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## Graphical Abstract

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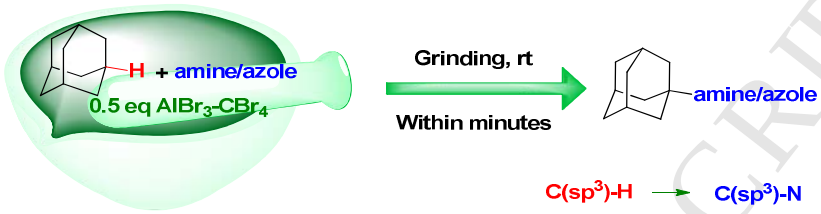

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# Solvent-free and direct C($sp^3$)-H amination of adamantanes by grinding

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ABSTRACT

A facile, direct and environmentally benign conversion of C($sp^3$)-H bonds to C($sp^3$)-N bonds using substoichiometric amount of aprotic superelectrophiles polyhalomethane-$AlX_3$ has been achieved by grinding under solvent-free conditions at room temperature in air. It is a general and simple method for the direct amination of adamantanes, and a series of aminoadamantanes of azoles, arylamines or heteroarylamines were obtained in good to excellent yields. The advantages of this amination are atom economy, solvent-free, chemoselectivity, short reaction time and high yields.



## 1. Introduction

Aminoadamantanes represent a valuable class of compounds with structural and functional motifs that are prevalent in many biologically active natural products, pharmaceuticals and materials. For example, 1-aminoadamantane hydrochloride (amantadine) and 1-(1-adamanty)ethanamine (rimantadine) have proved to be efficient medicines against influenza.[1a,1b] Recently, azolo-adamantanes were found to be new potent antiviral agents against influenza displaying a broad spectrum of activity and low toxicity.[1c-1e] As a result of steric environment of adamantane, the ligands containing aminoadamantane fragment have become important ones for the homodimerization reactions of terminal olefins,[2a,2b] ethylene polymerization,[2c] alkene isomerization,[2d] enyne cyclization,[2e] and suzuki cross-coupling reactions.[2f] Also, 1,2,4-triazole functionalized adamantanes are known to be useful molecular engineers for the synthesis of metal organic framework (MOF) materials.[3]

The traditional routes for the formation of C($sp^3$)-N bonds of adamantanes at the *tert*-carbons position are the nucleophilic substitution reactions,[1c,3,4] but these methods are usually not atom economic, thus generate substantial waste. Recently, the nitrene C-H insertion,[5] metal-nitrenoid,[6] and organo-nitrenoid direct aminations[7] have been reported for the direct C($sp^3$)-H amination of adamantanes. These methods often require special nitrene sources (*N*-tosylimino-$\lambda_3$-iodane, sulfamoyl azides, *N*-tosyloxycarbamates or aryl azides), directing groups, or strong oxidants, so they are not very simple and general methods for C($sp^3$)-N bond formation.

Recently, Solvent-free organic reactions have drawn considerable attention due to their environmentally benign protocols, short reaction time, occasionally-enhanced selectivity and convenient means of product purification.[8] Grinding technique, as a useful mechanochemistry approach, plays a pivotal role in various solvent-free reactions.[9] As aprotic superelectrophiles polyhalomethane-$AlX_3$ systems are able to generate carbocations effectively from saturated hydrocarbons under very mild condition, they are recognized as a unique possibility to the halogenation, dichlorophosphorylation, sul-furization, Ritter-type reaction and carbonylation with CO of cycloalkanes.[10] However, all the procedures employ conditions utilizing organic solvents. To the best of our knowledge, the solvent-free reaction for aprotic superelectrophiles polyhalo-methane-$AlX_3$ systems has not been disclosed.

In the continuation of our interest in the utilization of aprotic superelectrophiles systems in mechanochemical reactions, herein we report a general, environmentally friendly, effective and chemoselective method for the direct C($sp^3$)-H amination of adamantanes by employing a mixture of polyhalomethane-$AlX_3$ and amine by grinding under solvent-free conditions. It is worth mentioning that, very common nitrogen sources, such as azole, heteroarylamine and arylamine derivatives, are readily employed in this procedure.

## 2. Results and discussion

In our initial studies, adamantane (**1a**) and 1*H*-benzotriazole (**2b**) were chosen as model substrates to find a green, chemoselective and effective condition for the grinding reaction. As

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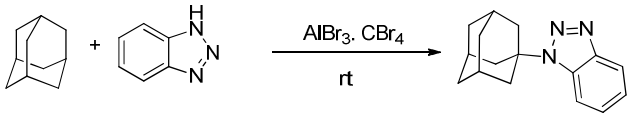
shown in Table 1, the activity of different Lewis acids, such as $FeCl_3$, $CoCl_2$, $BiCl_3$, $ZnBr_2$, $InBr_3$, $AlCl_3$ and $AlBr_3$, was scanned (entries 1–9). Gratifyingly, we found that the $AlX_3$-$CBr_4$ (X = Cl, Br) was an efficient catalyst to activate the C-H bond of adamantane in grinding condition, and the reaction using $AlBr_3$-$CBr_4$ as the catalyst resulted in higher yields than those using $AlCl_3$-$CBr_4$. Without $CBr_4$ in the system, the amination of adamantane could not occur (entry 10). It proved that the formation of polyhalomethane cation promoted by the strong Lewis acid played the key role in the grinding reaction. The 0.5 eq $AlBr_3$-$CBr_4$ was the best (entry 8). With the increasing of the amount of catalyst, the bromination of 1-adamantyl-1*H*-benzotriazole would occur (entry 9). It is worth mentioning that the mechanochemistry grinding is a considerable effective and environmentally friendly method compared with the solvent condition (entries 11, 12).

**Table 1** Opitimization Conditions

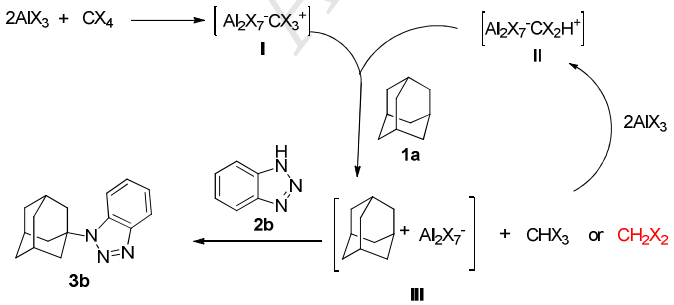



1a 2b 3b

| Entry | Lewis acid | Amount of Lewis acid (equiv) | Amount of $CBr_4$ (equiv) | Time (minute) | Yield (%) |
|---|---|---|---|---|---|
| 1 | $FeCl_3$ | 0.5 | 0.5 | 5 | 0[a] |
| 2 | $CoCl_2$ | 0.5 | 0.5 | 5 | 0[a] |
| 3 | $BiCl_3$ | 0.5 | 0.5 | 5 | 0[a] |
| 4 | $ZnBr_2$ | 0.5 | 0.5 | 5 | 0[a] |
| 5 | $InBr_3$ | 0.5 | 0.5 | 5 | 0[a] |
| 6 | $AlCl_3$ | 0.5 | 0.5 | 5 | 15[a, c] |
| 7 | $AlBr_3$ | 0.5 | 0.25 | 5 | 67[a, c] |
| 8 | $AlBr_3$ | 0.5 | 0.5 | 5 | 91[a, d] |
| 9 | $AlBr_3$ | 1 | 1 | 5 | 71[a, c] |
| 10 | $AlBr_3$ | 1 | 0 | 5 | 0[a] |
| 11 | $AlBr_3$ | 0.5 | 0.5 | 60 | trace[b] |
| 12 | $AlBr_3$ | 2 | 1 | 60 | 76[b, c] |

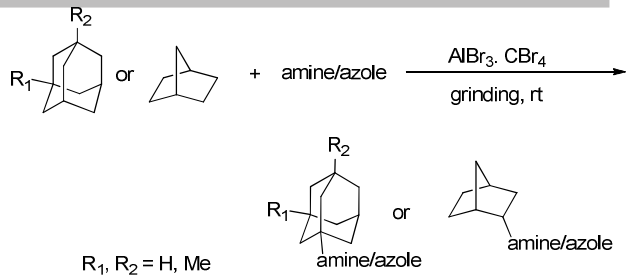
[a] Reaction conditions: adamantane (1 mmol) and 1*H*-benzotriazole (1 mmol).
[b] Reaction conditions: adamantane (1 mmol), 1*H*-benzotriazole (1 mmol) and $CH_2Br_2$ (5 ml).
[c] Isolated yield after purification by column chromatography.
[d] Isolated yield by filtration and recrystallisation.

The possible amination mechanism of adamantanes by polyhalomethane-$AlX_3$ is shown in the Scheme 1. Firstly, the superelectrophiles $[Al_2X_7]^-CX_3^+$ **I** are produced by the $CX_4$ and 2 *eq* $AlX_3$, then trihalomethyl cations are capable of hydride abstraction from AdH to generate $Ad^+$. The latter, in turn, can be converted into amination product. The newly generated $CX_3H$




**Scheme 1.** The possible amination mechanism of adamantanes by polyhalomethane-$AlX_3$

**Table 2** The amination of adamantanes and norbornane




| Entry | Amine/azole | Product | Time (min) | Yield (%) |
|---|---|---|---|---|
| 1 | 2a | 3a | 5 | 90[a,d] |
| 2 | 2b | 3b | 5 | 91[a,d] |
| 3 | 2c | 3c | 5 | 93[a,d] |
| 4 | 2d | 3d | 5 | 79[a,d] |
| 5 | 2e | 3e | 5 | 71[a,d] |
| 6 | 2f | 3f | 10 | 75[a,c] |
| 7 | 2g | 3g | 5 | 81[a,c] |
| 8 | 2h | 3h | 5 | 90[a,c] |
| 9 | 2i | 3i | 5 | 84[a,c] |
| 10 | 2j | 3j | 5 | 83[a,c] |
| 11 | 2k | 3k | 5 | 91[a,c] |
| 12 | 2l | 3l | 5 | 64[b,c] |
| 13 | **2b** | 3m | 5 | 89[a,d] |
| 14 | **2i** | 3n | 5 | 87[a,c] |
| 15 | **2k** | 3o | 5 | 92[a,c] |
| 16 | **2b** | 3p | 5 | 88[a,d] |
| 17 | **2h** | 3q | 5 | 79[a,c] |

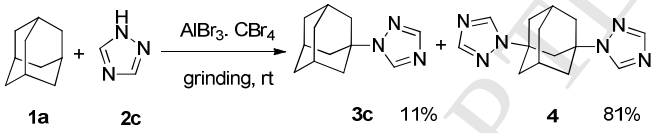
[a] Reaction conditions: cycloalkane (1 mmol), azole/ heteroarylamine/aromatic amine (1 mmol), $AlBr_3$ (0.5 mmol) and $CBr_4$ (0.5 mmol). [b] Reaction conditions: adamantane (2 mmol), 2,6-diaminopyridine (1 mmol) $AlBr_3$ (1 mmol) and $CBr_4$ (1 mmol). [c] Isolated yield after purification by column chromatography. [d] Isolated yield by filtration and recrystallisation.

can still react with $AlX_3$ to product superelectrophiles $[Al_2X_7]^-$ $CX_2H^+$ **II** which also can generate $Ad^+$ from AdH.[10c]

With these results in hand, we surveyed the scope of this reaction by subjecting a series of azole, arylamine and heteroaryl-amine compounds **2a-l** to react with adamantanes **1**, and the results were presented in Table 2. As summarized in Table 2, various azoles such as tetrazole, triazole and imidazole, were found to undergo the reaction well and selectively (entries 1-5). Compared to *N*-alkylation of tetrazole and benzotriazole in 1- or 2-position,[1e] the direct $sp^3$ C-H amination catalyzed by the superelectrophiles polyhalomethane-$AlX_3$ was highly selective *N*-alkylation in 1-position, and 1-adamantanylazoles **3a** and **3b** were synthesized. Adamantylation of 3-amino-1,2,4-triazole in the 1-position promoted by the superelectophiles polyhalo-methane-$AlX_3$ was similar to the nucleophilic substitution reaction.[4d]

Encouraged by these exciting results, subsequently we investigated the reaction of adamantane **1a** with a range of arylamine (entries 6-9). Generally, electron-deficient arylamine showed better results than electron-rich ones. The result was different from the conventional nucleophilic substitution reaction.[11] Heteroarylamines also provided good to excellent yields (entries 10-12). Bialkylation product of $N^2$,$N^6$-di(adamantanyl)-pyridine-2,6-diamine **3l** was obtained in the presence of 2 eq adamtance and 1eq $AlBr_3$-$CBr_4$. Additionally, dimethyladaman-tane **1b**, norbornane **1c** also could react with azoles, arylamines and heteroarylamines to give the corresponding amines ( entries 13-17).

When the reaction of adamantance **1a** and 1,2,4-triazole **2c** in 2 eq. $AlBr_3$-$CBr_4$, the expected 1-(1-adamantanyl)-1,2,4-triazole **3c** was obtained as minor product (11%), while an bifunctional product 1,3-di(1*H*-1,2,4-triazolyl)-adamantane **4** was the major one (81%) (Scheme 2). Perhaps the main reason is that, when 2 eq. $AlBr_3$-$CBr_4$ was used, the mono-substituted intermediate **3c** could react with excess of $CX_3^+$ to give the di-substituted product **4**. The structure of **4** has been undoubtedly confirmed by X-ray crystallographic analysis (Fig. 1).[12]




**Scheme 2.** The formation of the bifunctional product **4** catalyzed by $AlBr_3$-$CBr_4$ under grinding in one step

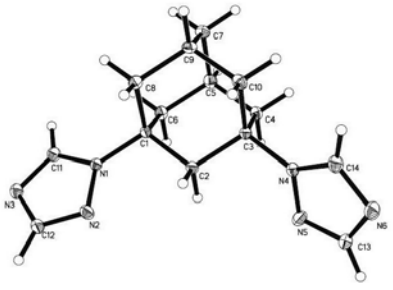
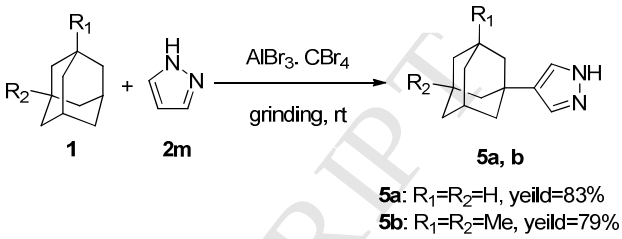


**Fig. 1.** ORTEP diagram of **4**

Pilar and his companions reported that, reaction of NH-pyrazoles with 1-bromoadamantane in a high pressure gave regioselectively 1-(1-adamantyl)- or 4-(1-adamantyl)-pyrazoles depending on the reaction temperature.[4c] We found that the direct C($sp^3$)-H amination catalyzed by the superelectrophiles polyhalomethane-$AlX_3$ was the highly selective synthesis of the 4-C substituted compound **5** (Scheme 3). The molecular structure of **5** had been confirmed by MS, $^1H$ and $^{13}C$ NMR spectra. The $^{13}C$ NMR spectra data (31.27 ppm or 31.17 ppm) of the connected carbon of 5 indicated the formation of C-C bond, while the chemical shift of the same carbon would be about 50~60 ppm if the C-N one was connected. The $^1H$ NMR chemical shifts of hydrogen on both 3- and 5-positions were equal, it confirmed that the structure of **5a** was symmetric and the connection between adamantane and pyrazole should be 1-position of adamantane and 4-position of pyrazole.




