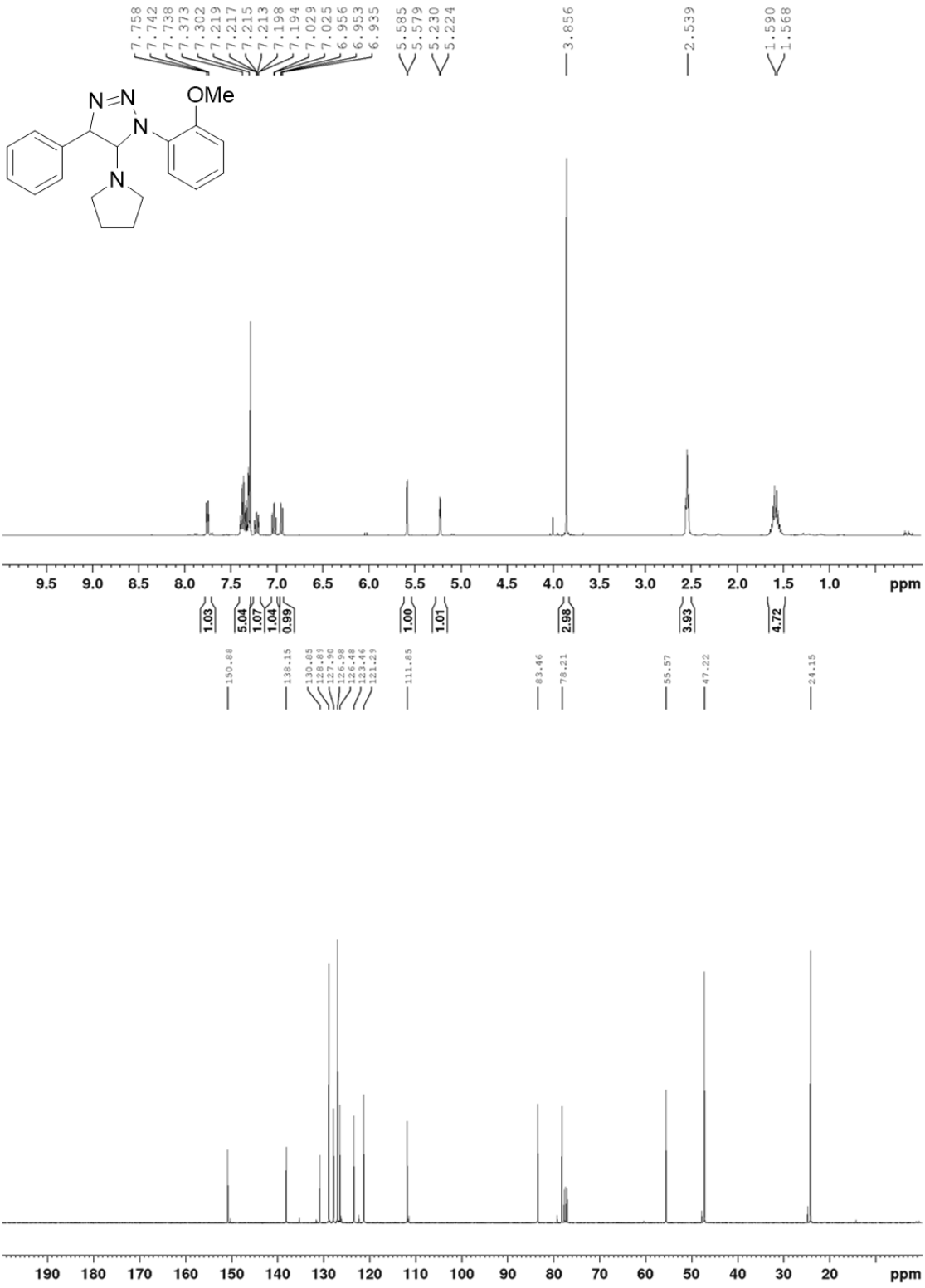
1-(4-methoxyphenyl)-4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazole (4nn)



