A One-pot Synthesis of Tetrazolones from Acid Chlorides: Understanding Functional Group Compatibility, and Application to the Late-Stage Functionalization of Marketed Drugs

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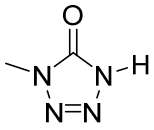
LITERATURE STRUCTURES CONTAINING A TETRAZOLONE MOTIF

The following sub-structure search was conducted within SciFinder® on 01st October 2014 to ascertain the number of compounds attached to a mono-substituted tetrazolone motif.



substructure search, locking all nitrogen, oxygen and hydrogen atoms

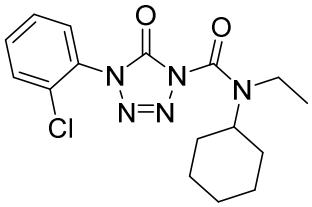
This resulted in 9410 substances contained within 269 references (when duplicates were removed). The results of this search can be found using the following link

https://scifinder.cas.org/scifinder/view/link_v1/answerset.html?l=guJIPNevZdEYhFK6sQswYGkco7YzXzXs2-pfH6Ki1yQ5q4Iv3_UQHnjzA1XKEO8UJbeTI_be1M2X8c-3iqIVTw

The 269 references consisted of 164 patents (or patent applications) and 105 journal articles.

Of the 164 patents (or patent applications), approximately 95 described the use of a tetrazolone within agrochemistry. Approximately 48 patents (or patent applications) described the use of a tetrazolone within medicinal chemistry. It should be noted that most of the 164 patent (or patent applications) synthesize a mono-substituted tetrazolone intermediate, like that shown in the substructure above, and then acylate, or alkylate, the mono-substituted tetrazolone to obtain 1,3-disubstituted tetrazolone final compounds.

Of the 105 journal articles, approximately 8 described applications of tetrazolones in agrochemistry, and approximately 14 described applications of tetrazolones in medicinal chemistry. Included in the agrochemistry articles were those describing research with the agrochemical, fentrazamide (YRC 2388).



Fentrazamide (YRC 2388)

IMPORTANT SAFETY NOTICE FOR ALL EXPERIMENTS

Azidotrimethylsilane (also known as trimethylsilylazide) is highly toxic and is potentially explosive.[1-4] Azidotrimethylsilane can also be hydrolyzed to hydrazoic acid (HN_3), a volatile, highly toxic and highly explosive substance.[2-4] Therefore, personnel should be well-versed in the safe-handling and safe disposal of azidotrimethylsilane before attempting to repeat any of the experiments described within this *Supplementary Information*.[4] It should be noted that all experiments were undertaken behind a blast shield, with personnel wearing appropriate protective clothing for working with azidotrimethylsilane, azide intermediates and tetrazolone products.

It should also be noted that the tetrazolone products arising from these reactions may also be potentially explosive, and possess unknown toxicities. Therefore, appropriate care and safety precautions should also be exercised when performing workups and purifications of the compounds described within this *Supplementary Information*.

1. For a Material Safety Data Sheet (MSDS) on azidotrmethylsilane, see: http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=155071&brand=ALDRICH&PageToGoToURL=http%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2F155071%3Flang%3Den

2. K. J. KerBeek, *Chem. Eng. News*, 1998, **76**, 6.

3. M. Jafarzadeh, *Synlett*, 2007, 2144-2145.

4. For a recent discussion regarding some important considerations when using, or scaling-up azide chemistry, see: F. González-Bobes, N. Kopp, L. Li, J. Deerberg, P. Sharma, S. Leung, M. Davies, J. Bush, J. Hamm, M. Hrytsak, *Org. Proc. Res. Develop.*, 2012, **16**, 2051-2057 and references cited therein.

GENERAL EXPERIMENTAL

All reagents and solvents were purchased from commercial suppliers and used without further purification. Reactions were monitored by thin-layer chromatography or high-performance liquid chromatography. NMR was performed on a 300 MHz NMR spectrometer and all chemical shifts are reported relative to a tetramethylsilane internal standard, or by referencing on the deuterated solvent. Reverse-phase high-performance liquid chromatography was performed on standard equipment and was coupled to diode array and mass spectra detectors – the mass-spectra detector operating under the electrospray ionization (ESI) mode. The column-gradient system was as follows

Column: Phenomenex Gemini 4.6 x 100 mm, C18, 5µm, 110Å

Column temperature 30°C

Sample temperature 15°C

Solvent A – 0.05% Formic acid in Water

Solvent B – 0.05% Formic acid in Acetonitrile

Flow rate – 1.5 mL/min

Gradient:

Time	A%	B%
0	95	5
10	0	100 (curve=6)
11.1	0	100
11.2	95	5
12.1	95	5

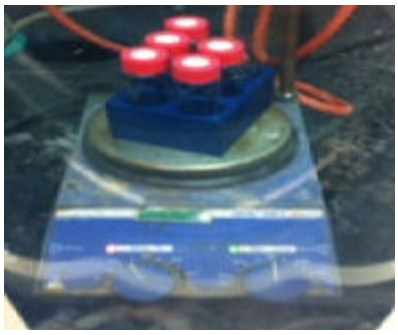
High resolution mass spectrometry were obtained on a LCT Premier XE mass spectrometer (time-of-flight) operating under the electrospray ionization mode. Mass analysis was performed in extended W-

mode using leucine enkephalin as reference lock mass (556.2771 Da for positive ion & 554.2615 Da for negative ion).

20 mL Vials with pressure-release caps were obtained from Chemglass (catalogue # CG-4912-05).

Supporting Figure 1. Photo of 20 mL vials with pressure-release tops.

Reactions could also be undertaken in parallel using the setup illustrated in Supporting Figure 2. The last position of the heating block is used to house a vial containing heat-resistant silicone oil. A thermocouple is then inserted in to the oil to control the temperature of the block.



Supporting Figure 2. Photo of reactions undertaken in parallel on heating block (behind a blast shield).

Note about the reactions: It is likely that the reactions described in this Supporting Information are complete within a short timeframe (2 hours) - e.g. see page S18. However, we typically undertake the majority of reactions at the end of a working day, and hence, leave them overnight for convenience.

PREPARATION OF 1-(2-BROMO-4-FLUOROPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 4

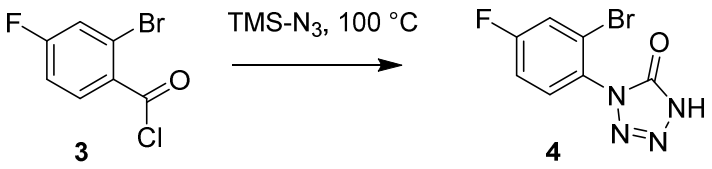


Table 1, entry 1: See 'Important safety notice for all experiments' (page S6); Blast shield employed

Azidotrimethylsilane (5 mL, 38.0 mmol) was added in one portion to 2-bromo-4-fluorobenzoyl chloride **3** (1.5 g, 6.3 mmol). The mixture was placed under nitrogen and then heated to 100 °C with stirring [Note: 100 °C refers to temperature of heating block]. The mixture was left to stir at 100 °C overnight. After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (50 mL) and H_2O (50 mL). The organic layer was then extracted with a saturated aqueous solution of $NaHCO_3$ (4 x 40 mL) [Note: extraction continued until TLC showed all tetrazolone product removed from the organic layer]. EtOAc (50 mL) was added to the combined $NaHCO_3$ layers, and the pH was adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned, and the aqueous layer extracted with EtOAc (1 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under vacuum to afford the product (1.34 g, 82%) as a solid.

^{1}H NMR (DMSO-d_6, 300MHz): δ 7.90 (dd, J = 8.4, 2.7 Hz, 1H), 7.77 (dd, J = 8.7, 5.7 Hz, 1H), 7.52-7.45 (m, 1H), -1.2 (br. s, 1H)

^{19}F NMR (DMSO-d_6, MHz): - 107.6 (dd, J = 13.8, 7.6 Hz)

^{13}C NMR (DMSO-d_6, 75MHz): δ 164.2 (d, J = 251 Hz), 150.7, 132.0 (d, J = 9.3 Hz), 128.7 (d, J = 3.8 Hz), 122.6 (d, J = 11.0 Hz), 121.0 (d, J = 26 Hz), 116.4 (d, J = 23 Hz)

m/z = 257.28 $[M-H]^+$ for ^{79}Br

HRMS (EI): $[M-H]^+$ calc'd for $C_7H_4BrFN_4O$ *m/z* 256.9474, found 256.9527

Table 1, entry 2:

The above reaction could be repeated using 4.5 equivalents of azidotrimethylsilane (3.75 mL) to give the product (1.24 g , 76%) as a solid.

Table 1, entry 3:

The above reaction could be repeated using 3.0 equivalents of azidotrimethylsilane (2.5 mL) to give the product (0.6 g , 37%) as a solid. Also isolated from the EtOAc layer after extraction with saturated $NaHCO_3$ was a symmetrical urea by-product, *bis*-(2-bromo-4-fluorphenyl)urea.

Data for *bis*-(2-bromo-4-fluorphenyl)urea

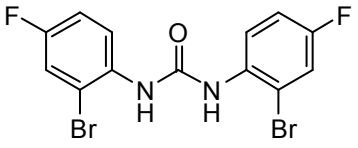
^{1}H NMR (DMSO-d_6, 300MHz): δ 8.82 (br. s, 2H), 7.88 (dd, J = 9.0, 5.7 Hz, 2H), 7.57 (dd, J = 8.7, 3.0 Hz, 2H), 7.22 (ddd, J = 9.0, 8.1, 3.0, Hz, 2H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 159.2 (d, J = 244 Hz), 152.7, 133.7 (d, J = 3.3 Hz), 125.1 (d, J = 8.3 Hz), 119.4 (d, J = 25 Hz), 115.0 (d, J = 22 Hz), 114.8 (d, J = 10 Hz)

m/z = 407.26 $[M+H]^+$ and 405.37 $[M-H]^+$

HRMS (EI): $[M+H]^+$ calc'd for $C_{13}H_8Br_2F_2N_2O$ *m/z* 404.9050, found 404.9047; *m/z* 406.9030, found 406.9025; *m/z* 408.9011, found 408.9003

HRMS (EI): $[M-H]^+$ calc'd for $C_{13}H_8Br_2F_2N_2O$ *m/z* 402.8893, found 402.8912; *m/z* 404.8873, found 404.8815; *m/z* 406.8854, found 406.8802



bis-(2-bromo-4-fluorphenyl)urea

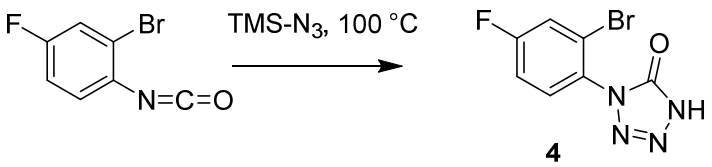
Table 1, entry 4: Note: For large-scale reactions, the mixtures are only placed under a nitrogen atmosphere after cessation of the gas evolution

The above reaction was repeated on a large-scale using azidotrimethylsilane (65 mL, 494 mmol) and 2-bromo-4-fluorobenzoyl chloride **3** (20.4 g, 85.9 mmol). The mixture was heated slowly and evolution of a gas (presumably, arising from a Curtius rearrangement) was noted from 50-60 °C (block temperature), which became a vigorous evolution when the block temperature was raised to *ca*. 65 °C. The mixture was removed from the heat at a block temperature of *ca*. 70 °C, and when gas evolution subsided, was re-subjected to heating stepwise from *ca*. 70 °C to 90 °C. The mixture was stirred at 90 °C overnight. Usual workup, partitioning between EtOAc (200 mL) and H_2O (100 mL) and then extracting the organic layer with a saturated solution of $NaHCO_3$ (5 x 150 mL), followed by acidification and extraction with EtOAc, gave the product (19.9 g, 89%) as a solid.

A separate reaction using 20.0g of 2-bromo-4-fluorobenzoyl chloride **3** and 47 mL of azidotrimethylsilane (4.0 equivalents) gave the product (17.4 g, 80%) as a solid.

A separate reaction using 36g of 2-bromo-4-fluorobenzoyl chloride **3** and 120 mL of azidotrimethylsilane (6.0 equivalents) gave the product (37 g, 94%) as a solid. For this reaction, the mixture was heated slowly to *ca*. 55 °C, whereupon the evolution of gas became regular. Evolution of gas stopped after *ca*. 15 min at 55 °C. The mixture was then slowly heated to 90-95 °C (block temperature), placed under a nitrogen atmosphere and stirred overnight.

PREPARATION OF 1-(2-BROMO-4-FLUOROPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 4 FROM COMMERCIALLY-AVAILABLE 2-BROMO-4-FLUORO-1-ISOCYANOATOBENZENE



See 'Important safety notice for all experiments' (page S6); Blast shield employed

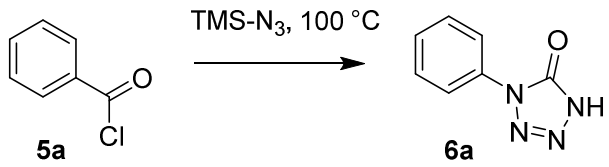
Azidotrimethylsilane (10 mL, 76 mmol) was added in one portion to 2-bromo-4-fluoro-1-isocyanatobenzene (3.0 g, 13.9 mmol). The mixture was placed under nitrogen and then heated to 90 °C with stirring [Note: 90 °C refers to temperature of heating block]. The mixture was left to stir at 90 °C overnight. After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (50 mL) and a saturated aqueous solution of $NaHCO_3$ (100 mL). The organic layer was extracted with a further quantity of saturated aqueous $NaHCO_3$ (1 x 50 mL). EtOAc (100 mL) was added to the combined $NaHCO_3$ layers, and the pH was adjusted to < 3 using 2N HCl with efficient stirring. The aqueous and organic layers were partitioned, and the organic layer was dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford the product (3.44 g, 95%) as a solid.

A separate reaction was repeated using 20.0g of 2-bromo-4-fluoro-1-isocyanatobenzene (92.6 mmol) and 50 mL of azidotrimethylsilane (380 mmol; *ca*. 4.0 equivalents) to give the product (20.1 g, 84%) after workup.

Note: Experiments with related starting materials have indicated that the isocyanate to tetrazolone formation is complete within ca. 2 hours. Therefore, it is likely that the reaction of acid chlorides to tetrazolones is similarly complete within a few hours, since it is observed that the Curtius rearrangement occurs quickly (evolution of gas complete within 15-30 min). However, we typically

undertake the majority of reactions at the end of a working day, and hence, leave them overnight for convenience.

PREPARATION OF 1-PHENYL-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6A



See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and benzoyl chloride (422 mg, 3.0 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The mixture was then stirred at 100 °C overnight (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic layer was extracted with a further quantity of saturated aqueous $NaHCO_3$ (1 x 10 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (20 mL) was added to the combined $NaHCO_3$ layers, and the pH was adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford the product (369 mg, 76%) as a solid. A sample was recrystallized from EtOAc.

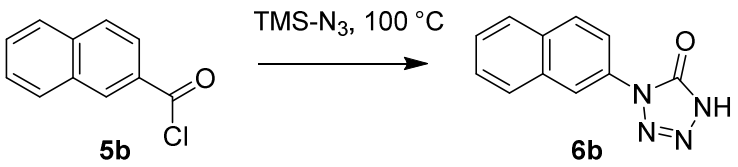
^{1}H NMR (DMSO-d_6, 300MHz): δ 7.85-7.81 (m, 2H), 7.57-7.50 (m, 2H), 7.41 (dt, J = 7.5, 1.5 Hz, 1H), -1.3 (br. s, 1H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 150.3, 134.2, 129.5, 127.6, 119.5

m/z = 163.18 $[M+H]^+$ and 161.24 $[M-H]^+$

HRMS (EI): $[M-H]^+$ calc'd for $C_7H_6N_4O$ *m/z* 161.0463, found 161.0532

PREPARATION OF 1-(NAPHTHALEN-2-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6B



See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and 2-naphthoyl chloride (572 mg, 3.0 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The mixture was then stirred at 100 °C overnight (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic layer was extracted with a further quantity of saturated aqueous $NaHCO_3$ (1 x 10 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (20 mL) was added to the combined $NaHCO_3$ layers, and the pH was adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford the product (419 mg, 66%) as a solid. A sample was recrystallized from EtOAc.

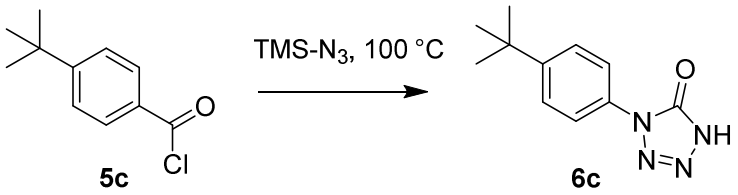
^{1}H NMR (DMSO-d_6, 300MHz): δ 8.42 (d, J = 2.1 Hz, 1H), 8.09 (d, J = 8.7 Hz, 1H), 8.02-7.93 (m, 3H), 7.60-7.52 (m, 2H), -1.1 (br. s, 1H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 150.4, 132.7, 131.8, 131.6, 129.5, 128.1, 127.8, 127.2, 126.6, 118.1, 117.0

m/z = 216.36 $[M+H]^+$ and 215.45 $[M-H]^+$

HRMS (EI): $[M+H]^+$ calc'd for $C_{11}H_8N_4O$ *m/z* 213.0776, found 213.0764

PREPARATION OF 1-(4-(*TERT*-BUTYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6C



See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and 4-(*tert*-butyl)benzoyl chloride (590 mg, 3.0 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The mixture was then stirred at 100 °C overnight (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (20 mL) and a saturated aqueous solution of $NaHCO_3$ (20 mL). The organic layer was extracted with a further quantity of saturated aqueous $NaHCO_3$ (10 x 15 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (40 mL) was added to the combined $NaHCO_3$ layers, and the pH was adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 40 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford the product (401 mg, 61%) as a solid.

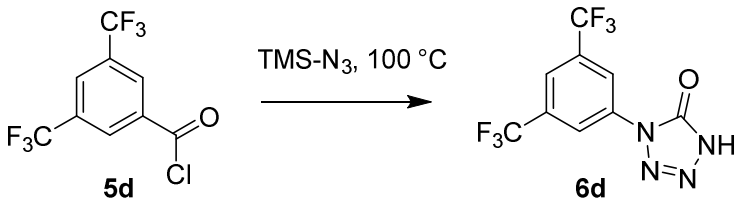
^{1}H NMR (DMSO-d_6, 300MHz): δ 7.74 (dt, J = 8.7, 2.4 Hz, 2H), 7.57 (dt, J = 8.7, 2.4 Hz, 2H), 1.29 (s, 9H), -1.3 (br. s, 1H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 150.3, 139.0, 131.7, 126.2, 119.5, 34.4, 31.0

m/z = 219.31$[M+H]^+$ and 217.38 $[M-H]^+$

HRMS (EI): $[M-H]^+$ calc'd for $C_{11}H_{14}N_4O$ *m/z* 217.1089, found 213.1139

PREPARATION OF 1-(3,5-BIS(TRIFLUOROMETHYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6D



See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and 3,5-bis(trifluoromethyl)benzoyl chloride (830 mg, 3.0 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The mixture was then stirred at 100 °C overnight (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). This base-acid extraction did not work for this compound (only 20 mg obtained after acidification / extraction), and the tetrazolone remained in the organic (EtOAc) layer. Therefore, the organic layer from the initial partition above was concentrated under vacuum and purified by column chromatography on silica gel using hexane / EtOAc as eluent (ISCO Combiflash System) to give the product (503 mg, 56%) as a solid.

^{1}H NMR (DMSO-d_6, 300MHz): δ 8.48 (s, 2H), 8.14 (s, 1H), -1.2 (br. s, 1H)

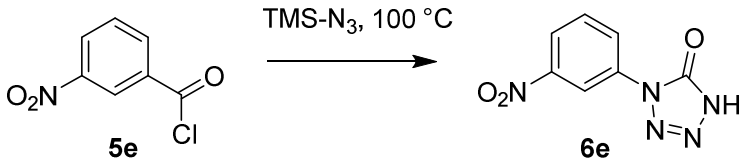
^{19}F NMR (DMSO-d_6, 282MHz): δ -61.8 (s)

^{13}C NMR (DMSO-d_6, 75MHz): δ 150.4, 136.0, 131.7 (q, J = 33 Hz), 124.6 (q, J = 271 Hz), 120.6 (m), 118.9 (m)

m/z = 297.36 $[M-H]^+$

HRMS (EI): $[M-H]^+$ calc'd for $C_9H_4F_6N_4O$ m/z 297.0211, found 297.0157

PREPARATION OF 1-(3-NITROPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6E



See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and 3-nitrobenzoyl chloride (554 mg, 3.0 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The mixture was then stirred at 100 °C for 2 hr (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic layer was extracted with a further quantity of saturated aqueous $NaHCO_3$ (1 x 10 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (20 mL) was added to the combined $NaHCO_3$ layers, and the pH was adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford the product (560 mg, 90%) as a solid. A sample was recrystallized from EtOAc.

^{1}H NMR (DMSO-d_6, 300MHz): δ 8.69 (t, J = 4.2 Hz, 1H), 8.28-8.19 (m, 2H), 7.82 (t, J = 8.3 Hz, 1H),

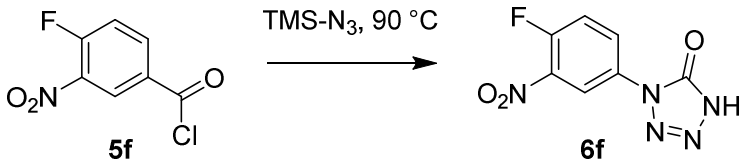
-1.0 (br. s, 1H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 150.1, 148.1, 135.1, 131.2, 124.8, 121.8, 113.2

m/z = 208.25 $[M+H]^+$ and 206.30 $[M-H]^+$

HRMS (EI): $[M-H]^+$ calc'd for $C_7H_5N_5O_3$ *m/z* 206.0314, found 206.0398

PREPARATION OF 1-(4-FLUORO-5-NITROPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6F



See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (7.9 mL, 60 mmol) and 4-fluoro-5-nitrobenzoyl chloride (2.04 g, 10 mmol) in a round bottom flask with reflux condenser was heated slowly from room temperature to 90 °C under an atmosphere of nitrogen (block temperature). The mixture was then stirred at 90 °C overnight. After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (50 mL) and H_2O (50 mL). The organic layer was extracted with a saturated aqueous solution of $NaHCO_3$ (3 x 50 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (100 mL) was added to the combined $NaHCO_3$ layers, and the pH was adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned and the organic layer was dried ($MgSO_4$), filtered and the solvent removed under vacuum to afford the product (1.96 g) as a solid. ^{1}H NMR analysis indicated that the product was *ca*. 80-90% purity with approximately 10-20% of 4-fluoro-3-nitrobenzoic acid as a contaminant. Adjusting the yield for purity gives *ca*. 70% of desired product.

A sample of the above material was recrystallized from EtOAc to provide pure material.