**Scheme 3.** Forming C-C bond catalyzed by $AlBr_3$-$CBr_4$ under grinding

## 3. Conclusions

In summary, we have developed an efficient, chemoselectivity and environmentally benign method for the amination of adamantanes in a substoichiometric amount of $AlX_3$-polyhalomethane by grinding under solvent-free condition. The purification of amination products is very simple. In the meanwhile, this method make it possible for the bifunctional reaction by direct C($sp^3$)-H amination in one step, and offers significant advantage of time efficiency, ease of manipulation and atom economy.

## 4. Experimental section

### 4.1 General information

All the reactions were carried out at room temperature that is 15-20 □. Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. All reactions were conducted by grinding in a mortar and pestle. Melting points were determined using XT4 microscope melting point apparatus (uncorrected). Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrophotometer with KBr pellets. $^1H$ and $^{13}C$ NMR spectra were recorded at a Bruker 400 (400 MHz) spectrometer with TMS as the internal standard. Mass spectra were recorded on a ZAB-HS mass spectrometer using ESI ionization. Elemental analyses were performed on an Elementar Vario EL.

### 4.2 General Procedure for synthesis of compounds 3 and 5

A mixture of the appropriate adamantane/norbornane (1 mmol), amine (1 mmol), $AlBr_3$ (0.5 mmol) and $CBr_4$ (0.5 mmol) was ground in a mortar and pestle at room temperature till the completion of reaction as indicated by TLC (5-10 min). The product of azole derivatives were purified by recrystallisation from ethyl alcohol, and the other amine derivatives were purified by column chromatography using ethyl acetate and petroleum ether mixtures as the mobile phase.

*4.2.1. 1-((3s,5s,7s)-adamantan-1-yl)-1H-tetrazole (**3a**).* White crystal; m.p. 135-136 ℃; IR (KBr, *v*, $cm^{-1}$): 3348, 3148, 3121, 2913, 2855, 1626, 1556, 1453; $^1H$ NMR (400MHz, $CDCl_3$) ($\delta$, ppm): 1.83 (6H, s, Ad-H), 2.27 (6H, s, Ad-H), 2.31 (3H, s, Ad-H), 8.63 (1H, s, tetrazole-H); $^{13}C$ NMR (100 MHz, $CDCl_3$) ($\delta$, ppm): 29.2 (3C), 35.6 (3C), 42.5 (3C), 59.7, 139.3; ESI-MS (*m/z*)

= 205.2 ([M+H]$^+$).

*4.2.2. 1-((3s,5s,7s)-adamantan-1-yl)-1H-benzo[d][1,2,3]triazole (**3b**).* White crystal; m.p. 164-165 ℃; IR (KBr, *v*, cm$^{-1}$): 3051, 2918, 2849, 1671, 1620, 1454, 740; $^1$H NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.91 (6H, s, Ad-H), 2.38 (3H, s, Ad-H), 2.56 (6H, s, Ad-H), 7.36 (1 H, td, J = 7.6, 1.6 Hz, benzotriazole-H), 7.45 (1 H, td, J = 7.2, 0.8 Hz, benzotriazole-H), 7.85 (1 H, d, J = 8.0 Hz, benzotriazole-H), 8.11 (1 H, d, J = 9.2 Hz, benzotriazole-H); $^{13}$C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 29.3 (3C), 35.7 (3C), 42.8 (3C), 61.6, 112.5, 120.4, 123.4, 126.3, 131.7, 147.0; ESI-MS (*m/z*) = 254.2 ([M+H]$^+$).

*4.2.3. 1-((3s,5s,7s)-adamantan-1-yl)-1H-1,2,4-triazole (**3c**).* White crystal; m.p. 87-88 ℃; IR (KBr, *v*, cm$^{-1}$): 3119, 2909, 2861, 1742, 1498, 1276; $^1$H NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.78 (6H, s, Ad-H), 2.17 (6H, s, Ad-H), 2.24 (3H, s, Ad-H), 7.93 (1H, s, triazole-H), 8.12 (1H, s, triazole-H); $^{13}$C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 29.3 (3C), 36.0 (3C), 42.6 (3C), 58.6, 139.4, 151.3; ESI-MS (*m/z*) = 204.2 ([M+H]$^+$).

*4.2.4. 1-((3s,5s,7s)-adamantan-1-yl)-1H-1,2,4-triazol-3-amine (**3d**).*White crystal; m.p. 223-225 ℃; IR (KBr, *v*, cm$^{-1}$): 3349, 3183, 2909, 2855, 1646, 1557; $^1$H NMR (400MHz, DMSO-$d_6$) (*δ*, ppm): 1.68 (6H, s, Ad-H), 2.01 (6H, s, Ad-H), 2.13 (3H, s, Ad-H), 5.15 (2H, s, N-H), 7.94 (1H, s, azole-H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) (*δ*, ppm): 28.7 (3C), 35.5 (3C), 41.8 (3C), 56.4, 138.7, 162.2; ESI-MS (*m/z*) = 219.2 ([M+H]$^+$).

*4.2.5. 1-((3s,5s,7s)-adamantan-1-yl)-1H-imidazole (**3e**).* White crystal; m.p. 110-112 ℃; IR (KBr, *v*, cm$^{-1}$): 3052, 2914, 2832, 1432, 933; $^1$H NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.77 (6H, s, Ad-H), 2.08 (6H, s, Ad-H), 2.24 (3H, s, Ad-H), 7.06 (1H, s, imidazole-H), 7.08 (1H, s, imidazole-H), 7.64 (1H, s, imidazole-H); $^{13}$C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 29.5 (3C), 36.0 (3C), 43.8 (3C), 55.0, 115.3, 128.8, 133.6; ESI-MS (*m/z*) = 203.2 ([M+H]$^+$).

*4.2.6. (3s,5s,7s)-N-(p-tolyl)adamantan-1-amine (**3f**).* White crystal; m.p. 95-96 ℃; IR (KBr, *v*, cm$^{-1}$): 3408, 2909, 2848, 1609, 1517, 1449, 803; $^1$H NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.66 (6H, s, Ad-H), 1.82 (6H, s, Ad-H), 2.09 (3H, s, Ad-H), 2.26 (1H, s, Me-H), 6.74-6.77 (2H, m, phenyl-H), 6.97-7.00 (2H, m, phenyl-H); $^{13}$C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 20.6, 29.7 (3C), 36.5 (3C), 43.6 (3C), 52.4, 120.9 (2C), 129.2 (3C), 143.2; ESI-MS (*m/z*) = 242.3 ([M+H]$^+$).

*4.2.7. (3s,5s,7s)-N-(4-nitrophenyl)adamantan-1-amine (**3g**).* Yellow crystal; m.p. 169-170 ℃; IR (KBr, *v*, cm$^{-1}$): 3371, 2919, 2850, 1595, 1535, 1450, 1275; $^1$H NMR (400MHz, DMSO-$d_6$) (*δ*, ppm): 1.64-1.69 (6H, m, Ad-H), 1.96 (6H, s, Ad-H), 2.09 (3H, s, Ad-H), 6.84 (2H, d, J = 9.2 Hz, phenyl-H), 7.92 (2H, d, J = 9.2 Hz, phenyl-H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) (*δ*, ppm): 29.6 (3C), 36.5 (3C), 41.7 (3C), 53.3, 112.5 (2C), 126.1 (2C), 137.3, 150.0; ESI-MS (*m/z*) = 273.0 ([M+H]$^+$).

*4.2.8. (3s,5s,7s)-N-(3-nitrophenyl)adamantan-1-amine (**3h**).* Yellow crystal; m.p. 125-126 ℃; IR (KBr, *v*, cm$^{-1}$): 3413, 2906, 2849, 1621, 1577, 1529, 1338; $^1$H NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.63 (6H, s, Ad-H), 1.86 (6H, s, Ad-H), 2.08 (3H, s, Ad-H), 6.89-6.92 (1H, m, phenyl-H), 7.13-7.19 (1H, m, phenyl-H), 7.43-7.45 (1H, m, phenyl-H), 7.48-7.49 (1H, m, phenyl-H); $^{13}$C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 29.6 (3C), 36.3 (3C), 42.9 (3C), 53.0, 110.4, 112.2, 122.5, 129.4, 149.2, 150.5; ESI-MS (*m/z*) = 273.3 ([M+H]$^+$).

*4.2.9. 2-((3s,5s,7s)-adamantan-1-ylamino)benzonitrile (**3i**).* White crystal; m.p. 153-154 ℃; IR (KBr, *v*, cm$^{-1}$): 3395, 2917, 2846, 2209, 1603, 1579, 1519, 1465, 741; $^1$H NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.70 (6H, s, Ad-H), 1.99 (6H, s, Ad-H), 2.15 (3H, s, Ad-H), 4.38 (1H, s, N-H), 6.61-6.65 (1H, m, phenyl-H), 7.01 (1H, d, J = 9.6 Hz, phenyl-H), 7.28-7.32 (1H, m, phenyl-H), 7.36 (1H, d, J = 8.0 Hz, phenyl-H); $^{13}$C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 29.6 (3C), 36.3 (3C), 42.6 (3C), 52.7, 97.7, 114.7, 116.4, 118.3, 133.2, 133.4, 149.1; ESI-MS (*m/z*) = 253.2 ([M+H]$^+$).

*4.2.10. N-((3s,5s,7s)-adamantan-1-yl)pyridin-2-amine (**3j**).* White crystal; m.p. 171-172 ℃; IR (KBr, *v*, cm$^{-1}$): 3372, 3011, 2904, 2847, 1602, 1507, 1485; $^1$H NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.70 (6H, s, Ad-H), 2.04 (6H, s, Ad-H), 2.12 (3H, s, Ad-H), 4.48 (1H, s, N-H), 6.48-6.53 (2H, m, pyridine-H), 7.32-7.37 (1H, m, pyridine-H), 8.03 (1H, d, J=3.6 Hz, pyridine-H); $^{13}$C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 29.1 (3C), 35.6 (3C), 41.7 (3C), 56.4, 112.3, 114.5, 138.4, 147.8, 156.9; ESI-MS (*m/z*) = 229.2 ([M+H]$^+$).

*4.2.11. 2-((3s,5s,7s)-adamantan-1-ylamino)nicotinonitrile (**3k**).* White crystal; m.p. 169-170 ℃; IR (KBr, *v*, cm$^{-1}$): 3359, 3003, 2902, 2849, 2219, 1591, 1576, 1506, 1461, 1415; $^1$H NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.73 (6H, s, Ad-H), 2.13 (3H, s, Ad-H), 2.16 (6H, s, Ad-H), 4.93 (1H, s, N-H), 6.51-6.54 (1H, m, pyridine-H), 7.58-7.60 (1H, m, pyridine-H), 8.22-8.24 (1H, m , pyridine-H); $^{13}$C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 29.7 (3C), 36.5 (3C), 41.8 (3C), 53.2, 91.9, 111.2, 117.8, 141.3, 152.1, 158.5; ESI-MS (*m/z*) = 254.2 ([M+H]$^+$).

*4.2.12. $N^2$,$N^6$-di((3s,5s,7s)-adamantan-1-yl)pyridine-2,6-diamine (**3l**).* Green crystal; m.p. 144-145 ℃; IR (KBr, *v*, cm$^{-1}$): 3393, 3323, 2905, 2849, 1591, 1498, 1452; $^1$H NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.67 (12H, s, Ad-H), 2.05 (12H, s, Ad-H), 2.09 (6H, s, Ad-H), 4.13 (2H, s, N-H), 5.73 (2H, d, J = 7.6 Hz, pyridine-H), 7.07 (1H, t, J = 7.6 Hz, pyridine-H); $^{13}$C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 29.7 (6C), 36.5 (6C), 42.6 (6C), 49.3, 51.3, 97.2 (2C), 137.9, 157.0 (2C); ESI-MS (*m/z*) = 378.5 ([M+H]$^+$); Anal. Calcd for $C_{25}H_{35}N_3$: C, 79.53; H, 9.34; N, 11.13; Found: C, 79.31; H, 9.27; N, 11.08.

*4.2.13. 1-((1r,3R,5S,7r)-3,5-dimethyladamantan-1-yl)-1H-benzo[d][1,2,3]triazole (**3m**).* White crystal; m.p. 104-105 ℃; IR (KBr, *v*, cm$^{-1}$): 3103, 2915, 2848, 1611, 1454, 750; $^1$H NMR (400MHz, $CDCl_3$) (*δ*, ppm): 0.98 (6H, s, Me-H), 1.35 (2H, s, Ad-H), 1.46-1.58 (4H, m, Ad-H), 2.10-2.20 (4H, m, Ad-H), 2.35 (2H, s, Ad-H), 2.37-2.39 (1H, m, Ad-H), 7.32 (1 H, td, J = 7.2, 0 Hz, benzotriazole-H), 7.41 (1 H, td, J = 7.4, 1.2 Hz, benzotriazole-H), 7.78 (1 H, d, J = 8.0 Hz, benzotriazole-H), 8.07 (1 H, d, J = 8.4 Hz, benzotriazole-H); $^{13}$C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 30.1 (2C), 32.9, 40.6 (2C), 42.4 (3C), 48.0 (2C), 50.4, 63.1, 112.3, 120.3, 123.3, 126. 2, 131.6, 146.8; ESI-MS (*m/z*) = 282.1 ([M+H]$^+$); Anal. Calcd for $C_{18}H_{23}N_3$: C, 76.83; H, 8.24; N, 14.93; Found: C, 76.65; H, 8.12; N, 14.81.

*4.2.14. 2-(((1r,3R,5S,7r)-3,5-dimethyladamantan-1-yl)amino)-benzonitrile (**3n**).* White crystal; m.p. 75-76 ℃; IR (KBr, *v*, cm$^{-1}$): 3403, 2945, 2893, 2205, 1605, 1576, 1514, 1463; $^1$H NMR (400MHz, $CDCl_3$) (*δ*, ppm): 0.90 (6H, s, Me-H), 1.20 (2H, s, Ad-H), 1.33-1.42 (4H, m, Ad-H), 1.57-1.68 (4H, m, Ad-H), 1.85 (2H, s, Ad-H), 2.21-2.23 (1H, m, Ad-H), 4.45 (1H, s, N-H), 6.64-6.68 (1H, m, phenyl-H), 7.00 (1H, d, J = 8.8 Hz, phenyl-H), 7.30-7.34 (1H, m, phenyl-H), 7.38 (1H, d, J = 8.0 Hz, phenyl-H); $^{13}$C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 30.3 (2C), 32.7, 41.0 (2C), 42.6 (3C), 48.7 (2C), 50.6, 54.5, 95.3, 114.9, 116.6, 120.9, 133.2, 133.4, 152.0; ESI-MS (*m/z*) = 281.1 ([M+H]$^+$); Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99; Found: C, 81.25; H, 8.52; N, 9.91.

*4.2.15. 2-(((1r,3R,5S,7r)-3,5-dimethyladamantan-1-yl)amino)-nicotinonitrile (**3o**).* White crystal; m.p. 70-71 ℃; IR (KBr, *v*, cm$^{-1}$): 3398, 2941, 2843, 2215, 1591, 1575, 1416; $^1$H NMR

(400MHz, $CDCl_3$) (*δ*, ppm): 0.88 (6H, s, Me-H), 1.18-1.20 (2H, m, Ad-H), 1.30-1.44 (4H, m, Ad-H), 1.73-1.84 (4H, m, Ad-H), 2.00 (2H, s, Ad-H), 2.17-2.19 (1H, m, Ad-H), 4.93 (1H, s, N-H), 6.51-6.54 (1H, m, pyridine-H), 7.57-7.59 (1H, m, pyridine-H), 8.22-8.24 (1H, m , pyridine-H); $^{13}$C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 30.2 (2C), 32.5, 40.1 (2C), 42.7 (3C), 47.7 (2C), 50.6, 54.7, 100.7, 111.2, 117.2, 141.1, 152.2, 160.5; ESI-MS (*m/z*) = 282.3 ($[M+H]^+$); Anal. Calcd for $C_{18}H_{23}N_3$: C, 76.83; H, 8.24; N, 14.93; Found: C, 76.65; H, 8.32; N, 14.91.

