# Organic Syntheses

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

REGIOSELECTIVE SYNTHESIS OF 1,3,5-TRISUBSTITUTED PYRAZOLES BY THE REACTION OF *N*-MONOSUBSTITUTED HYDRAZONES WITH NITROOLEFINS
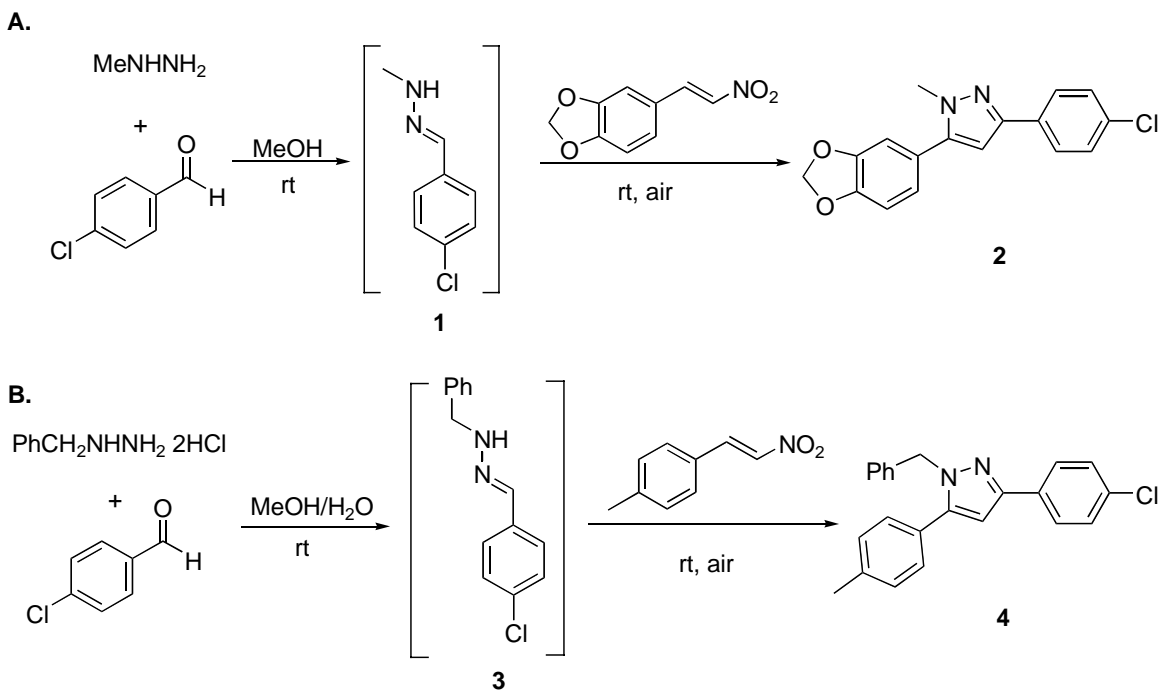
Submitted by Xiaohu Deng and Neelakandha S. Mani.[1]
Checked by Kay M. Brummond, Daitao Chen and Josh Osbourn.[2]

1. Procedure

A.   *5-Benzo[1,3]dioxol-5-yl-3-(4-chlorophenyl)-1-methyl-1H-pyrazole (2)*. A 500-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer (fitted with a 7.5-cm glass paddle), a condenser (open to the atmosphere) and a rubber septum is charged with 4-chlorobenzaldehyde (5.00 g, 35.5 mmol, 1.25 equiv) and MeOH (200 mL) (Note 1). Methylhydrazine (1.9 mL, 1.66 g, 35.5 mmol, 1.25 equiv) is added to this solution dropwise via syringe over 3 min (Note 1). After 2 h at room temperature, the formation of hydrazone **1** is complete (Note 2). The septum is removed and 3,4-methylenedioxy-β-nitrostyrene (5.50 g, 28.5 mmol) is added as a solid in one portion (Note 3). The reaction mixture is stirred at room temperature open to air for 72 h (Notes 4-6). The condenser is replaced with a 125-mL, pressure-equalizing addition funnel and water

(60 mL) is added to the mixture over 20 min. The resulting suspension is stirred at room temperature for an additional 1 h. The yellow solid that is formed is collected on a 250-mL fritted glass Büchner funnel by vacuum filtration (washing with ca. 30 mL of 1:1 MeOH/H_2O) and is suction-dried overnight. The yellow solid is dissolved in a minimum amount of boiling MeOH, then after being cooled to room temperature, the product is collected by suction filtration in 125-mL fritted glass Büchner funnel as a fine brown powder (6.07 g, 19.3 mmol, 68%) (Note 7).

B. *1-Benzyl-3-(4-chlorophenyl)-5-p-tolyl-1H-pyrazole (4).* In a 500-mL, one-necked, round-bottomed flask equipped with a 3.8-cm, egg-shaped Teflon-coated magnetic stirring bar and a condenser, 4-chlorobenzaldehyde (4.86 g, 34.5 mmol, 1.25 equiv) is dissolved in MeOH (150 mL) and then water (10 mL) is added (Note 8). Benzylhydrazine dihydrochloride (6.75 g, 34.5 mmol, 1.25 equiv) is added in one portion (Note 9). After stirring the mixture at room temperature for 3 h, hydrazone **3** is formed (Note 10). 4-Methyl-β-nitrostyrene (4.51 g, 27.7 mmol) (Note 11) is added in one portion and the reaction solution is stirred at room temperature open to air until complete (Notes 12, 13). The condenser is replaced with a 125-mL, pressure-equalizing addition funnel and water (50 mL) is slowly added into the mixture over 20 min and the resulting white suspension is stirred at room temperature for an additional 1 h. The resulting white solid is collected on a 250-mL fritted glass Büchner funnel by vacuum filtration (washing with ca. 30 mL of 1:1 MeOH/H_2O) and is suction-dried (ca. 10 min). The solid is transferred into a 50-mL, round-bottomed flask and further dried under vacuum at room temperature for 8 h. The title compound is obtained as a white solid (9.12 g, 25.3 mmol, 92%) (Note 14).

2. Notes

1. 4-Chlorobenzaldehyde (97% purity) and methylhydrazine (98% purity) were purchased from Aldrich. Methanol (HPLC grade) was purchased from EMD. All reagents were used as received without further purification. HPLC t_R = 8.68 min (Note 2) for 4-chlorobenzaldehyde.

2. The checkers monitored the progress of the reaction by ^{1}H NMR spectroscopy. (Typical procedure for ^{1}H NMR analysis: an aliquot of the reaction mixture was transferred into an NMR tube via pipette. The NMR tube was fitted with a rubber septum, connected to a vacuum with a needle, the solvent was evaporated and the residue was dissolved in $CDCl_3$). NMR

data for hydrazone **1**; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 3.01 (s, 3 H), 7.34 (d, *J* = 8.5 Hz, 2 H), 7.49 (s, 1 H), 7.52 (d, *J* = 8.5 Hz, 2 H). The submitters monitored the formation of hydrazone **1** by HPLC analysis. All HPLC analyses were performed on a Hewlett Packard 1100 (Agilent ZORBAX® Eclipse XDB-C8, 5 μm, 4.6 x 150 mm, 1 mL/min, acetonitrile/water with 0.05% trifluoroacetic acid :   1% acetonitrile/99% water to 99% acetonitrile/1% water ramp over 8 min, then hold at 99% acetonitrile/1% water) HPLC t_R = 7.43 min for **1**.