^{1}H NMR (DMSO-d_6, 300MHz): δ 8.63 (dd, J = 9.6, 2.7 Hz, 1H), 8.25 (ddd, J = 9.3, 3.9, 2.7 Hz, 1H), 7.80 (dd, J = 11.1, 9.0 Hz, 1H), -1.0 (br. s, 1H)

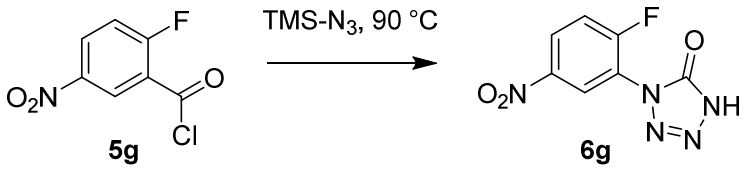
^{19}F NMR (DMSO-d_6, 272MHz): δ -119.7 (m)

^{13}C NMR (DMSO-d_6, 75MHz): δ 154.9 (d, J = 261 Hz), 150.2, 136.9 (d, J = 8 Hz), 130.6 (d, J = 3 Hz), 127.0 (d, J = 9 Hz), 120.1 (d, J = 23 Hz), 116.6 (d, J = 3 Hz)

m/z = 226.24 $[M+H]^+$ and 224.32 $[M-H]^+$

HRMS (EI): $[M-H]^+$ calc'd for $C_7H_4FN_5O_3$ *m/z* 224.0220, found 224.0227

PREPARATION OF 1-(2-FLUORO-5-NITROPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6G



See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (19.7 mL, 150 mmol) and 2-fluoro-5-nitrobenzoyl chloride (5.1 g, 25 mmol) in a round bottom flask with reflux condenser was heated slowly from room temperature to 90 °C (block temperature) (note: evolution of nitrogen is observed from 70 °C). The mixture was then stirred at 90 °C for 5-6 hr (TLC indicated complete reaction). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (100 mL) and a saturated aqueous solution of $NaHCO_3$ (150 mL). The organic layer was extracted with a further quantity of saturated aqueous $NaHCO_3$ (1 x 50 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (200 mL) was added to the combined $NaHCO_3$ layers, and the pH was adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (1 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under vacuum to afford the product (4.8 g, 86%) as a solid. A sample was recrystallized from EtOAc.

^{1}H NMR (DMSO-d_6, 300MHz): δ 8.66-8.63 (m, 1H), 8.49-8.43 (m, 1H), 7.82 (t, J = 7.5 Hz, 1H), -1.0 (br. s, 1H)

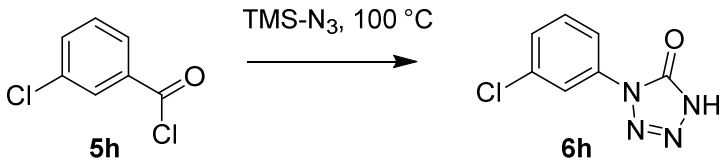
^{19}F NMR (DMSO-d_6, 272MHz): δ -110.4 (m)

^{13}C NMR (DMSO-d_6, 75MHz): δ 160.9 (d, J = 262 Hz), 150.5, 144.0 (d, J = 3.1 Hz), 127.2 (d, J = 9.9 Hz), 123.4 (d, J = 2.2 Hz), 121.6 (d, J = 13.7 Hz), 118.7 (d, J = 22.1 Hz)

m/z = 226.24 $[M+H]^+$ and 224.30 $[M-H]^+$

HRMS (EI): $[M-H]^+$ calc'd for $C_7H_4FN_5O_3$ *m/z* 224.0220, found 224.0231

PREPARATION OF 1-(3-CHLOROPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6H



See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and 3-chlorobenzoyl chloride (525 mg, 3.0 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The mixture was then stirred at 100 °C overnight (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic layer was extracted with a further quantity of saturated aqueous $NaHCO_3$ (1 x 10 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (20 mL) was added to the combined $NaHCO_3$ layers, and the pH was adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford the product (355 mg, 60%) as a solid. A sample was recrystallized from EtOAc.

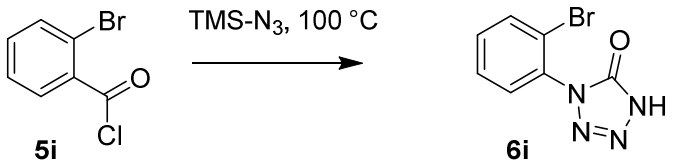
^{1}H NMR (DMSO-d_6, 300MHz): δ 7.92 (t, J = 2.1 Hz, 1H), 7.82 (ddd, J = 8.2, 2.1, 1.2 Hz, 1H), 7.59 (t, J = 8.3 Hz, 1H), 7.46 (ddd, J = 8.1, 2.1, 0.9 Hz, 1H), -1.1 (br. s, 1H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 150.1, 135.4, 133.7, 131.3, 127.3, 118.7, 117.6

m/z = 197.30 $[M+H]^+$ and 195.38 $[M-H]^+$ for ^{35}Cl

HRMS (EI): $[M+H]^+$ calc'd for $C_7H_5ClN_4O$ *m/z* 195.0074, found 195.0099

PREPARATION OF 1-(2-BROMOPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6i



See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and 2-bromobenzoyl chloride (590 mg, 3.0 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The mixture was then stirred at 100 °C for 24hr (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (20 mL) and a saturated aqueous solution of $NaHCO_3$ (20 mL). The organic layer was extracted with a further quantity of saturated aqueous $NaHCO_3$ (1 x 20 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (30 mL) was added to the combined $NaHCO_3$ layers, and the pH was adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford the product (546 mg, 76%) as a solid. A sample was recrystallized from EtOAc.

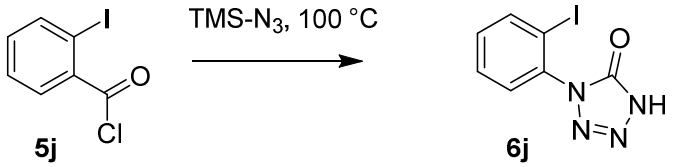
^{1}H NMR (DMSO-d_6, 300MHz): δ 7.89 (dd, J = 8.1, 1.5 Hz, 1H), 7.68 (dd, J = 7.8, 2.1 Hz, 1H), 7.61-7.50 (m, 2H), -1.3 (br. s, 1H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 150.7, 133.5, 132.4, 131.9, 130.3, 129.0, 121.3

m/z = 239.24 $[M-H]^+$

HRMS (EI): $[M-H]^+$ calc'd for $C_7H_5BrN_4O$ m/z 238.9568, found 238.9577

PREPARATION OF 1-(2-IODOPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6J



See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and 2-iodobenzoyl chloride (799 mg, 3.0 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The mixture was then stirred at 100 °C overnight (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic layer was extracted with a further quantity of saturated aqueous $NaHCO_3$ (1 x 10 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (20 mL) was added to the combined $NaHCO_3$ layers, and the pH was adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford the product (567 mg, 66%) as a solid. A sample was recrystallized from EtOAc.

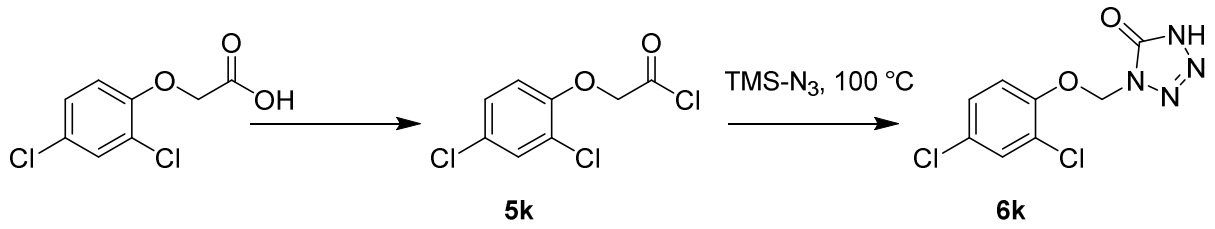
^{1}H NMR (DMSO-d_6, 300MHz): δ 8.07 (m, 1H), 7.61-7.57 (m, 2H), 7.38-7.29 (m, 1H), -1.3 (br. s, 1H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 150.5, 139.6, 135.5, 132.3, 129.6, 129.6, 98.2

m/z = 289.31 $[M+H]^+$ and 287.42 $[M-H]^+$

HRMS (EI): $[M+H]^+$ calc'd for $C_7H_5IN_4O$ *m/z* 289.9586, found 289.9588

PREPARATION OF 1-((2,4-DICHLOROPHENOXY)METHYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6K



5k **6k**

Oxalyl chloride (2.0 M in CH_2Cl_2; 3.0 mL, 6.0 mmol) was added dropwise over 2-3 min to a stirred suspension of 2,4-dichlorophenoxyacetic acid, also known as 2,4-D (663 mg, 3.0 mmol) and DMF (1-2drops) in CH_2Cl_2 (6 mL) at 0 °C under nitrogen. After complete addition, the mixture was allowed to warm to room temperature and stirred over a weekend (note: a solution develops after warming to rt; reaction left over a weekend as did not want to undertake the next step on a Friday evening). The mixture was concentrated under vacuum to leave the acid chloride **5k**, which was used directly in the tetrazolone-forming step below (yield assumed quantitative = 718 mg).

See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and 2,4-dichlorophenoxyacetyl chloride (718 mg, 3.0 mmol) was heated from room temperature to 100 °C (block temperature) in a round bottom flask with reflux condenser under an atmosphere of nitrogen. The mixture was then stirred at 100 °C for 3 hours. After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (30 mL) and a saturated solution of $NaHCO_3$ (30 mL). The organic layer was extracted with a saturated solution of $NaHCO_3$ (1 x 30 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (30 mL) was added to the filtrate and the pH was adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford the crude product (600 mg) of *ca.* 90% purity. The crude product was purified by column chromatography on silica gel (ISCO Combiflash)

using CH_2Cl_2 / MeOH (1:0 to 9:1) as eluent to give pure product (336 mg, 43%) as a solid. Less pure product (*ca*. 130 mg) was also obtained from the column, but was not purified further.

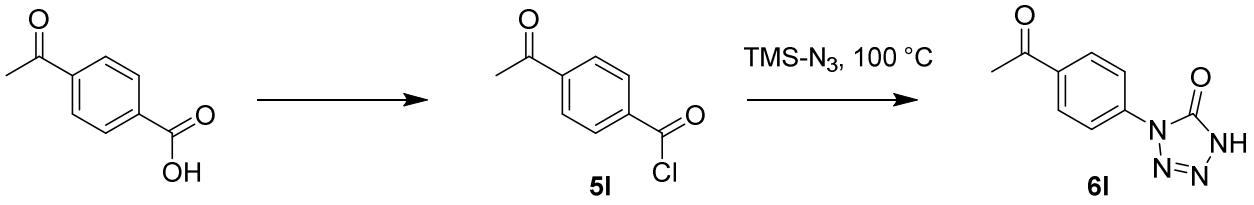
^{1}H NMR (DMSO-d_6, 300MHz): δ 7.59 (d, J = 2.4 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.43 (dd, J = 8.7, 2.4 Hz, 1H), 5.94 (s, 2H), -1.4 (br. s, 1H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 151.3, 150.6, 129.7, 128.3, 127.2, 124.2, 118.6, 71.2

m/z = 261.30 $[M+H]^+$ and 259.37 $[M-H]^+$ for ^{35}Cl

HRMS (EI): $[M-H]^+$ calc'd for $C_8H_6Cl_2N_4O_2$ *m/z* 258.9789, found 258.9795

PREPARATION OF 1-(4-ACETYLPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6L



Oxalyl chloride (2.0 M in CH_2Cl_2; 3.0 mL, 6.0 mmol) was added dropwise over 2-3 min to a stirred suspension of 4-acetylbenzoic acid (493 mg, 3.0 mmol) and DMF (1-2drops) in CH_2Cl_2 (6 mL) at 0 °C under nitrogen. After complete addition, the mixture was allowed to warm to room temperature and stirred overnight. The mixture was concentrated under vacuum to leave the acid chloride **5l**, which was used directly in the tetrazolone-forming step below (yield assumed quantitative = 548 mg).

See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and 4-acetylbenzoyl chloride (548 mg, 3.0 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The mixture was then stirred at 100 °C overnight (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (100 mL) and a 1:1 mixture of saturated $NaHCO_3$ (75 mL) and H_2O (75 mL). The organic layer was extracted with a 1:1 mixture of saturated $NaHCO_3$ (25 mL) and H_2O (25 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. The aqueous layer was filtered to remove minor insoluble items and then EtOAc (100 mL) was added to the filtrate. The pH was adjusted to < 3 using 6N HCl with efficient stirring (care: if an azidohydrin is formed from the reaction, then treatment with acid may release HCN). The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 75 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford the crude product (445 mg) of *ca*.

90-95% purity. The crude product was purified by column chromatography on silica gel (ISCO Combiflash) using CH_2Cl_2 / MeOH (1:0 to 9:1) as eluent to give the product (360 mg, 59%) as a solid.

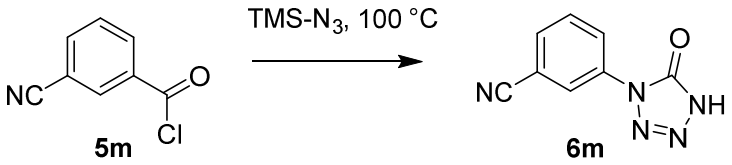
^{1}H NMR (DMSO-d_6, 300MHz): δ 8.11 (d, J = 7.2 Hz, 2H), 8.02 (d, J = 9.0 Hz, 2H), 2.58 (s, 3H), -1.0 (br. s, 1H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 196.8, 150.1, 137.8, 135.1, 129.7, 118.3, 26.7

m/z = 203.30 $[M-H]^+$

HRMS (EI): $[M+H]^+$ calc'd for $C_9H_8N_4O_2$ *m/z* 205.0726, found 205.0721

PREPARATION OF 1-(3-CYANOPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6M



See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and 3-cyanobenzoyl chloride (497 mg, 3.0 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The mixture was then stirred at 100 °C overnight (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic layer was extracted with a further quantity of saturated aqueous $NaHCO_3$ (1 x 10 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (20 mL) was added to the combined $NaHCO_3$ layers, and the pH was adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford the product (505 mg, 90%) as a solid. A sample was recrystallized from EtOAc

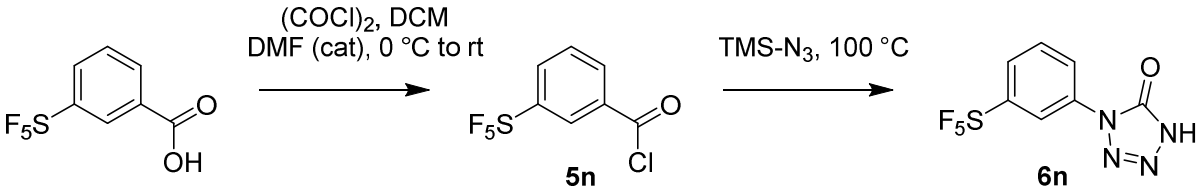
^{1}H NMR (DMSO-d_6, 300MHz): δ 8.26 (m, 1H), 8.16 (ddd, J = 8.7, 2.4, 1.2 Hz, 1H), 7.87 (dt, J = 7.8, 2.7 Hz, 1H), 7.48 (dt, J = 8.3, 0.6 Hz, 1H), -1.1 (br. s, 1H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 150.1, 134.9, 131.1, 131.0, 123.7, 122.1, 117.9, 112.4

m/z = 188.30 $[M+H]^+$ and 186.42 $[M-H]^+$

HRMS (EI): $[M-H]^+$ calc'd for $C_8H_5N_5O$ m/z 186.0486, found 186.0427

PREPARATION OF 1-(3-(PENTAFLUOROSULFANYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6N



Oxalyl chloride (2.0 M in CH_2Cl_2; 0.75 mL, 1.5 mmol) was added dropwise over 2-3 min to a stirred suspension of 3-(pentafluorosulfanyl)benzoic acid (248 mg, 1.0 mmol) and DMF (2-3drops) in CH_2Cl_2 (3 mL) at 0 °C under nitrogen. After complete addition, the mixture was stirred at 0 °C for 1 hr then allowed to warm to room temperature and stirred for 3 hr. The mixture was concentrated under vacuum to leave the acid chloride **5n**, which was used directly in the tetrazolone-forming step below (yield assumed quantitative = 267 mg).

See 'Important safety notice for all experiments' (page S6); Blast shield employed

Note: 18 equivalent of TMS-N_3 were used in order to ensure complete coverage of the material in a vial with pressure-release cap

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and 3-(pentafluorosulfanyl)benzoyl chloride (267 mg, 1.0 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The mixture was then stirred at 100 °C overnight (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (20 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic layer was extracted with a further quantity of saturated aqueous $NaHCO_3$ (8 x 10 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (30 mL) was added to the combined $NaHCO_3$ layers, and the pH was adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford the product (187 mg, 65%) as a solid.

^{1}H NMR (DMSO-d_6, 300MHz): δ 8.40 (t, J = 2.1 Hz, 1H), 8.14 (d, J = 8.1 Hz, 1H), 7.92-7.96 (m, 1H), 7.80 (t, J = 8.6 Hz, 1H), -1.1 (br. s, 1H)

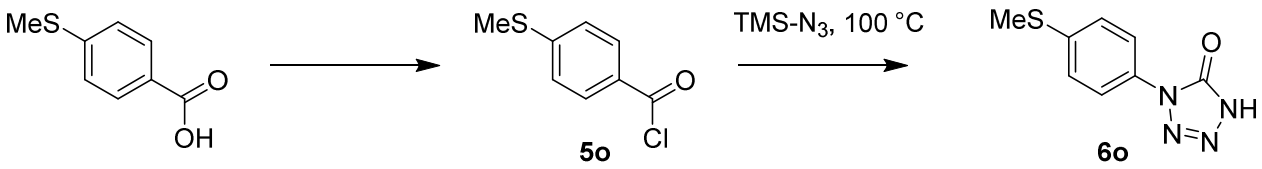
^{19}F NMR (DMSO-d_6, 272MHz): δ -114.4 (quin., J = 145 Hz), -136.2 (d, J = 145 Hz)

^{13}C NMR (DMSO-d_6, 75MHz): δ 153.0 (quin., J = 17.3 Hz), 150.2, 134.7, 130.9, 124.5 (quin., J = 4.7 Hz), 123.0, 116.1 (quin., J = 5.0 Hz)

m/z = 287.45 $[M-H]^+$

HRMS (EI): $[M-H]^+$ calc'd for $C_7H_5F_3N_4OS$ *m/z* 287.0026, found 287.0059

PREPARATION OF 1-(4-(METHYLTHIO)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6O



Oxalyl chloride (2.0 M in CH_2Cl_2; 3.0 mL, 6.0 mmol) was added dropwise over 2-3 min to a stirred suspension of 4-(methylthio)benzoic acid (505 mg, 3.0 mmol) and DMF (1-2drops) in CH_2Cl_2 (6 mL) at 0 °C under nitrogen. After complete addition, the mixture was allowed to warm to room temperature and stirred overnight. The mixture was concentrated under vacuum to leave the acid chloride **5o**, which was used directly in the tetrazolone-forming step below (yield assumed quantitative = 560 mg).

See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and 4-(methylthio)benzoyl chloride (560 mg, 3.0 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The mixture was then stirred at 100 °C overnight (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (100 mL) and a 1:1 mixture of saturated $NaHCO_3$ (50 mL) and H_2O (50 mL). The organic layer was extracted with a further quantity of saturated aqueous $NaHCO_3$ (2 x 30 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (75 mL) was added to the combined $NaHCO_3$ layers, and the pH was carefully adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford a crude residue containing product (*ca*. 93% purity). The residue was purified by column chromatography on silica gel (ISCO Combiflash) using CH_2Cl_2 / MeOH (1:0 to 9:1) as eluent to give the product (473 mg, 73%) as a solid.

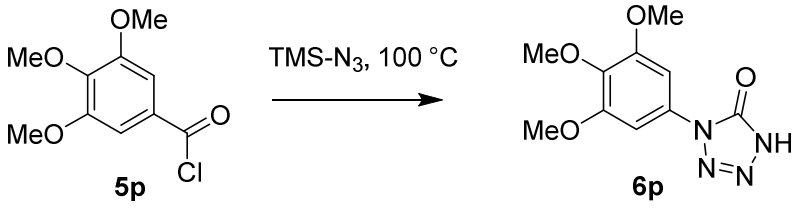
^{1}H NMR (DMSO-d_6, 300MHz): δ 7.78-7.73 (m, 2H), 7.42-7.38 (m, 2H), 2.49 (s, 3H), -1.3 (br. s, 1H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 150.2, 137.9, 131.1, 126.6, 120.1, 14.7

m/z = 209.27 $[M+H]^+$ and 207.41 $[M-H]^+$

HRMS (EI): $[M+H]^+$ calc'd for $C_8H_8N_4OS$ *m/z* 209.0497, found 209.0482

PREPARATION OF 1-(3,4,5-TRIMETHOXYPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6P



See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and 3,4,5-trimethoxybenzoyl chloride (692 mg, 3.0 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The mixture was then stirred at 100 °C overnight (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic layer was extracted with a further quantity of saturated aqueous $NaHCO_3$ (1 x 10 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (20 mL) was added to the combined $NaHCO_3$ layers, and the pH was carefully adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford a crude residue containing product and carboxylic acid impurity. The residue was purified by column chromatography on silica gel (ISCO Combiflash) using hexanes / EtOAc (1:0 to 0:1) as eluent to give the product (155 mg, 20%) as a solid.

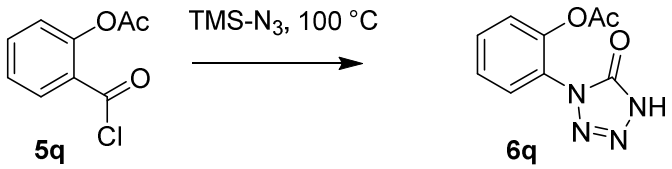
^{1}H NMR (DMSO-d_6, 300MHz): δ 7.14 (s, 2H), 3.79 (s, 6H), 3.67 (s, 3H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 153.3, 150.3, 136.6, 130.1, 97.6, 60.2, 56.1

m/z = 253.34 $[M+H]^+$ and 251.39 $[M-H]^+$

HRMS (EI): $[M+H]^+$ calc'd for $C_{10}H_{12}N_4O_4$ *m/z* 253.0937, found 253.0933

PREPARATION OF 2-(5-OXO-4,5-DIHYDRO-1*H*-TETRAZOL-1YL)PHENYL ACETATE 6Q



See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and 2-chlorocarbonyl)phenyl acetate (566 mg, 3.0 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The mixture was then stirred at 100 °C overnight (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic layer was extracted with a further quantity of saturated aqueous $NaHCO_3$ (1 x 10 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (20 mL) was added to the combined $NaHCO_3$ layers, and the pH was carefully adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford a crude residue containing product and other impurities. The residue was purified by column chromatography on silica gel (ISCO Combiflash) using hexanes / EtOAc (1:0 to 0:1) as eluent to give the product (367 mg, 56%) as a solid.

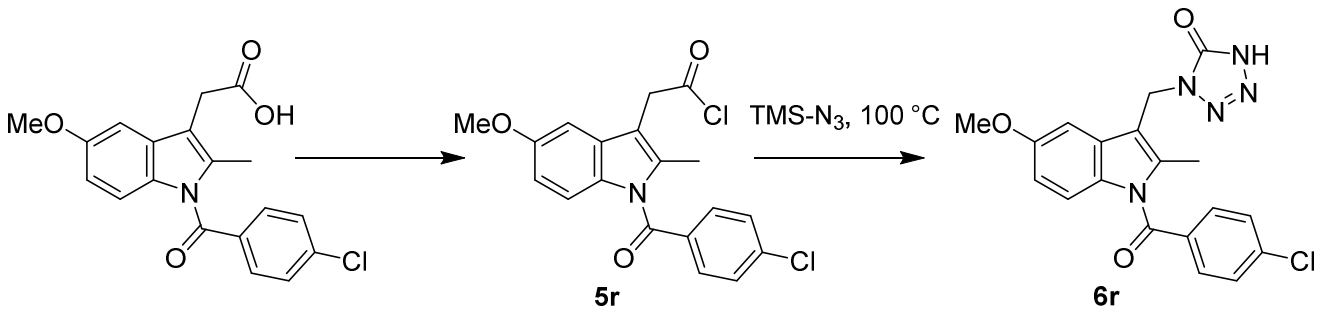
^{1}H NMR (DMSO-d_6, 300MHz): δ 7.66-7.54 (m, 2H), 7.50-7.38 (m, 2H), 2.16 (s, 3H), -1.3 (br. s, 1H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 168.2, 150.5, 144.4, 130.5, 126.9, 126.7, 125.4, 124.6, 20.6

m/z = 219.45 $[M-H]^+$

HRMS (EI): $[M-H]^+$ calc'd for $C_9H_8N_4O_3$ *m/z* 219.0518, found 219.0507

PREPARATION OF 1-((1-(4-CHLOROBENZOYL)-5-METHOXY-1*H*-INDOL-3-YL)METHYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6R



Oxalyl chloride (2.0 M in CH_2Cl_2; 2.3 mL, 4.6 mmol) was added dropwise over 2-3 min to a stirred suspension of 2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetic acid, also known as Indomethacin (1.07 g, 3.0 mmol) and DMF (1-2drops) in CH_2Cl_2 (9 mL) at 0 °C in a vial with pressure-release top. After complete addition, the mixture was allowed to warm to room temperature and stirred at room temperature for *ca*. 60 min. The mixture was concentrated under vacuum to leave the acid chloride **5r**, which was used directly in the tetrazolone-forming step below after drying on a high vacuum for 30 min (yield assumed quantitative = 1.13 g).