*4.2.16. 1-((1R,4S)-bicyclo[2.2.1]heptan-2-yl)-1H-benzo[d][1,2,3] triazole (**3p**).* White crystal; m.p. 75-76 ℃; IR (KBr, *v*, $cm^{-1}$): 3062, 2960, 2867, 1613, 1453, 741; $^1$H NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.31-1.47 (4H, m, norbornane-H), 1.61-1.77 (2H, m, norbornane-H), 1.96-2.03 (2H, m, norbornane-H), 2.55-2.70 (2H, m, norbornane-H), 4.56-4.59 (1H, m, norbornane-H), 7.35 (1 H, td, J = 7.6, 0.0 Hz, benzotriazole-H), 7.45 (1 H, td, J = 7.2, 0.8 Hz, benzotriazole-H), 7.53 (1 H, d, J = 9.2 Hz, benzotriazole-H), 8.04 (1 H, d, J = 8.0 Hz, benzotriazole-H); $^{13}$C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 27.1, 28.7, 35.9, 36.0, 37.3, 42.9, 61.9, 109.7, 119.9, 123.8, 126.8, 133.0, 146.2; ESI-MS (*m/z*) = 214.1 ($[M+H]^+$).

*4.2.17. (1R,4S)-N-(3-nitrophenyl)bicyclo[2.2.1]heptan-2-amine (**3q**).* Yellow crystal; m.p. 65-66 ℃; IR (KBr, *v*, $cm^{-1}$): 3413, 2960, 2867, 1621, 1571, 1534, 1332; $^1$H NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.18-1.23 (4H, m, norbornane-H), 1.43-1.56 (3H, m, norbornane-H), 1.77-1.82 (1H, m, norbornane-H), 2.19-2.25 (2H, m, norbornane-H), 3.19 (1H, m, norbornane-H), 3.87 (1H, s, NH), 6.72-6.75 (1H, m, phenyl-H), 7.15-7.19 (1H, m, phenyl-H), 7.39-7.41 (1H, m, phenyl-H), 7.46-7.47 (1H, m, phenyl-H); $^{13}$C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 26.4, 28.4, 35.5, 35.7, 41.0, 41.2, 56.5, 106.7, 111.5, 119.0, 129.7, 148.3, 149.6; ESI-MS (*m/z*) = 233.2 ($[M+H]^+$).

*4.2.18. 4-((3s,5s,7s)-adamantan-1-yl)-1H-pyrazole (**5a**).* White crystal; m.p. 208-210 ℃; IR (KBr, *v*, $cm^{-1}$): 3155, 2902, 2846, 1449, 958; $^1$H NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.76 (6H, s, Ad-H), 1.86 (6H, s, Ad-H), 2.04 (3H, s, Ad-H), 4.73 (1H, s, N-H), 7.44 (2H, s, pyrazole-H); $^{13}$C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 28.7 (3C), 31.2, 36.8 (3C), 44.2 (3C), 130.1, 130.2, 133.2; ESI-MS (*m/z*) = 203.2 ($[M+H]^+$).

*4.2.19. 4-((1r,3R,5S,7r)-3,5-dimethyladamantan-1-yl)-1H-pyrazole (**5b**).* White crystal; m.p. 114-117 ℃; IR (KBr, *v*, $cm^{-1}$): 3143, 2941, 2843, 1443, 954; $^1$H NMR (400MHz, $CDCl_3$) (*δ*, ppm): 0.90 (6H, s, Me-H), 1.21 (2H, s, Ad-H), 1.37-1.45 (4H, m, Ad-H), 1.67-1.82 (4H, m, Ad-H), 2.05 (2H, s, Ad-H), 2.27-2.29 (1H, m, Ad-H), 4.68 (1H, s, N-H), 7.43 (2H, s, pyrazole-H); $^{13}$C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 30.0 (2C), 31.1, 32.9, 40.6 (2C), 42.4 (3C), 48.0 (2C), 50.4, 130.0, 130.1, 133.2; ESI-MS (*m/z*) = 231.3 ($[M+H]^+$); Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16; Found: C, 78.18; H, 9.54; N, 12.21.

### 4.3 General Procedure for synthesis of compounds 4

A mixture of the appropriate adamantane (1 mmol), 1*H*-1,2,4-triazole (2 mmol), $AlBr_3$ (2 mmol) and $CBr_4$ (2 mmol) was ground in a mortar and pestle at room temperature for 10 minutes. The product of azole derivatives were purified by column chromatography using ethyl acetate and petroleum ether mixtures as the mobile phase.

*4.3.1. (1s,3s,5s,7s)-1,3-di(1H-1,2,4-triazol-1-yl)adamantine (**4**).* White crystal; m.p. 174-176 ℃; IR (KBr, v, cm-1): 3131, 2936, 2860, 1501, 1279; $^1$H NMR (400MHz, $CDCl_3$) (δ, ppm): 1.84 (2H, s, Ad-H), 2.21-2.32 (8H, m, Ad-H), 2.61 (4H, s, Ad-H), 7.96 (2H, s, triazole-H), 8.16 (2H, s, triazole-H); $^{13}$C NMR (100 MHz, $CDCl_3$) (δ, ppm): 29.6 (2C), 34.5, 41.2 (4C), 47.2, 59.4 (2C), 139.4, 151.6; ESI-MS (m/z) = 271.2 ($[M+H]^+$); Anal. Calcd for $C_{14}H_{18}N_6$: C, 62.20; H, 6.71; N, 31.09; Found: C, 62.18; H, 6.64; N, 31.15.

### Acknowledgments

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12. Full details have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-947577 (**4**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).

**Supplementary Material**

Experimental procedures and compound characterization data are available. Supplementary data related to this article can be found at xxxxxx .

# Supporting Information

# Solvent-free and direct sp3 C-H amination of unfunctionalized adamantanes promoted by grinding

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## Contents

## General Information

All the reactions were carried out at room temperature that is 15-20 □. Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. All reactions were conducted by grinding in a mortar and pestle. Melting points were determined using XT4 microscope melting point apparatus (uncorrected). Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrophotometer with KBr pellets. $^{1}$H and $^{13}$C NMR spectra were recorded at a Bruker 400 (400 MHz) spectrometer with TMS as the internal standard. Mass spectra were recorded on a ZAB-HS mass spectrometer using ESI ionization. Elemental analyses were performed on an Elementar Vario EL.

## General Procedure for synthesis

### General Procedure for synthesis of compounds 3 and 5

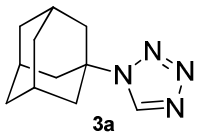
A mixture of the appropriate adamantane/norbornane (1 mmol), azole/heteroarylamine/arylamine (1 mmol), $AlBr_3$ (0.5 mmol) and $CBr_4$ (0.5 mmol) was ground in a mortar and pestle at room temperature till the completion of reaction as indicated by TLC (5-10 min). The product of azole derivatives were purified by recrystallisation from ethyl alcohol, and the heteroaryl/ arylamine derivatives were purified by column chromatography using ethyl acetate and petroleum ether mixtures as the mobile phase.

### General Procedure for synthesis of compound 4

A mixture of the appropriate adamantane (1 mmol), 1*H*-1,2,4-triazole (2 mmol), $AlBr_3$ (2 mmol) and $CBr_4$ (2 mmol) was ground in a mortar and pestle at room temperature for 10 minutes. The product of azole derivatives were purified by column chromatography using ethyl acetate and petroleum ether mixtures as the mobile phase.

## Spectra Data for the Products

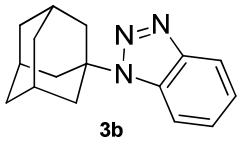
**1-((3*s*,5*s*,7*s*)-adamantan-1-yl)-1*H*-tetrazole (3a)**




3a

White crystal; m.p. 135-136 ℃; IR (KBr, *v*, cm$^{-1}$): 3348, 3148, 3121, 2913, 2855, 1626, 1556, 1453; $^{1}$H NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.83 (6H, s, Ad-H), 2.27 (6H, s, Ad-H), 2.31 (3H, s, Ad-H), 8.63 (1H, s, tetrazole-H); $^{13}$C NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 29.23 (3C), 35.61 (3C), 42.59 (3C), 59.72, 139.30; ESI-MS (*m/z*) = 205.2 ([M+H]$^{+}$).

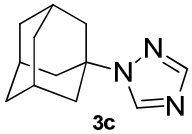
**1-((3*s*,5*s*,7*s*)-adamantan-1-yl)-1*H*-benzo[*d*][1,2,3]triazole (3b)**



3b

White crystal; m.p. 164-165 ℃; IR (KBr, *v*, $cm^{-1}$): 3051, 2918, 2849, 1671, 1620, 1454, 740; $^1H$ NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.91 (6H, s, Ad-H), 2.38 (3H, s, Ad-H), 2.56 (6H, s, Ad-H), 7.36 (1 H, td, J = 7.6, 1.6 Hz, benzotriazole-H), 7.45 (1 H, td, J = 7.2, 0.8 Hz, benzotriazole-H), 7.85 (1 H, d, J = 8.0 Hz, benzotriazole-H), 8.11 (1 H, d, J = 9.2 Hz, benzotriazole-H); $^{13}C$ NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 29.31 (3C), 35.70 (3C), 42.84 (3C), 61.67, 112.50, 120.43, 123.43, 126.31, 131.74, 147.06; ESI-MS (*m/z*) = 254.2 ($[M+H]^+$).

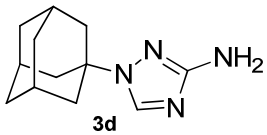
**1-((3*s*,5*s*,7*s*)-adamantan-1-yl)-1*H*-1,2,4-triazole (3c)**



3c

White crystal; m.p. 87-88 ℃; IR (KBr, *v*, $cm^{-1}$): 3119, 2909, 2861, 1742, 1498, 1276; $^1H$ NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.78 (6H, s, Ad-H), 2.17 (6H, s, Ad-H), 2.24 (3H, s, Ad-H), 7.93 (1H, s, triazole-H), 8.12 (1H, s, triazole-H); $^{13}C$ NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 29.39 (3C), 36.04 (3C), 42.68 (3C), 58.63, 139.49, 151.31; ESI-MS (*m/z*) = 204.2 ($[M+H]^+$).

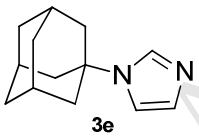
**1-((3*s*,5*s*,7*s*)-adamantan-1-yl)-1*H*-1,2,4-triazol-3-amine (3d)**



3d

White crystal; m.p. 223-225 ℃; IR (KBr, *v*, $cm^{-1}$): 3349, 3183, 2909, 2855, 1646, 1557; $^1H$ NMR (400MHz, DMSO-$d_6$) (*δ*, ppm): 1.68 (6H, s, Ad-H), 2.01 (6H, s, Ad-H), 2.13 (3H, s, Ad-H), 5.15 (2H, s, N-H), 7.94 (1H, s, azole-H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) (*δ*, ppm): 28.71 (3C), 35.57 (3C), 41.83 (3C), 56.41, 138.74, 162.26; ESI-MS (*m/z*) = 219.2 ($[M+H]^+$).

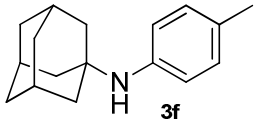
**1-((3*s*,5*s*,7*s*)-adamantan-1-yl)-1*H*-imidazole (3e)**



3e

White crystal; m.p. 110-112 ℃; IR (KBr, *v*, $cm^{-1}$): 3052, 2914, 2832, 1432, 933; $^1H$ NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.77 (6H, s, Ad-H), 2.08 (6H, s, Ad-H), 2.24 (3H, s, Ad-H), 7.06 (1H, s, imidazole-H), 7.08 (1H, s, imidazole-H), 7.64 (1H, s, imidazole-H); $^{13}C$ NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 29.51 (3C), 36.07 (3C), 43.87 (3C), 55.02, 115.34, 128.81, 133.63; ESI-MS (*m/z*) = 203.2 ($[M+H]^+$).

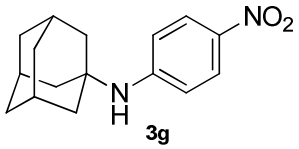
**(3*s*,5*s*,7*s*)-*N*-(p-tolyl)adamantan-1-amine (3f)**



**3f**

White crystal; m.p. 95-96 ℃; IR (KBr, *v*, $cm^{-1}$): 3408, 2909, 2848, 1609, 1517, 1449, 803; $^1H$ NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.66 (6H, s, Ad-H), 1.82 (6H, s, Ad-H), 2.09 (3H, s, Ad-H), 2.26 (1H, s, Me-H), 6.74-6.77 (2H, m, phenyl-H), 6.97-7.00 (2H, m, phenyl-H); $^{13}C$ NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 20.64, 29.76 (3C), 36.51 (3C), 43.65 (3C), 52.47, 120.96 (2C), 129.28 (3C), 143.20; ESI-MS (*m/z*) = 242.3 ($[M+H]^+$).

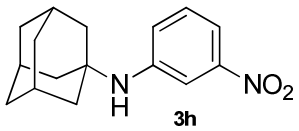
**(3*s*,5*s*,7*s*)-*N*-(4-nitrophenyl)adamantan-1-amine (3g)**



**3g**

Yellow crystal; m.p. 169-170 ℃; IR (KBr, *v*, $cm^{-1}$): 3371, 2919, 2850, 1595, 1535, 1450, 1275; $^1H$ NMR (400MHz, DMSO-$d_6$) (*δ*, ppm): 1.64-1.69 (6H, m, Ad-H), 1.96 (6H, s, Ad-H), 2.09 (3H, s, Ad-H), 6.84 (2H, d, J = 9.2 Hz, phenyl-H), 7.92 (2H, d, J = 9.2 Hz, phenyl-H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) (*δ*, ppm): 29.63 (3C), 36.58 (3C), 41.71 (3C), 53.38, 112.55 (2C), 126.11 (2C), 137.34, 150.03; ESI-MS (*m/z*) = 273.0 ($[M+H]^+$).

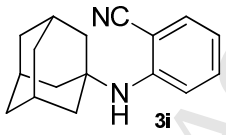
**(3*s*,5*s*,7*s*)-*N*-(3-nitrophenyl)adamantan-1-amine (3h)**



**3h**

Yellow crystal; m.p. 125-126 ℃; IR (KBr, *v*, $cm^{-1}$): 3413, 2906, 2849, 1621, 1577, 1529, 1338; $^1H$ NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.63 (6H, s, Ad-H), 1.86 (6H, s, Ad-H), 2.08 (3H, s, Ad-H), 6.89-6.92 (1H, m, phenyl-H), 7.13-7.19 (1H, m, phenyl-H), 7.43-7.45 (1H, m, phenyl-H), 7.48-7.49 (1H, m, phenyl-H); $^{13}C$ NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 29.67 (3C), 36.39 (3C), 42.92 (3C), 53.08, 110.43, 112.26, 122.52, 129.43, 149.23, 150.59; ESI-MS (*m/z*) = 273.3 ($[M+H]^+$).