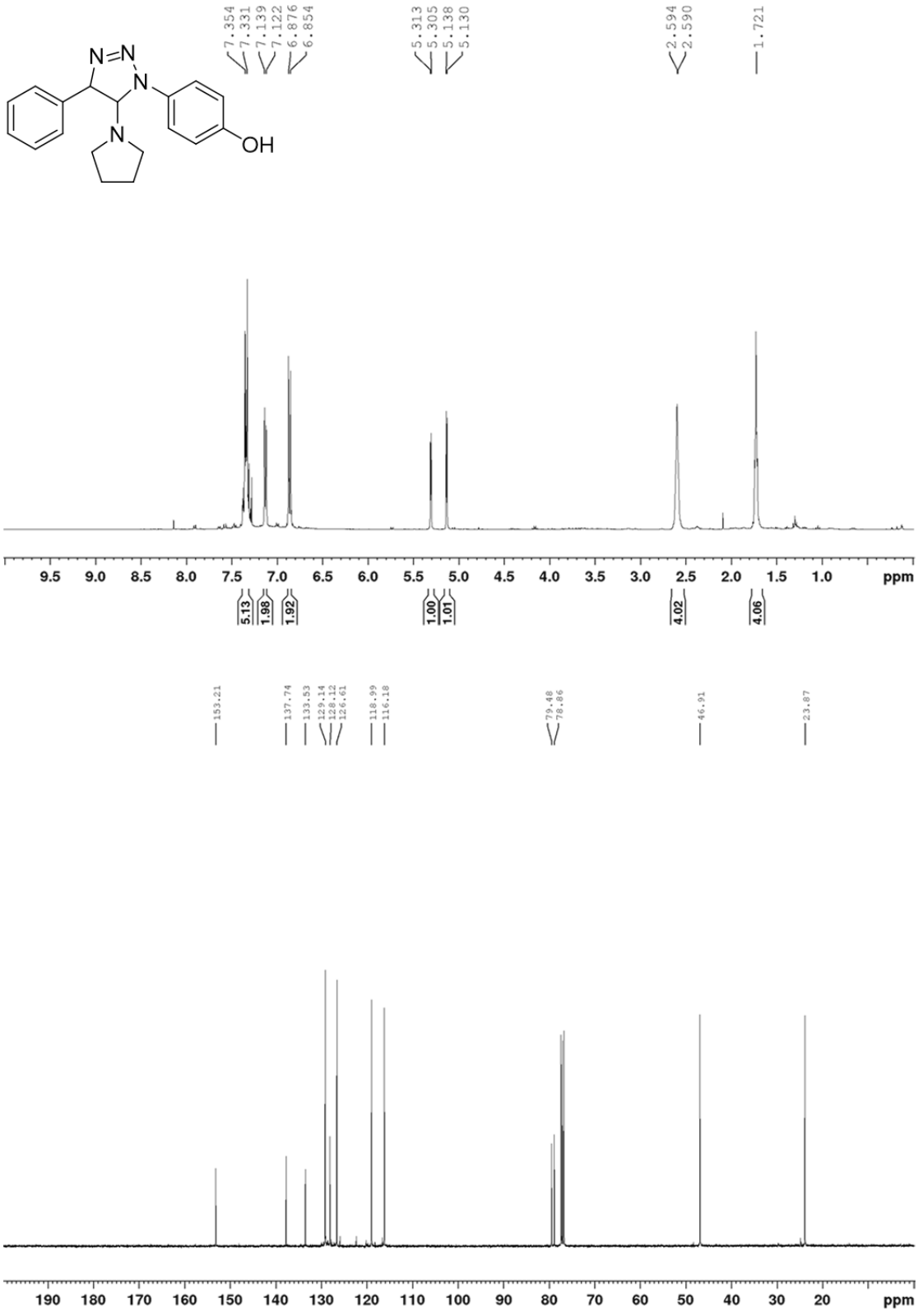
1-(3-methoxyphenyl)-4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazole (4no)



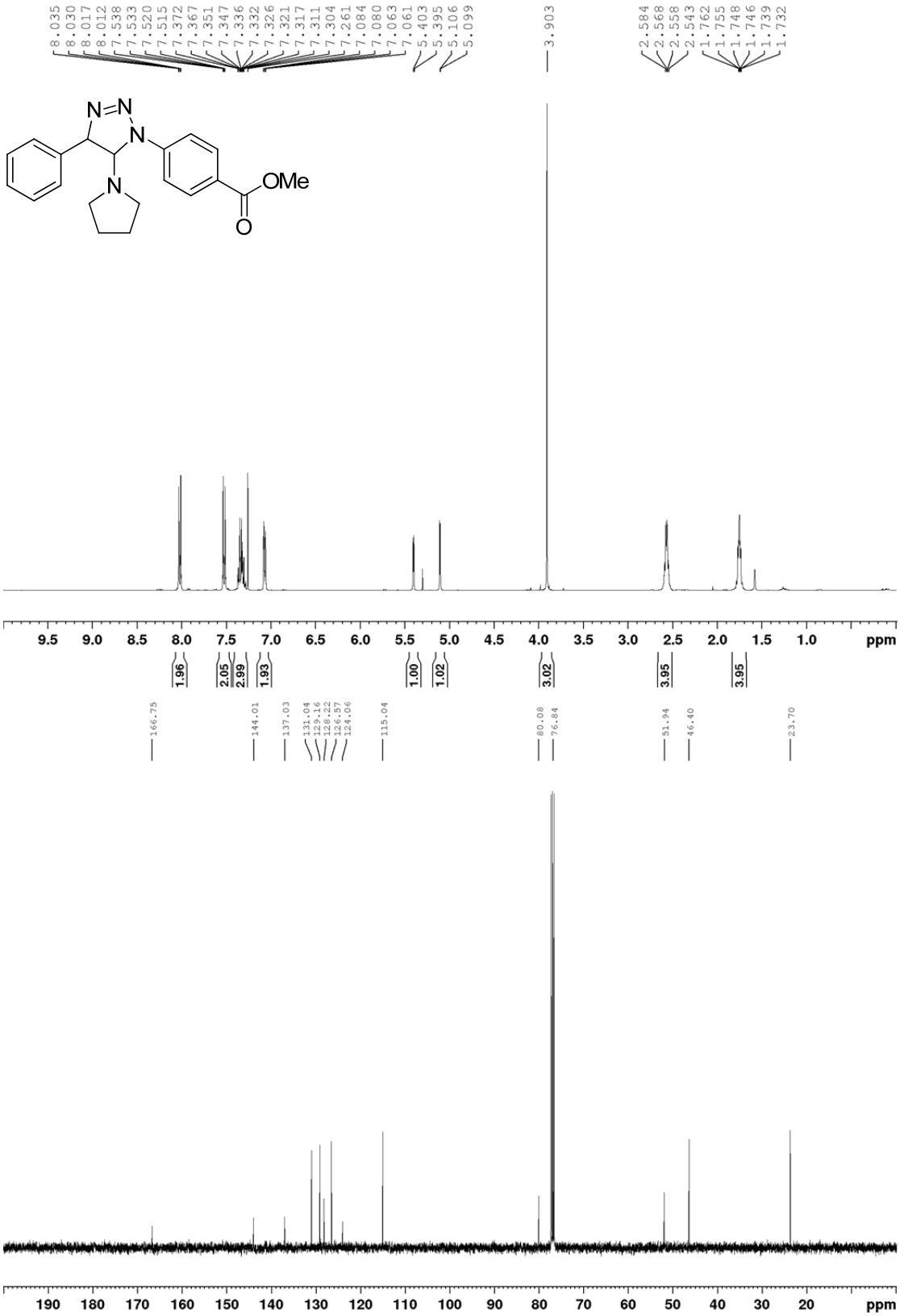
1-(2-methoxyphenyl)-4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazole (4np)