See 'Important safety notice for all experiments' (page S6); Blast shield employed

Note: 4.8 mL (12 equiv.) of azidotrimethylsilane used in order to give sufficient volume for acid chloride to dissolve

A stirred mixture of azidotrimethylsilane (4.8 mL, 18 mmol) and 2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetyl chloride (1.13 g, 3.0 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The temperature was lowered to 90 °C and the mixture was stirred at 90 °C overnight (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and then the mixture was dry-loaded on to silica gel by evaporation from EtOAc. The mixture was purified by column chromatography on silica gel (ISCO Combiflash) using hexanes / EtOAc (1:0 to 0:1) as eluent to the product (0.98 g, 82%) as a solid.

^{1}H NMR (DMSO-d_6, 300MHz): δ 7.69-7.60 (m, 4H), 7.21 (d, J = 2.4 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 6.73 (dd, J = 9.0, 2.4 Hz, 1H), 5.17 (s, 2H), 3.73 (s, 3H), 2.39 (s, 3H), -1.6 (br. s, 1H)

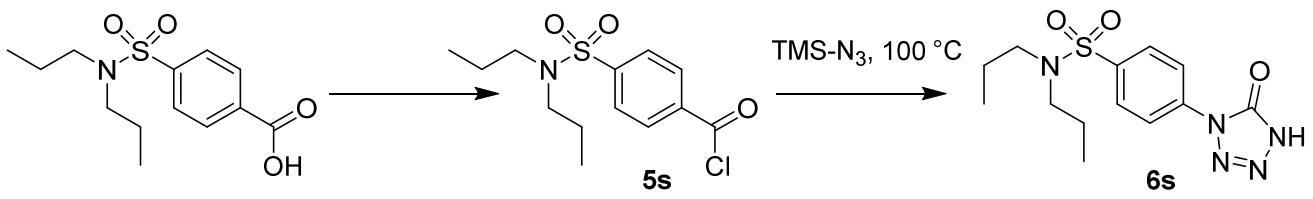
^{13}C NMR (DMSO-d_6, 75MHz): δ 168.0, 155.6, 151.6, 137.9, 137.2, 133.7, 131.3, 130.3, 129.3, 129.1, 114.7, 113.4, 111.6, 101.6, 55.3, 37.1, 13.0

m/z = 398.41 $[M+H]^+$ and 396.53 $[M-H]^+$

HRMS (EI): $[M+H]^+$ calc'd for $C_{19}H_{16}ClN_5O_3$ *m/z* 398.1020, found 398.1034

HRMS (EI): $[M-H]^+$ calc'd for $C_{19}H_{16}ClN_5O_3$ *m/z* 396.0863, found 396.0823

PREPARATION OF 4-(5-OXO-4,5-DIHYDRO-1*H*-TETRAZOL-1-YL)-DIPROPYLBENZENESULFONAMIDE 6S



Oxalyl chloride (2.0 M in CH_2Cl_2; 3.0 mL, 6.0 mmol) was added dropwise over 2-3 min to a stirred suspension of 4-(*N*,*N*-dipropylsulfamoyl)benzoic acid (856 mg, 3.0 mmol) and DMF (1-2drops) in CH_2Cl_2 (6 mL) at 0 °C under nitrogen. After complete addition, the mixture was allowed to warm to room temperature and stirred overnight. The mixture was concentrated under vacuum to leave the acid chloride **5s**, which was used directly in the tetrazolone-forming step below (yield assumed quantitative = 911 mg).

See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and 4-(*N*,*N*-dipropylsulfamoyl)benzoyl chloride (911 mg, 3.0 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The mixture was then stirred at 100 °C overnight (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (30 mL) and an aqueous saturated $NaHCO_3$ (30 mL). The organic layer was extracted with a further quantity of saturated aqueous $NaHCO_3$ (8 x 30 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (60 mL) was added to the combined $NaHCO_3$ layers, and the pH was carefully adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford the product (665 mg, 68%) as a solid.

^{1}H NMR (DMSO-d_6, 300MHz): δ 8.13-8.08 (m, 2H), 7.98-7.93 (m, 2H), 3.03 (t, J = 7.7 Hz, 2H), 1.47 (app. sextet, J = 7.4 Hz, 2H), 0.79 (t, J = 7.4 Hz, 3H), -1.1 (br. s, 1H)

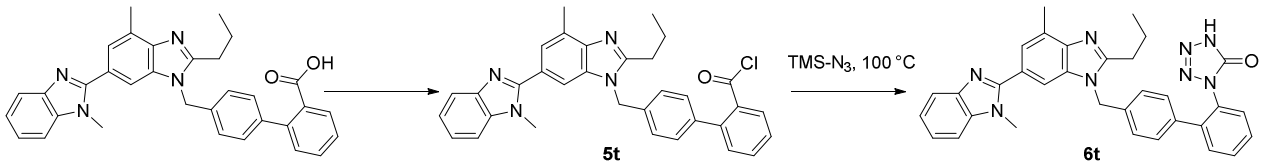
^{13}C NMR (DMSO-d_6, 75MHz): δ 150.1, 137.8, 137.3, 128.4, 119.0, 49.6, 21.6, 11.0

m/z = 326.35 $[M+H]^+$ and 324.43 $[M-H]^+$

HRMS (EI): $[M+H]^+$ calc'd for $C_{13}H_{19}N_5O_3S$ *m/z* 326.1287, found 326.1257

HRMS (EI): $[M-H]^+$ calc'd for $C_{13}H_{19}N_5O_3S$ *m/z* 324.1130, found 324.1116

PREPARATION OF 1-(4'-((1,7-DIMETHYL-2'-PROPYL-1*H*,3'*H*-[2,5'-DIBENZO[*D*]IMIDAZOL]-3'-YL)METHYL-[1,1'-BIPHENYL-2-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6T



Oxalyl chloride (2.0 M in CH_2Cl_2; 0.75 mL, 1.5 mmol) was added dropwise over 2-3 min to a stirred suspension of 4'-((1,7-dimethyl-2'-propyl-1*H*,3'*H*-[2,5'-dibenzo[*d*]imidazol]-3'-yl)methyl-[1,1'-biphenyl)-2-carboxylic acid, also known as Telmisartan (514 mg, 1.0 mmol) and DMF (3 drops) in CH_2Cl_2 (6 mL) at 0 °C under nitrogen. After complete addition, the mixture was stirred at 0 °C for 10 min, then allowed to warm to room temperature and stirred for 30 min (a yellow then orange solution develops). The mixture was concentrated under vacuum, then fresh CH_2Cl_2 (2 mL) was added to the residue and the mixture concentrated under vacuum again to leave the acid chloride **5t**, which was used directly in the tetrazolone-forming step below, after drying on a high vacuum for 15 min (yield assumed quantitative = 533 mg).

See 'Important safety notice for all experiments' (page S6); Blast shield employed

Note: 4.8 mL (36 equiv.) of azidotrimethylsilane used in order to give sufficient volume for the reaction

A stirred mixture of azidotrimethylsilane (4.8 mL, 36 mmol) and 4'-((1,7-dimethyl-2'-propyl-1*H*,3'*H*-[2,5'-dibenzo[*d*]imidazol]-3'-yl)methyl-[1,1'-biphenyl)-2-carbonyl chloride (533 mg, 1.0 mmol) was heated from room temperature to 100 °C (block temperature) in a round bottom flask with reflux condenser under an atmosphere of nitrogen. The mixture was then stirred at 100 °C for 2 hours. After cooling, the mixture was concentrated under vacuum and MeOH was added to the residue. The mixture was dry-loaded on to silica gel and then purified by column chromatography on silica gel (ISCO Combiflash) using CH_2Cl_2 / MeOH (1:0 to 92:8) as eluent to give the pure product (87 mg) and mixed fractions. The mixed fractions were re-purified by column chromatography on silica gel (ISCO

Combiflash) using CH_2Cl_2 / MeOH (1:0 to 92:8) as eluent to give the product (97 mg) as a solid. Total yield of product = 184 mg (33%). Also obtained, was a faster-eluting unidentified by-product (181 mg).

^{1}H NMR (DMSO-d_6, 300MHz): δ 7.73 (s, 1H), 7.64-7.47 (m, 7H), 7.29-7.11 (m, 6H), 5.58 (s, 2H), 3.80 (s, 3H), 2.86 (t, J = 7.5 Hz, 2H), 2.61 (s, 3H), 1.75 (sextet, J = 7.5 Hz, 2H), 0.94 (t, J = 7.5 Hz, 3H), -1.5 (br. s, 1H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 156.2, 154.0, 151.3, 142.6, 142.4, 139.2, 136.7, 136.7, 136.6, 134.7, 130.9, 130.7, 130.3, 128.8, 128.6, 128.6, 128.3, 126.8, 123.3, 123.2, 122.1, 121.8, 118.6, 110.4, 109.1, 45.9, 31.7, 28.7, 20.7, 16.4, 13.8

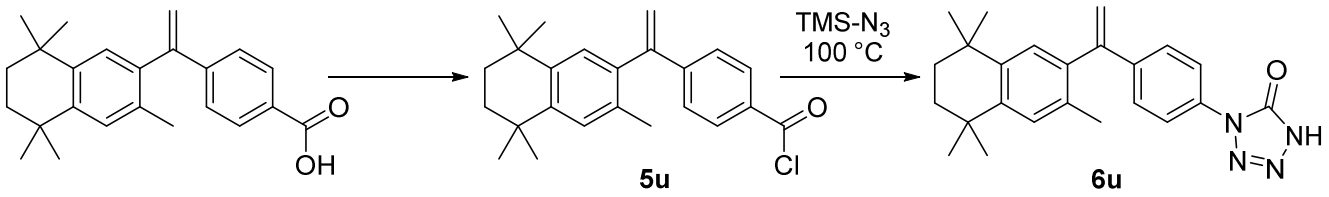
m/z = 555.66 $[M+H]^+$ and 553.75 $[M-H]^+$

HRMS (EI): $[M+H]^+$ calc'd for $C_{33}H_{30}N_8O$ *m/z* 555.2621, found 555.2585

HRMS (EI): $[M-H]^+$ calc'd for $C_{33}H_{30}N_8O$ *m/z* 553.2465, found 553.2411

A separate HRMS (EI) obtained: $[M+H]^+$ calc'd for $C_{33}H_{30}N_8O$ *m/z* 555.2621, found 555.2633

PREPARATION OF 1-(4-(1-(3,5,5,8,8-PENTAMETHYL-5,6,7,8-TETRAHYDRONAPHTHALEN-2-YL)VINYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6U



Oxalyl chloride (2.0 M in CH_2Cl_2; 0.38 mL, 0.75 mmol) was added dropwise over 1 min to a stirred suspension of 4-(1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)vinyl)benzoic acid, also known as Bexarotene (175 mg, 0.5 mmol) and DMF (1-2drops) in CH_2Cl_2 (5 mL) at 0 °C under nitrogen. After complete addition, the mixture was allowed to warm to room temperature and for 2 hr. The mixture was concentrated under vacuum to leave the acid chloride **5u**, which was used directly in the tetrazolone-forming step below (yield assumed quantitative = 184 mg).

See 'Important safety notice for all experiments' (page S6); Blast shield employed

Note: 1.0 mL (15 equiv.) of azidotrimethylsilane used in order to give sufficient volume for the reaction

A stirred mixture of azidotrimethylsilane (1.0 mL, 7.5 mmol) and 4-(1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)vinyl)benzoyl chloride (184 mg, 0.5 mmol) was heated from room temperature to 100 °C (block temperature) in a 10 mL round-bottom flask under an atmosphere of nitrogen. The mixture was then stirred at 100 °C for 2 hr, by which time LC/MS and TLC analysis indicates completion of the reaction. After cooling, CH_2Cl_2 and MeOH was added to the mixture, which was then dry-loaded on to silica gel and purified by column chromatography on silica gel (ISCO Combiflash) using hexanes / EtOAc (1:0 to 0:1) as eluent to give the product (173 mg, 89%) as a solid.

^{1}H NMR (DMSO-d_6, 300MHz): δ 7.82-7.79 (m, 2H), 7.39-7.36 (m, 2H), 7.13 (s, 1H), 7.06 (s, 1H), 5.84 (s, 1H), 5.18 (s, 1H), 1.91 (s, 3H), 1.63 (br. s, 4H), 1.24 (s, 6H), 1.21 (s, 6H), -1.0 (br. s, 1H)

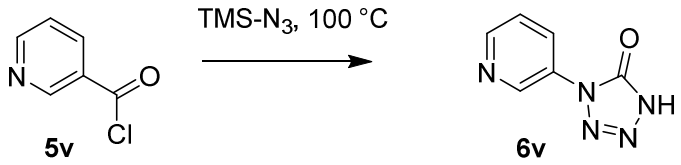
^{13}C NMR (DMSO-d_6, 75MHz): δ 150.2, 147.9, 143.7, 141.8, 138.3, 137.9, 133.4, 132.1, 127.9, 127.3, 127.1, 119.5, 115.9, 34.7, 34.6, 33.6, 33.5, 31.7, 31.6, 19.5

m/z = 389.63 $[M+H]^+$ and 387.68 $[M-H]^+$

HRMS (EI): $[M+H]^+$ calc'd for $C_{24}H_{28}N_4O$ *m/z* 389.2341, found 389.2344

HRMS (EI): $[M-H]^+$ calc'd for $C_{24}H_{28}N_4O$ *m/z* 387.2185, found 387.2211

PREPARATION OF 1-(PYRIDIN-3-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6V



See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and nicotinoyl chloride hydrochloride (425 mg, 2.4 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The mixture was then stirred at 100 °C overnight (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic layer was extracted with a further quantity of saturated aqueous $NaHCO_3$ (1 x 10 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (20 mL) was added to the combined $NaHCO_3$ layers, and the pH was adjusted to < 3 using 6N HCl with efficient stirring. Once acidified, the aqueous layer was re-adjusted to pH 6-7 using saturated $NaHCO_3$. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford the product (330 mg, 65%) as a solid. A sample was recrystallized from EtOAc.

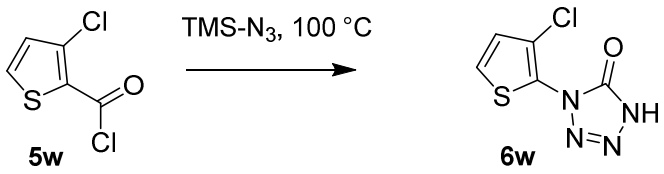
^{1}H NMR (DMSO-d_6, 300MHz): δ 9.04 (d, J = 2.1 Hz, 1H), 8.60 (d, J = 4.5 Hz, 1H), 8.22 (ddd, J = 8.4, 2.7, 1.5 Hz, 1H), 7.58 (dd, J = 8.4, 4.8, Hz, 1H), -1.1 (br. s, 1H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 150.4, 148.5, 140.7, 131.1, 127.1, 12.2

m/z = 162.20 $[M-H]^+$

HRMS (EI): $[M+H]^+$ calc'd for $C_6H_5N_5O$ *m/z* 164.0572, found 164.0542

PREPARATION OF 1-(3-CHLOROTHIOPHEN-2-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6W



See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and 3-chlorothiophene-2-carbonyl chloride (543 mg, 3.0 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The mixture was then stirred at 100 °C overnight (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic layer was extracted with a further quantity of saturated aqueous $NaHCO_3$ (1 x 10 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (20 mL) was added to the combined $NaHCO_3$ layers, and the pH was adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford a mixture of the desired product and 3-chlorothiophene-2-carboxylic acid. This mixture was purified by column chromatography on silica gel (ISCO Combiflash) using hexanes / EtOAc (1:0 to 0:1) as eluent to give the product (185 mg, 30%) as a solid [also obtained from the column was 3-chlorothiophene-2-carboxylic acid (20mg)].

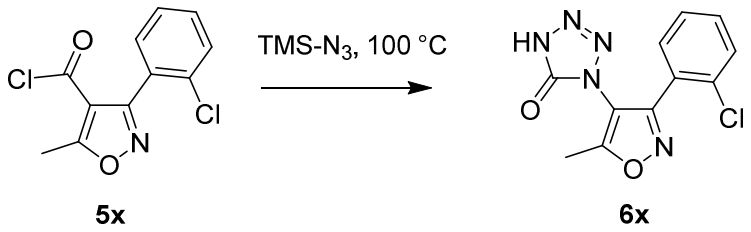
^{1}H NMR (DMSO-d_6, 300MHz): δ 7.88 (d, J = 6.0 Hz, 1H), 7.25 (d, J = 6.0 Hz, 1H), -1.1 (br. s, 1H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 150.5, 128.0, 126.6, 125.8, 123.6

m/z = 203.26 $[M+H]^+$ and 201.37 $[M-H]^+$

HRMS (EI): $[M-H]^+$ calc'd for $C_5H_3ClN_4OS$ *m/z* 200.9638, found 200.9674

PREPARATION OF 1-(3-(2-CHLOROPHENYL)5-METHYLISOXAZOL-4-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6X



See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and 3-(2-chlorophenyl)-5-methylisoxazole-4-carbonyl chloride (768 mg, 3.0 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The mixture was then stirred at 100 °C overnight (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic layer was extracted with a further quantity of saturated aqueous $NaHCO_3$ (1 x 10 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (20 mL) was added to the combined $NaHCO_3$ layers, and the pH was adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford the product (713 mg, 86%) as a solid. A sample was recrystallized from EtOAc.

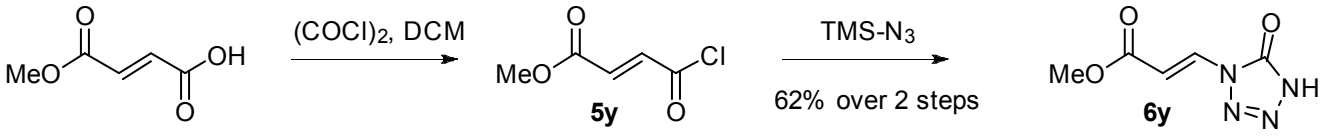
^{1}H NMR (DMSO-d_6, 300MHz): δ 7.58-7.44 (m, 4H), 2.55 (s, 3H), -1.2 (br. s, 1H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 167.4, 157.9, 150.8, 132.7, 132.1, 130.3, 128.2, 126.2, 115.5, 111.6

m/z = 278.36 $[M+H]^+$ and 276.51 $[M-H]^+$

HRMS (EI): $[M+H]^+$ calc'd for $C_{11}H_8ClN_5O_2$ *m/z* 278.0445, found 278.0450

PREPARATION OF METHYL (*E*)-3-(5-OXO-4,5-DIHYDRO-1*H*-TETRAZOL-1-YL)ACRYLATE 6Y



Oxalyl chloride (2.0 M in CH_2Cl_2; 15.2 mL, 30.3 mmol) was added dropwise over 2-3 min to a stirred suspension of monomethyl fumarate (2.63 g, 20.2 mmol) in CH_2Cl_2 (80 mL) at 0 °C under nitrogen. After complete addition, the mixture was stirred at 0 °C for 5min then allowed to warm to room temperature and stirred for 3 hr (a yellow solution develops). A small aliquot was removed and quenched with MeOH – TLC indicated no acid remaining. The mixture was concentrated under vacuum and CH_2Cl_2 (50 mL) was added to the residue and the mixture concentrated under vacuum once more to leave the acid chloride **5w**, which was used directly in the tetrazolone-forming step below (yield assumed quantitative = 3.0 g).

See 'Important safety notice for all experiments' (page S6); Blast shield employed

Azidotrimethylsilane (16.1 mL, 121.2 mmol) was added in one portion to the acid chloride from the above procedure (3.0 g, 20.2 mmol) at room temperature (gas evolution was noted). The mixture was place under nitrogen and heated from room temperature to 100 °C (block temperature), then stirred at 100 °C for 90 min. After cooling to room temperature, the excess solvent was removed under vacuum to leave a crude residue. EtOAC (150 mL) and saturated $NaHCO_3$ (150 mL) were added to the residue. A solid was noticed, so the mixture was filtered. The filter cake was dissolved in H_2O (350 mL) and then combined with the saturated $NaHCO_3$ layer of the filtrate. EtOAc (150 mL) was added to the combined aqueous system described above, and the mixture was acidified to *ca*. pH 3 with 1N HCl. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent removed under vacuum to leave a crude residue (2.6 g; *ca*. 90% purity of desired product). The residue was purified by column

chromatography on silica gel using CH_2Cl_2 / MeOH (1:0 to 9:1) as eluent to give the product (2.14 g, 62% over 2 steps) as a solid.

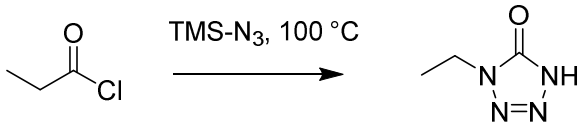
^{1}H NMR (DMSO-d_6, 300MHz): δ 7.73 (d, J = 14.4 Hz, 1H), 6.49 (d, J = 14.4 Hz, 1H), 3.71 (s, 3H), -1.0 (br. s, 1H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 165.7, 149.8, 132.3, 106.3, 51.9

m/z = 169.34 $[M-H]^+$

HRMS (EI): $[M+H]^+$ calc'd for $C_5H_6N_4O_3$ m/z 171.0518, found 171.0522

PREPARATION OF 1-ETHYL-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6Z



5z **6z**

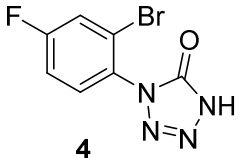
See 'Important safety notice for all experiments' (page S6); Blast shield employed

A stirred mixture of azidotrimethylsilane (2.4 mL, 18 mmol) and propionyl chloride (278 mg, 3.0 mmol) was heated from room temperature to 100 °C (block temperature) in a sealed vial with pressure-release cap. The mixture was then stirred at 100 °C overnight (Note: pressure develops during heating). After cooling, the mixture was concentrated under vacuum and the residue partitioned between EtOAc (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic layer was extracted with a further quantity of saturated aqueous $NaHCO_3$ (1 x 10 mL) [note: organic layer assessed by TLC to ascertain if tetrazolone product completely removed. If tetrazolone still present in organic layer, then further extractions with saturated $NaHCO_3$ are used]. EtOAc (20 mL) was added to the combined $NaHCO_3$ layers, and the pH was adjusted to < 3 using 6N HCl with efficient stirring. The aqueous and organic layers were partitioned and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent removed under vacuum to afford the product (49 mg, 14%) as a solid.