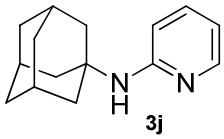
**2-((3*s*,5*s*,7*s*)-adamantan-1-ylamino)benzonitrile (3i)**



**3i**

White crystal; m.p. 153-154 ℃; IR (KBr, *v*, $cm^{-1}$): 3395, 2917, 2846, 2209, 1603, 1579, 1519, 1465, 741; $^1H$ NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.70 (6H, s, Ad-H), 1.99 (6H, s, Ad-H), 2.15 (3H, s, Ad-H), 4.38 (1H, s, N-H), 6.61-6.65 (1H, m, phenyl-H), 7.01 (1H, d, J = 9.6 Hz, phenyl-H), 7.28-7.32 (1H, m, phenyl-H), 7.36 (1H, d, J = 8.0 Hz, phenyl-H); $^{13}C$ NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 29.66 (3C), 36.36 (3C), 42.61 (3C), 52.76, 97.79, 114.73, 116.44, 118.31, 133.20, 133.45, 149.18; ESI-MS (*m/z*) = 253.2 ($[M+H]^+$).

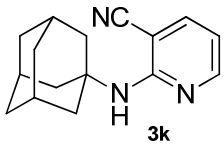
***N*-((3*s*,5*s*,7*s*)-adamantan-1-yl)pyridin-2-amine (3j)**



3j

White crystal; m.p. 171-172 ℃; IR (KBr, *v*, $cm^{-1}$): 3372, 3011, 2904, 2847, 1602, 1507, 1485; $^1H$ NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.70 (6H, s, Ad-H), 2.04 (6H, s, Ad-H), 2.12 (3H, s, Ad-H), 4.48 (1H, s, N-H), 6.48-6.53 (2H, m, pyridine-H), 7.32-7.37 (1H, m, pyridine-H), 8.03 (1H, d, J=3.6 Hz, pyridine-H); $^{13}C$ NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 29.10 (3C), 35.63 (3C), 41.77 (3C), 56.43, 112.31, 114.54, 138.40, 147.82, 156.97; ESI-MS (*m/z*) = 229.2 ($[M+H]^+$).

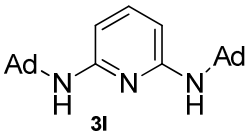
**2-((3*s*,5*s*,7*s*)-adamantan-1-ylamino)nicotinonitrile (3k)**



3k

White crystal; m.p. 169-170 ℃; IR (KBr, *v*, $cm^{-1}$): 3359, 3003, 2902, 2849, 2219, 1591, 1576, 1506, 1461, 1415; $^1H$ NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.73 (6H, s, Ad-H), 2.13 (3H, s, Ad-H), 2.16 (6H, s, Ad-H), 4.93 (1H, s, N-H), 6.51-6.54 (1H, m, pyridine-H), 7.58-7.60 (1H, m, pyridine-H), 8.22-8.24 (1H, m , pyridine-H); $^{13}C$ NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 29.73 (3C), 36.56 (3C), 41.81 (3C), 53.28, 91.93, 111.29, 117.87, 141.30, 152.10, 158.54; ESI-MS (*m/z*) = 254.2 ($[M+H]^+$).

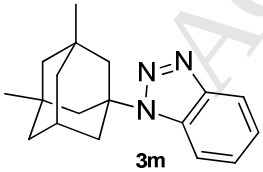
***N*$^2$,*N*$^6$-di((3*s*,5*s*,7*s*)-adamantan-1-yl)pyridine-2,6-diamine (3l)**



3l

Green crystal; m.p. 144-145 ℃; IR (KBr, *v*, $cm^{-1}$): 3393, 3323, 2905, 2849, 1591, 1498, 1452; $^1H$ NMR (400MHz, $CDCl_3$) (*δ*, ppm): 1.67 (12H, s, Ad-H), 2.05 (12H, s, Ad-H), 2.09 (6H, s, Ad-H), 4.13 (2H, s, N-H), 5.73 (2H, d, J = 7.6 Hz, pyridine-H), 7.07 (1H, t, J = 7.6 Hz, pyridine-H); $^{13}C$ NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 29.73 (6C), 36.58 (6C), 42.60 (6C), 49.37, 51.30, 97.29 (2C), 137.94, 157.01 (2C); ESI-MS (*m/z*) = 378.5 ($[M+H]^+$); Anal. Calcd for $C_{25}H_{35}N_3$: C, 79.53; H, 9.34; N, 11.13; Found: C, 79.31; H, 9.27; N, 11.08.

**1-((1*r*,3*R*,5*S*,7*r*)-3,5-dimethyladamantan-1-yl)-1*H*-benzo[*d*][1,2,3]triazole (3m)**

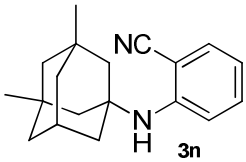


3m

White crystal; m.p. 104-105 ℃; IR (KBr, *v*, $cm^{-1}$): 3103, 2915, 2848, 1611, 1454, 750; $^1H$ NMR (400MHz, $CDCl_3$) (*δ*, ppm): 0.98 (6H, s, Me-H), 1.35 (2H, s, Ad-H), 1.46-1.58 (4H, m, Ad-H), 2.10-2.20 (4H, m, Ad-H), 2.35 (2H, s, Ad-H), 2.37-2.39 (1H, m, Ad-H), 7.32 (1 H, td, J = 7.2, 0 Hz, benzotriazole-H), 7.41 (1 H, td, J = 7.4, 1.2 Hz, benzotriazole-H), 7.78 (1 H, d, J = 8.0 Hz, benzotriazole-H), 8.07 (1 H, d, J = 8.4 Hz, benzotriazole-H);

$^{13}$C NMR (100 MHz, $CDCl_3$) ($\delta$, ppm): 30.10 (2C), 32.90, 40.67 (2C), 42.49 (3C), 48.02 (2C), 50.43, 63.11, 112.36, 120.33, 123.34, 126. 25, 131.66, 146.89; ESI-MS (*m/z*) = 282.1 ($[M+H]^+$); Anal. Calcd for $C_{18}H_{23}N_3$: C, 76.83; H, 8.24; N, 14.93; Found: C, 76.65; H, 8.12; N, 14.81.

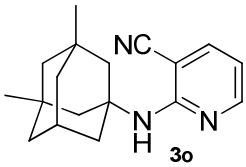
**2-(((1*r*,3*R*,5*S*,7*r*)-3,5-dimethyladamantan-1-yl)amino)benzonitrile (3n)**



3n

White crystal; m.p. 75-76 ℃; IR (KBr, *v*, $cm^{-1}$): 3403, 2945, 2893, 2205, 1605, 1576, 1514, 1463; $^1$H NMR (400MHz, $CDCl_3$) ($\delta$, ppm): 0.90 (6H, s, Me-H), 1.20 (2H, s, Ad-H), 1.33-1.42 (4H, m, Ad-H), 1.57-1.68 (4H, m, Ad-H), 1.85 (2H, s, Ad-H), 2.21-2.23 (1H, m, Ad-H), 4.45 (1H, s, N-H), 6.64-6.68 (1H, m, phenyl-H), 7.00 (1H, d, J = 8.8 Hz, phenyl-H), 7.30-7.34 (1H, m, phenyl-H), 7.38 (1H, d, J = 8.0 Hz, phenyl-H); $^{13}$C NMR (100 MHz, $CDCl_3$) ($\delta$, ppm): 30.31 (2C), 32.79, 41.08 (2C), 42.65 (3C), 48.73 (2C), 50.62, 54.56, 95.35, 114.92, 116.67, 120.94, 133.20, 133.47, 152.02; ESI-MS (*m/z*) = 281.1 ($[M+H]^+$); Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99; Found: C, 81.25; H, 8.52; N, 9.91.

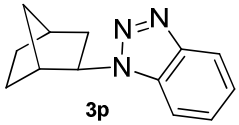
**2-(((1*r*,3*R*,5*S*,7*r*)-3,5-dimethyladamantan-1-yl)amino)nicotinonitrile (3o)**



3o

White crystal; m.p. 70-71 ℃; IR (KBr, *v*, $cm^{-1}$): 3398, 2941, 2843, 2215, 1591, 1575, 1416; $^1$H NMR (400MHz, $CDCl_3$) ($\delta$, ppm): 0.88 (6H, s, Me-H), 1.18-1.20 (2H, m, Ad-H), 1.30-1.44 (4H, m, Ad-H), 1.73-1.84 (4H, m, Ad-H), 2.00 (2H, s, Ad-H), 2.17-2.19 (1H, m, Ad-H), 4.93 (1H, s, N-H), 6.51-6.54 (1H, m, pyridine-H), 7.57-7.59 (1H, m, pyridine-H), 8.22-8.24 (1H, m , pyridine-H); $^{13}$C NMR (100 MHz, $CDCl_3$) ($\delta$, ppm): 30.23 (2C), 32.59, 40.16 (2C), 42.75 (3C), 47.73 (2C), 50.69, 54.77, 100.71, 111.23, 117.29, 141. 19, 152.24, 160.53; ESI-MS (*m/z*) = 282.3 ($[M+H]^+$); Anal. Calcd for $C_{18}H_{23}N_3$: C, 76.83; H, 8.24; N, 14.93; Found: C, 76.65; H, 8.32; N, 14.91.

**1-((1*R*,4*S*)-bicyclo[2.2.1]heptan-2-yl)-1*H*-benzo[*d*][1,2,3]triazole (3p)**

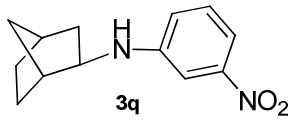


3p

White crystal; m.p. 75-76 ℃; IR (KBr, *v*, $cm^{-1}$): 3062, 2960, 2867, 1613, 1453, 741; $^1$H NMR (400MHz, $CDCl_3$) ($\delta$, ppm): 1.31-1.47 (4H, m, norbornane-H), 1.61-1.77 (2H, m, norbornane-H), 1.96-2.03 (2H, m, norbornane-H), 2.55-2.70 (2H, m, norbornane-H), 4.56-4.59 (1H, m, norbornane-H), 7.35 (1 H, td, J = 7.6, 0.0 Hz,

benzotriazole-H), 7.45 (1 H, td, J = 7.2, 0.8 Hz, benzotriazole-H), 7.53 (1 H, d, J = 9.2 Hz, benzotriazole-H), 8.04 (1 H, d, J = 8.0 Hz, benzotriazole-H); $^{13}$C NMR (100 MHz, $CDCl_3$) ($\delta$, ppm): 27.11, 28.76, 35.95, 36.00, 37.36, 42.96, 61.93, 109.76, 119.91, 123.88, 126.81, 133.02, 146.26; ESI-MS (*m/z*) = 214.1 ($[M+H]^+$).

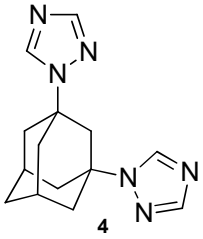
**(1*R*,4*S*)-*N*-(3-nitrophenyl)bicyclo[2.2.1]heptan-2-amine (3q)**



3q

Yellow crystal; m.p. 65-66 ℃; IR (KBr, *v*, $cm^{-1}$): 3413, 2960, 2867, 1621, 1571, 1534, 1332; $^1$H NMR (400MHz, $CDCl_3$) ($\delta$, ppm): 1.18-1.23 (4H, m, norbornane-H), 1.43-1.56 (3H, m, norbornane-H), 1.77-1.82 (1H, m, norbornane-H), 2.19-2.25 (2H, m, norbornane-H), 3.19 (1H, m, norbornane-H), 3.87 (1H, s, NH), 6.72-6.75 (1H, m, phenyl-H), 7.15-7.19 (1H, m, phenyl-H), 7.39-7.41 (1H, m, phenyl-H), 7.46-7.47 (1H, m, phenyl-H); $^{13}$C NMR (100 MHz, $CDCl_3$) ($\delta$, ppm): 26.42, 28.45, 35.56, 35.75, 41.02, 41.24, 56.59, 106.70, 111.52, 119.05, 129.73, 148.30, 149.68; ESI-MS (*m/z*) = 233.2 ($[M+H]^+$).

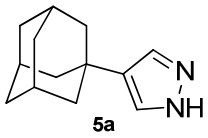
**(1*s*,3*s*,5*s*,7*s*)-1,3-di(1*H*-1,2,4-triazol-1-yl)adamantine (4)**



4

White crystal; m.p. 174-176 ℃; IR (KBr, v, cm-1): 3131, 2936, 2860, 1501, 1279; $^1$H NMR (400MHz, $CDCl_3$) (δ, ppm): 1.84 (2H, s, Ad-H), 2.21-2.32 (8H, m, Ad-H), 2.61 (4H, s, Ad-H), 7.96 (2H, s, triazole-H), 8.16 (2H, s, triazole-H); $^{13}$C NMR (100 MHz, $CDCl_3$) (δ, ppm): 29.69 (2C), 34.59, 41.22 (4C), 47.23, 59.48 (2C), 139.45, 151.67; ESI-MS (m/z) = 271.2 ($[M+H]^+$); Anal. Calcd for $C_{14}H_{18}N_6$: C, 62.20; H, 6.71; N, 31.09; Found: C, 62.18; H, 6.64; N, 31.15.

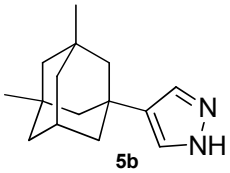
**4-((3*s*,5*s*,7*s*)-adamantan-1-yl)-1*H*-pyrazole (5a)**



5a

White crystal; m.p. 208-210 ℃; IR (KBr, *v*, $cm^{-1}$): 3155, 2902, 2846, 1449, 958; $^1$H NMR (400MHz, $CDCl_3$) ($\delta$, ppm): 1.76 (6H, s, Ad-H), 1.86 (6H, s, Ad-H), 2.04 (3H, s, Ad-H), 4.73 (1H, s, N-H), 7.44 (2H, s, pyrazole-H); $^{13}$C NMR (100 MHz, $CDCl_3$) ($\delta$, ppm): 28.78 (3C), 31.27, 36.84 (3C), 44.28 (3C), 130.14, 130.25, 133.29; ESI-MS (*m/z*) = 203.2 ($[M+H]^+$).