3.   3,4-Methylenedioxy-β-nitrostyrene (98% purity) was purchased from Alfa Aesar and used as received. HPLC t_R = 8.83 min (Note 2).

4.   Air is essential for the reaction to proceed.

5.   The reaction time is dependent upon the scale and the stirring speed. ^{1}H NMR analysis of small aliquots is desirable to follow the reaction progress. The submitters reported a reaction time of 40 h for a 5 g reaction; the checkers observe a reaction time of 72 h for the same reaction scale.

6.   As the reaction proceeds 3,4-methylenedioxy-β-nitrostyrene slowly dissolves and the product precipitates, evidenced by a brown heterogeneous mixture turning homogeneous and a yellow precipitate forming after 1-2 h.

7.   The product displayed the following physicochemical properties: mp 117-120 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 3.90 (s, 3 H), 6.05 (s, 2 H), 6.52 (s, 1 H), 6.91-6.92 (m, 3 H), 7.37 (dt, *J* = 9.0, 2.0 Hz, 2 H), 7.75 (dt, *J* = 9.0, 2.0 Hz, 2 H); ^{13}C NMR (125.7 MHz, CDCl$_3$) δ: 37.7, 101.7, 103.3, 108.8, 109.4, 122.9, 124.3, 126.9, 129.0, 132.2, 133.5, 145.1, 148.1, 148.2, 149.5; IR (film) cm^{-1}: 2895 (w), 1554 (w), 1478 (s); MS *m/z* (relative intensity): 312 (M$^+$, 100%); HRMS-ESI *m/z*: [M]$^+$ calcd for C$_{17}$H$_{13}$ClN$_2$O$_2$ 312.0666; found, 312.0663. Anal. Calcd for C$_{17}$H$_{13}$ClN$_2$O$_2$: C, 65.29; H, 4.19; N, 8.96. Found: C, 65.09; H, 4.13; N, 9.00. The submitters reported HPLC t_R = 10.47 min. The crude pyrazole (prior to recrystallization) is contaminated with a small amount of the 1,4-addition product (*E*)-1-(1-(benzo[d][1,3]dioxol-5-yl)-2-nitroethyl)-2-(4-chlorobenzylidene)-1-methylhydrazine as evidenced by the three resonances: 5.41 (dd, *J* = 13.2, 9.5 Hz, 1 H), 4.98 (dd, *J* = 9.5, 4.8 Hz, 1 H), 4.60 (dd, *J* = 13.2, 4.8, 1 H). For complete characterization of the 1,4-addition product see the original disclosure of this procedure by the authors.[3]

8.   Water (distilled) is necessary for hydrazone and pyrazole formation when the HCl salt of the hydrazine is used.

9. Benzylhydrazine dihydrochloride (97% purity) was purchased from Aldrich and used as received.

10. The checkers monitored the progress of the reaction by ^{1}H NMR spectroscopy. (Typical procedure for ^{1}H NMR analysis: an aliquot of the reaction mixture was transferred into an NMR tube via pipette. The NMR tube was fitted with a rubber septum, connected to a vacuum with a needle, the solvent was evaporated and the residue was dissolved in $CDCl_3$.) NMR data for hydrazone **3**; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.44 (s, 2 H), 5.74 (br s, 1 H), 7.30 (d, J = 8.5 Hz, 2 H), 7.32-7.28 (m, 1 H), 7.36-7.37 (m, 4 H), 7.48 (d, J = 8.5 Hz, 2 H), 7.55 (s, 1 H). The submitters reported the HPLC t_R = 10.05 min for **3** (Note 2).

11. 4-Methyl-β-nitrostyrene (98% purity) was purchased from Alfa Aesar and used as received. HPLC t_R = 9.42 min (Note 2).

12. Whereas the submitters report a 48 h reaction time, the checkers observed a reaction time of 88 to 92 h. The progress of the reaction was monitored by ^{1}H NMR spectroscopy.

13. As the reaction proceeds the product precipitates as a white solid after ca. 1-2 h.

14. No purification is necessary for 1-benzyl-3-(4-chlorophenyl)-5-*p*-tolyl-1*H*-pyrazole (**4**). The product displayed the following physicochemical properties:: mp 132-133 °C; HPLC t_R =11.99 min (Note 2); R_f = 0.43 (hexanes/EtOAc, 4/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.40 (s, 3 H), 5.38 (s, 2 H), 6.61 (s, 1 H), 7.11 (d, J = 7.0 Hz, 2 H), 7.21-7.32 (m, 7 H), 7.38 (dt, J = 9.0, 2.0 Hz, 2 H), 7.80 (dt, J = 9.0, 2.0 Hz, 2 H); ^{13}C NMR (125.7 MHz, CD_2Cl_2) δ: 21.5, 53.4, 103.7, 126.9, 127.1, 127.6, 127.7, 128.8, 129.0 (2C), 129.6, 132.3, 133.5, 137.9, 139.0, 146.0, 150.1; IR (film) cm^{-1}: 3028 (w), 2929 (w), 1490 (w), 1436 (s); MS m/z (relative intensity): 358 (M$^+$, 80%), 239 (26%), 91 (100%); HRMS-ESI m/z: [M]$^+$ calcd for $C_{23}H_{19}ClN_2$ 358.1237; found, 358.1225; Anal. Calcd for $C_{23}H_{19}ClN_2$, C, 76.98; H, 5.34; N, 7.81. Found: C, 76.85; H, 5.34; N, 7.84. The submitters reported greater than 98% purity based upon HPLC analysis and t_R = 11.99 min (Note 2).

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Substituted pyrazoles are important synthetic targets in the pharmaceutical industry.[4] Regioselective synthesis of the pyrazole ring remains a significant challenge for organic chemists.[5] Inspired by the literature precedent reactions of hydrazones and nitroolefins[6] we developed a general, one-pot, regioselective synthesis of substituted pyrazoles from N-monosubstituted hydrazones and nitro-olefins.

The outcome of the reaction depended upon the nature of solvents used (Table 1). Non-polar solvents such as toluene are not a good choice for the reaction, with no reaction being observed. Aprotic polar solvents generally favored the formation of Michael addition product **3**, with the exception of CH_2Cl_2. Protic polar solvents favored the formation of pyrazole **2**. Although AcOH and CH_2Cl_2 also afforded high **2:3** ratios, the reaction in alcoholic solvents such as MeOH and EtOH was much cleaner and provided the best yields of **2**.