^{1}H NMR (DMSO-d_6, 300MHz): δ 3.86 (q, J = 7.3 Hz, 2H), 1.26 (t, J = 7.3 Hz, 3H), -1.7 (br. s, 1H)

^{13}C NMR (DMSO-d_6, 75MHz): δ 151.6, 38.7, 13.7

LC DATA FOR 1-(2-BROMO4-FLUOROPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 4



4

Openlynx Report - Page 1

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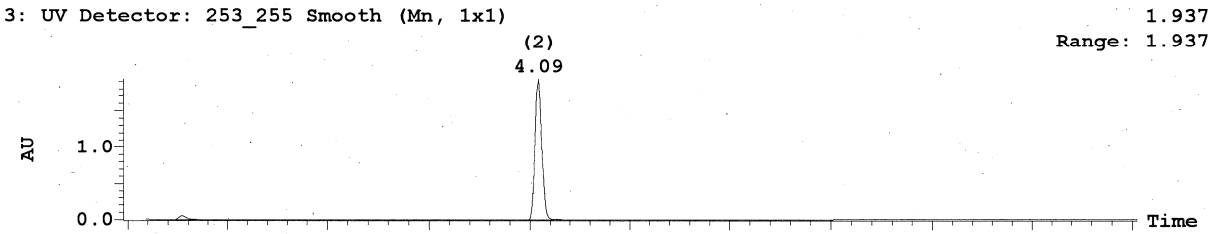
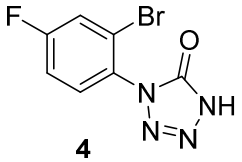
Time:17:03:11 Zed: Method:10min

Printed: Thu Aug 08 17:16:22 2013



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		0.54	4e+003	2.58	0	5e+004	
2		4.09	1e+005	97.42	0	2e+006	

^{1}H NMR FOR 1-(2-BROMO4-FLUOROPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 4



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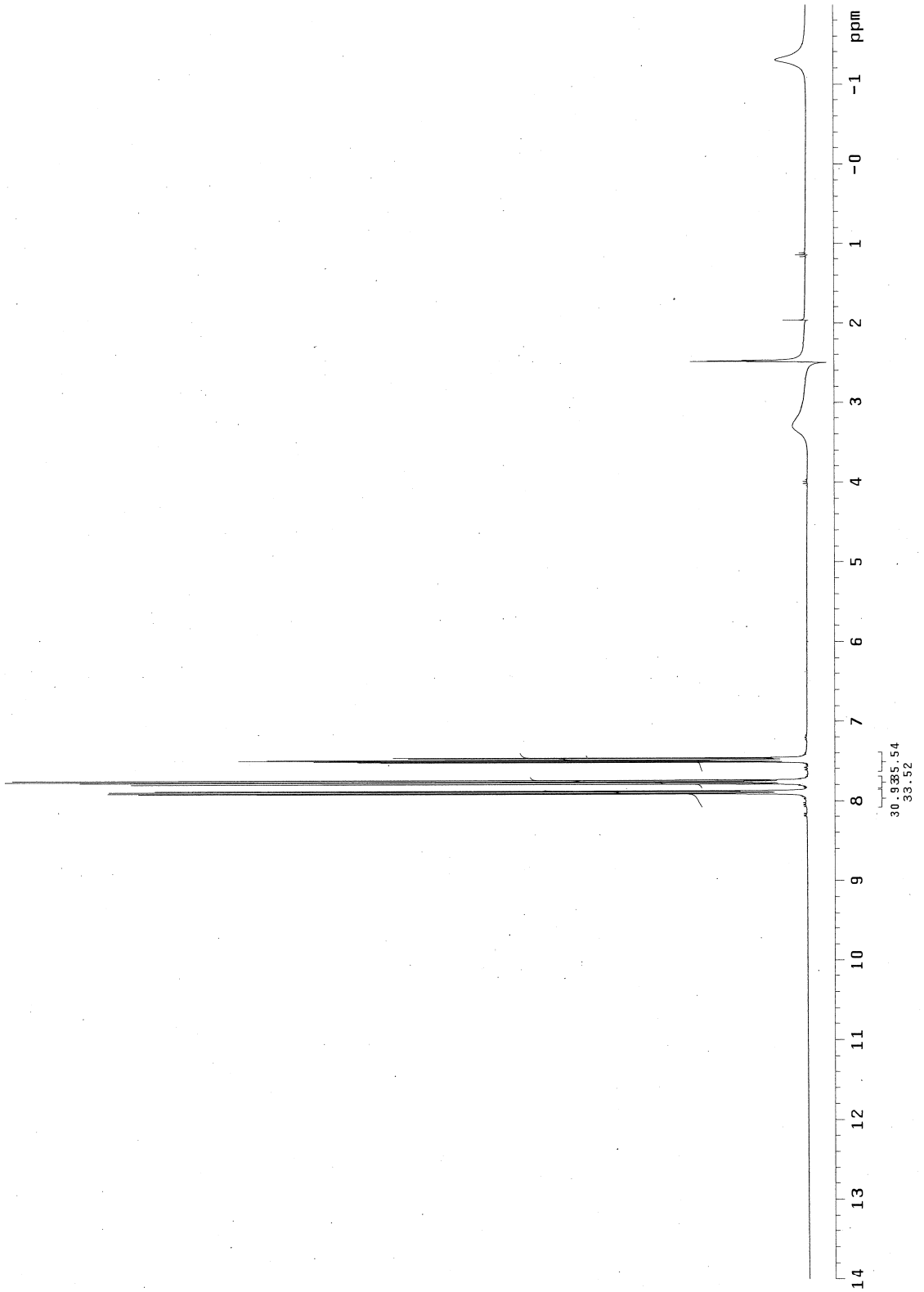
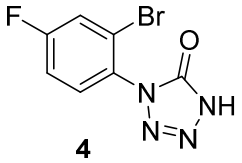


^{19}F NMR FOR 1-(2-BROMO4-FLUOROPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 4



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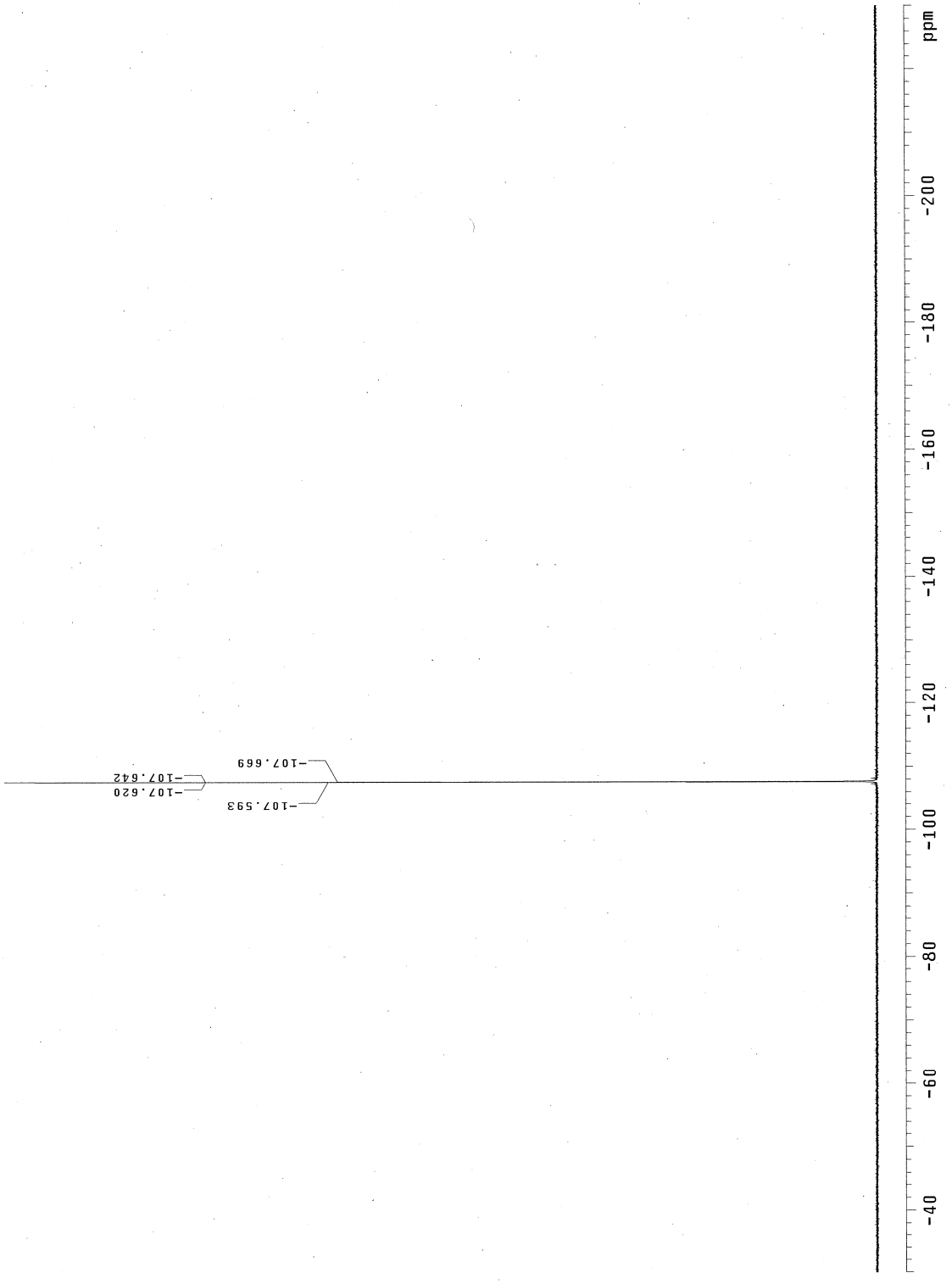
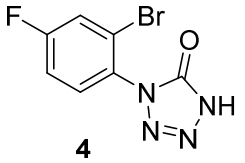
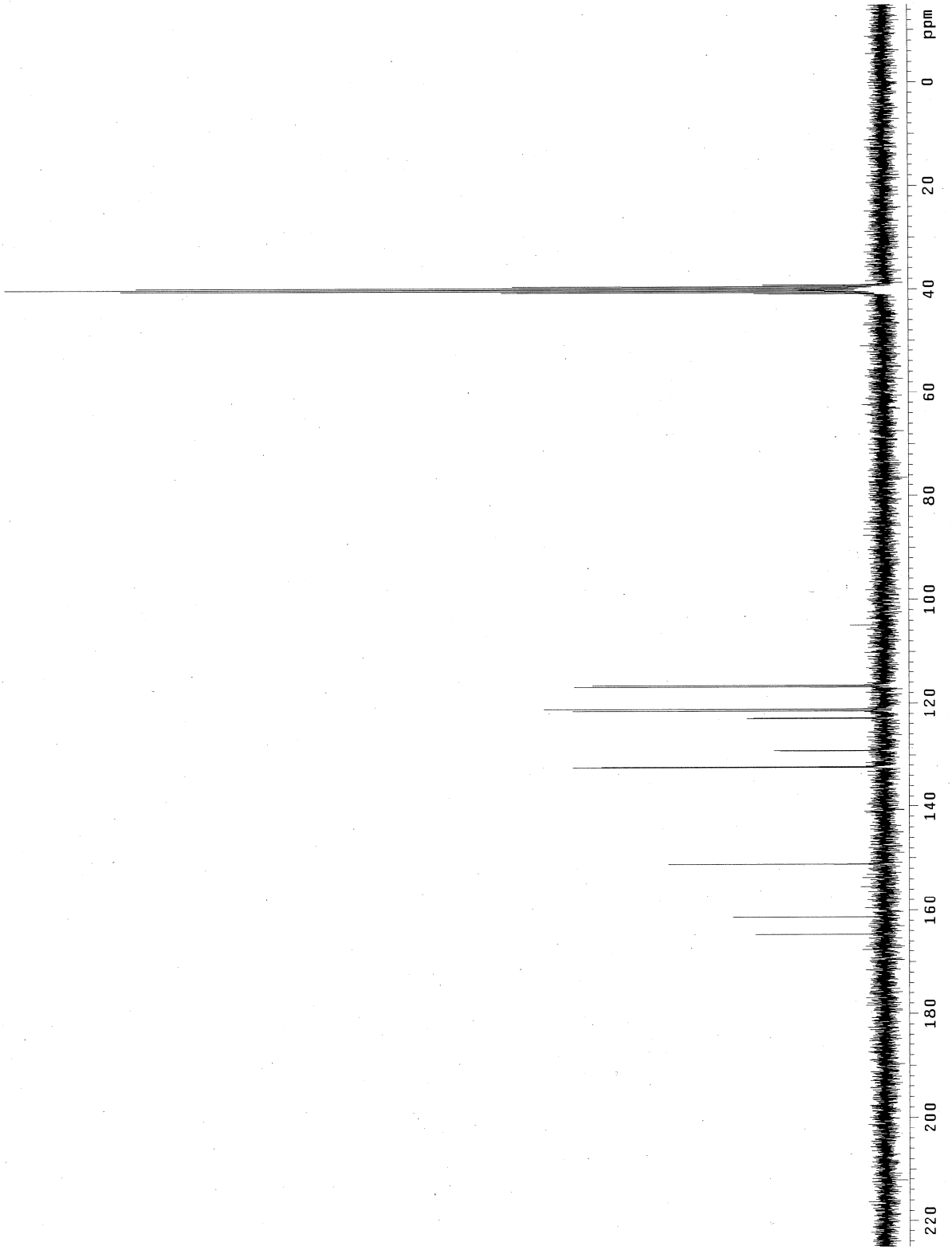


^{13}C NMR FOR 1-(2-BROMO4-FLUOROPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 4



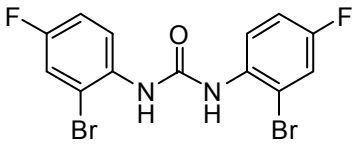
4



LC DATA FOR SYMMETRICAL UREA *BIS*-(2-BROMO-4-FLUORPHENYL)UREA

BY-PRODUCT ISOLATED FROM OPTIMIZATION REACTION IN TABLE 1, ENTRY 3

[NOTE: TWO LC ARE SHOWN DUE TO SIGNIFICANT TAILING WITH FIRST METHOD]

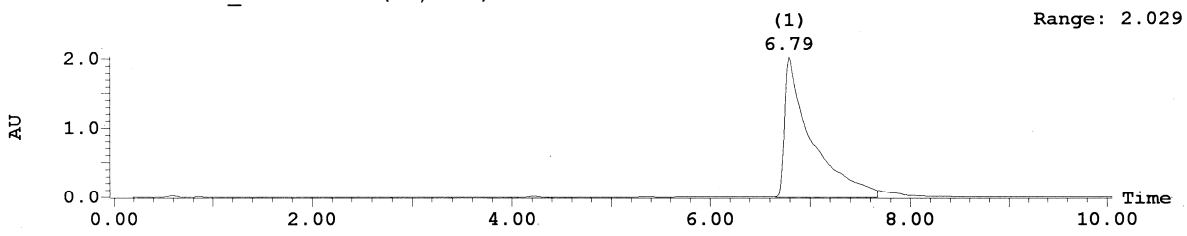


Openlynx Report - Page 1

Vial:1:A,9 File:MD1569-081B Date:12-Nov-2013
Time:13:15:22 Zed: Method:10min

Printed: Tue Nov 12 13:26:42 2013

3: UV Detector: 253_255 Smooth (Mn, 1x1) 2.029
Range: 2.029



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		6.79	6e+005	100.00	1	2e+006	

Openlynx Report - Page 1

Sample: 12 Vial:1:12 ID:
File:1569-081B Date:13-Nov-2013 Time:3::3::3
Description:3min

Printed: Wed Nov 13 15:17:55 2013

Sample Report:

Vial 1:12 ID File 1569-081B Date 13-Nov-2013 Time 3::3::3 Description 3min

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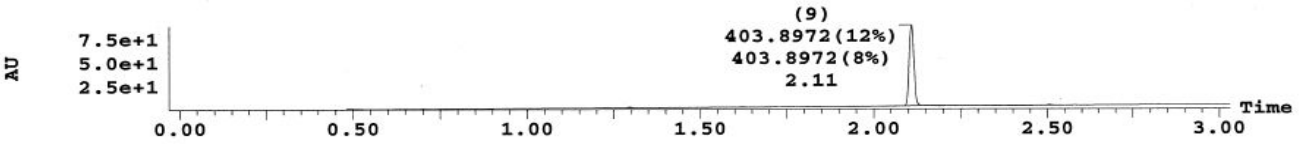
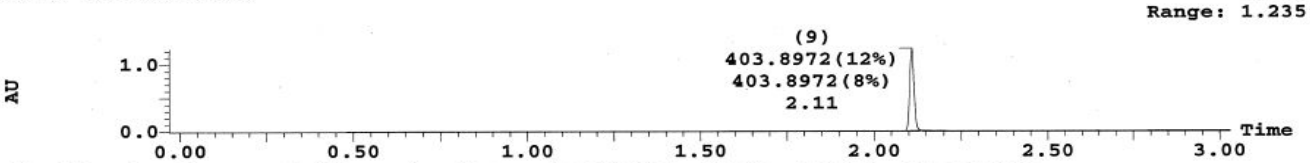
Range: 8.821e+1

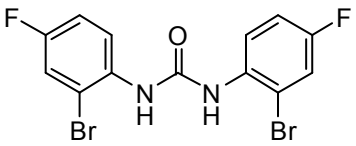


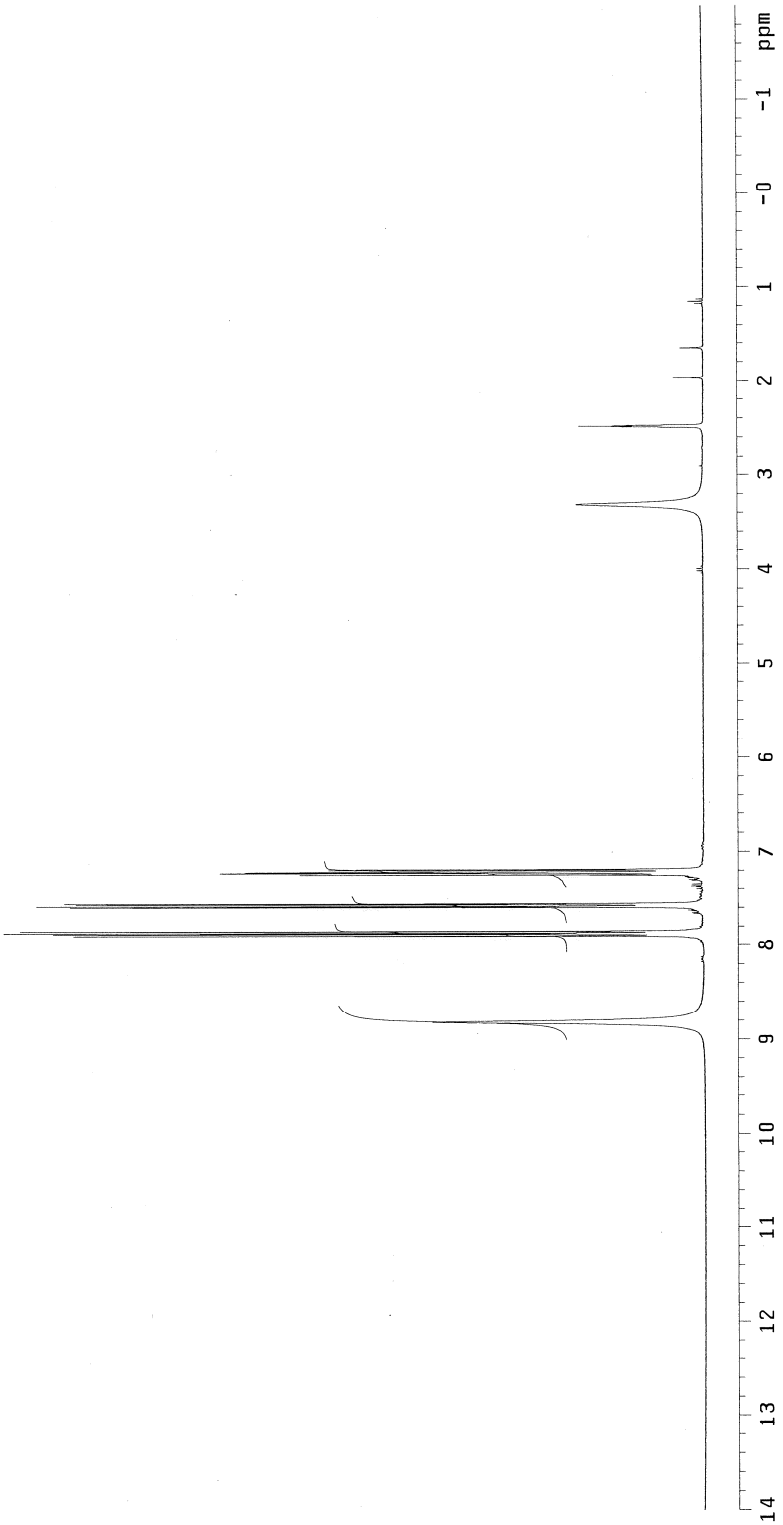
5: UV Detector: 254 1.235
Range: 1.235



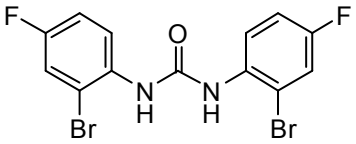
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
5		1.30	1e+001	0.07	0	7e+002	
8		2.00	3e+001	0.19	0	1e+003	
9	Tentative	2.11	2e+004	99.59	0	1e+006	403.90, 403.90
10		2.25	1e+001	0.07	0	6e+002	
12		2.65	1e+001	0.07	0	1e+003	

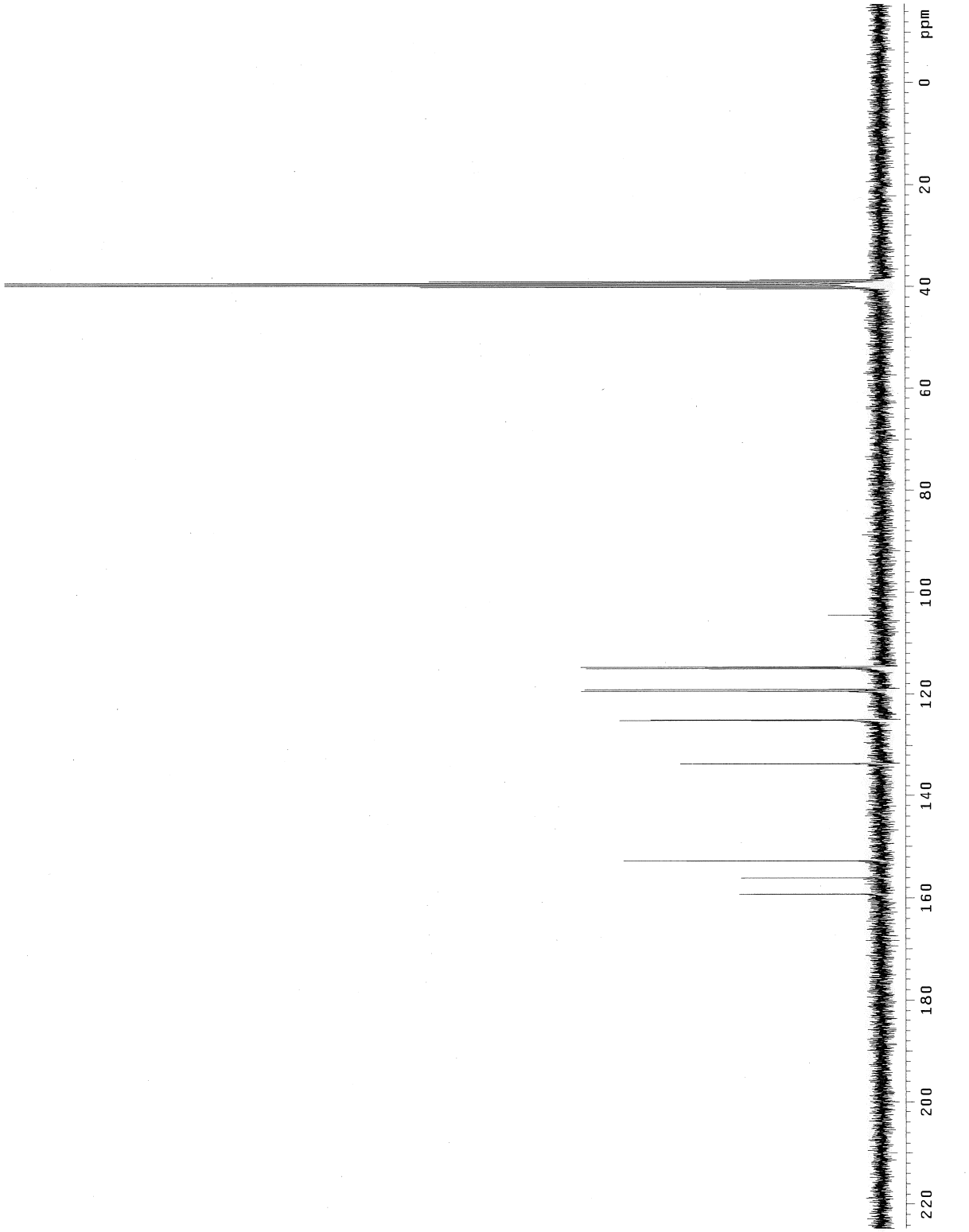
^{1}H NMR FOR SYMMETRICAL UREA *BIS*-(2-BROMO-4-FLUORPHENYL)UREA (BY-PRODUCT ISOLATED FROM OPTIMIZATION REACTION IN TABLE 1, ENTRY 3)