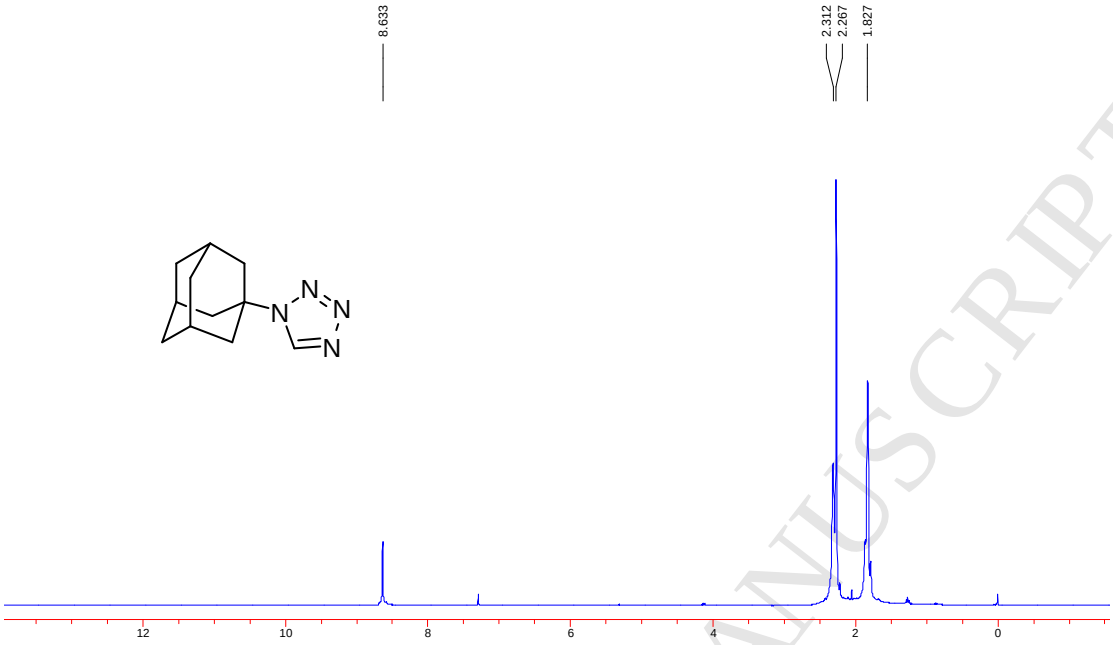
**4-((1*r*,3*R*,5*S*,7*r*)-3,5-dimethyladamantan-1-yl)-1*H*-pyrazole (5b)**

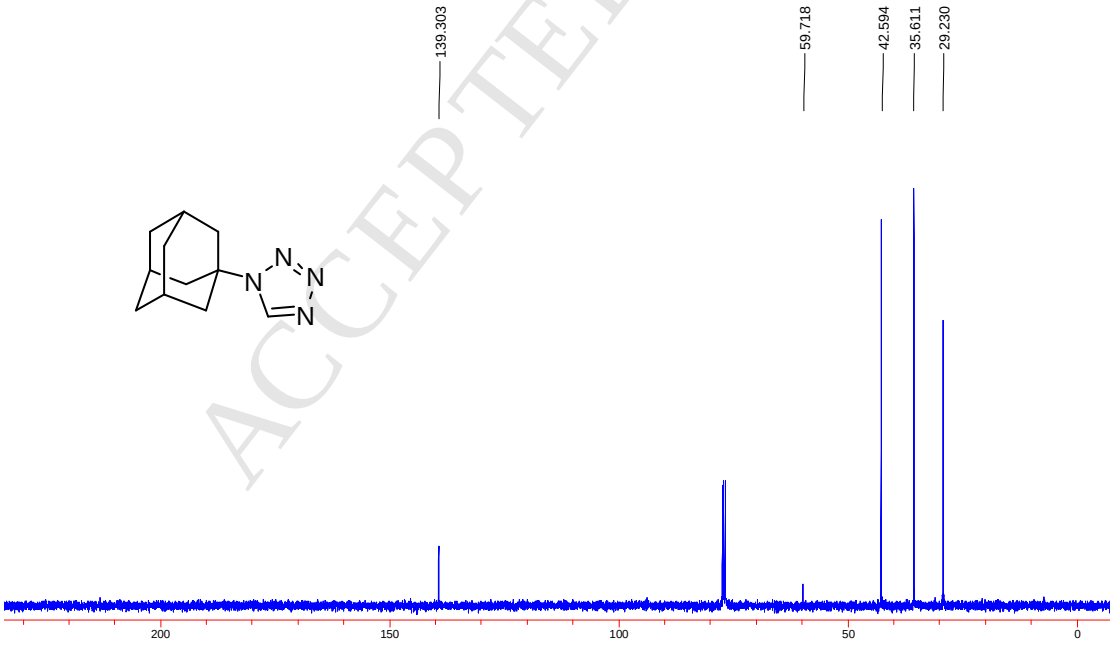


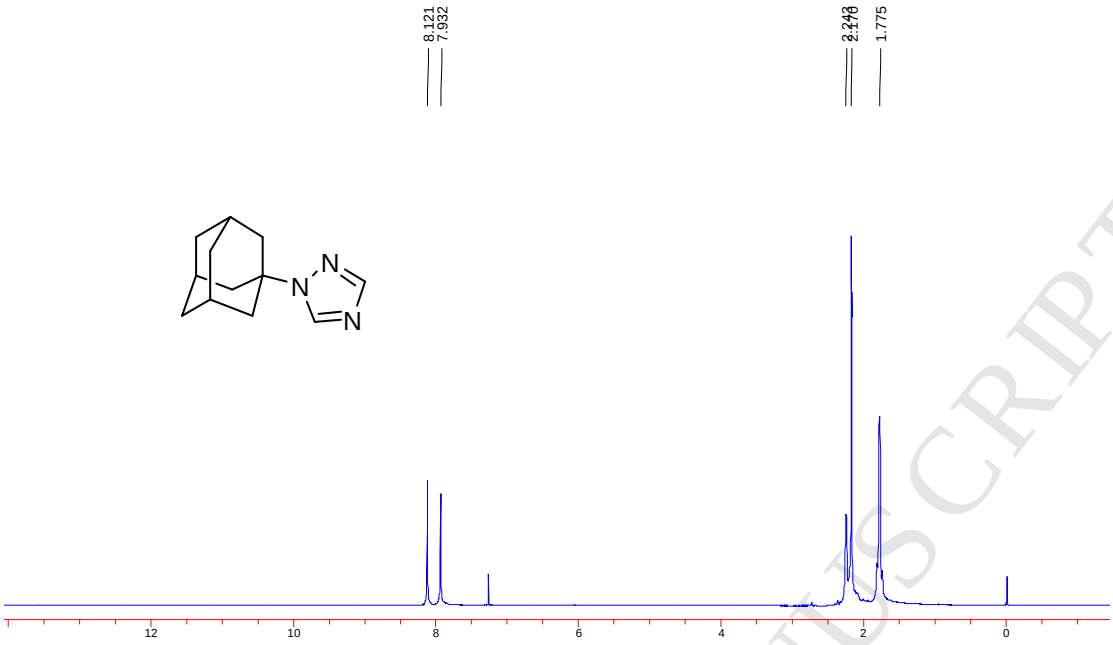

**5b**

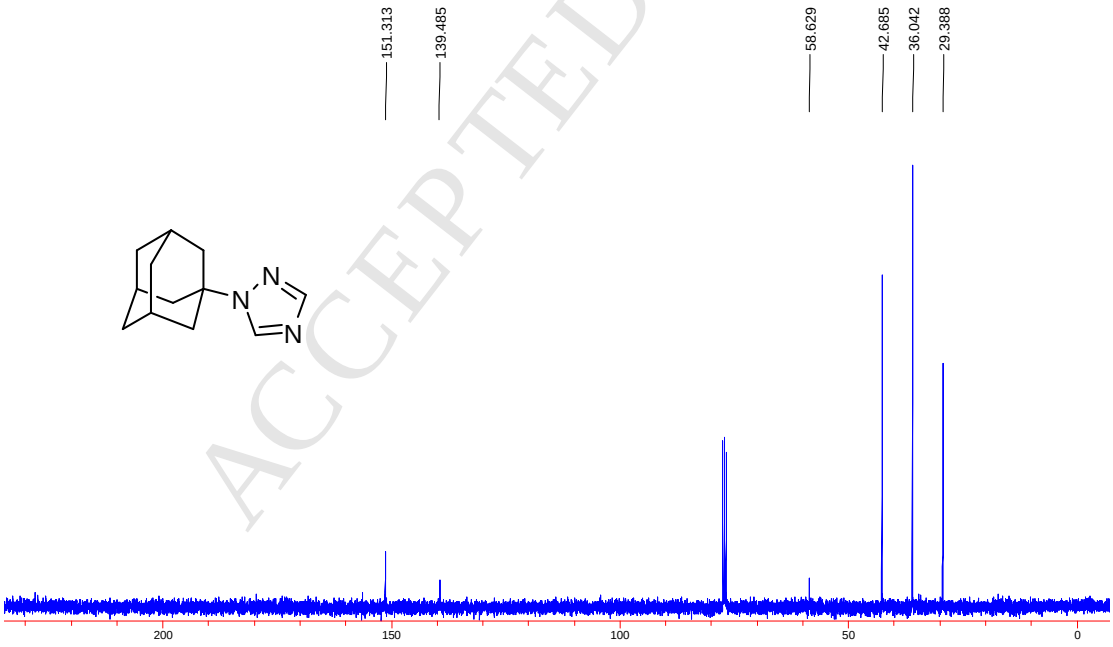
White crystal; m.p. 114-117 ℃; IR (KBr, *v*, $cm^{-1}$): 3143, 2941, 2843, 1443, 954; $^{1}H$ NMR (400MHz, $CDCl_3$) (*δ*, ppm): 0.90 (6H, s, Me-H), 1.21 (2H, s, Ad-H), 1.37-1.45 (4H, m, Ad-H), 1.67-1.82 (4H, m, Ad-H), 2.05 (2H, s, Ad-H), 2.27-2.29 (1H, m, Ad-H), 4.68 (1H, s, N-H), 7.43 (2H, s, pyrazole-H); $^{13}C$ NMR (100 MHz, $CDCl_3$) (*δ*, ppm): 30.08 (2C), 31.17, 32.92, 40.69 (2C), 42.43 (3C), 48.00 (2C), 50.41, 130.09, 130.15, 133.27; ESI-MS (*m/z*) = 231.3 ($[M+H]^+$); Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16; Found: C, 78.18; H, 9.54; N, 12.21.

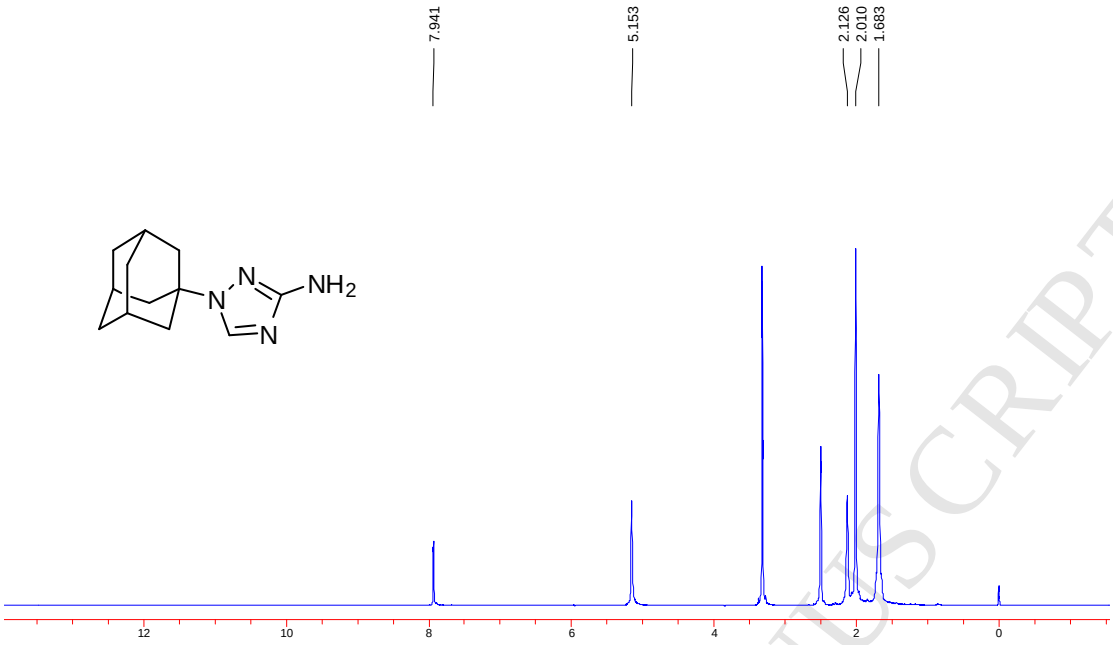
# $^{1}$H NMR and $^{13}$C NMR Spectra of products