Table 1. Solvent Effect on the Pyrazole Formation Reaction.
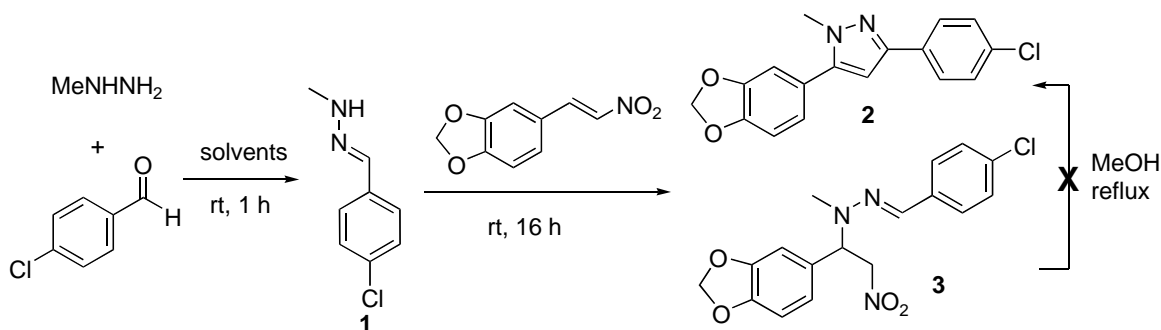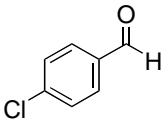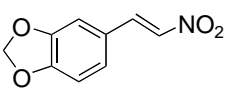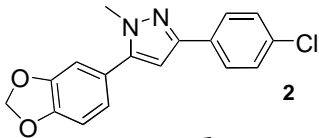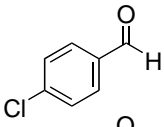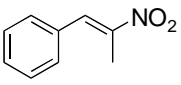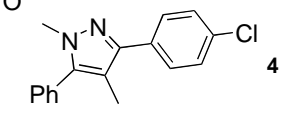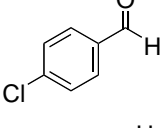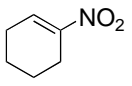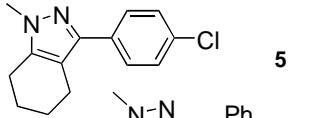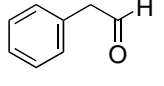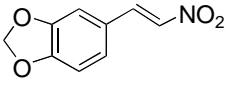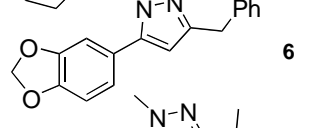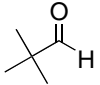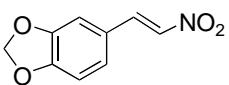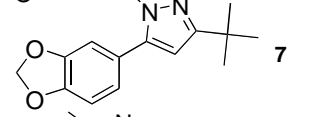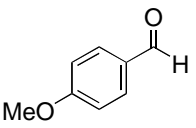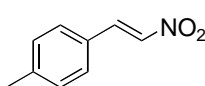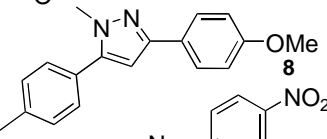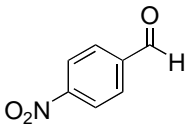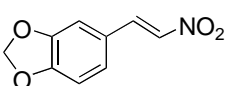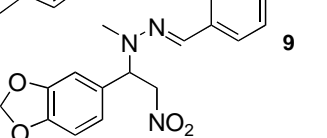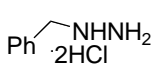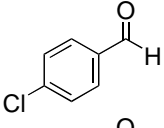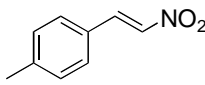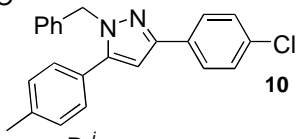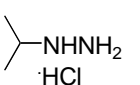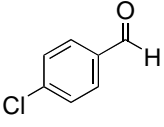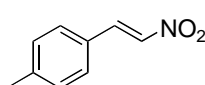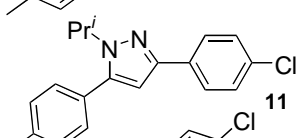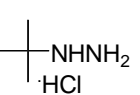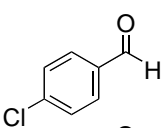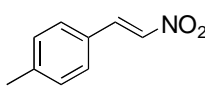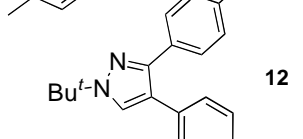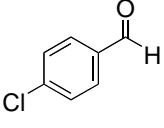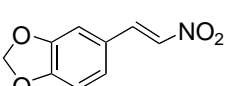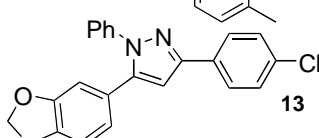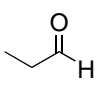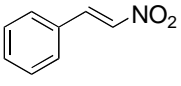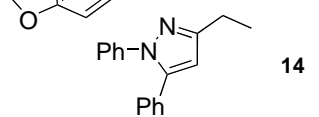
solvents	Et_2O	DMF	DMF/H_2O	$MeOH^b$	EtOH	IPA	AcOH
2:3 Ratio[a]	1:99	4:96	41:59	94:6	93:7	71:29	99:1

solvents	DCM	THF	EtOAc	CH_3CN^c	Toluene	Pyridine	Et_3N
2:3 Ratio[a]	94:6	6:94	20:80	8:92	0:0	10:90	9:91

(a) Determined by HPLC analysis at 254 nm (UV), not corrected; (b) The isolated yield of compound 2 was 83%; (c) The isolated yield of compound 3 was 90%.

This pyrazole formation reaction is fairly general with nitroolefins bearing various substituents at the R^3 and R^4 positions (Table 2). Steric effects at R^2 position play a small role; for example, sterically congested 2,2-dimethylpropionaldehyde affords pyrazole **7** in 56% yield (Entry 5). In contrast, electronic effects are prominent. Whereas electron-donating or

Table 2. Three-component Reaction for Pyrazole Synthesis
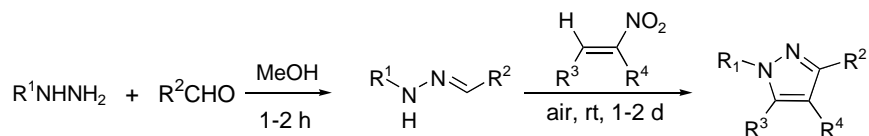
entry	hydrazine	aldehyde	nitro-olefin	product	yield
1	MeNHNH$_2$	4-Cl-C$_6$H$_4$CHO	benzodioxole-CH=CH-NO$_2$	**2**	83%
2	MeNHNH$_2$	4-Cl-C$_6$H$_4$CHO	Ph-CH=C(CH$_3$)-NO$_2$	**4**	92%
3	MeNHNH$_2$	4-Cl-C$_6$H$_4$CHO	1-nitrocyclohexene	**5**	81%
4	MeNHNH$_2$	PhCH$_2$CHO	benzodioxole-CH=CH-NO$_2$	**6**	82%
5	MeNHNH$_2$	(CH$_3$)$_3$CCHO	benzodioxole-CH=CH-NO$_2$	**7**	56%
6	MeNHNH$_2$	4-MeO-C$_6$H$_4$CHO	4-Me-C$_6$H$_4$-CH=CH-NO$_2$	**8**	72%
7	MeNHNH$_2$	4-O$_2$N-C$_6$H$_4$CHO	benzodioxole-CH=CH-NO$_2$	**9**	90%
8[a]	PhCH$_2$NHNH$_2$·2HCl	4-Cl-C$_6$H$_4$CHO	4-Me-C$_6$H$_4$-CH=CH-NO$_2$	**10**	90%
9[a,b]	(CH$_3$)$_2$CHNHNH$_2$·HCl	4-Cl-C$_6$H$_4$CHO	4-Me-C$_6$H$_4$-CH=CH-NO$_2$	**11**	26%
10[a,c]	(CH$_3$)$_3$CNHNH$_2$·HCl	4-Cl-C$_6$H$_4$CHO	4-Me-C$_6$H$_4$-CH=CH-NO$_2$	**12**	15%
11[c]	PhNHNH$_2$	4-Cl-C$_6$H$_4$CHO	benzodioxole-CH=CH-NO$_2$	**13**	42%
12	PhNHNH$_2$	CH$_3$CH$_2$CHO	Ph-CH=CH-NO$_2$	**14**	76%