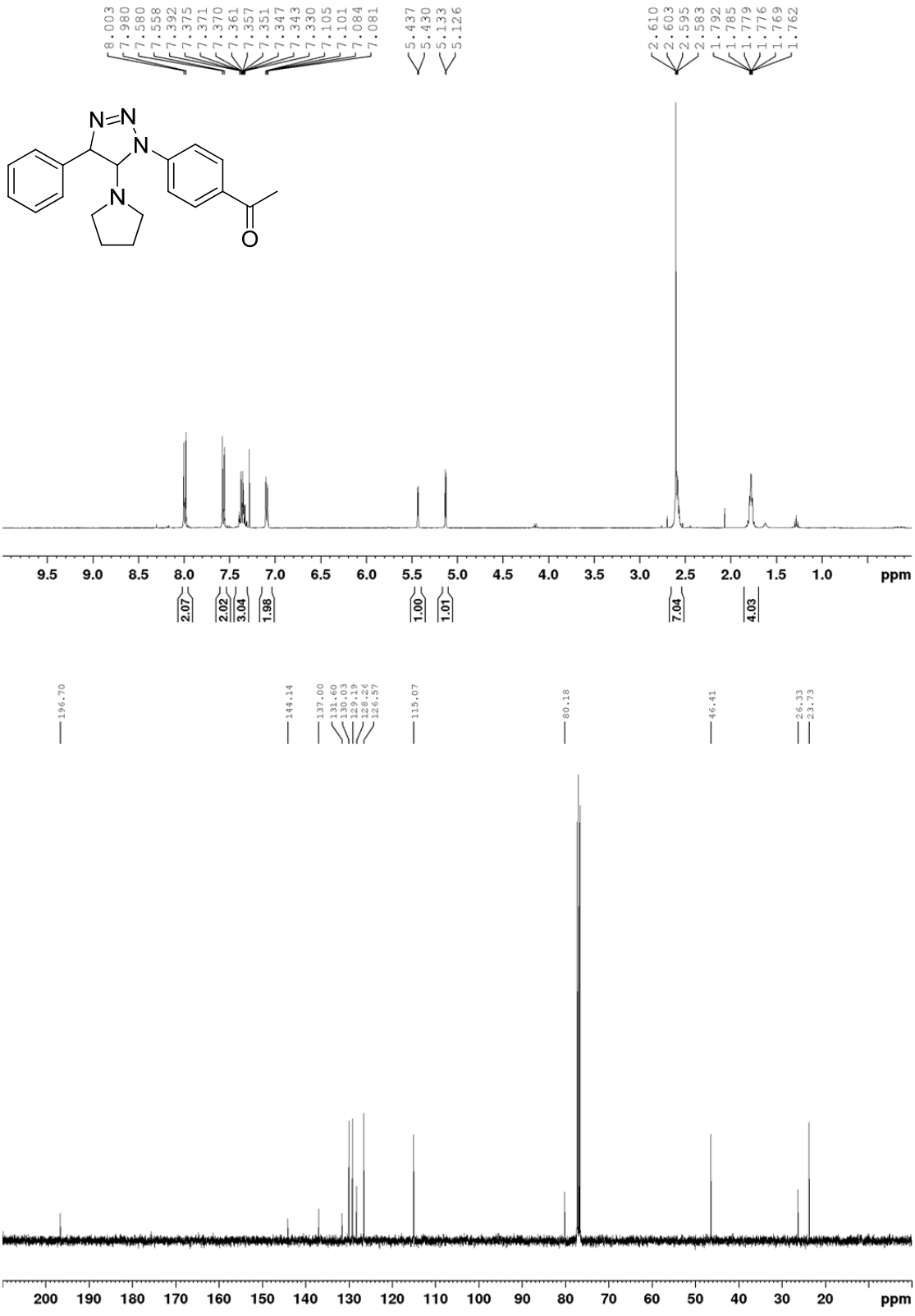
4-(4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)phenol (4nq)