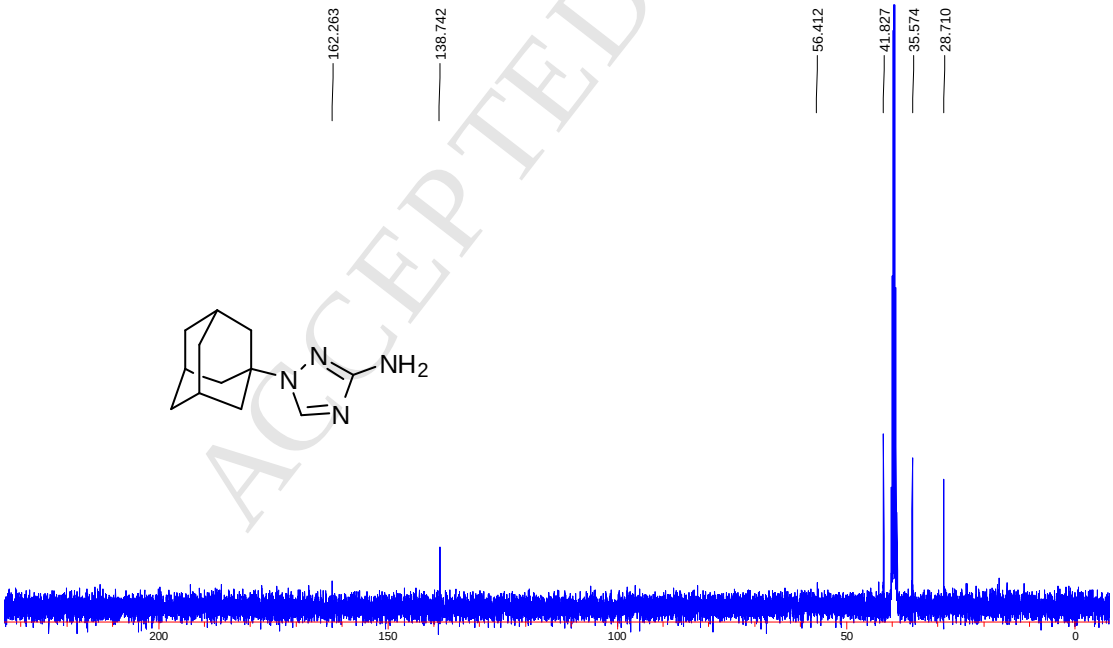


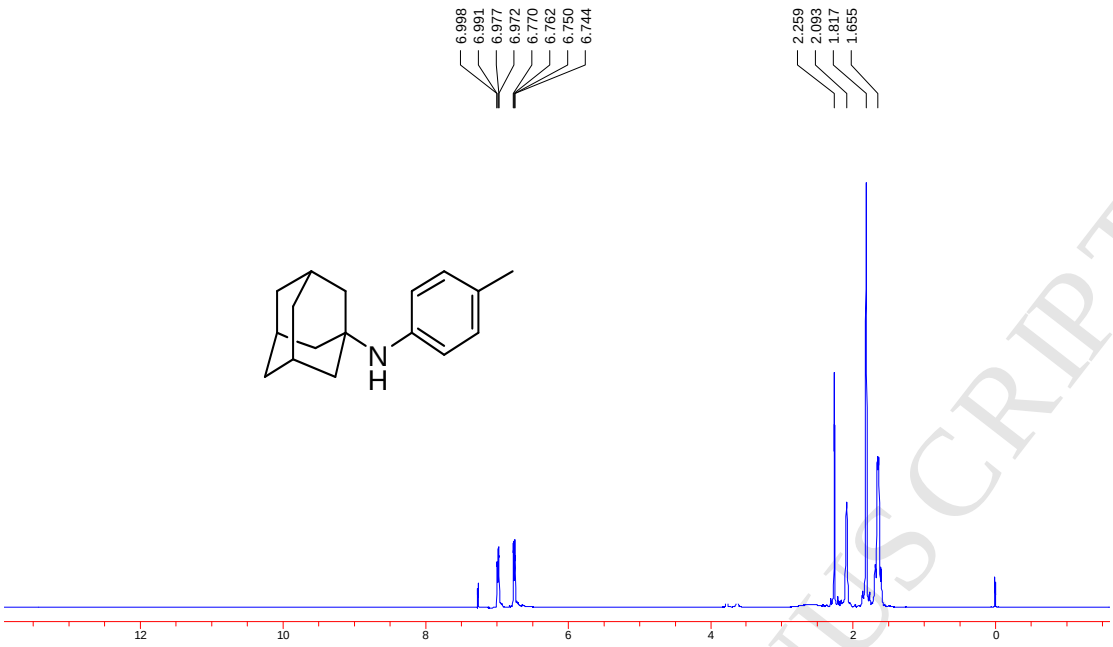



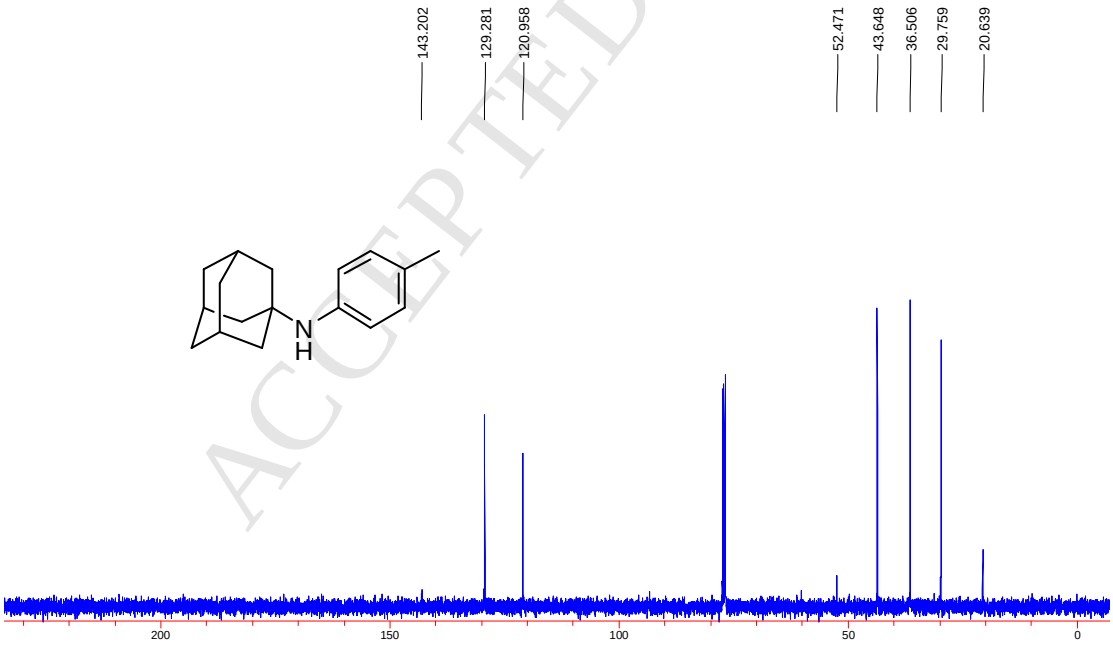


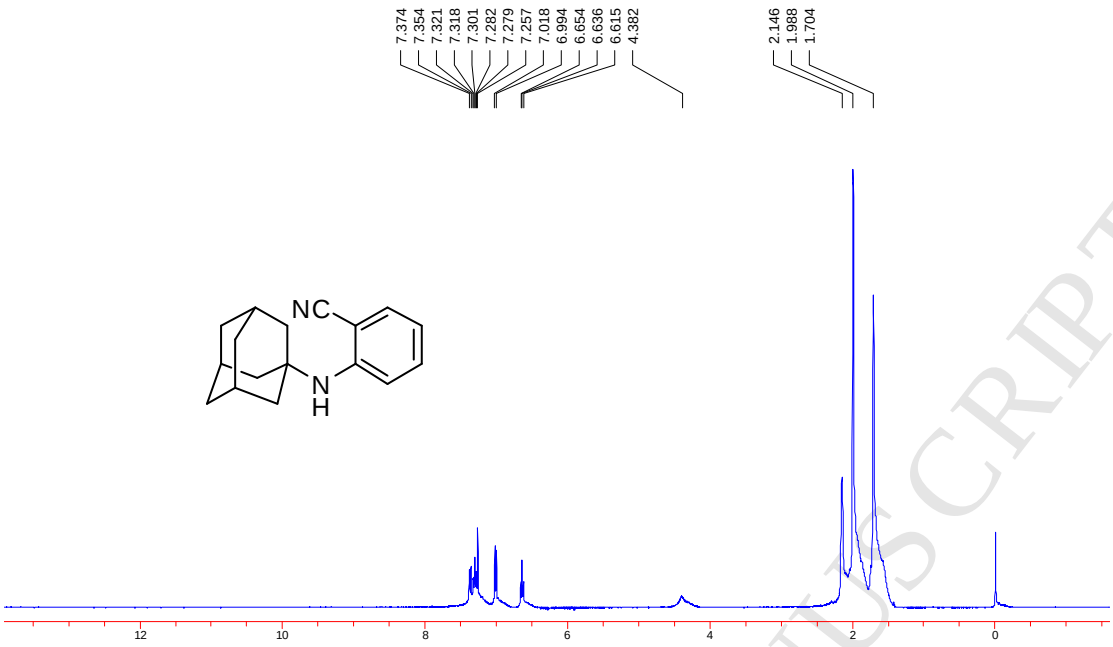



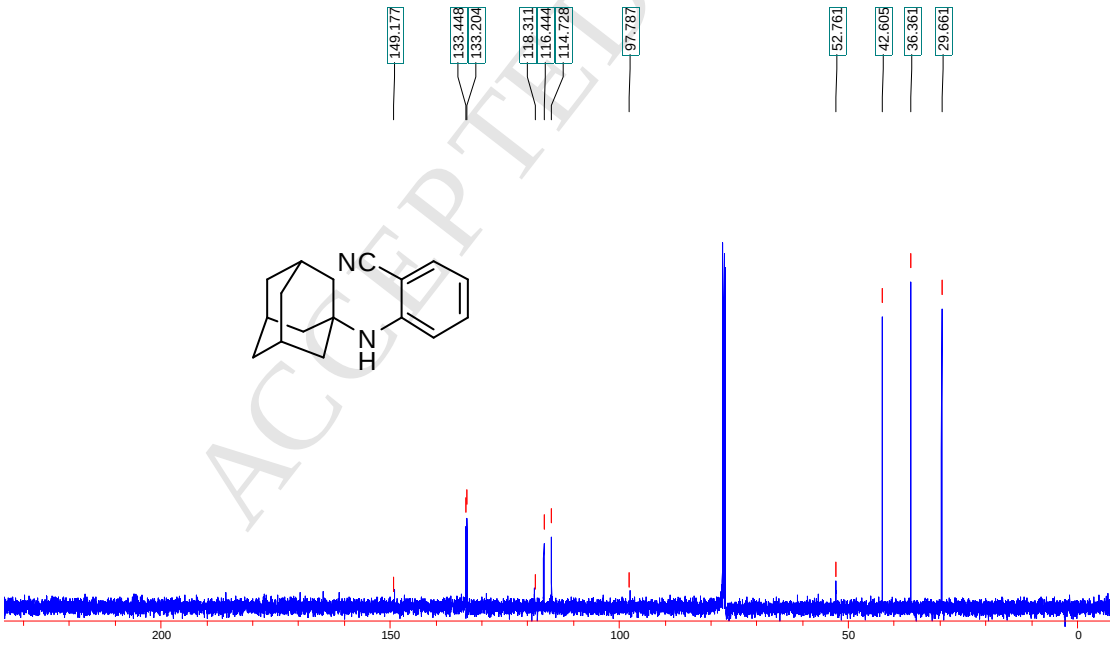


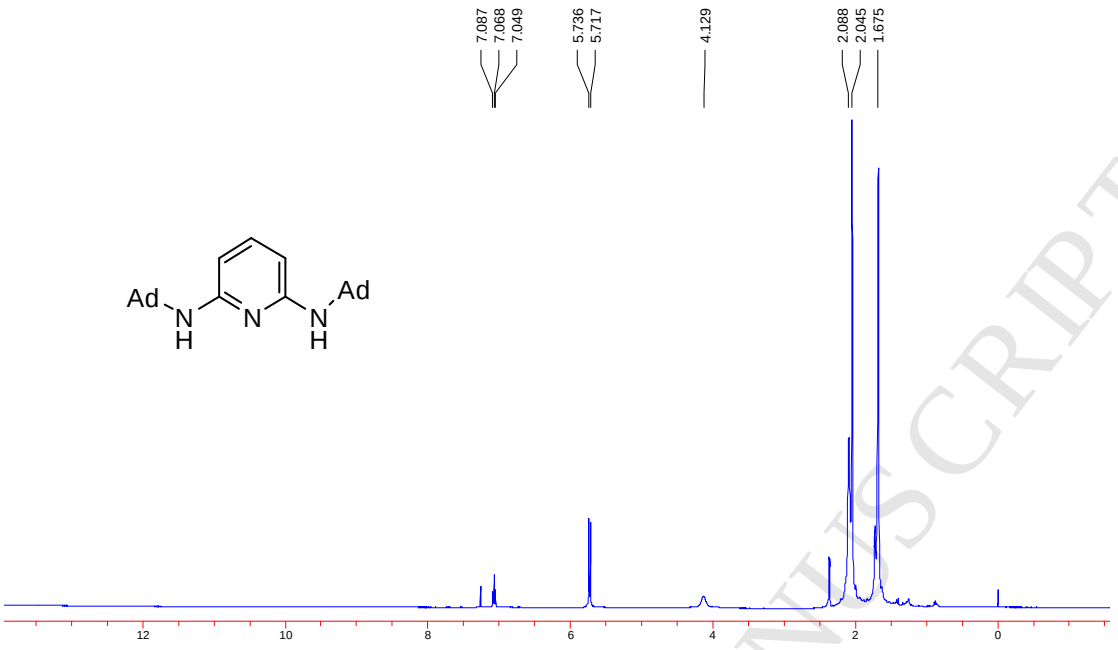



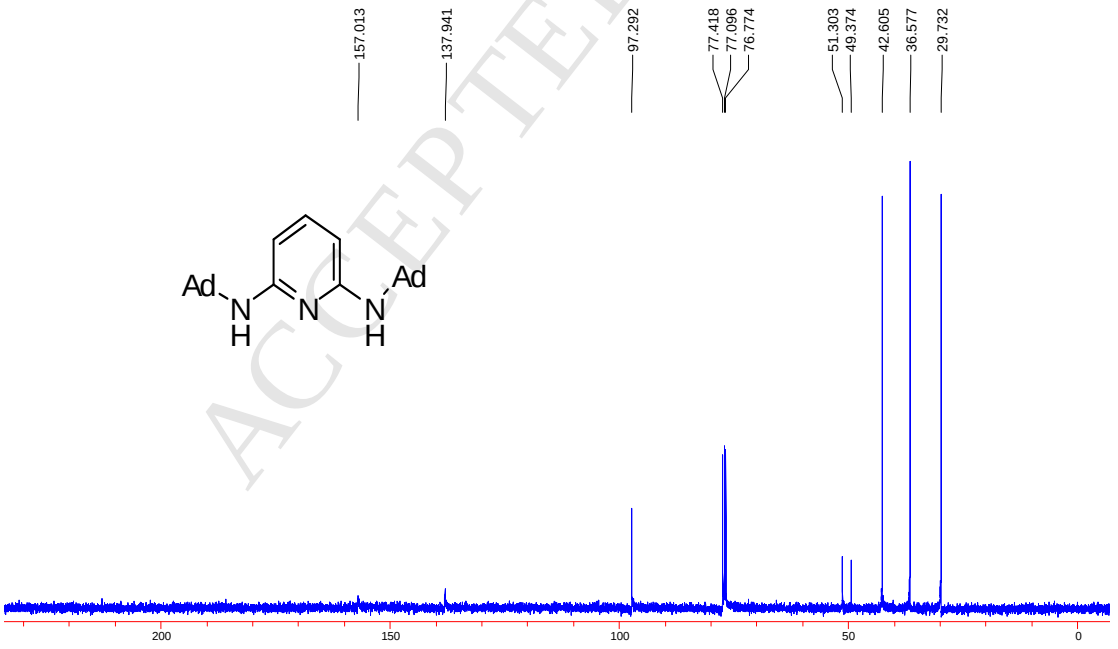


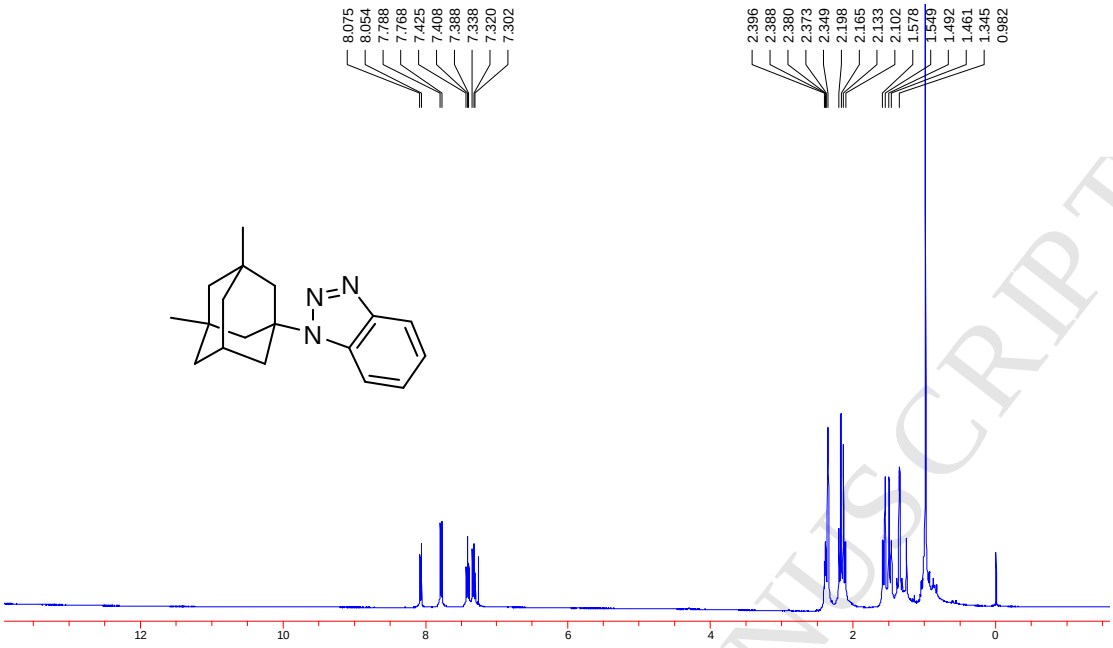



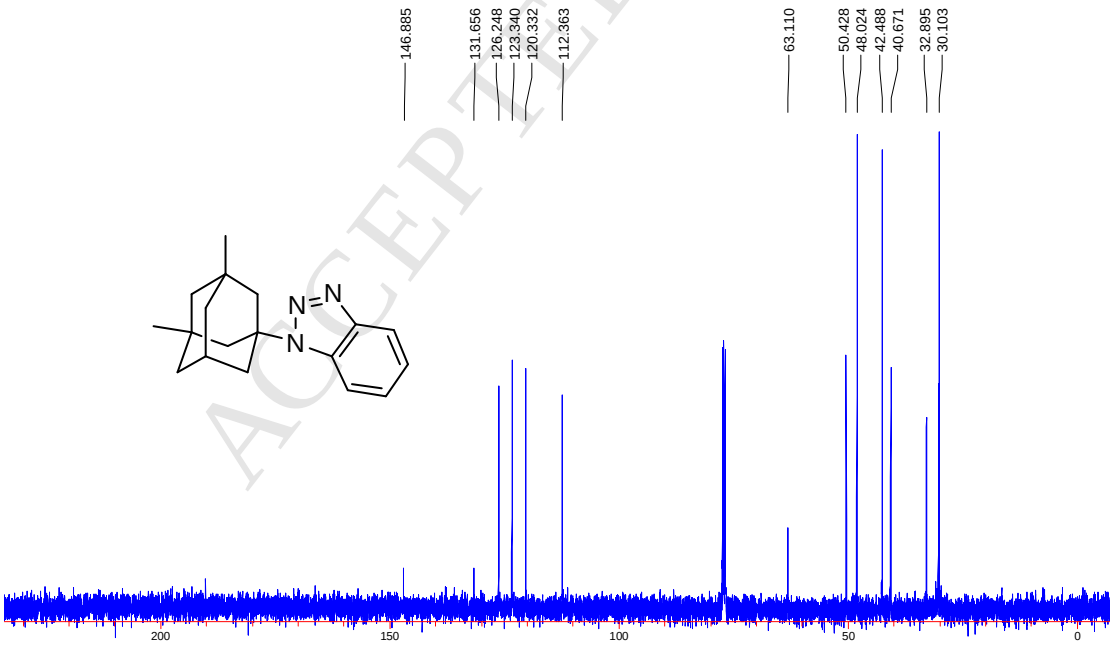


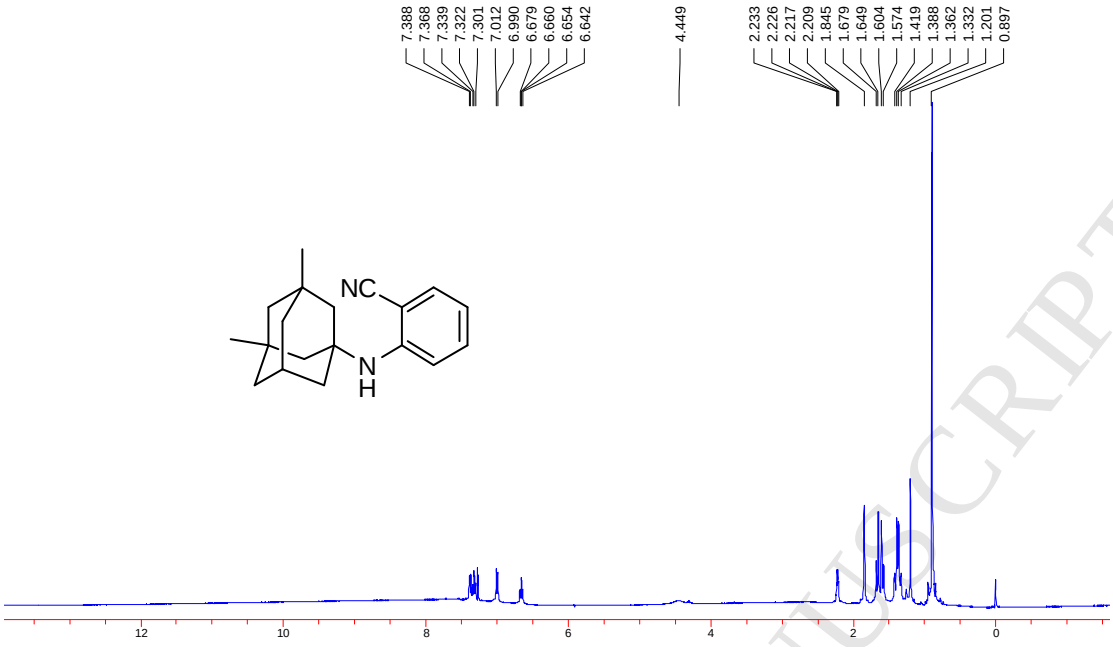



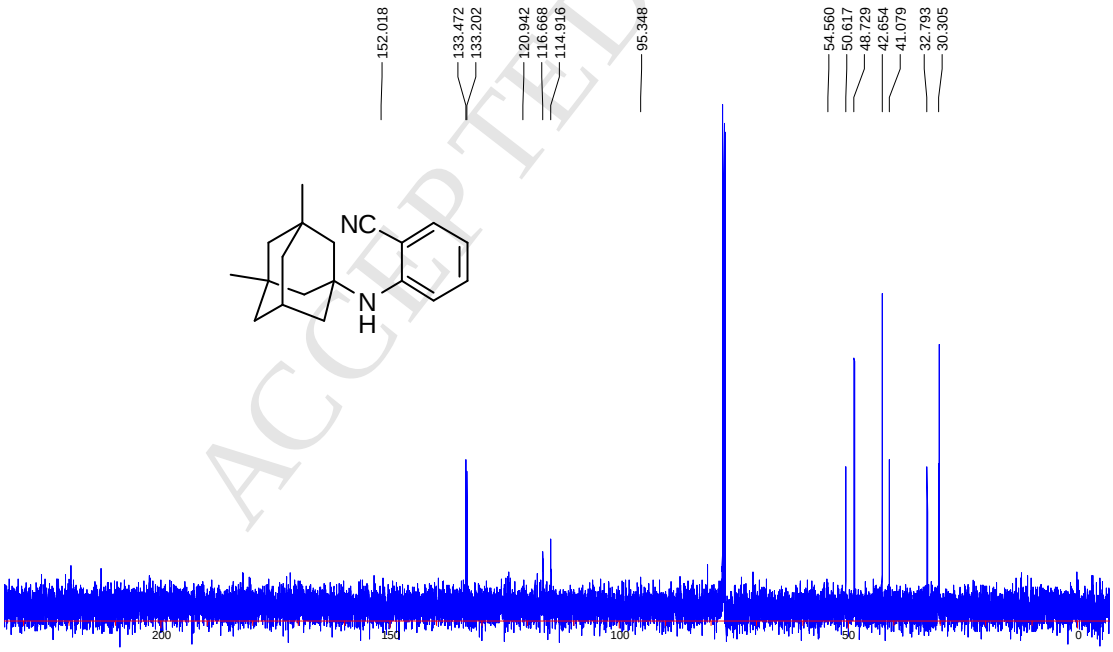