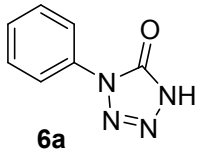


^{13}C NMR FOR SYMMETRICAL UREA *BIS*-(2-BROMO-4-FLUORPHENYL)UREA (BY-PRODUCT ISOLATED FROM OPTIMIZATION REACTION IN TABLE 1, ENTRY 3)





LC DATA FOR 1-PHENYL-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6A



6a

Openlynx Report - Page 1

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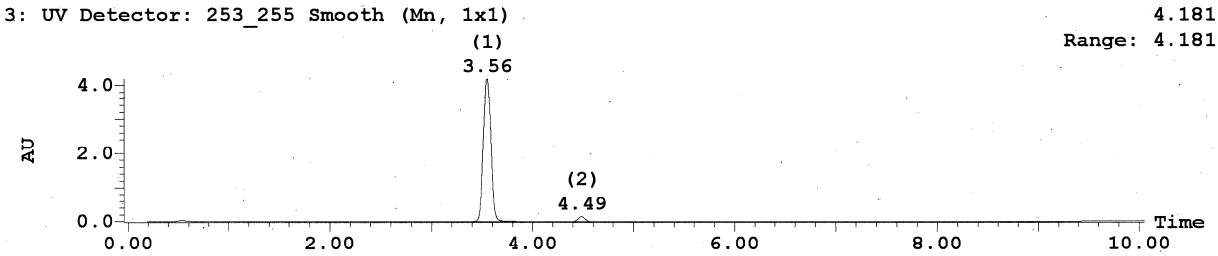
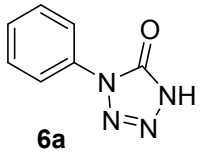
Time:17:29:51 Zed: Method:10min

Printed: Thu Aug 08 17:42:57 2013

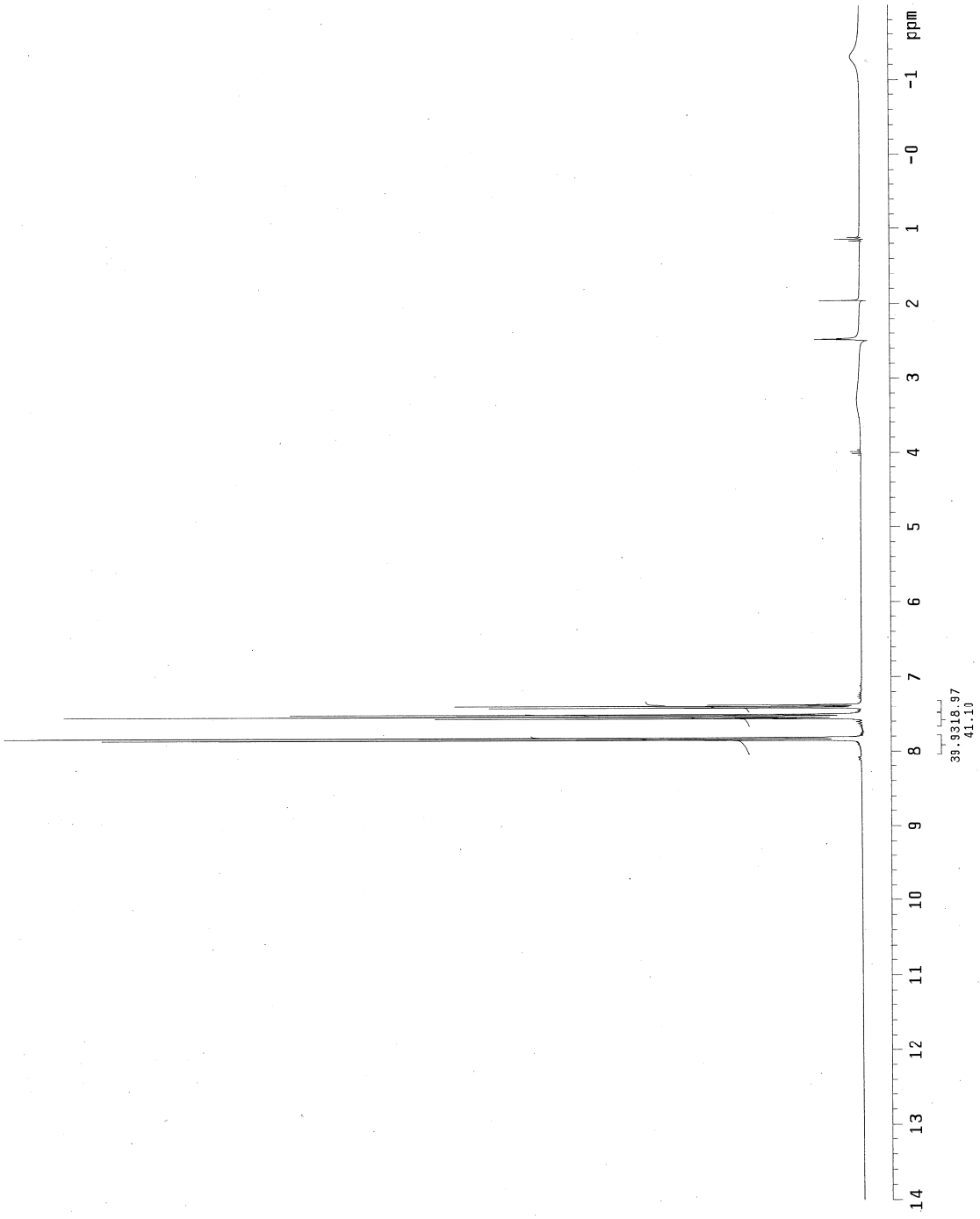


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		3.56	4e+005	97.11	1	4e+006	
2		4.49	1e+004	2.89	0	1e+005	

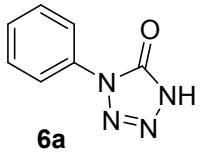
^{1}H NMR FOR 1-PHENYL-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6A



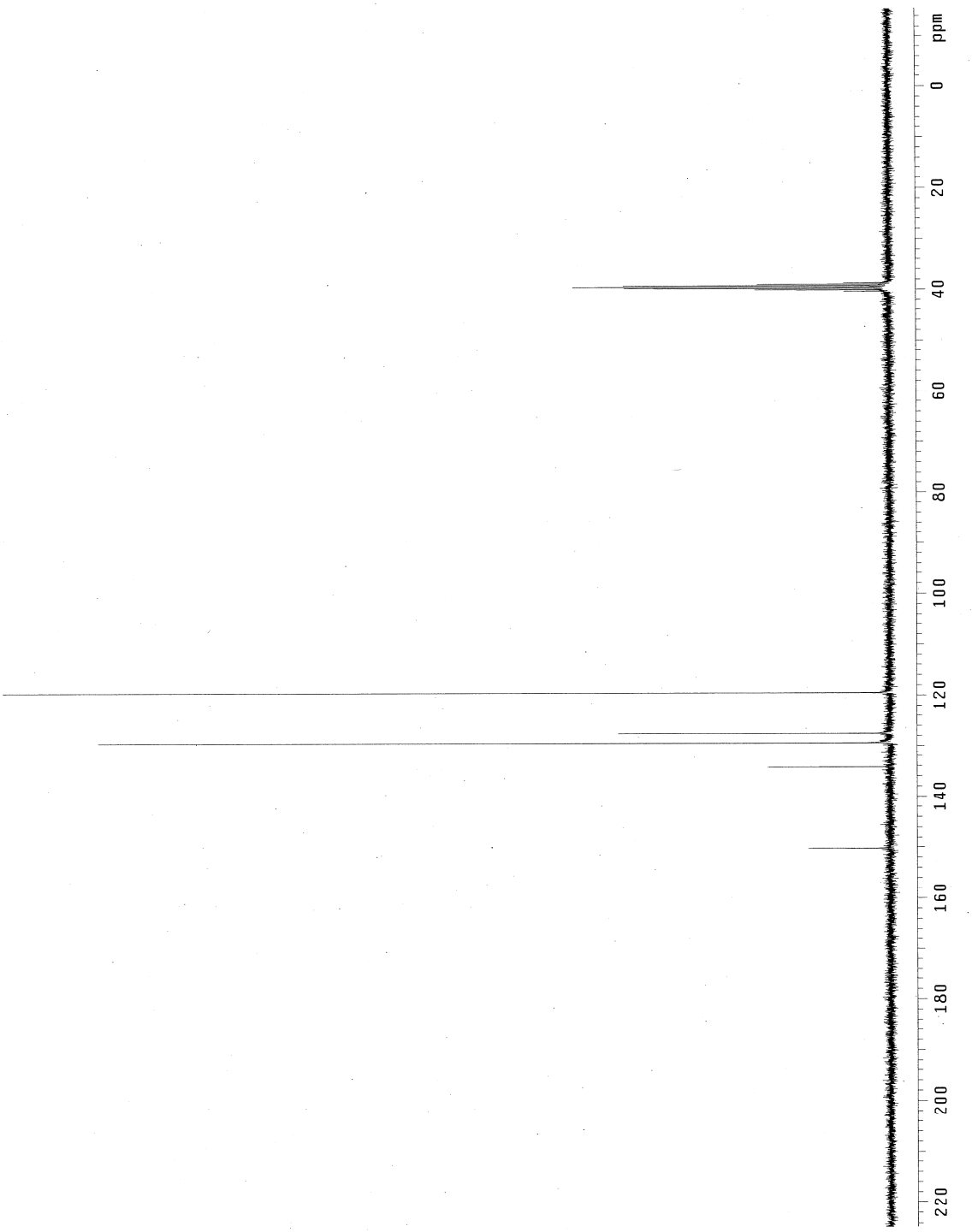
6a



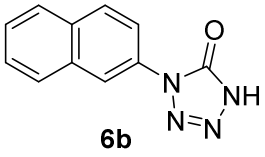
^{13}C NMR FOR 1-PHENYL-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6A



6a



LC DATA FOR 1-(NAPHTHALEN-2-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6B



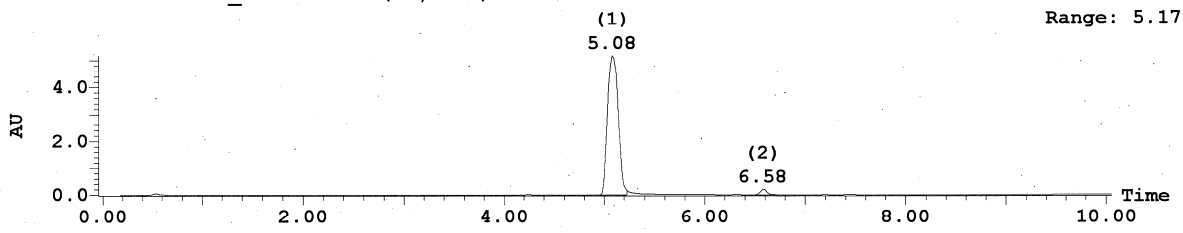
6b

Openlynx Report - Page 1

Vial:1:A,4 File:MD1740-176C Date:08-Aug-2013
Time:15:04:13 Zed: Method:10min

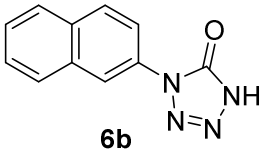
Printed: Thu Aug 08 15:17:31 2013

3: UV Detector: 253_255 Smooth (Mn, 1x1) 5.17
Range: 5.17

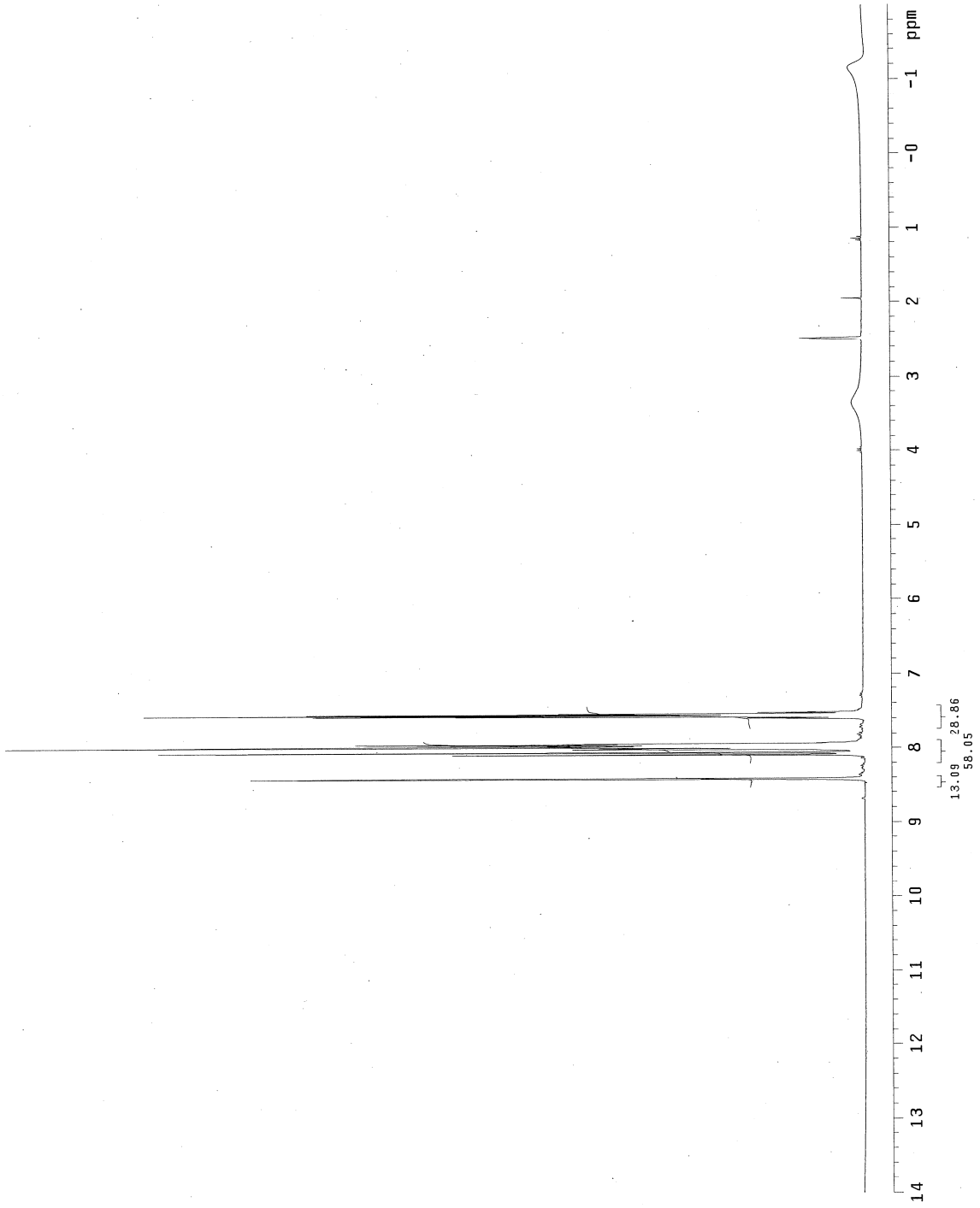


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		5.08	6e+005	97.56	0	5e+006	
2		6.58	2e+004	2.44	0	2e+005	

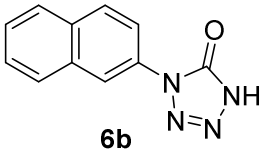
^{1}H NMR FOR 1-(NAPHTHALEN-2-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6B



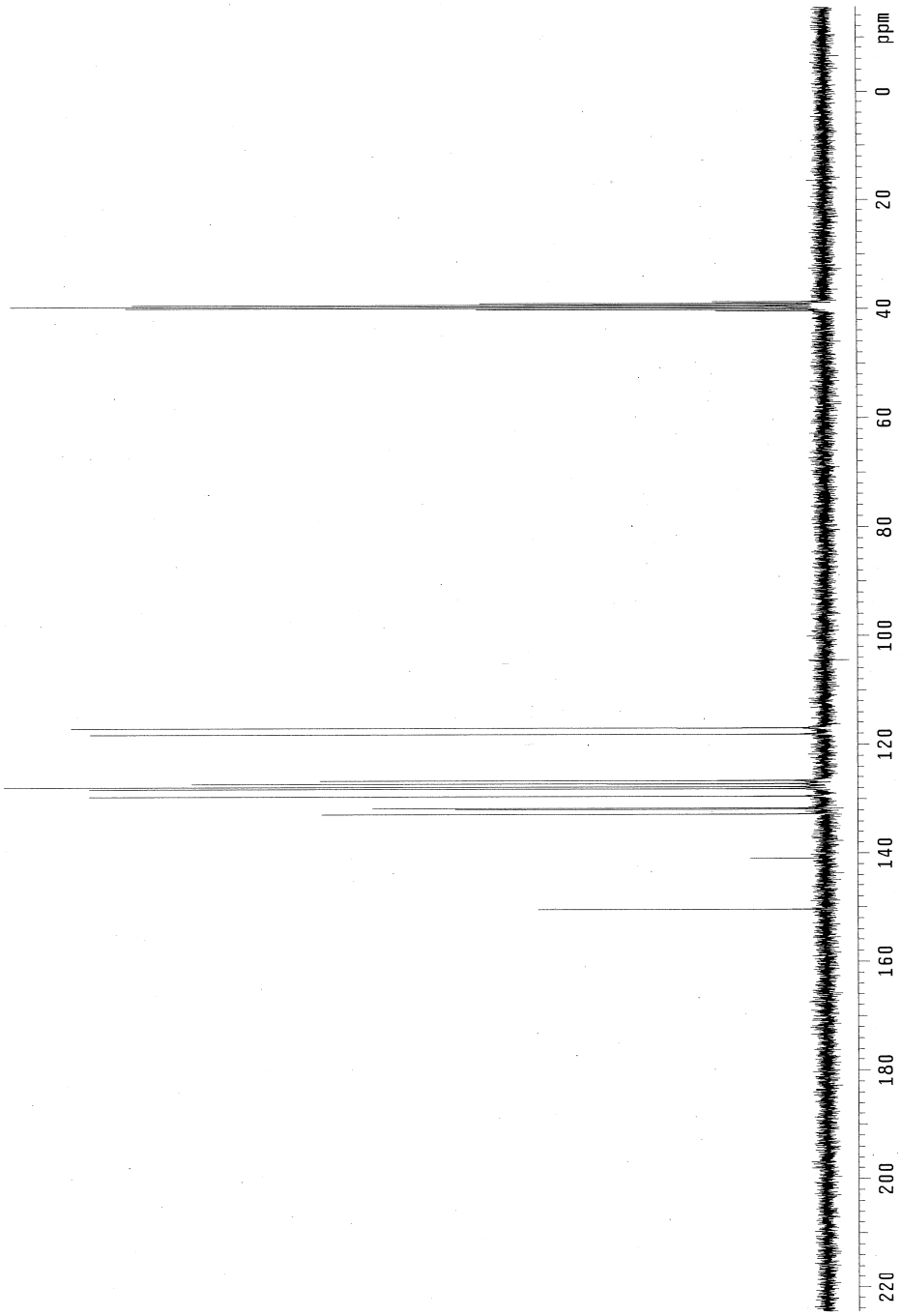
6b



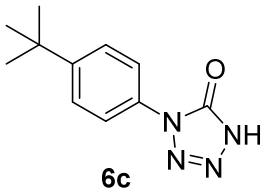
^{1}H NMR FOR 1-(NAPHTHALEN-2-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6B



6b



LC DATA FOR 1-(4-(*TERT*-BUTYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6C



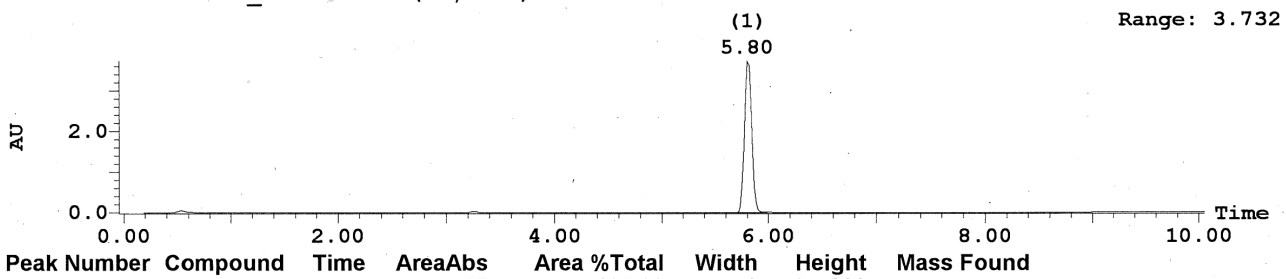
6c

Openlynx Report - Page 1

Vial:2:A,2 File:MD1740-178D Date:08-Aug-2013
Time:17:16:25 Zed: Method:10min

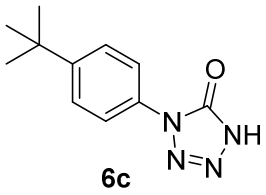
Printed: Thu Aug 08 17:29:49 2013

3: UV Detector: 253_255 Smooth (Mn, 1x1) 3.733
Range: 3.732

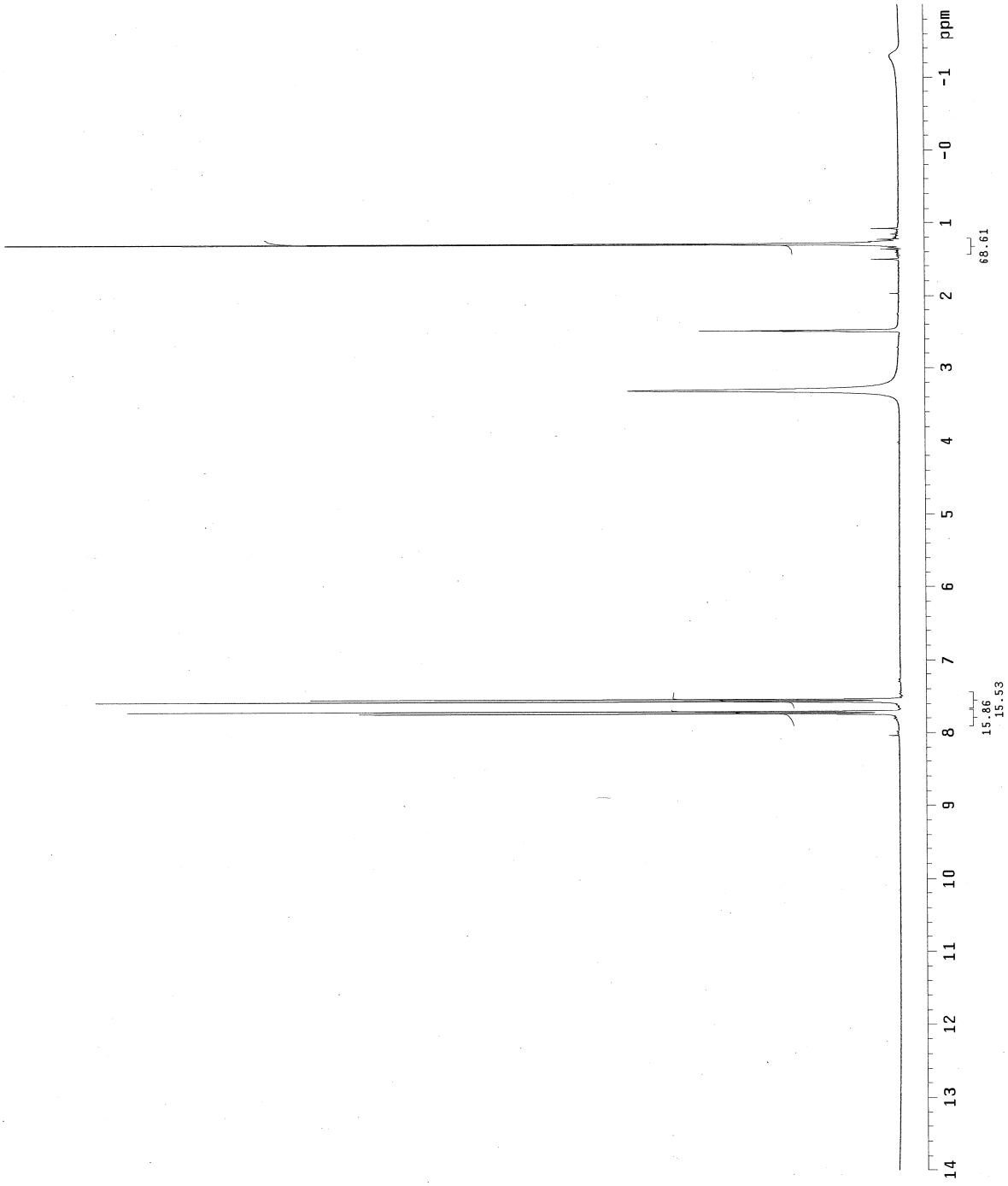


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		5.80	3e+005	100.00	0	4e+006	