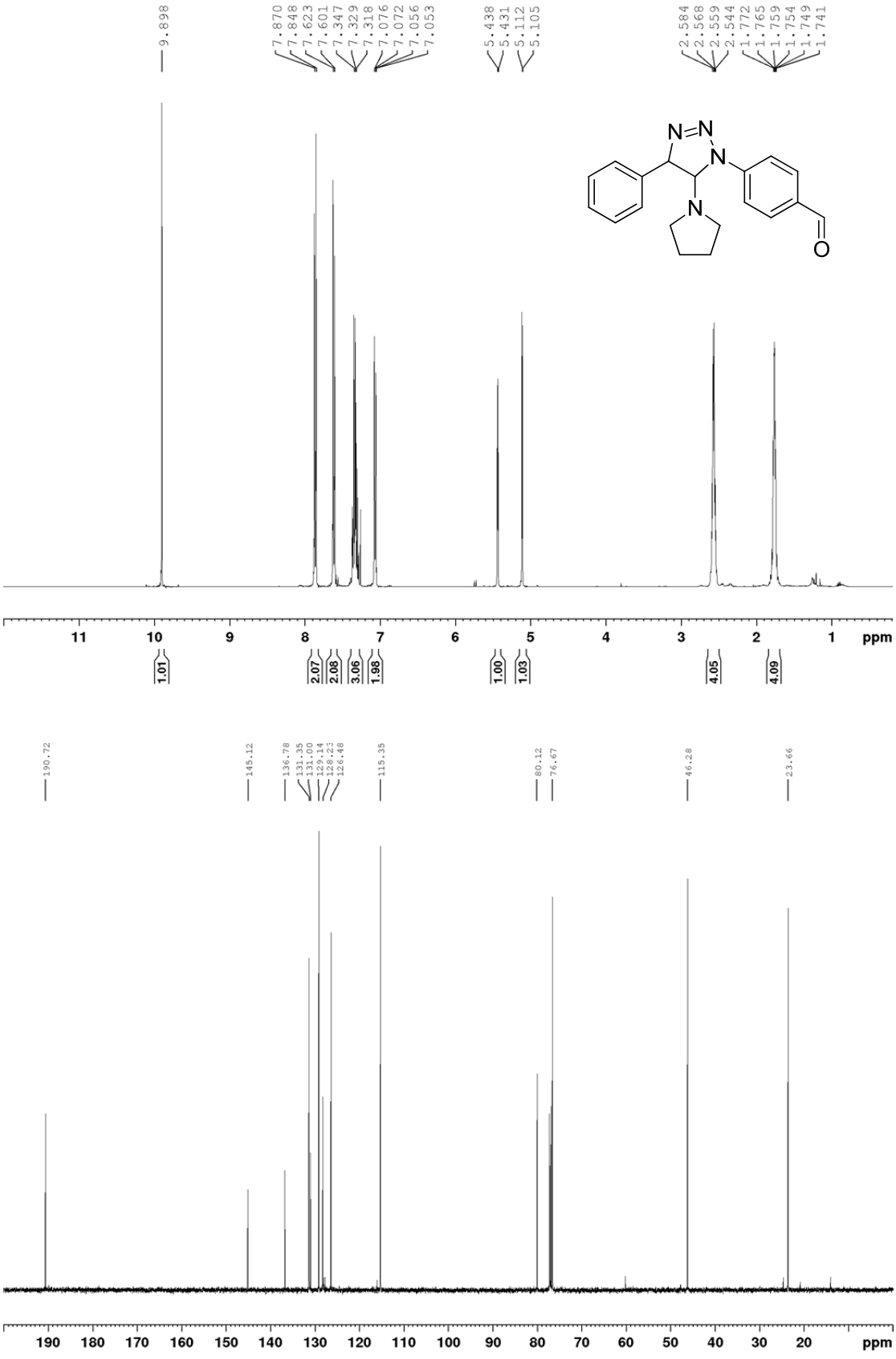
methyl 4-(4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)benzoate (4nr)



1-(4-(4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)phenyl)ethanone (4ns)