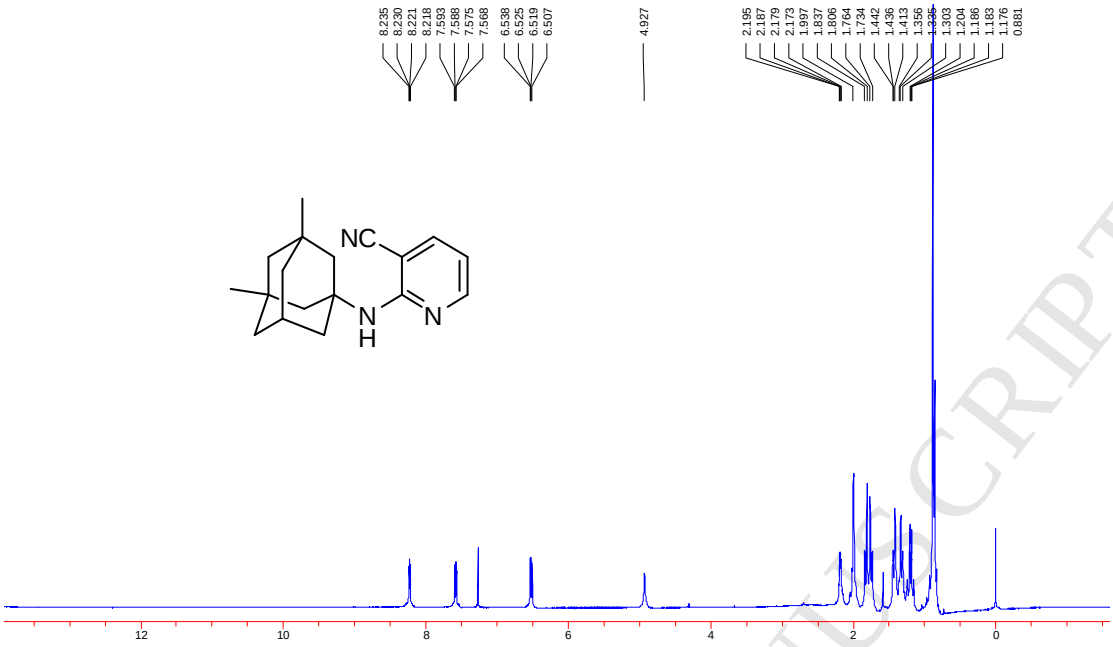



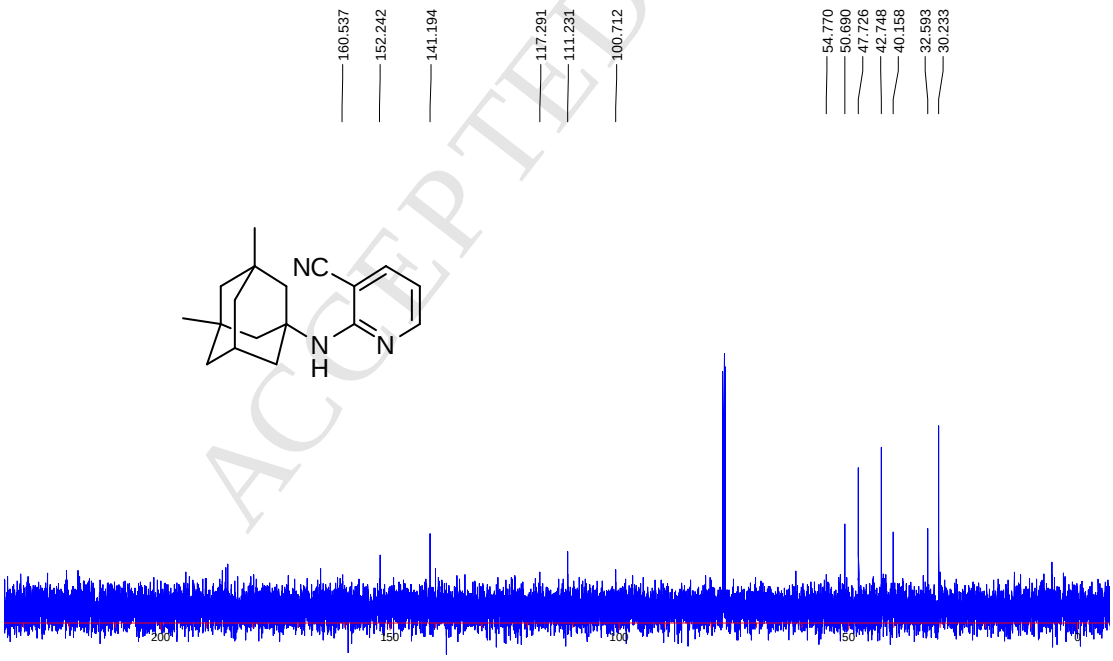


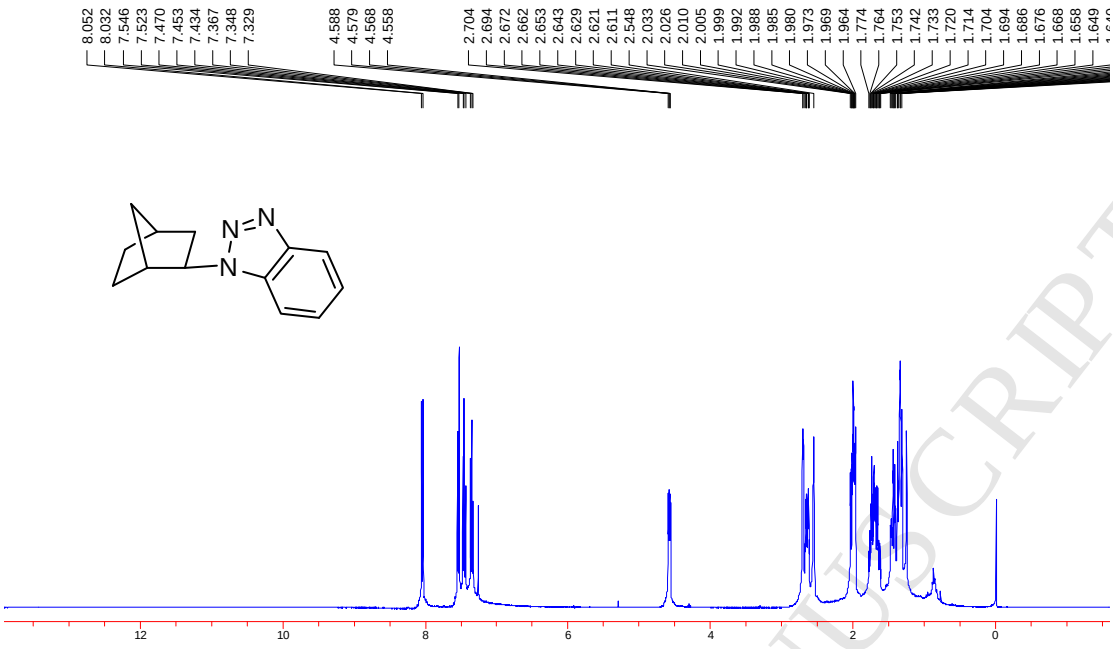



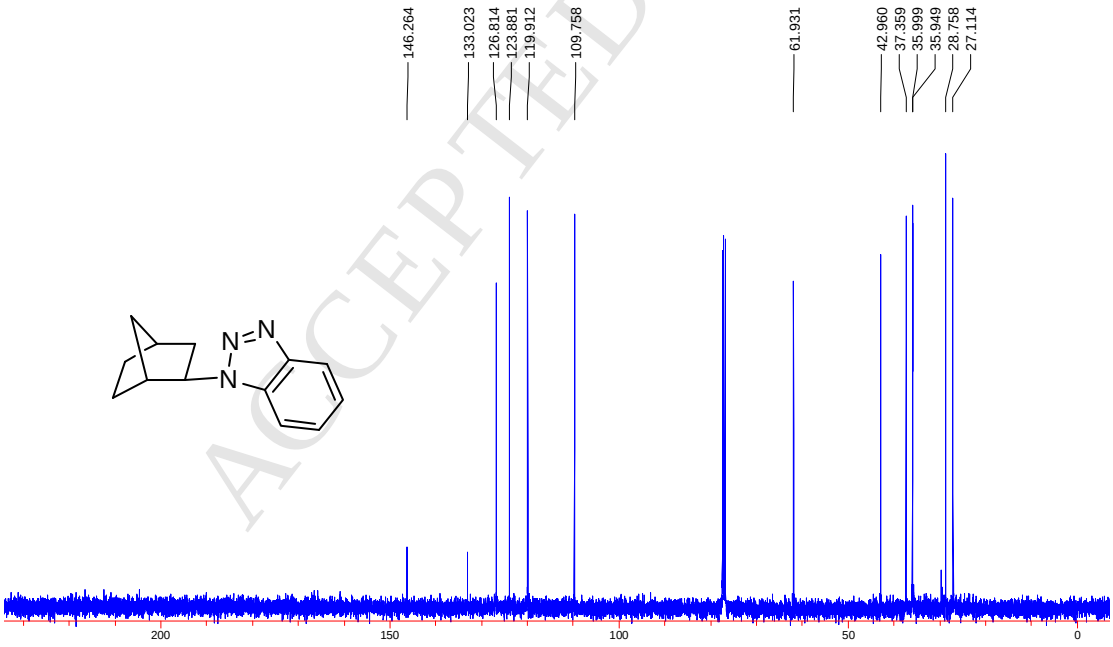


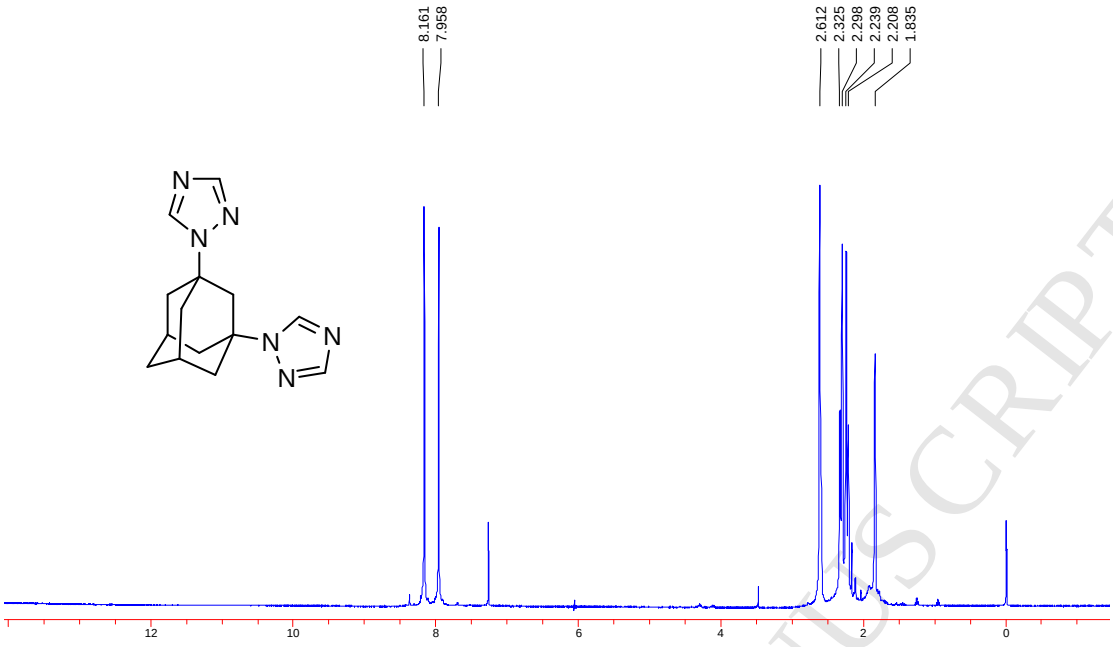



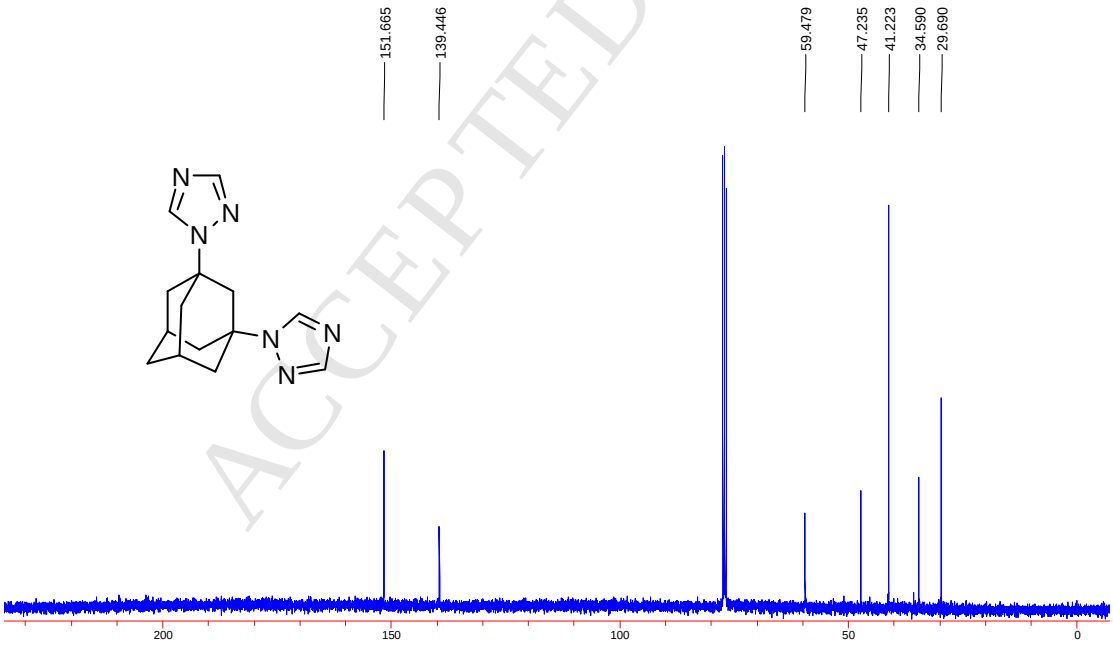


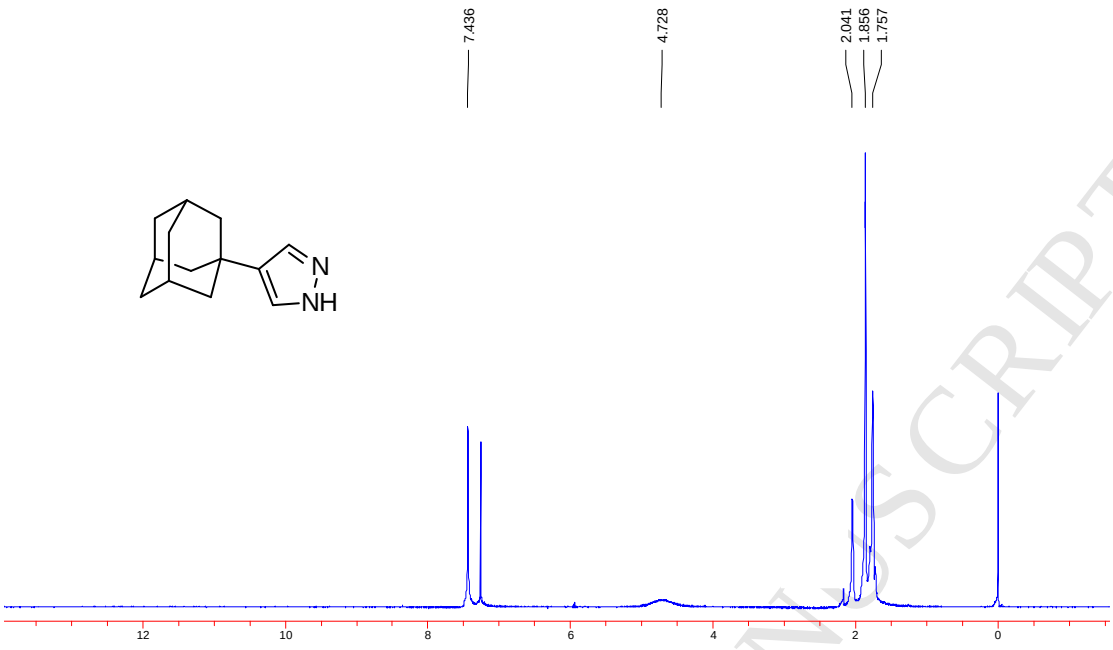



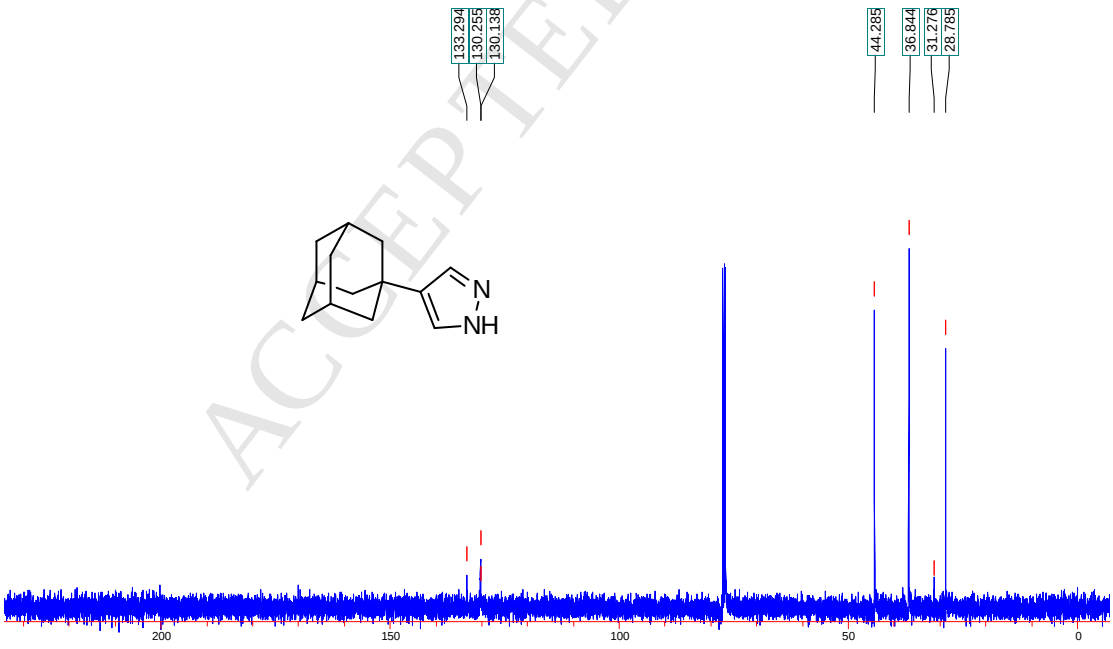


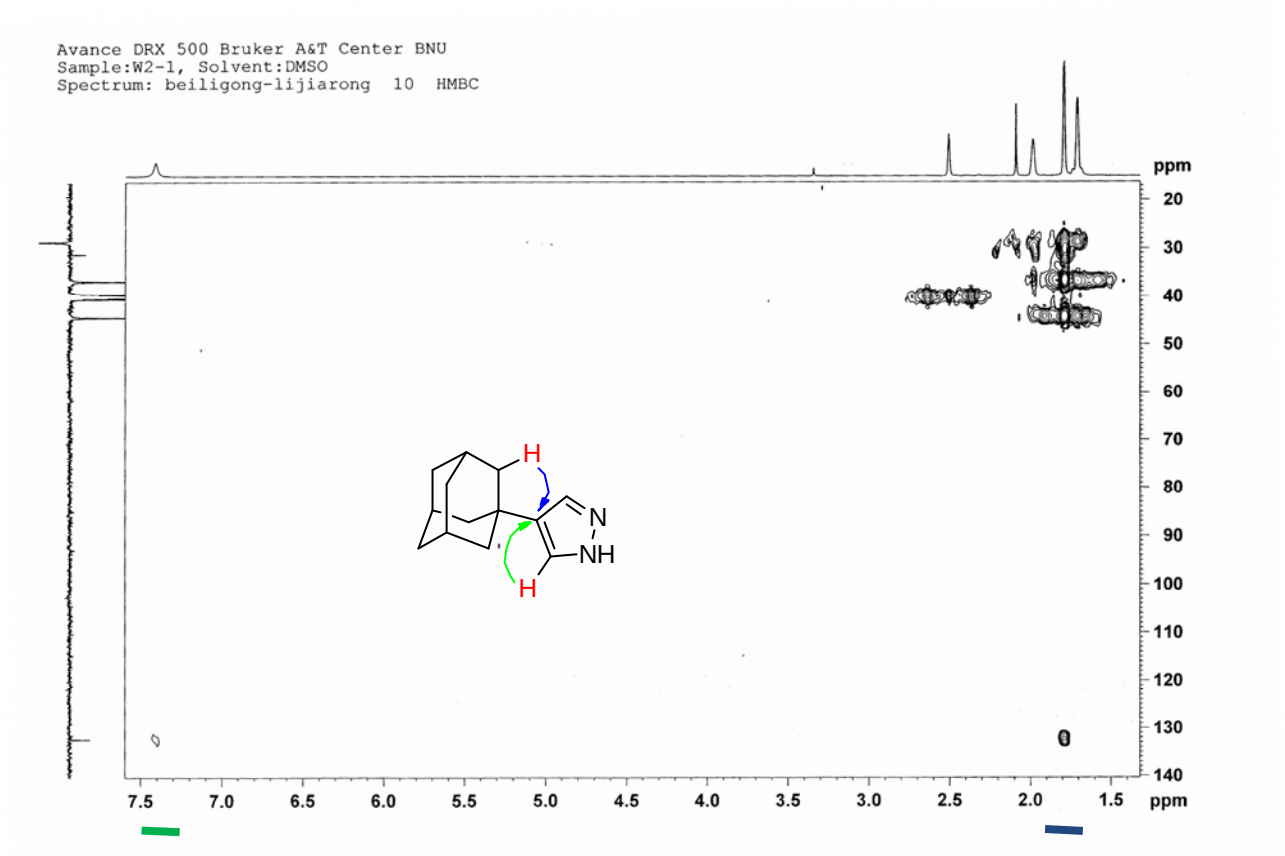





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60
70
80