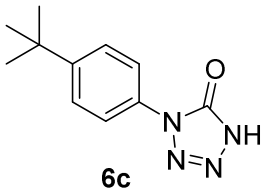
^{1}H NMR FOR 1-(4-(*TERT*-BUTYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6C



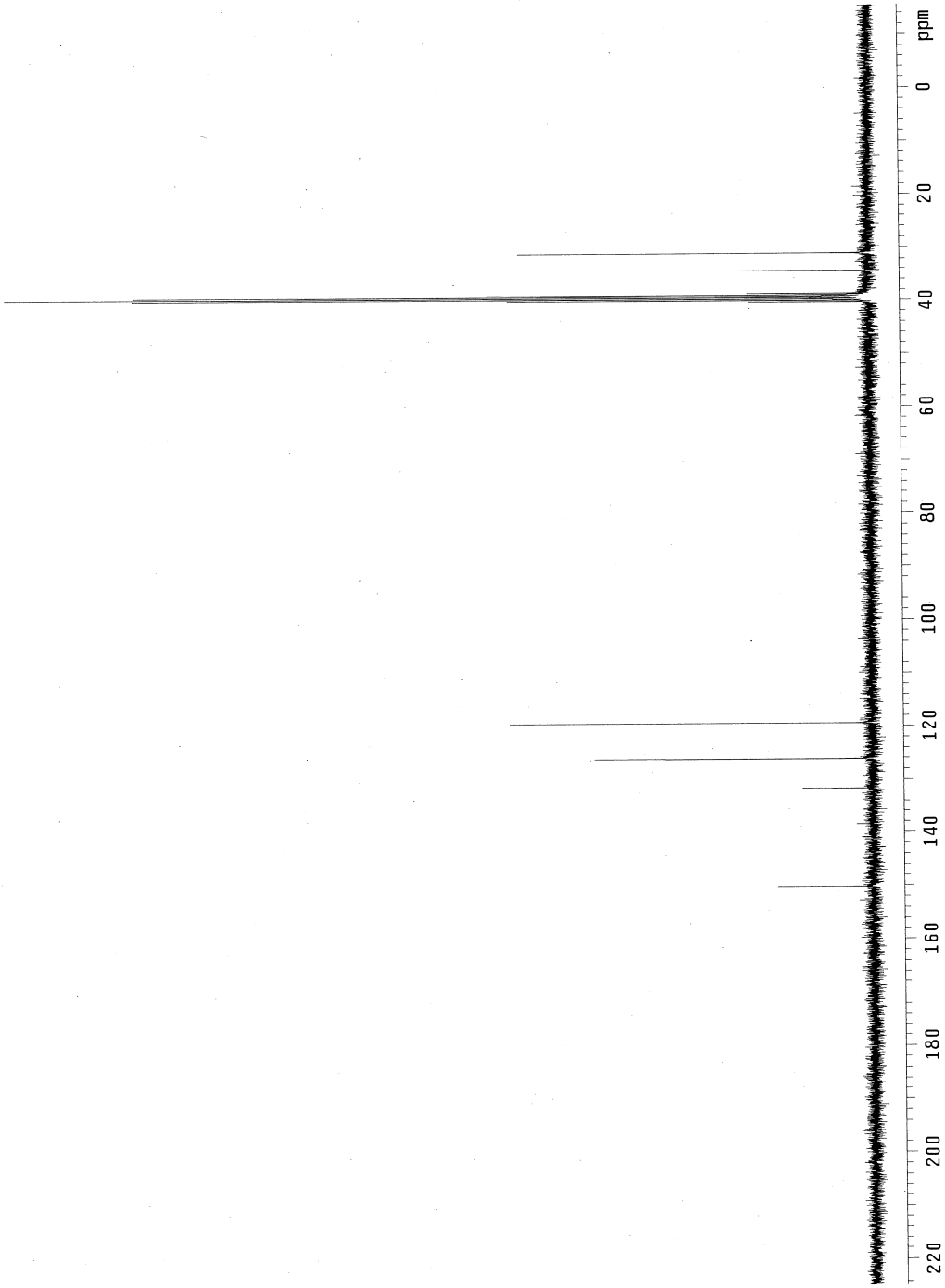
6c



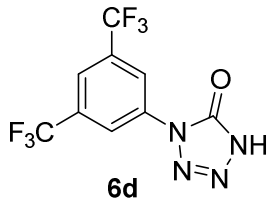
^{13}C NMR FOR 1-(4-(*TERT*-BUTYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6C



6c



LC DATA FOR 1-(3,5-BIS(TRIFLUOROMETHYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6D



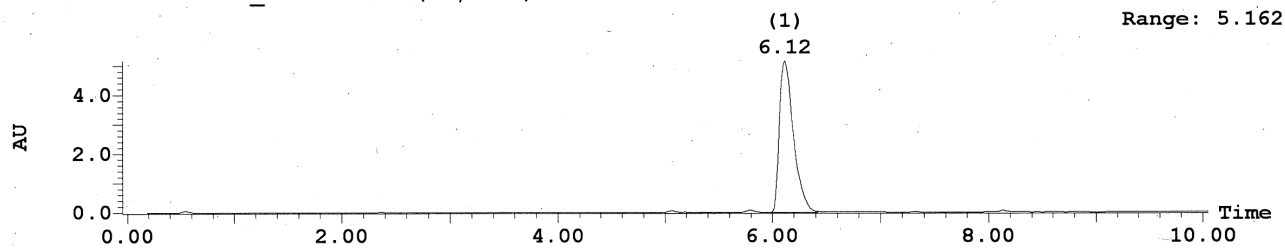
6d

Openlynx Report - Page 1

Vial:2:D,1 File:MD1740-176E Date:13-Aug-2013
Time:11:12:12 Zed: Method:10min

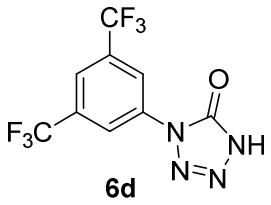
Printed: Tue Aug 13 11:25:36 2013

3: UV Detector: 253_255 Smooth (Mn, 1x1) 5.162
Range: 5.162

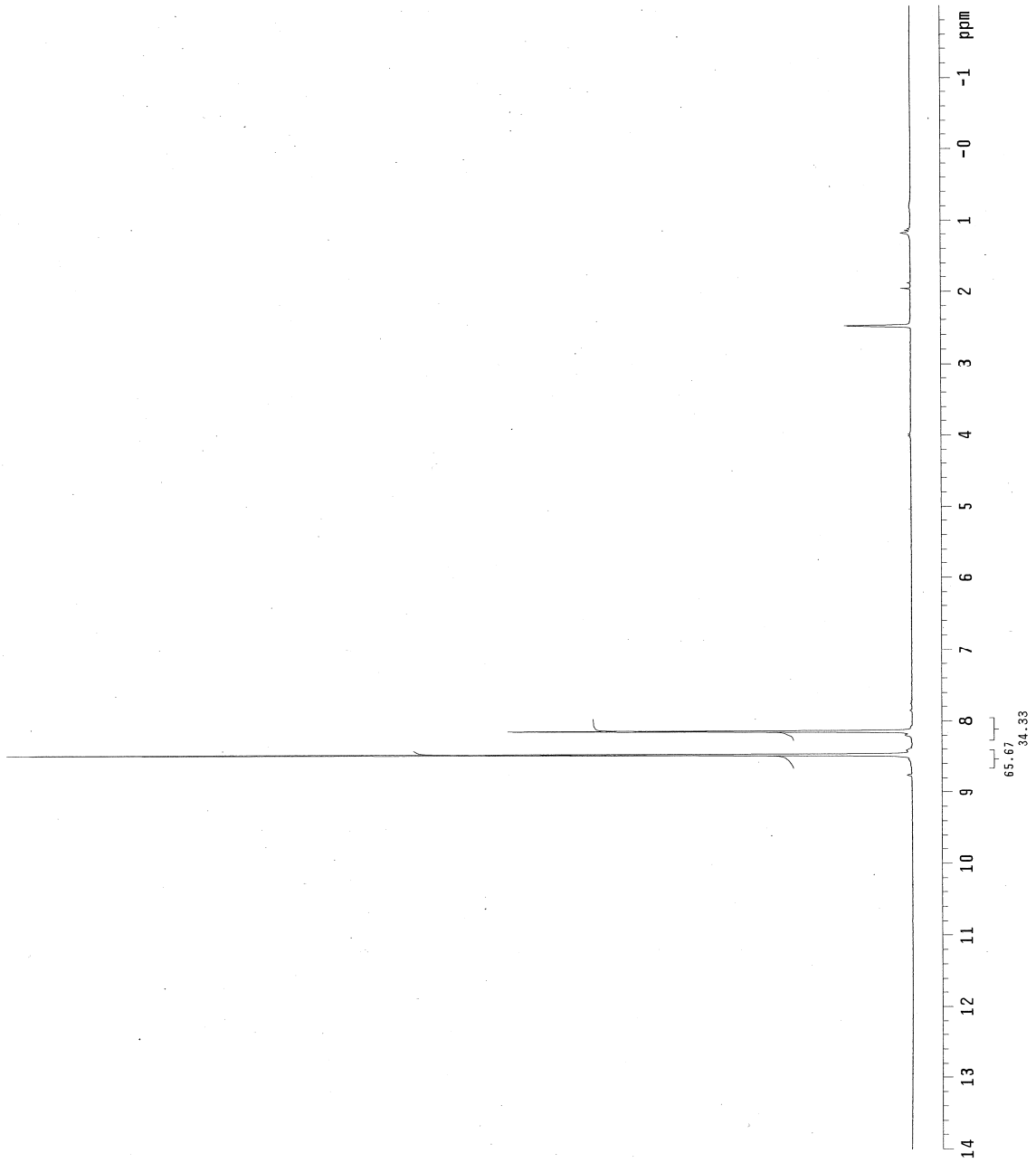


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		6.12	8e+005	100.00	0	5e+006	

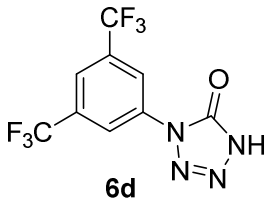
^{1}H NMR FOR 1-(3,5-BIS(TRIFLUOROMETHYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6D



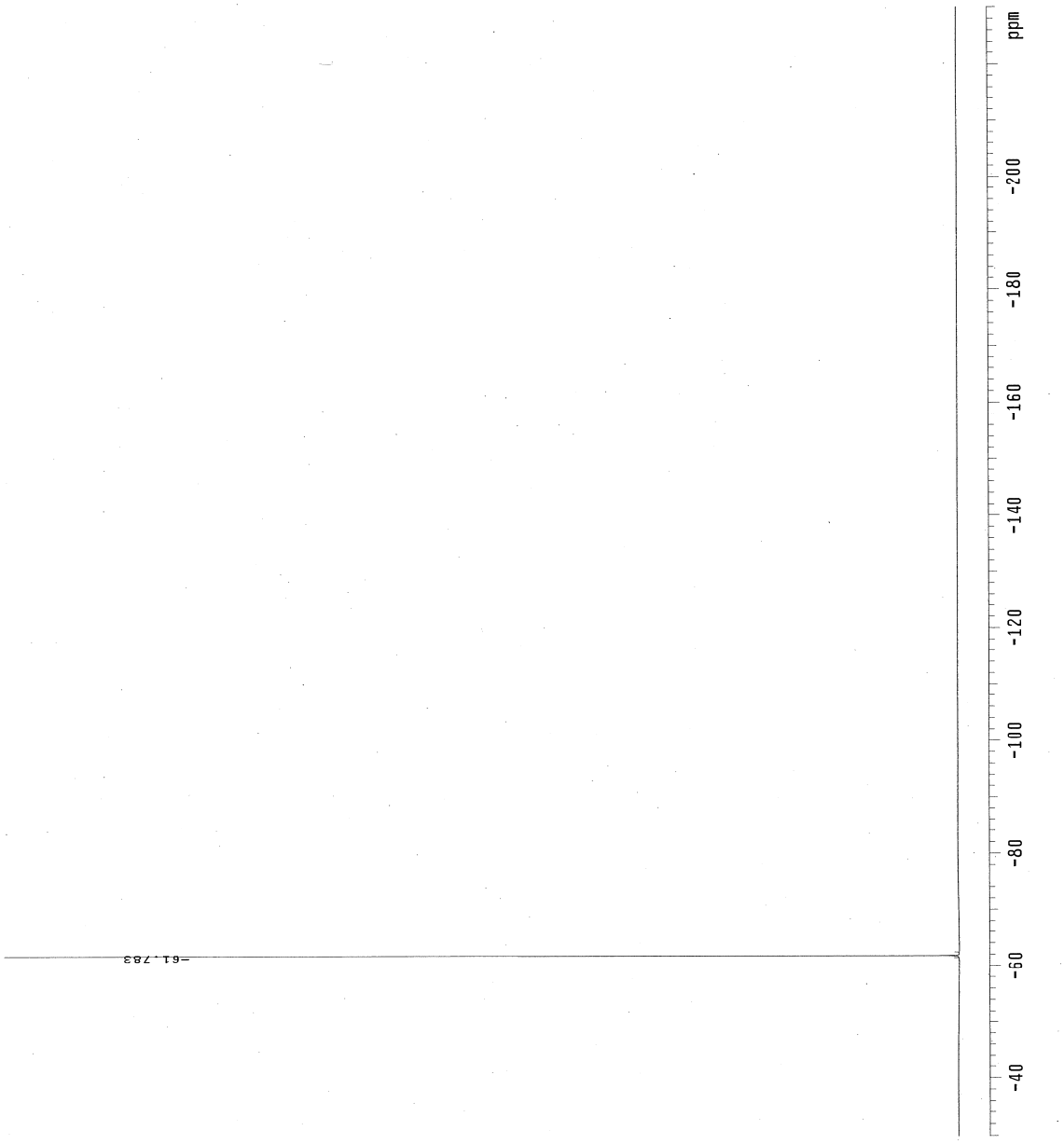
6d



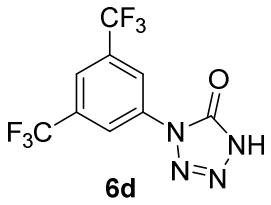
^{19}F NMR FOR 1-(3,5-BIS(TRIFLUOROMETHYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6D



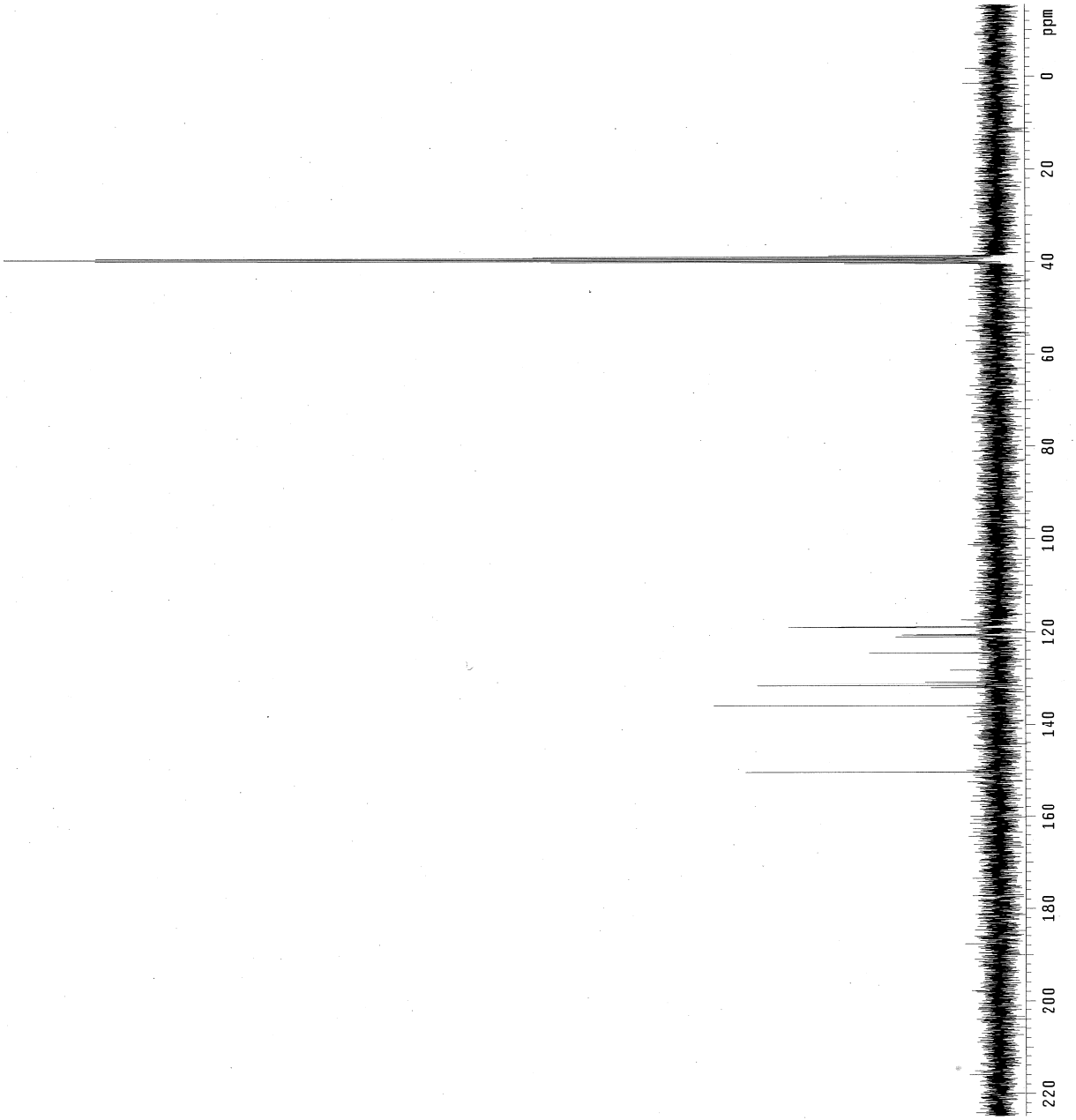
6d



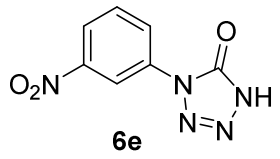
^{13}C NMR FOR 1-(3,5-BIS(TRIFLUOROMETHYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6D



6d



LC DATA FOR 1-(3-NITROPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6E



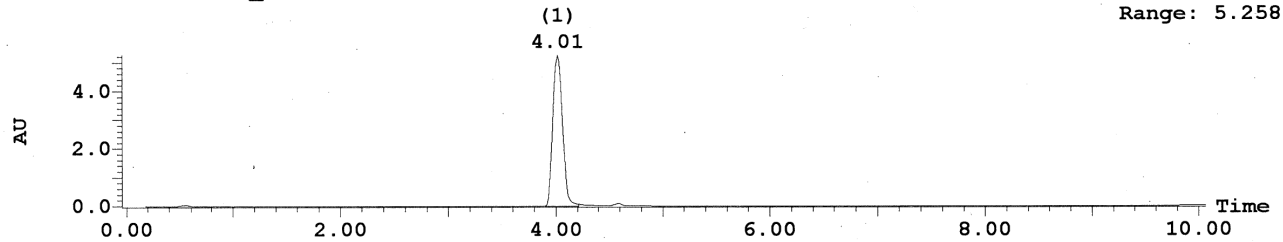
6e

Openlynx Report - Page 1

Vial:1:H,7 File:MD1740-183 Date:14-Aug-2013
Time:15:41:20 Zed: Method:10min

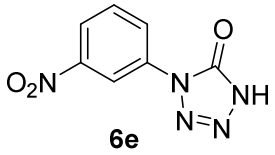
Printed: Wed Aug 14 15:54:28 2013

3: UV Detector: 253_255 Smooth (Mn, 1x1) 5.258
Range: 5.258

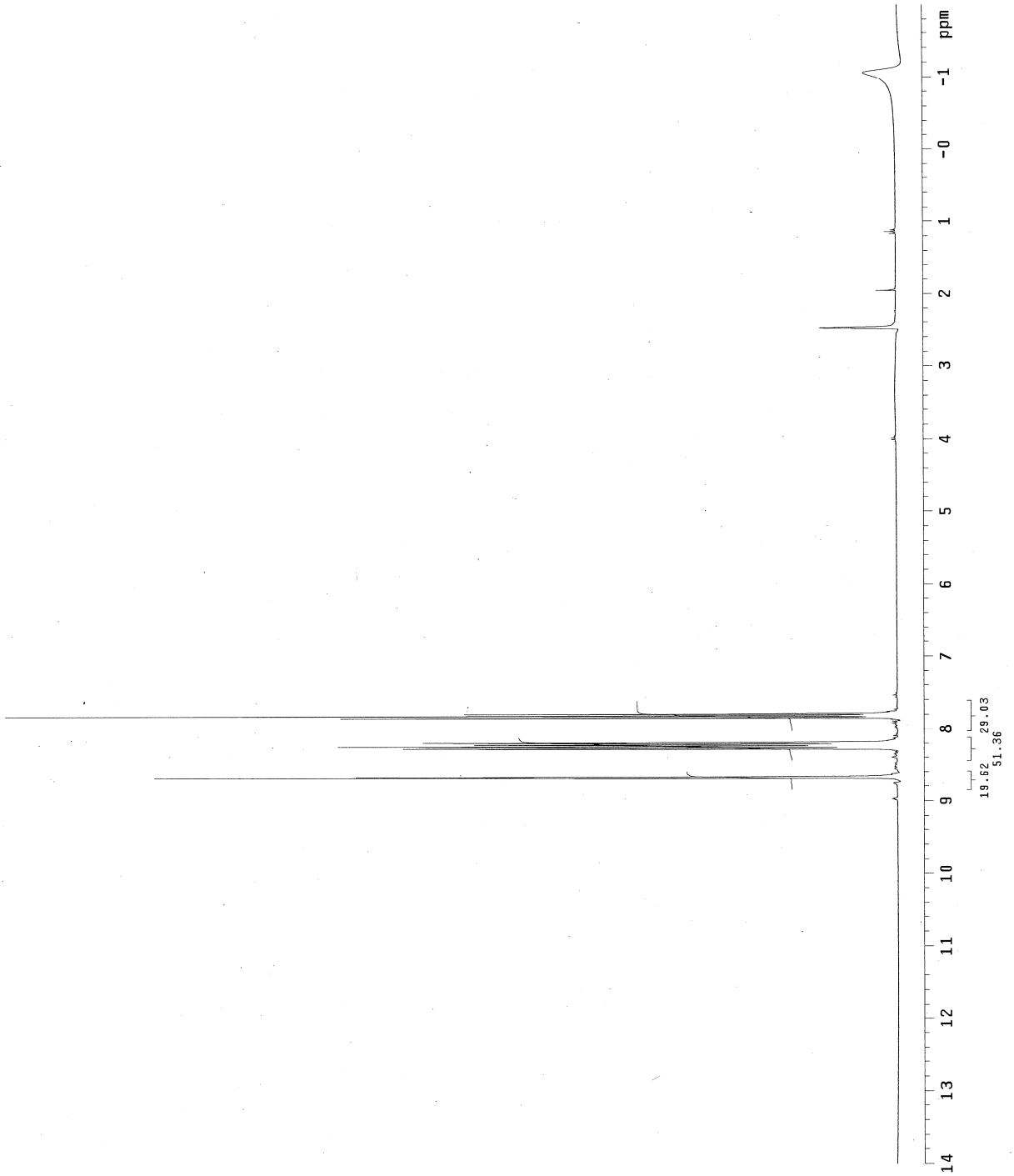


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		4.01	5e+005	100.00	0	5e+006	