(a) 10:1 MeOH/H2O was used as solvent; (b) room temperature, 7 days; (c) reflux, 4 days

slightly electron-withdrawing aldehydes provide pyrazole products smoothly, electron-demanding 4-nitrobenzaldehyde gives the Michael addition product **9** in 90% yield (Entry 7), which does not cyclize even at reflux temperature. At the R^1 position, both electronic and steric effects are important. The pyrazole formation reaction proceeds smoothly with primary alkyl hydrazones such as methyl hydrazones (Entries 1-7) and benzyl hydrazone (Entry 8). However, as the bulk of the R^1 group increases, the reaction slows or requires higher temperature. For example, with isopropylhydrazine, the pyrazole formation reaction was not complete after 7 days at room temperature with only 26% isolated yield (Entry 9). In the case of *tert*-butylhydrazine, after refluxing for 4 days, a different 1-*t*-butyl-3,4-diarylpyrazole isomer **12** was isolated in 15% yield (Entry 10). An electronic effect related to the hydrazone substituents is apparent with electron-deficient phenyl hydrazines. In entry 11, reflux temperature was required for 4 days to give 42% yield of pyrazole **13**. Interestingly, this effect can be moderated through the use of an electron-donating aldehyde such as propionaldehyde, which gives a 76% yield of pyrazole **14** at room temperature (Entry 12).

A possible reaction pathway has been proposed, as shown in Scheme 1. The first step is a reversible cycloaddition to give a 4-nitro-pyrazolidine intermediate, probably proceeding through a 1,3-dipole intermediate generated *in situ*, as proposed in literature on the reaction of hydrazones with

Scheme 1. Proposed Mechanism
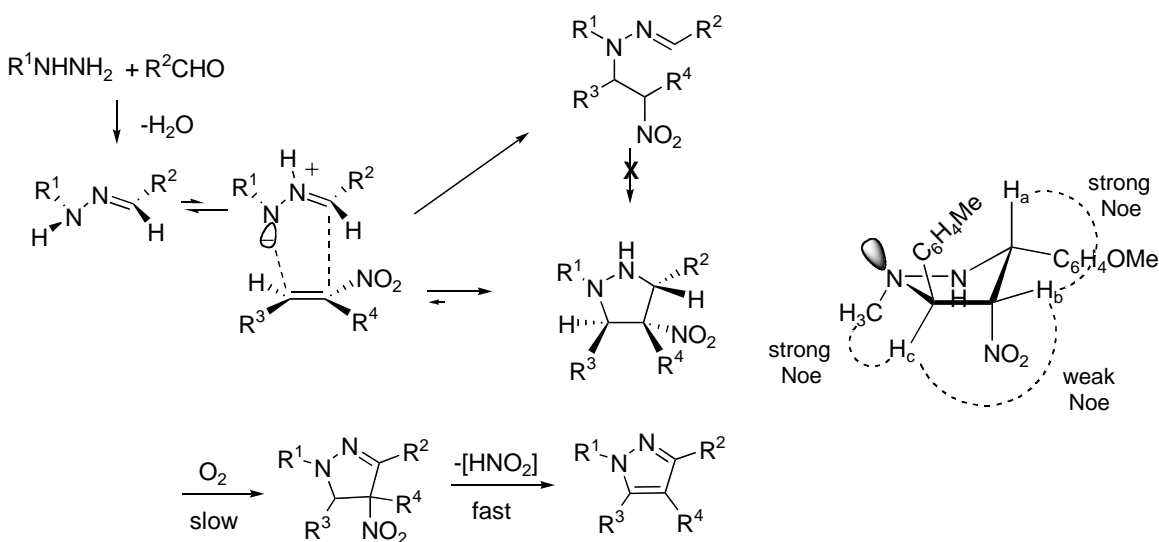
other electron-deficient olefins.[7] This process is in competition with an irreversible Michael addition process.[8] In one case, the key intermediate was directly observed on NMR experiments and was fully characterized. The key pyrazolidine intermediate then undergoes a slow oxidation by air, followed by a fast elimination of HNO_2[9] to afford the pyrazole product.

1. Johnson & Johnson Pharmaceutical R&D LLC, 3210 Merryfield Row, San Diego, CA 92121.
2. University of Pittsburgh, Department of Chemistry, Pittsburgh, PA 15260.
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Appendix
Chemical Abstracts Nomenclature;
(Registry Number)

4-Chlorobenzaldehyde; (104-88-1)

Methylhydrazine; (60-34-4)

Benzylhydrazine dihydrochloride; (20570-96-1)

(*E*)-3,4-Methylenedioxy-β-nitrostyrene; (22568-48-5)

trans-p-Methyl-β-nitrostyrene: Benzene, 1-methyl-4-[(1*E*)-2-nitroethenyl]-; (5153-68-4)

5-Benzo[1,3]dioxol-5-yl-3-(4-chloro-phenyl)-1-methyl-1*H*-pyrazole: 1*H*-Pyrazole, 5-(1,3-benzodioxol-5-yl)-3-(4-chlorophenyl)-1-methyl-; (908329-89-5)