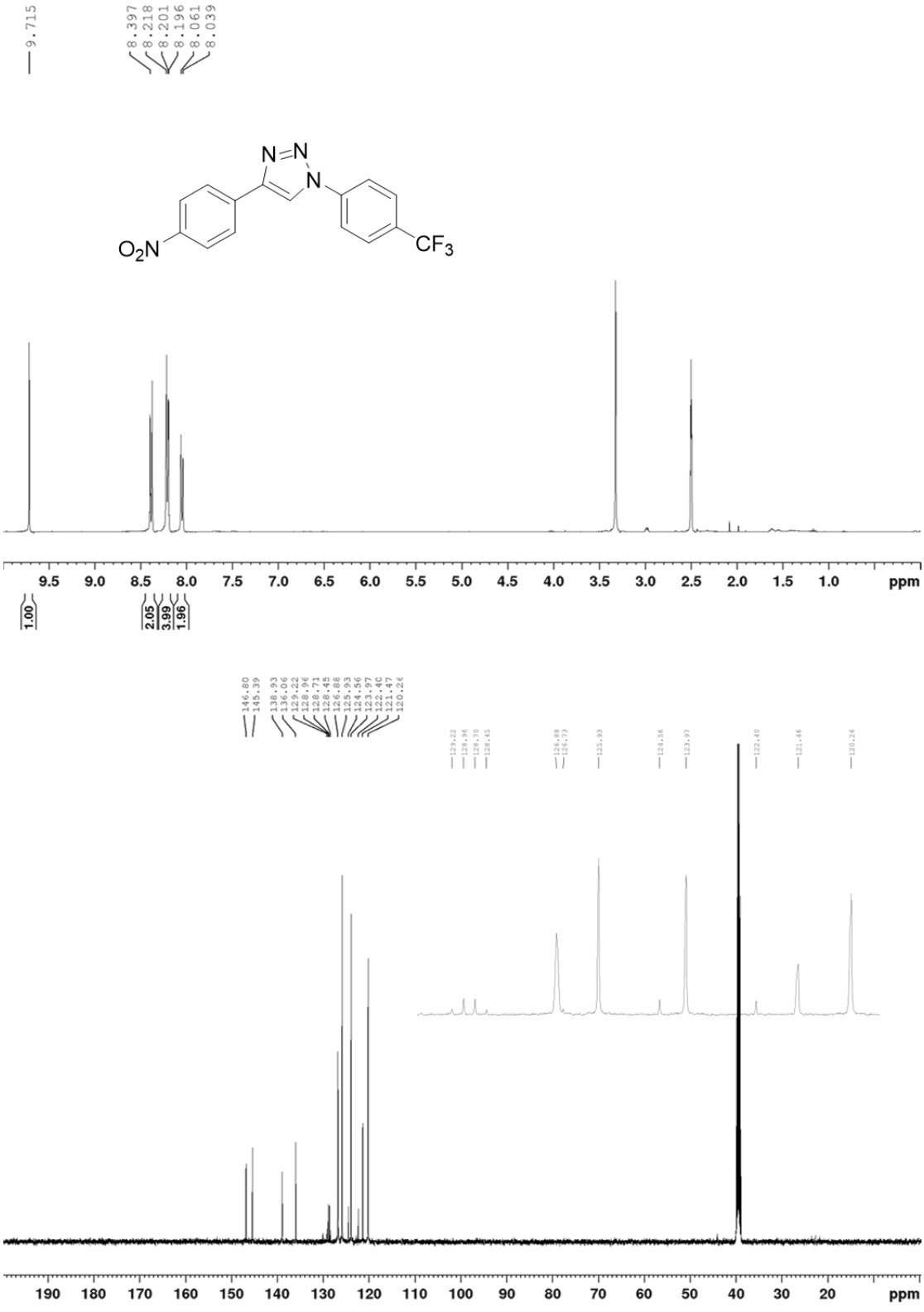


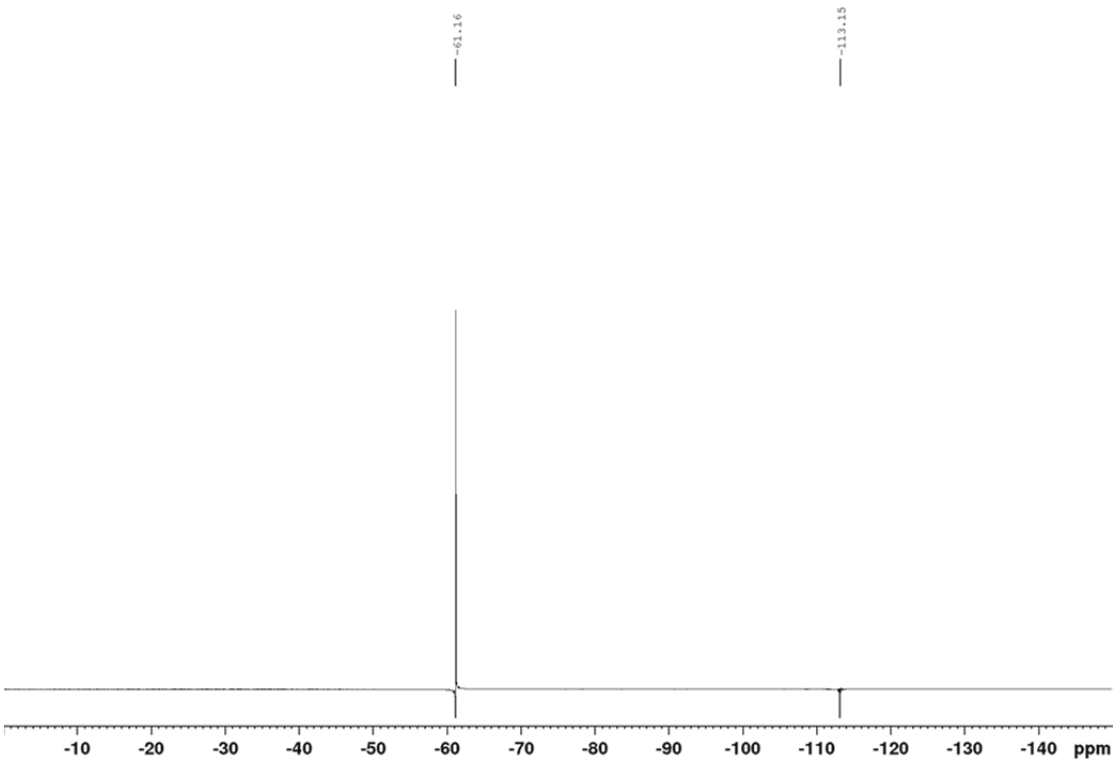
4-(4-phenyl-5-(pyrrolidin-1-yl)-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)benzaldehyde (4nt)