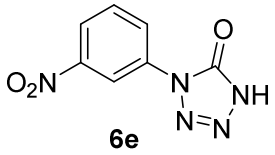
^{1}H NMR FOR 1-(3-NITROPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6E



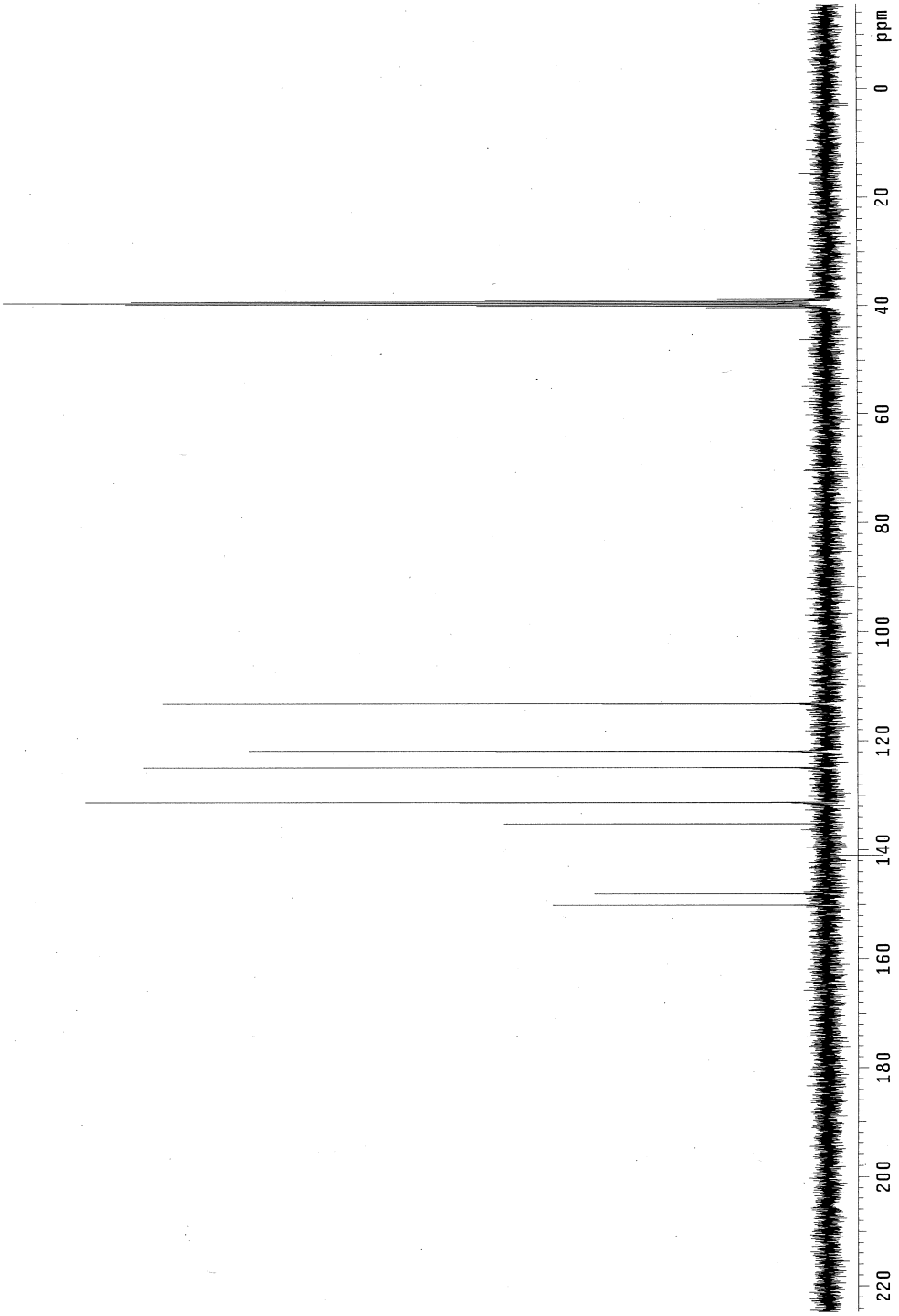
6e



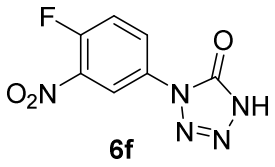
^{13}C NMR FOR 1-(3-NITROPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6E



6e



LC DATA FOR 1-(4-FLUORO-5-NITROPHENYLPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6F

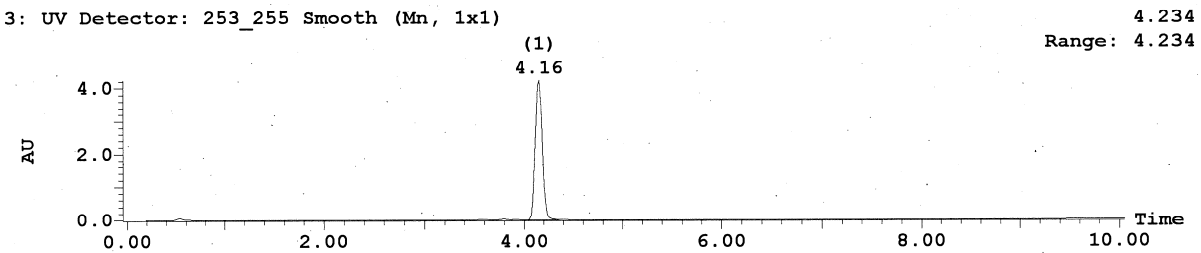


6f

Openlynx Report - Page 1

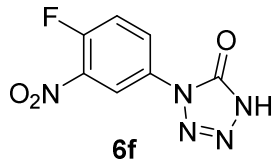
Vial:1:C,12 File:MD1740-180 Date:08-Aug-2013
Time:16:50:04 Zed: Method:10min

Printed: Thu Aug 08 17:03:09 2013

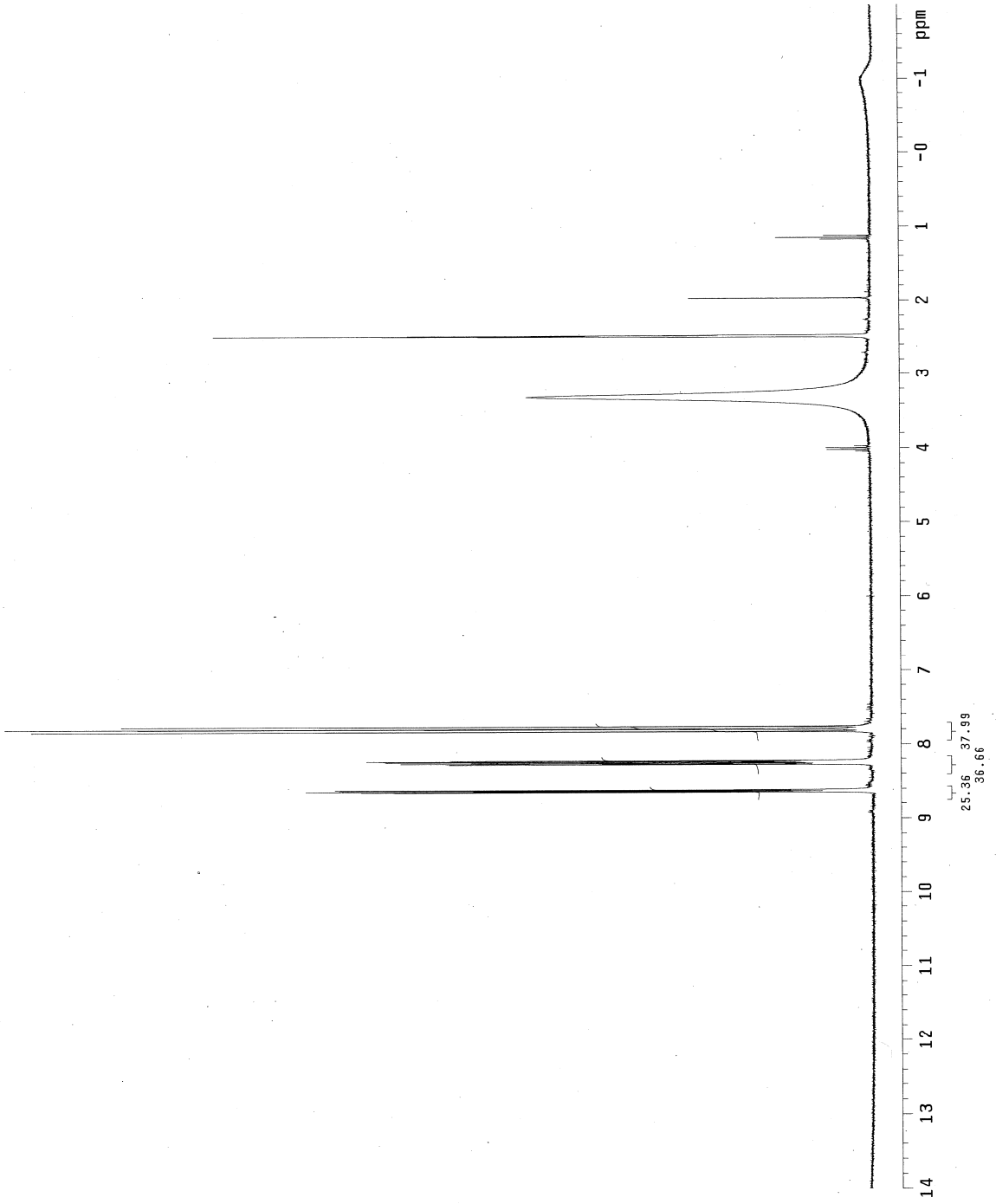


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		4.16	3e+005	100.00	0	4e+006	

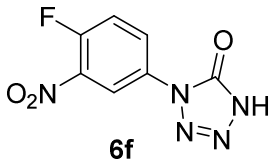
^{1}H NMR FOR 1-(4-FLUORO-5-NITROPHENYLPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6F



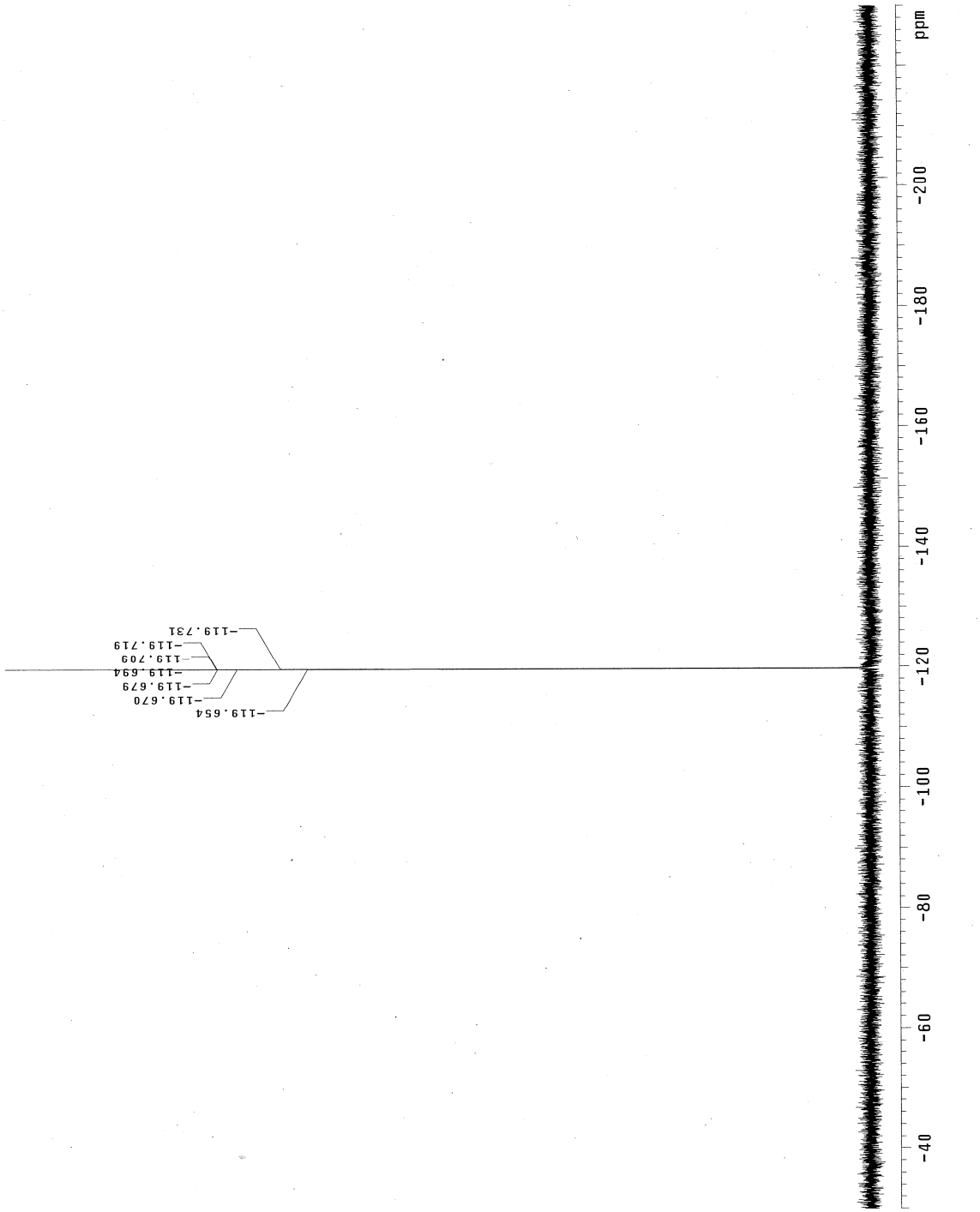
6f



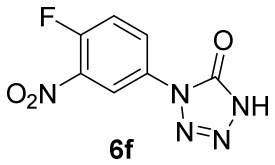
^{19}F NMR FOR 1-(4-FLUORO-5-NITROPHENYLPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6F



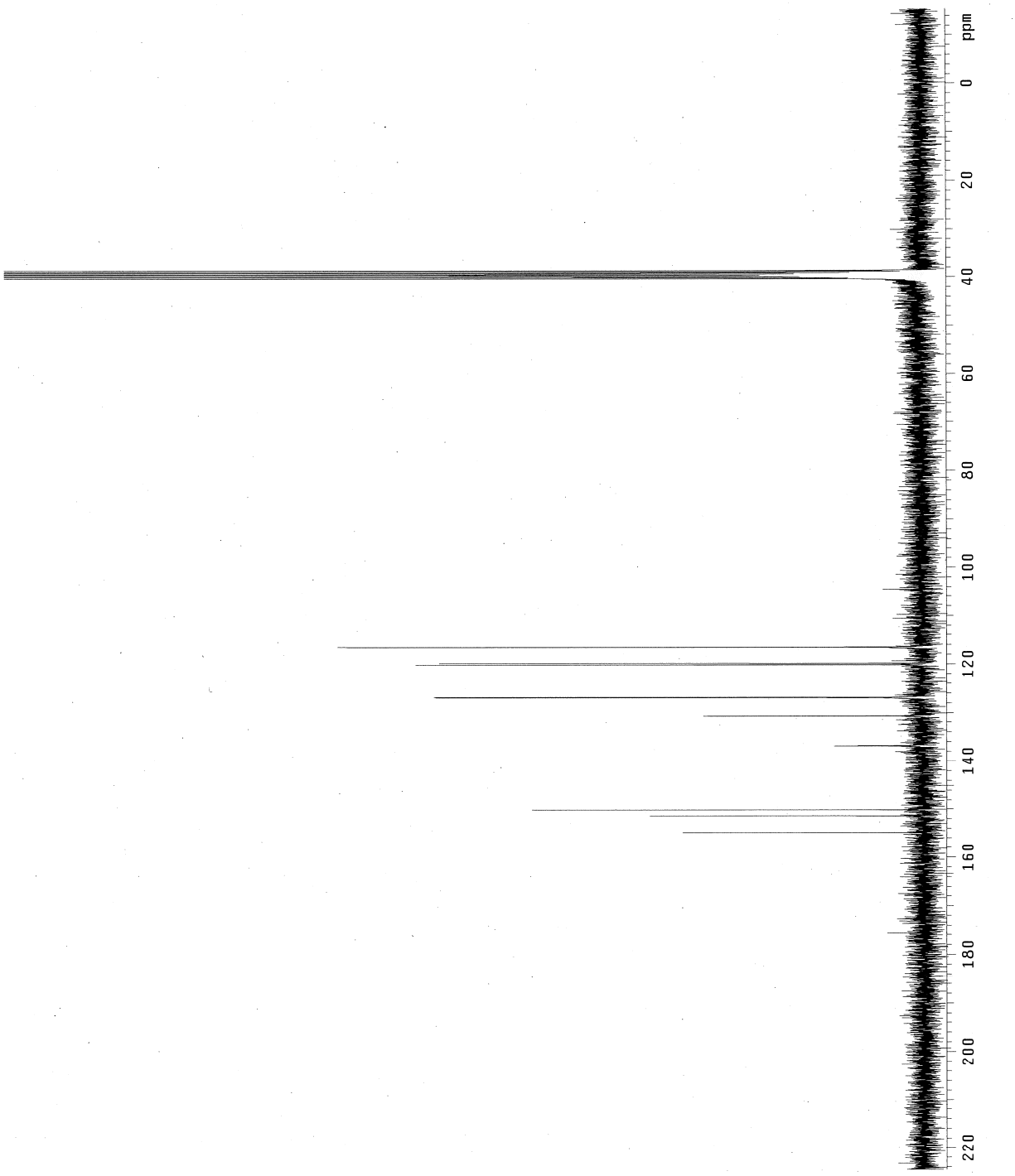
6f



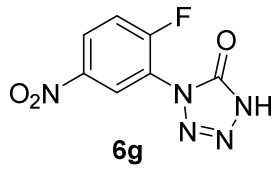
^{13}C NMR FOR 1-(4-FLUORO-5-NITROPHENYLPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6F



6f



LC DATA FOR 1-(2-FLUORO-5-NITROPHENYLPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6G

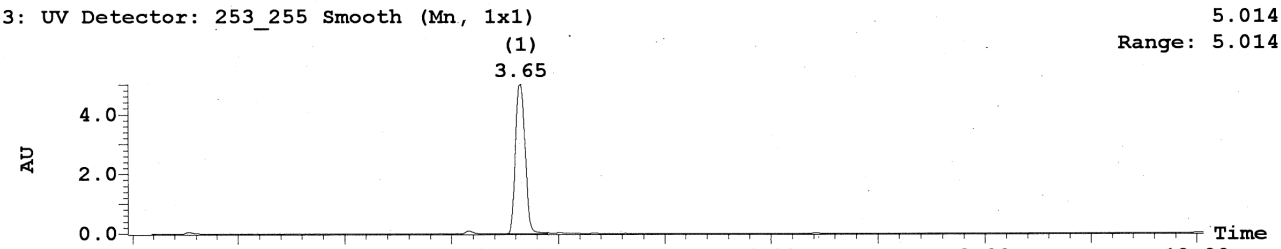


6g

Openlynx Report - Page 1

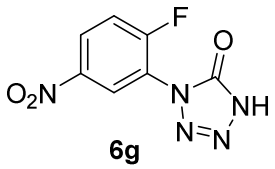
Vial:1:B,12 File:MD1740-179 Date:08-Aug-2013
Time:16:37:00 Zed: Method:10min

Printed: Thu Aug 08 16:50:02 2013

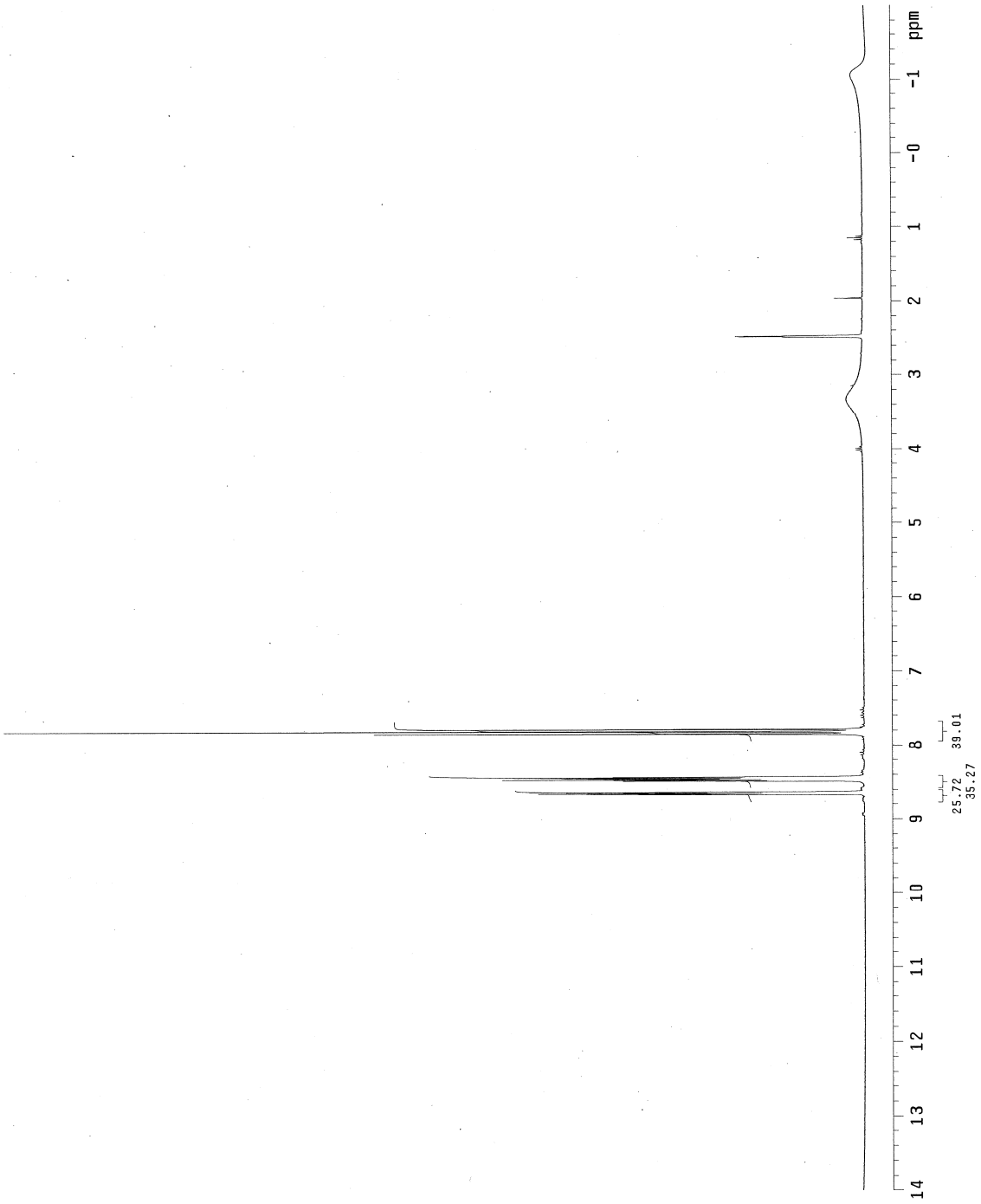


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		3.65	5e+005	100.00	0	5e+006	