1-Benzyl-3-(4-chloro-phenyl)-5-*p*-tolyl-1*H*-pyrazole: 1*H*-Pyrazole, 3-(4-chlorophenyl)-5-(4-methylphenyl)-1-(phenylmethyl)-; (908329-95-3)
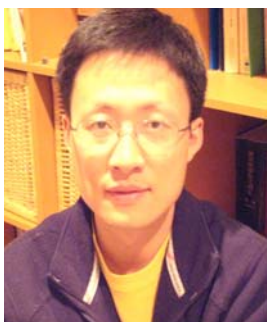
Xiaohu Deng was born in 1974 in Jingdezhen, China. He received a B.S. and a M.S. degree in chemistry under the supervision of Prof. Zi Gao from Fudan University in 1995 and 1997, respectively. After completing his doctoral dissertation in 2001 with Prof. Lanny S. Liebeskind at Emory University, he has been working in Johnson & Johnson Pharmaceutical R&D LLC in San Diego since. His research focuses on the design and development of practical synthetic methods to drug candidates.
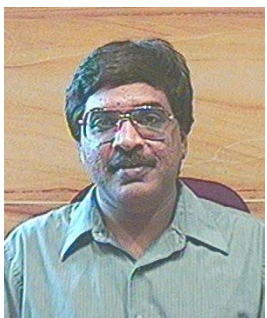
Neelakandha Mani was born in 1957 in Kozhikode, India. He completed his Bachelors in Chemistry at Malabar Christian College and Ph.D. at Indian Institute of Science Bangalore with G.S.R. Subba Rao. He spent 3 years with Anthony G.M. Barrett (Northwestern and Colorado State University) and 4 years with Craig A. Townsend (Johns Hopkins University) as post-doctoral researcher. After 5 years as a scientist at Council of Scientific and Industrial Research (CSIR), India and 3 years as a senior scientist at Ligand Pharmaceuticals he moved to Johnson & Johnson in 2000. His research interests include synthesis of heterocycles, design of practical routes to drug molecules and development of environmentally friendly synthetic methods.
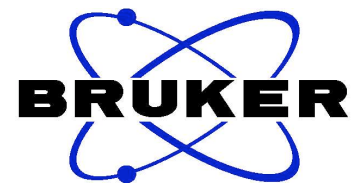
Daitao Chen was born in Sichuan, P.R. China in 1974. He received his B.Sc. in 1996 and M.S. in 1999 at Peking University. He then moved to Emory University and obtained his Ph.D. in 2004 under the guidance of Dr. Debra Mohler. After working as a post-doctoral researcher in Dr. Kay Brummond's group at the University of Pittsburgh, he joined Scynexis, Inc (RTP, NC) in 2007. He is currently working on the DNDi team as a research scientist.

Josh Osbourn was born in 1985 in Shinnston, West Virginia. In 2007, he graduated from West Virginia University with a B.S. degree in chemistry. During his time at WVU, he worked in the laboratory of Professor George O'Doherty and was supported through a Pfizer undergraduate research fellowship. In 2007, he entered the Ph.D. program at the University of Pittsburgh and is currently pursuing graduate studies in the laboratory of Professor Kay Brummond.
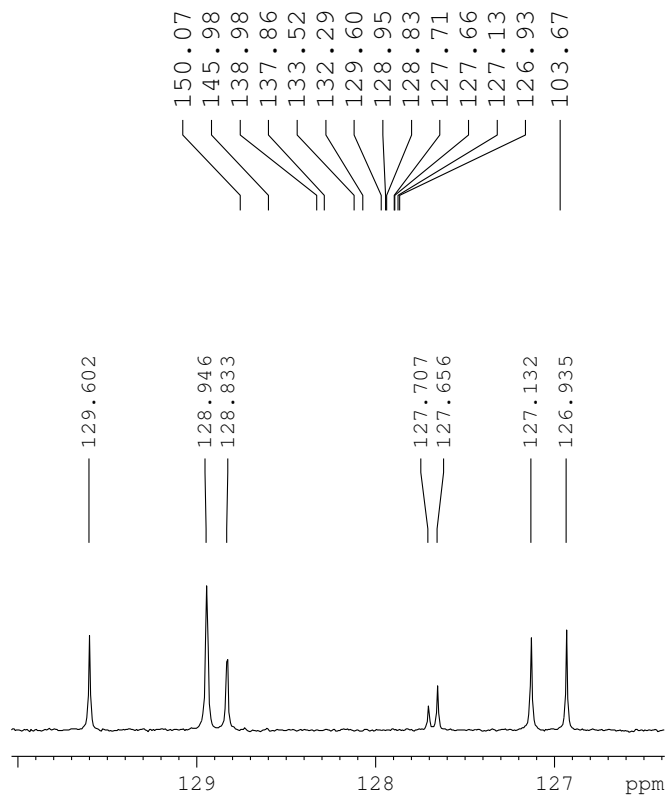
cdt-5-228

Peak labels (expansion top): 150.07, 145.98, 138.98, 137.86, 133.52, 132.29, 129.60, 128.95, 128.83, 127.71, 127.66, 127.13, 126.93, 103.67, 77.49, 77.23, 76.98, 53.44, 21.51

Inset expansion labels: 129.602, 128.946, 128.833, 127.707, 127.656, 127.132, 126.935

Structure label: 4

Current Data Parameters
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PROCNO   1

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PULPROG   zgpg
TD   65536
SOLVENT   CDCl3
NS   1592
DS   4
SWH   30030.029 Hz
FIDRES   0.458222 Hz
AQ   1.0912410 sec
RG   1149.4
DW   16.650 usec
DE   6.00 usec
TE   297.2 K
D1   10.00000000 sec
d11   0.03000000 sec
DELTA   9.89999962 sec
TD0   1