90
100
110
120
130
140
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7.0
6.5
6.0
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2.0
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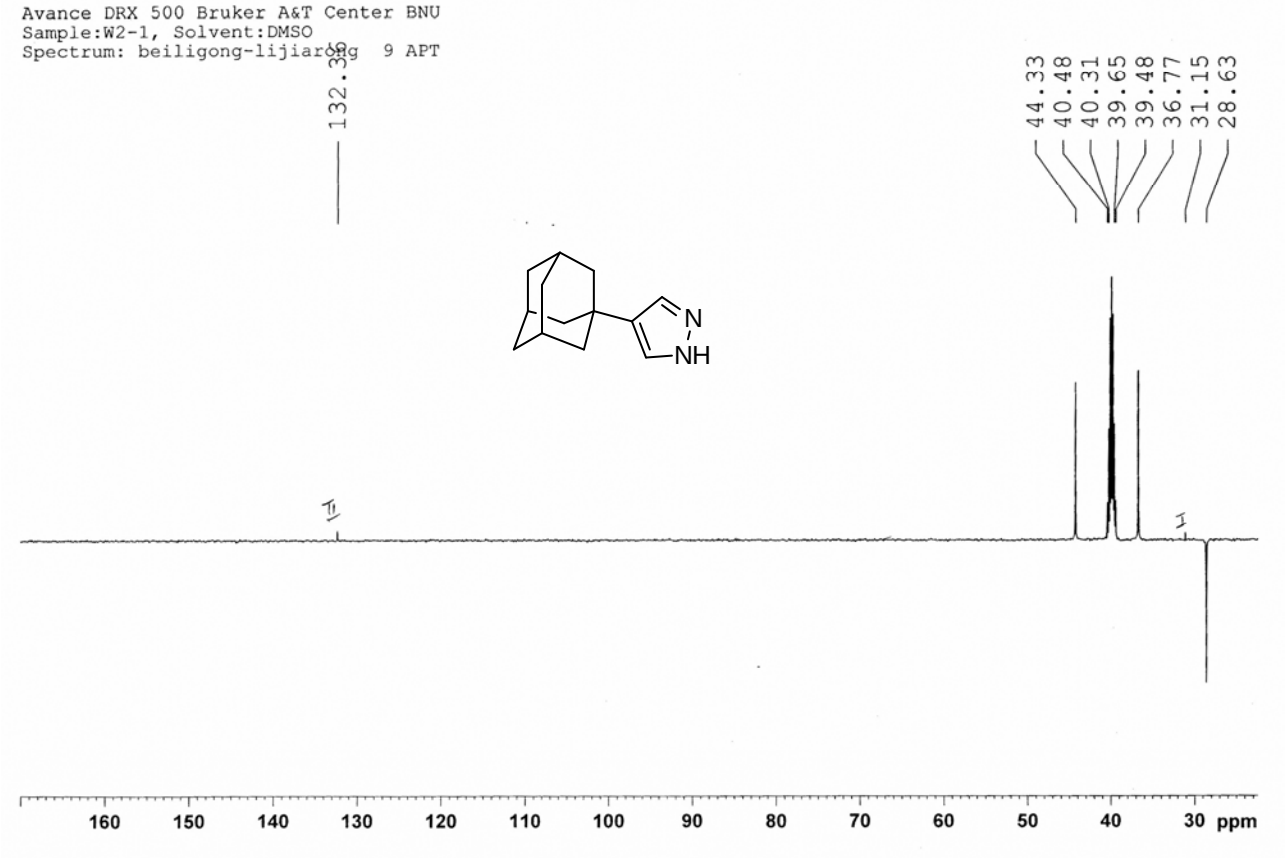
ppm
H
N
NH
H


Avance DRX 500 Bruker A&T Center BNU
Sample:W2-1, Solvent:DMSO
Spectrum: beiligong-lijiarong 9 APT
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NH
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ppm