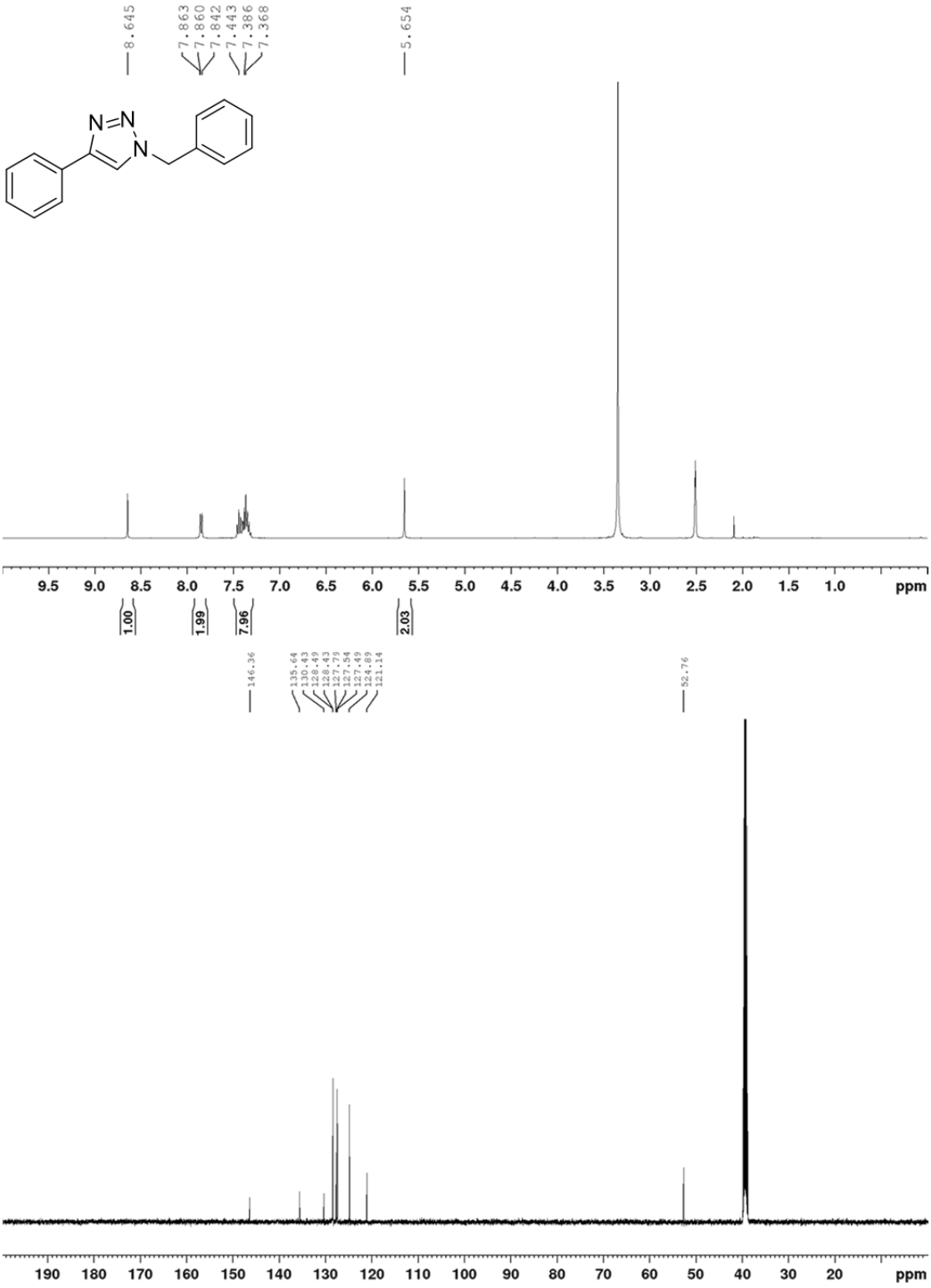
Triazoles

4-(4-nitrophenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (5ub)