======== CHANNEL f1 ========
NUC1   13C
P1   9.00 usec
PL1   -2.00 dB
SFO1   125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2   waltz16
NUC2   1H
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F2 - Processing parameters
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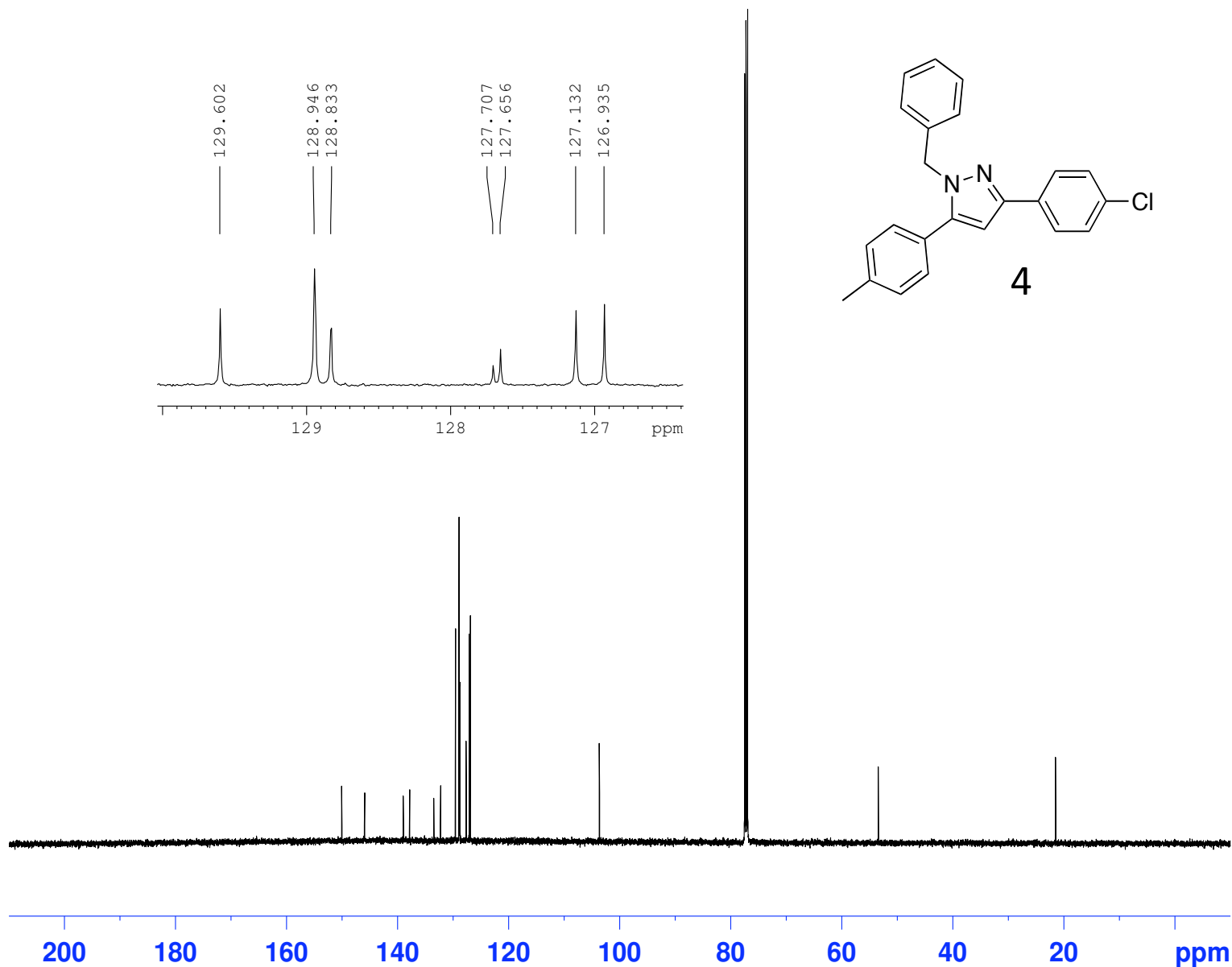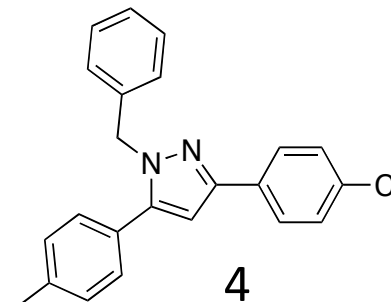SF   125.7577646 MHz
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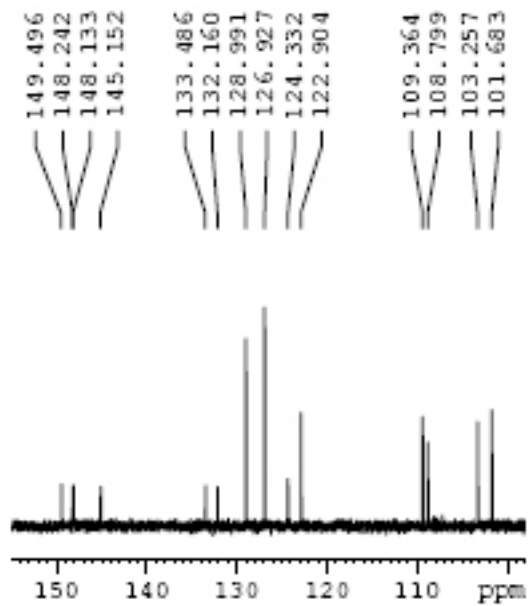GB   0
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cdt-5-218

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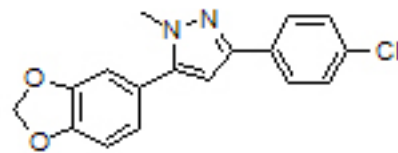122.904

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101.683

149.50
148.24
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145.15

133.49
132.16
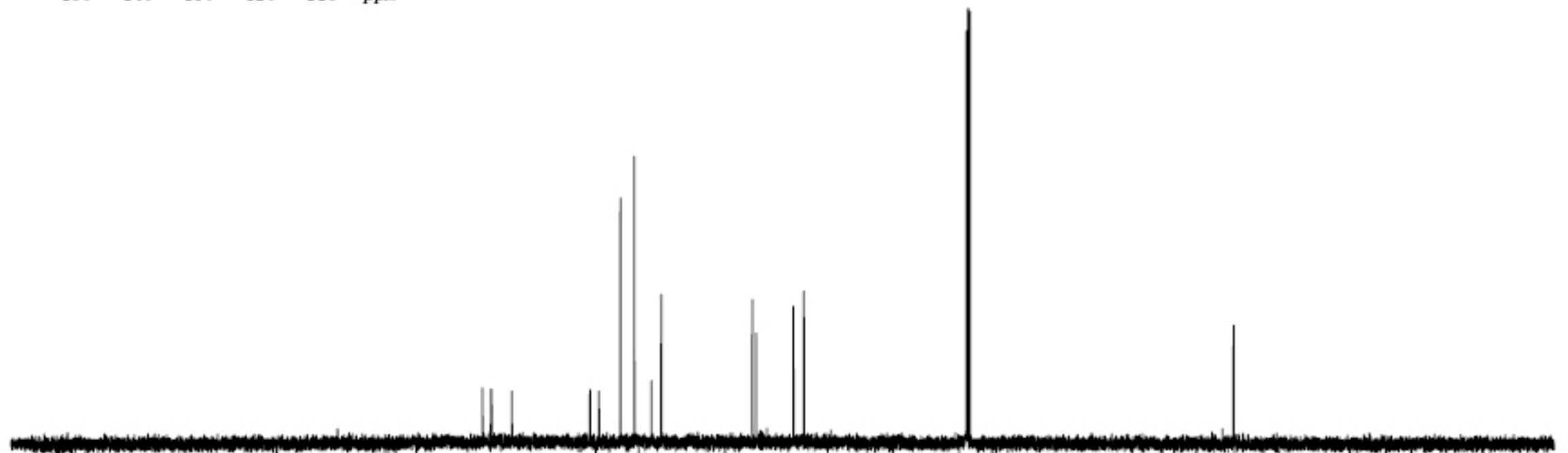128.99
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77.49
77.23
76.98