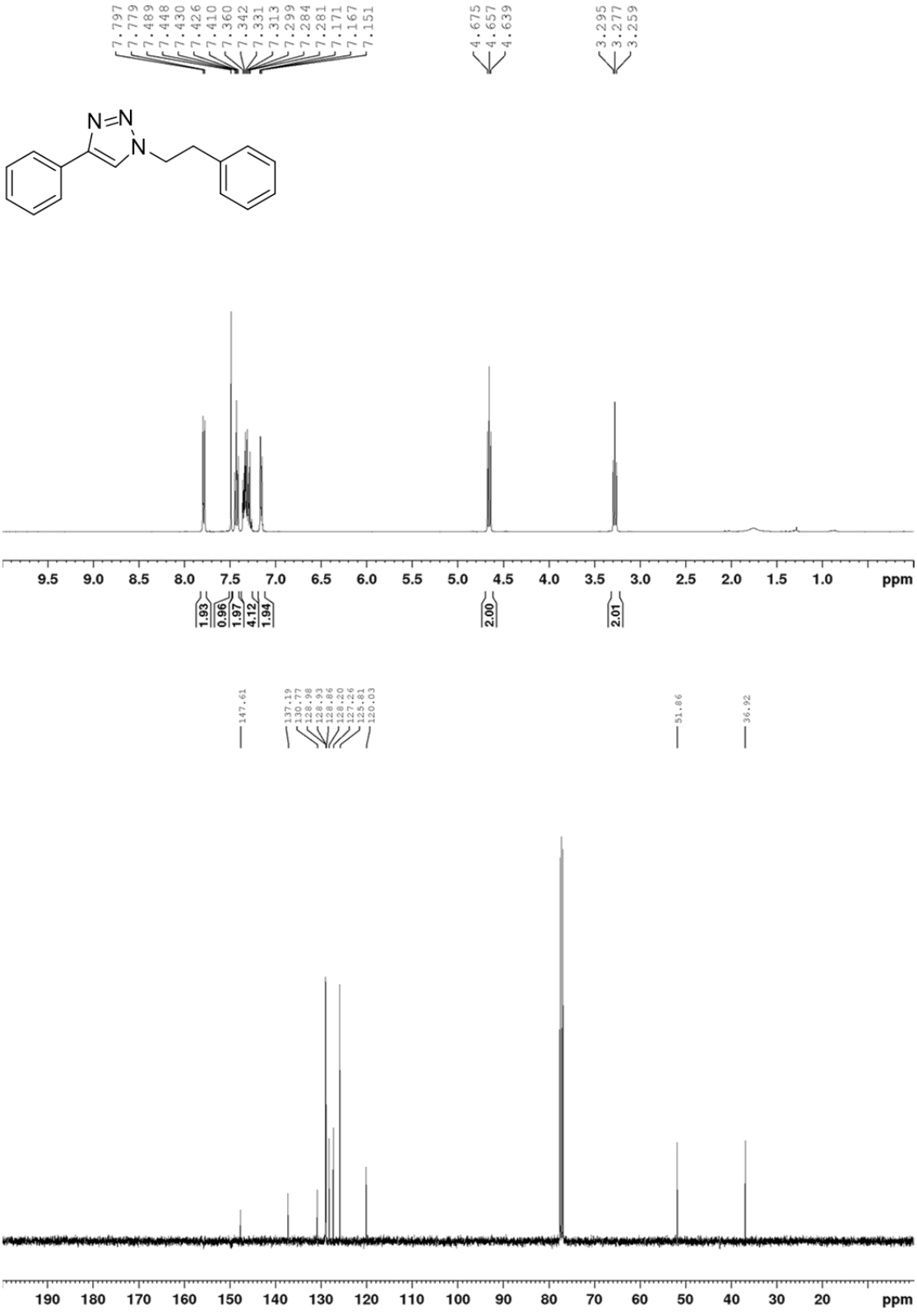



-61.16
-113.15
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
ppm

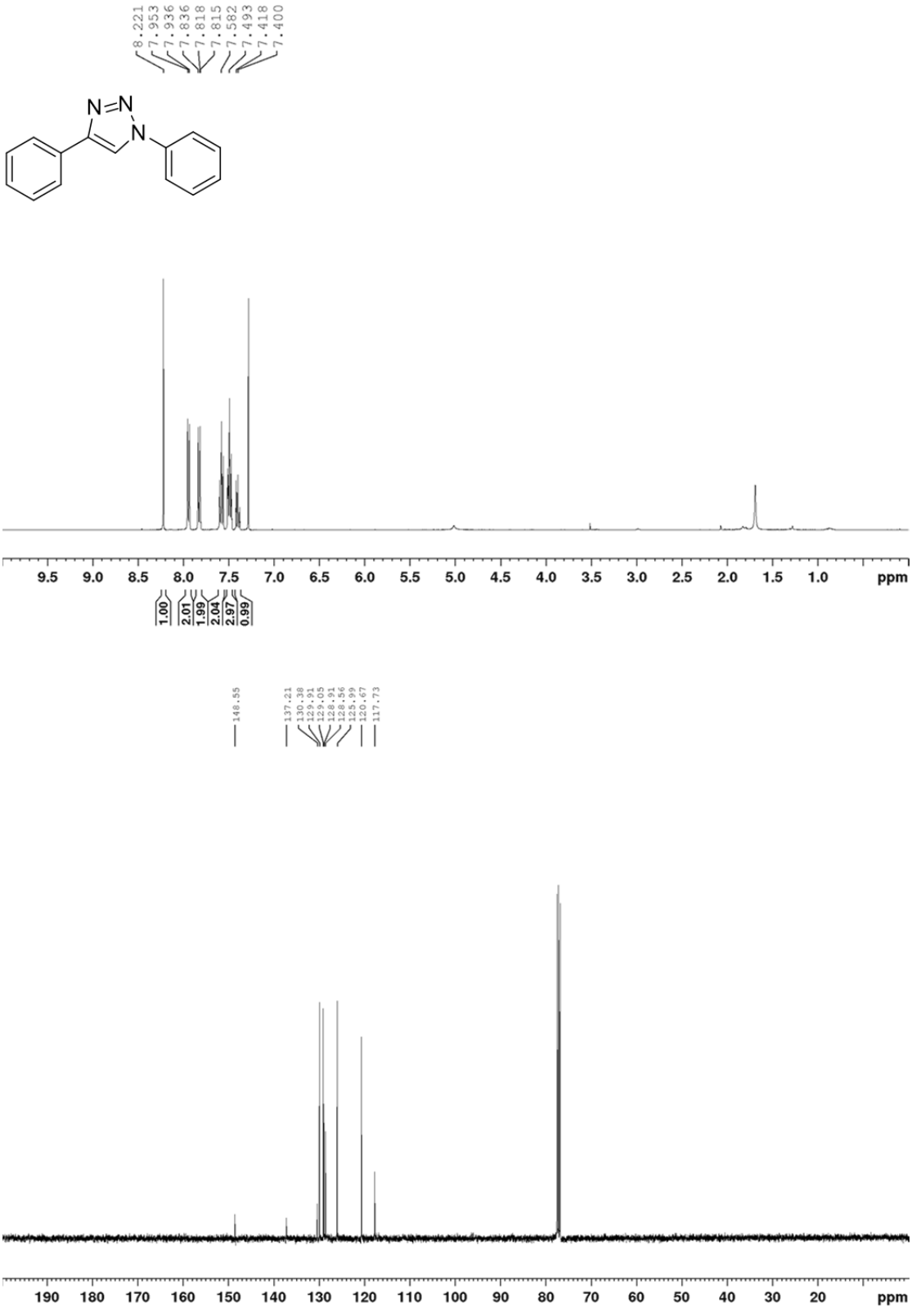
1-benzyl-4-phenyl-1*H*-1,2,3-triazole (5nu)