37.74
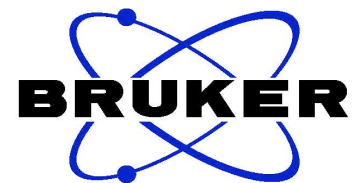
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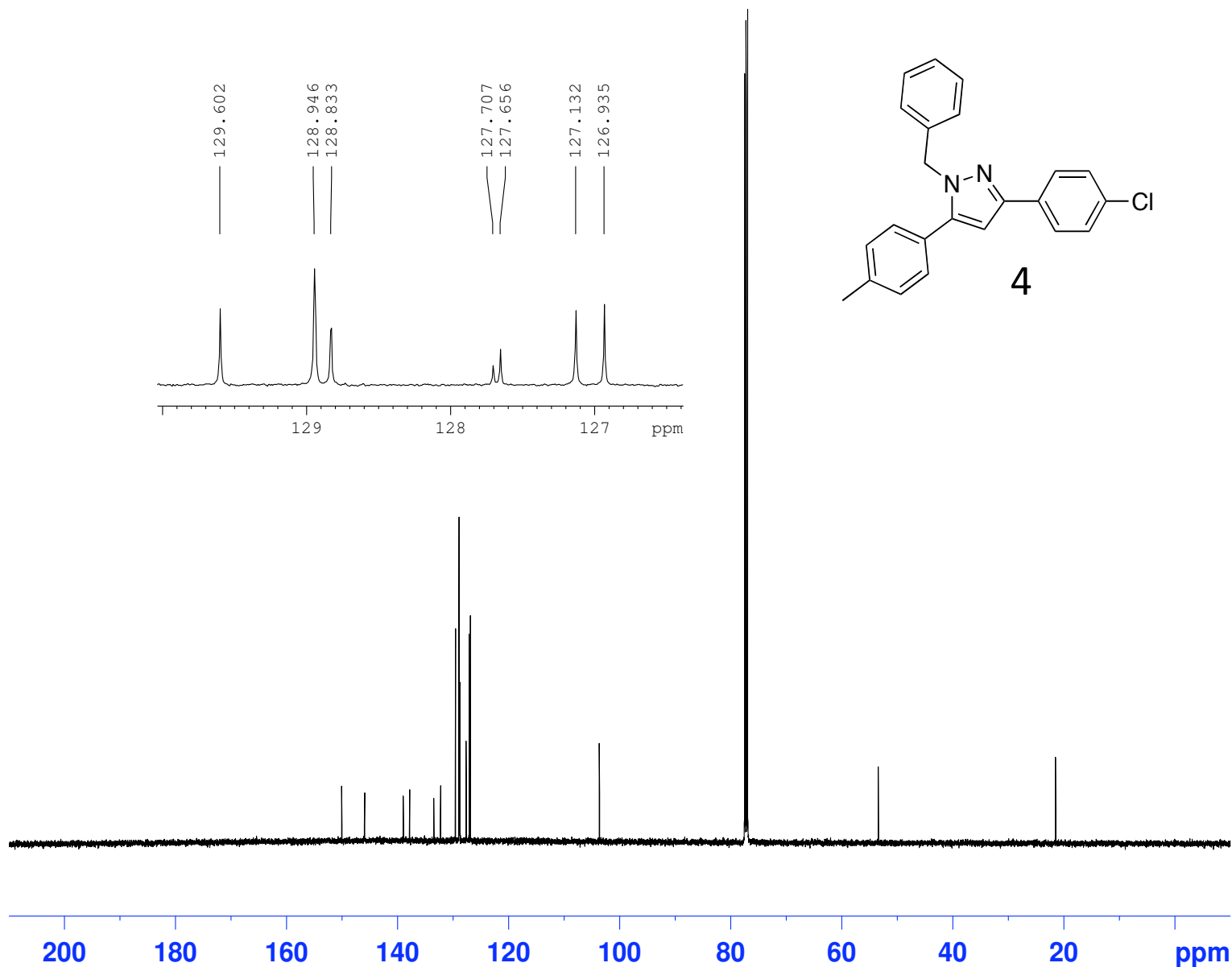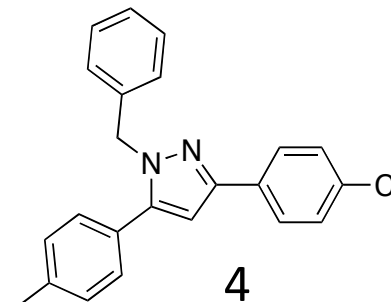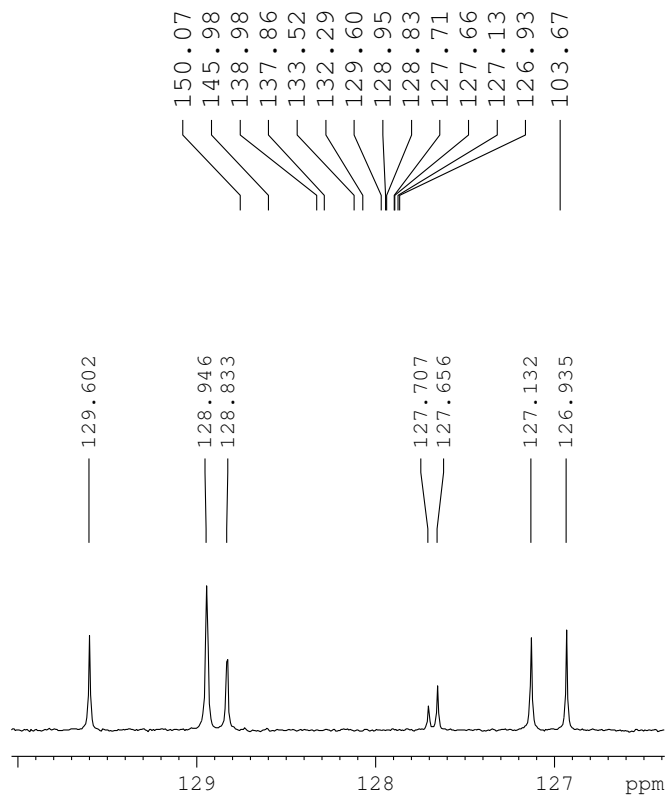210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

cdt-5-228

150.07
145.98
138.98
137.86
133.52
132.29
129.60
128.95
128.83
127.71
127.66
127.13
126.93
103.67

77.49
77.23
76.98

53.44

21.51

129.602
128.946
128.833
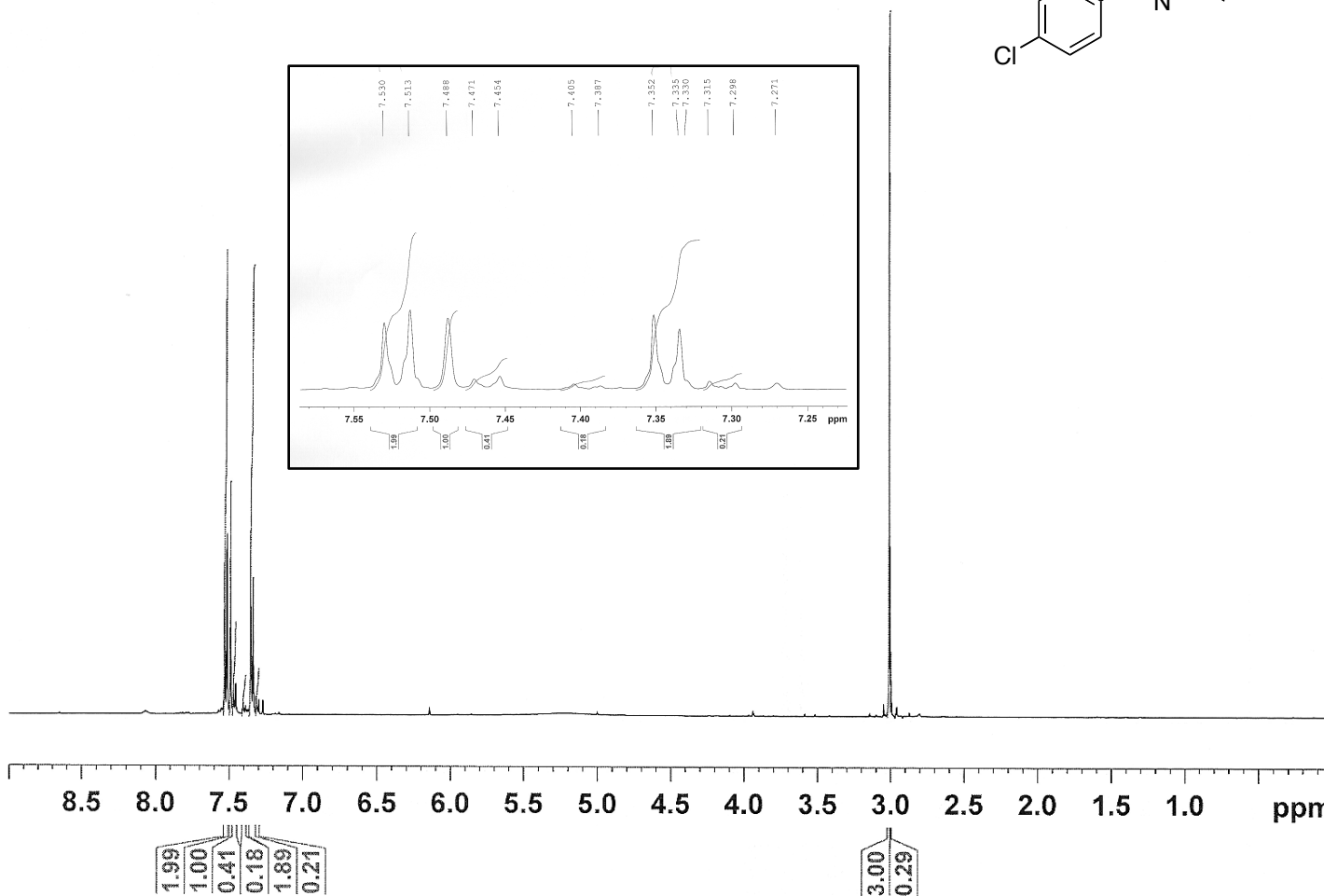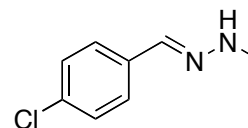127.707
127.656
127.132
126.935

4

200 180 160 140 120 100 80 60 40 20 ppm

cdt-6-18

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7.513
7.488
7.471
7.454
7.405
7.387
7.352
7.335
7.330
7.315
7.298
7.271

3.051
3.011
3.001
2.960

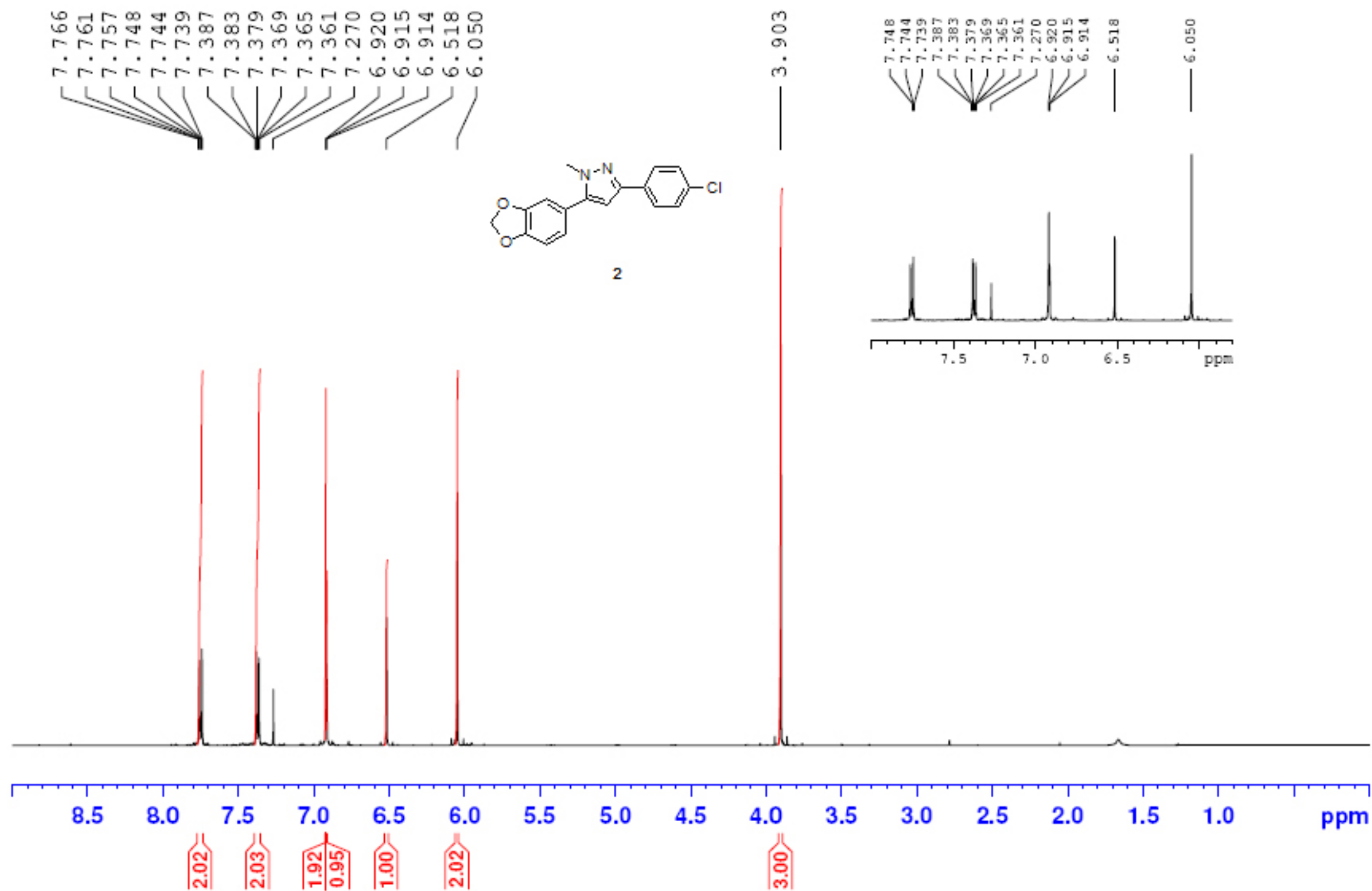Inset scale: 7.55 7.50 7.45 7.40 7.35 7.30 7.25 ppm
Inset integrals: 1.99 1.00 0.41 0.18 1.88 0.21

Main scale: 8.5 8.0 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 ppm

Main integrals: 1.99 1.00 0.41 0.18 1.89 0.21   3.00 0.29

cdt-5-218

7.766
7.761
7.757
7.748
7.744
7.739
7.387
7.383
7.379
7.369
7.365
7.361
7.270
6.920
6.915
6.914
6.518
6.050

3.903

7.748
7.744
7.739
7.387
7.383
7.379
7.369
7.365
7.361
7.270
6.920
6.915
6.914
6.518
6.050

2

8.5 8.0 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 ppm

2.02 2.03 1.92 0.95 1.00 2.02 3.00

cdt-6-19

7.513 7.490 7.473 7.414 7.405 7.375 7.366 7.351 7.348 7.343 7.334 7.324 7.312 7.295 7.284 7.270 5.740

4.476 4.448 4.436

1.578

Inset:
7.550 7.513 7.490 7.473 7.414 7.405 7.375 7.366 7.351 7.348 7.343 7.334 7.324 7.312 7.295 7.284 7.270

7.55   7.50   7.45   7.40   7.35   7.30   ppm
1.10   2.00   4.00   3.01

8.5 8.0 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 ppm

1.10 2.00 4.00 3.01   0.73   2.00