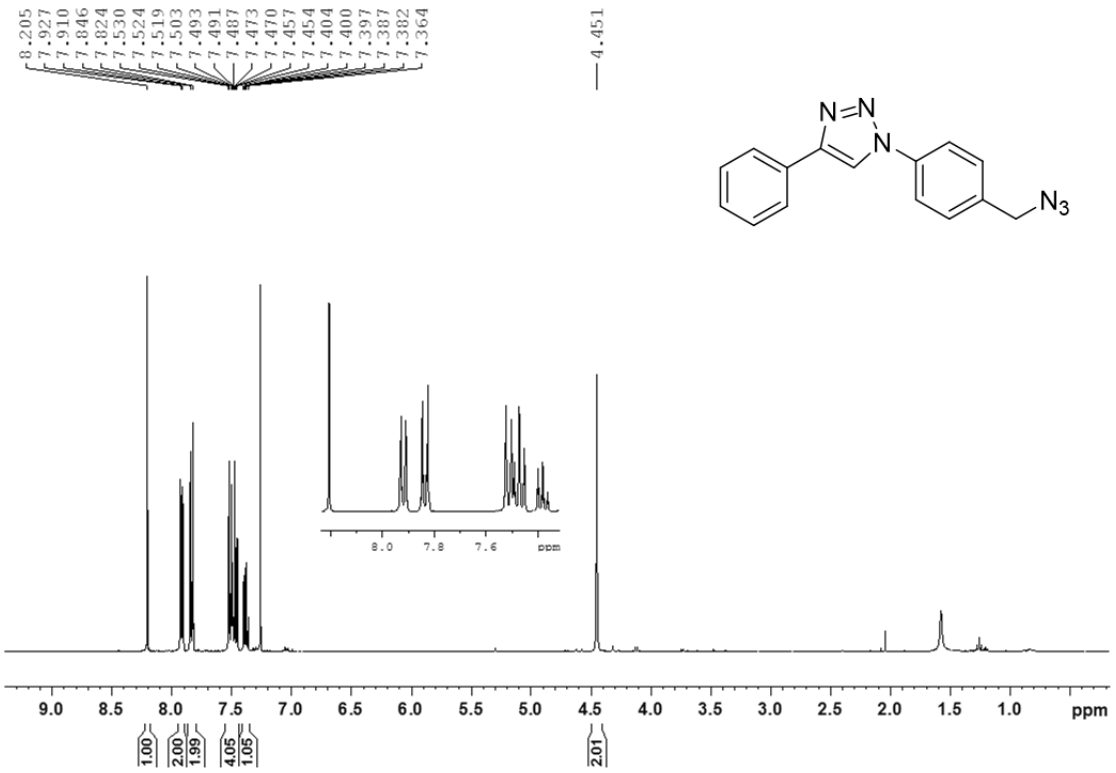
1-phenethyl-4-phenyl-1*H*-1,2,3-triazole (5nv)

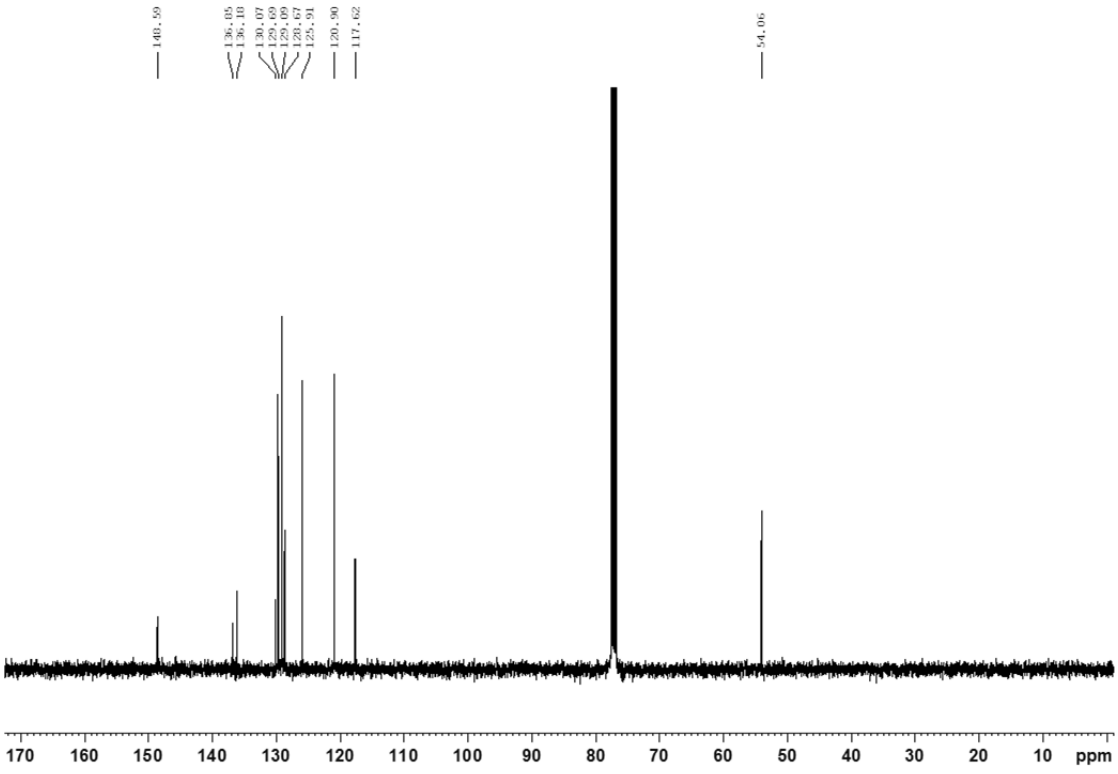


1,4-diphenyl-1*H*-1,2,3-triazole (5na)



1-(4-(azidomethyl)phenyl)-4-phenyl-1*H*-1,2,3-triazole (5ag)





4,4'-(1*H*-1,2,3-triazole-1,4-diyl)dibenzonitrile (5vk)