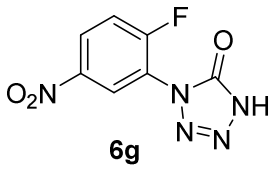
^{1}H NMR FOR 1-(2-FLUORO-5-NITROPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6G



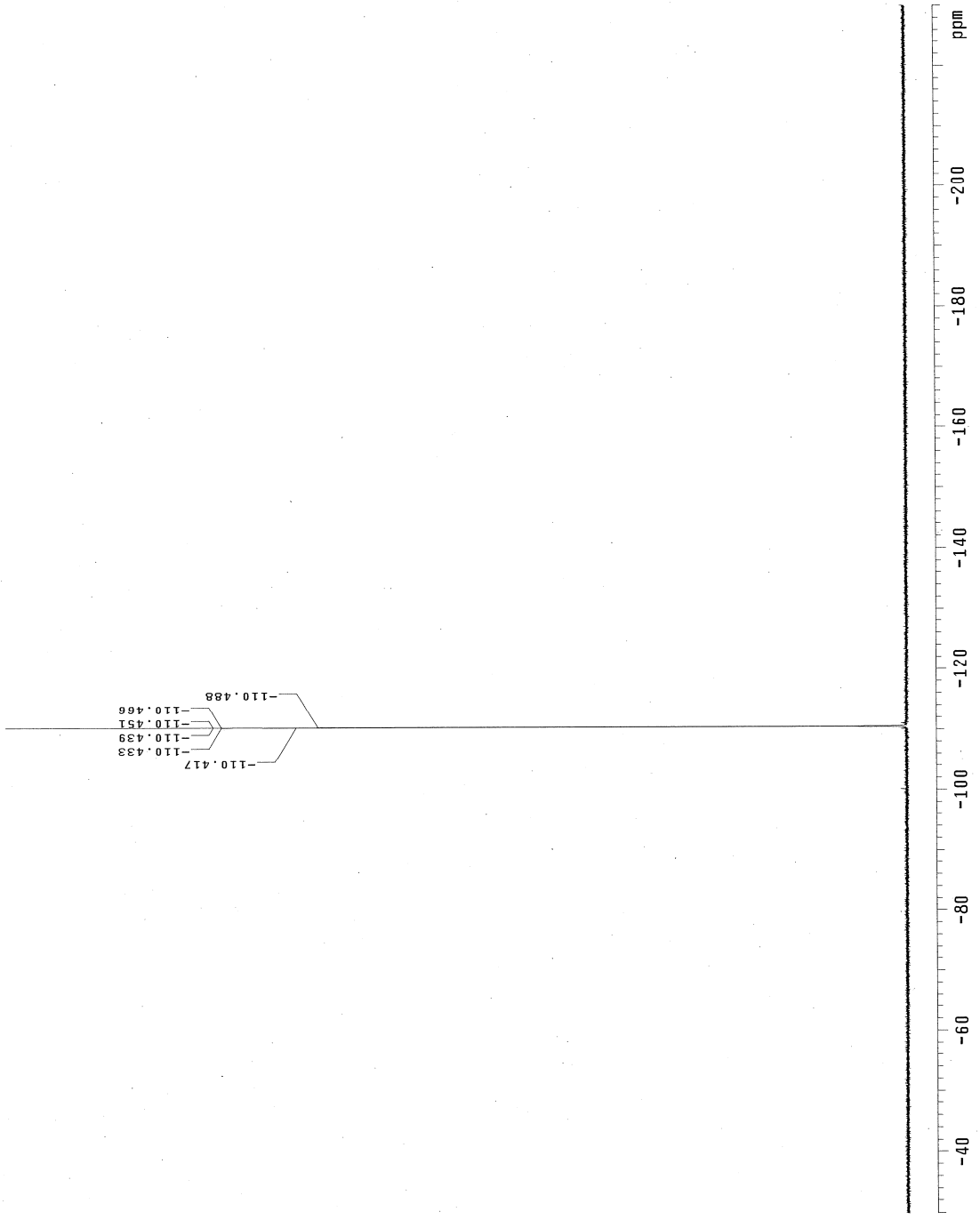
6g



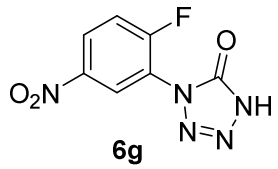
^{19}F NMR FOR 1-(2-FLUORO-5-NITROPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6G



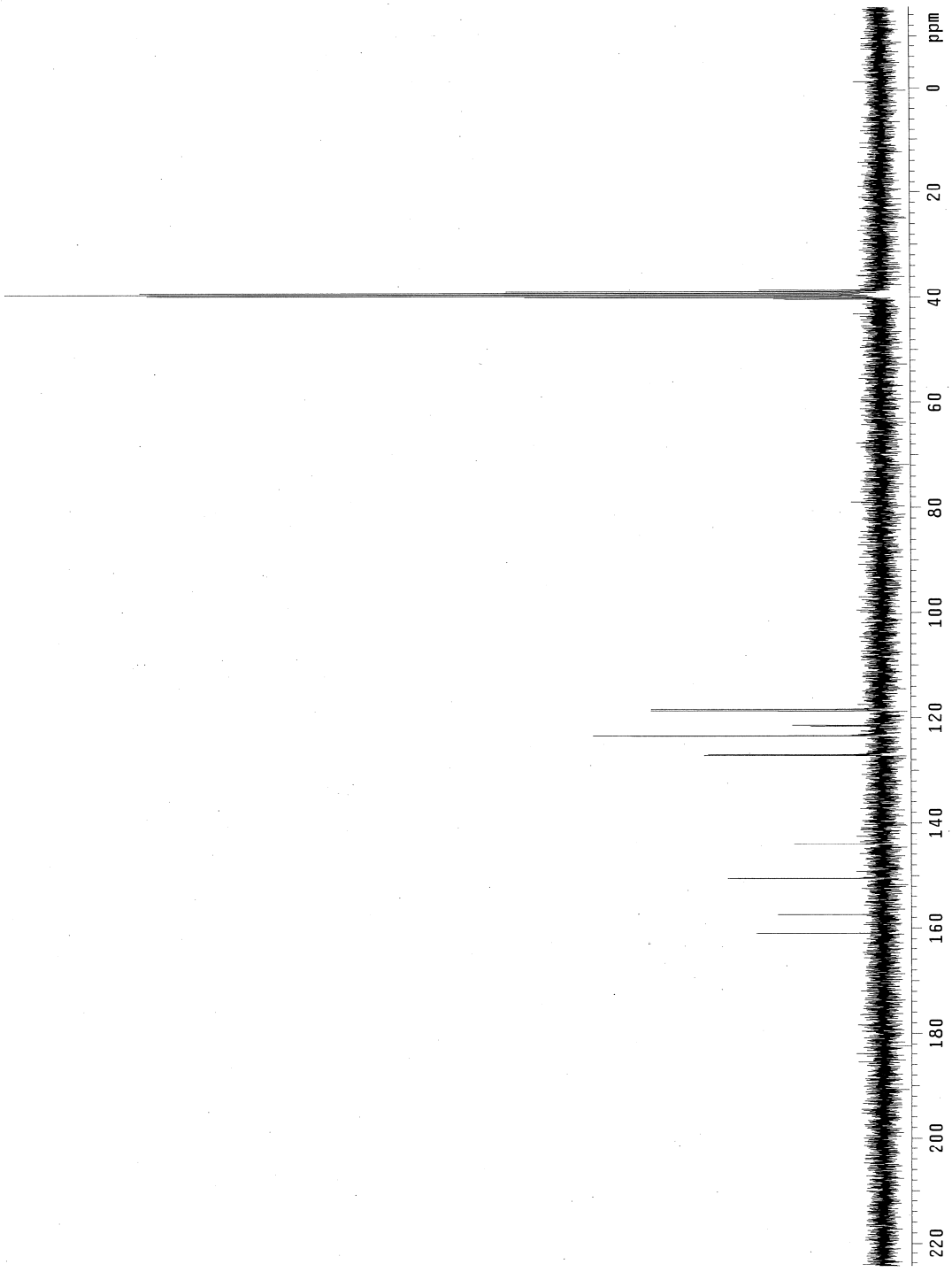
6g



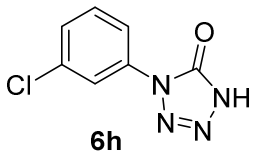
^{13}C NMR FOR 1-(2-FLUORO-5-NITROPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6G



6g



LC DATA FOR 1-(3-CHLOROPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6H



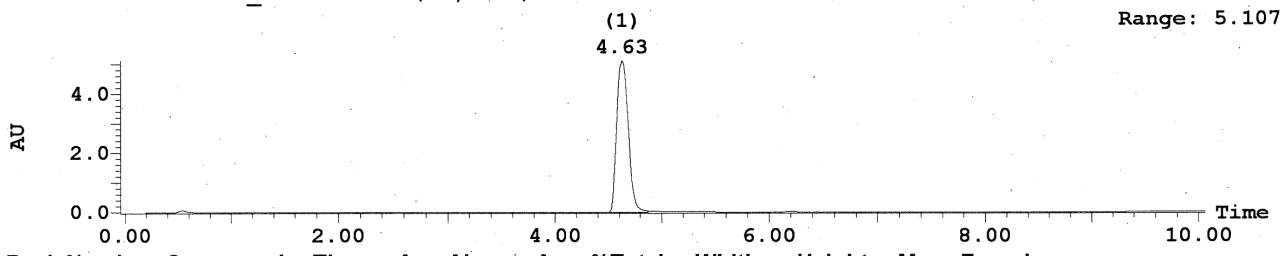
6h

Openlynx Report - Page 1

Vial:1:B,2 File:MD1740-172E Date:08-Aug-2013
Time:14:24:20 Zed: Method:10min

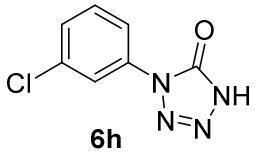
Printed: Thu Aug 08 14:37:45 2013

3: UV Detector: 253_255 Smooth (Mn, 1x1) 5.107
Range: 5.107

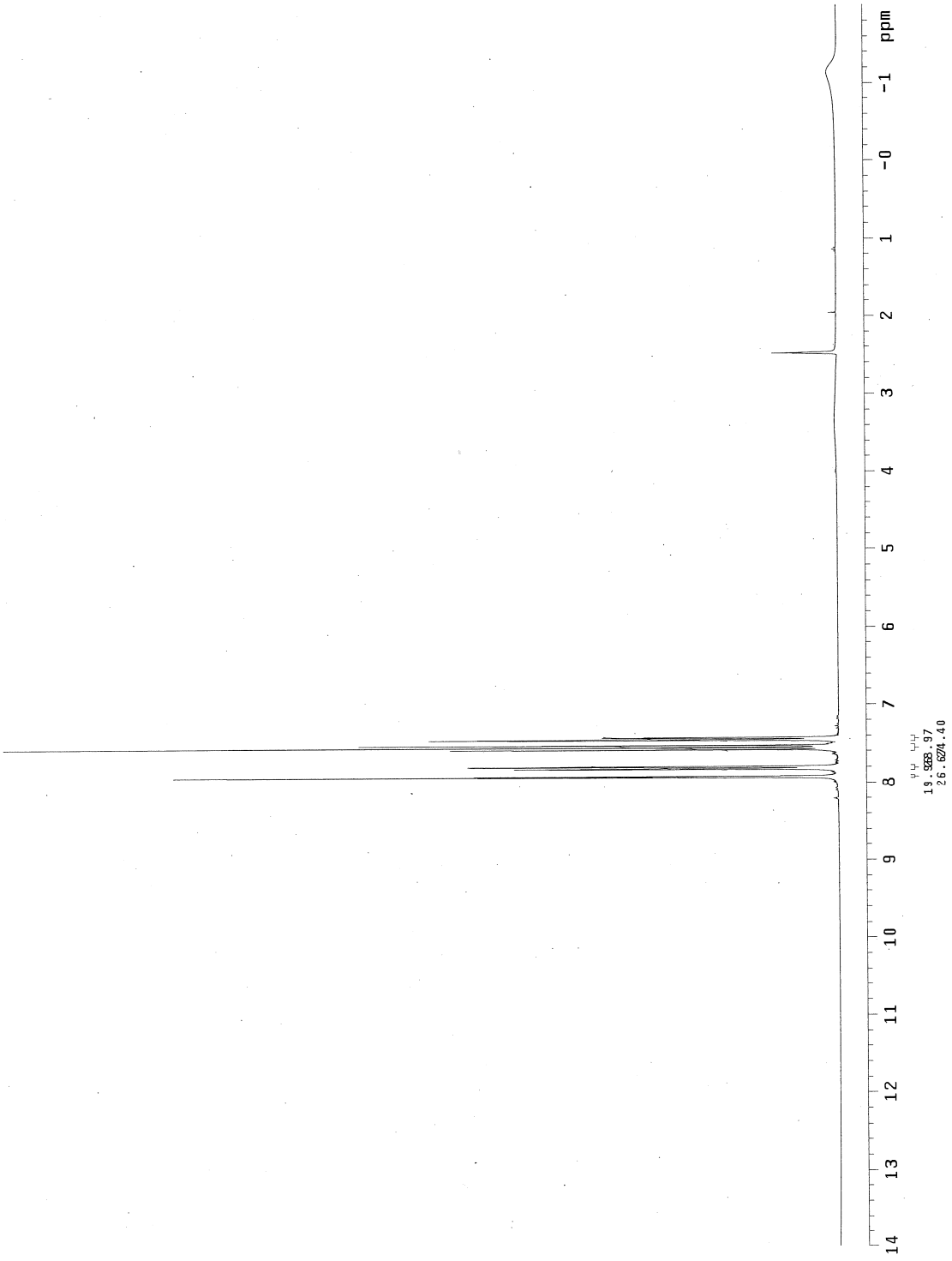


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		4.63	6e+005	100.00	0	5e+006	

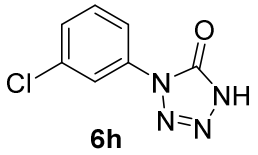
^{1}H NMR FOR 1-(3-CHLOROPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6H



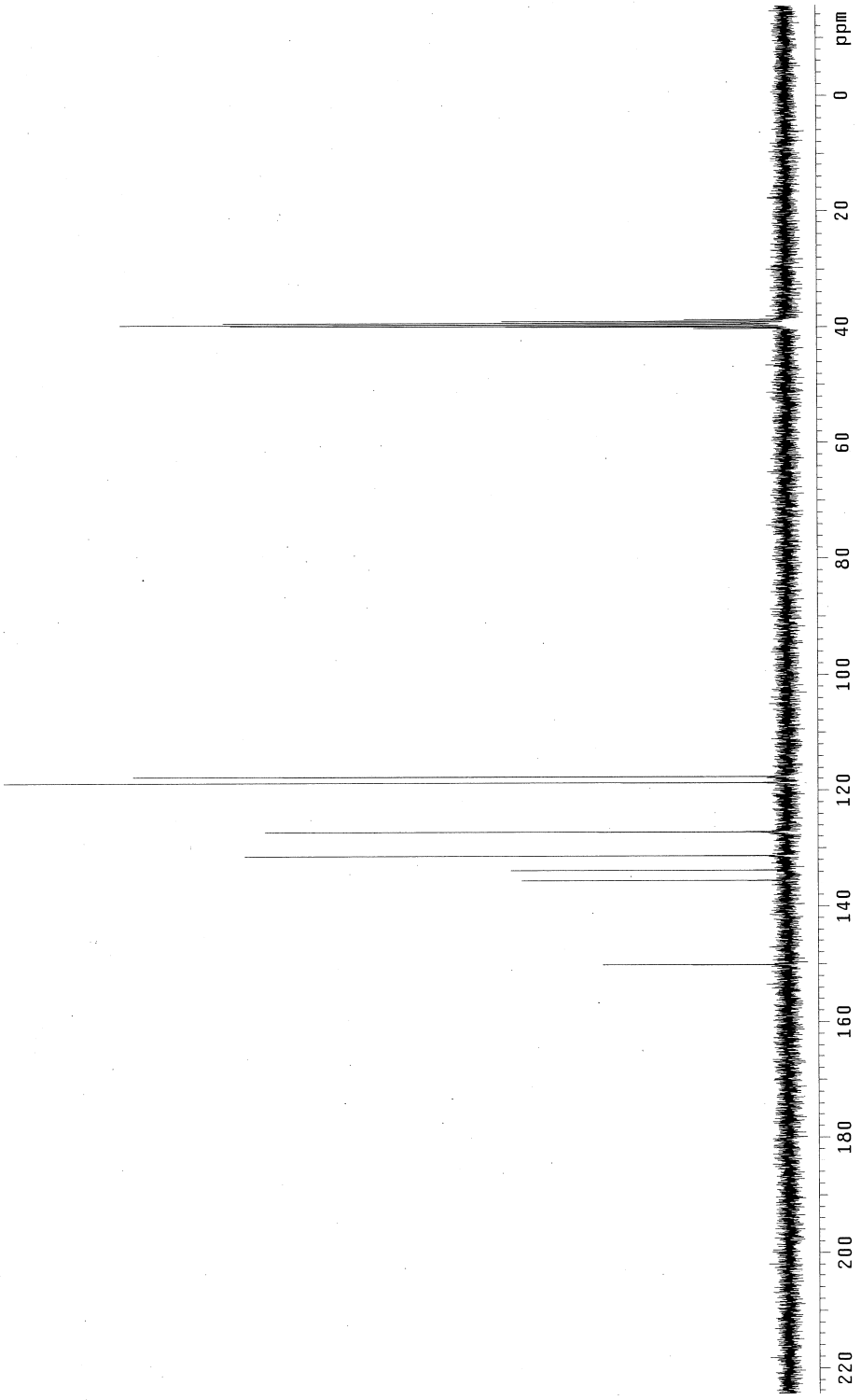
6h



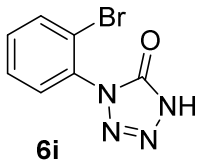
^{13}C NMR FOR 1-(3-CHLOROPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6H



6h



LC DATA FOR 1-(2-BROMOPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6I



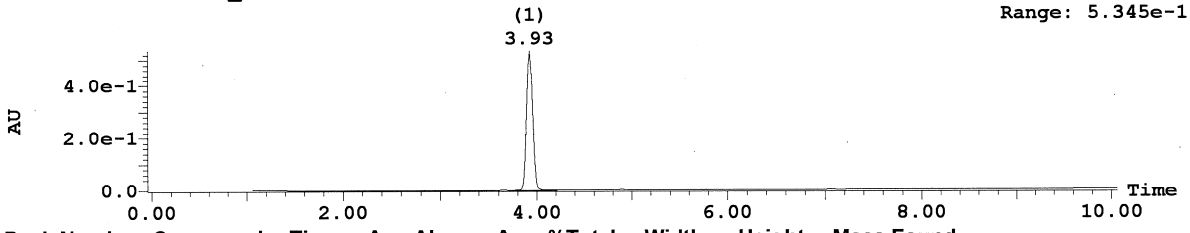
6i

Openlynx Report - Page 1

Vial:1:G,4 File:MD1856-018A2 Date:26-Mar-2014
Time:11:24:24 Zed: Method:10min

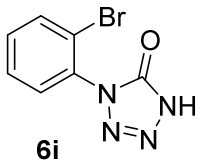
Printed: Wed Mar 26 11:37:27 2014

3: UV Detector: 253_255 Smooth (Mn, 1x1) 5.345e-1
Range: 5.345e-1

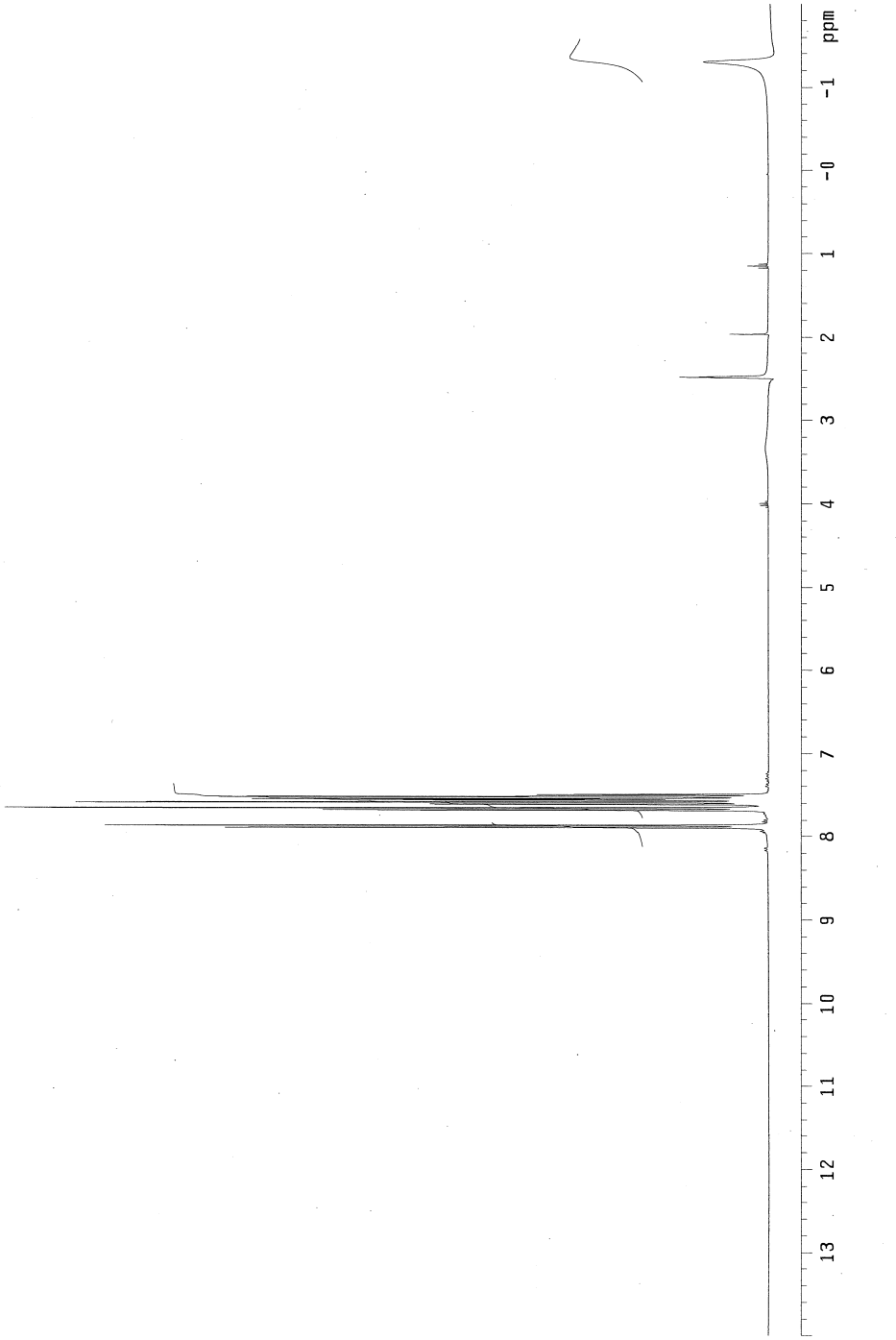


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		3.93	4e+004	100.00	0	5e+005	

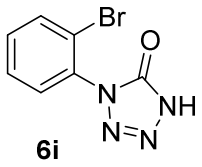
^{1}H NMR FOR 1-(2-BROMOPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6I



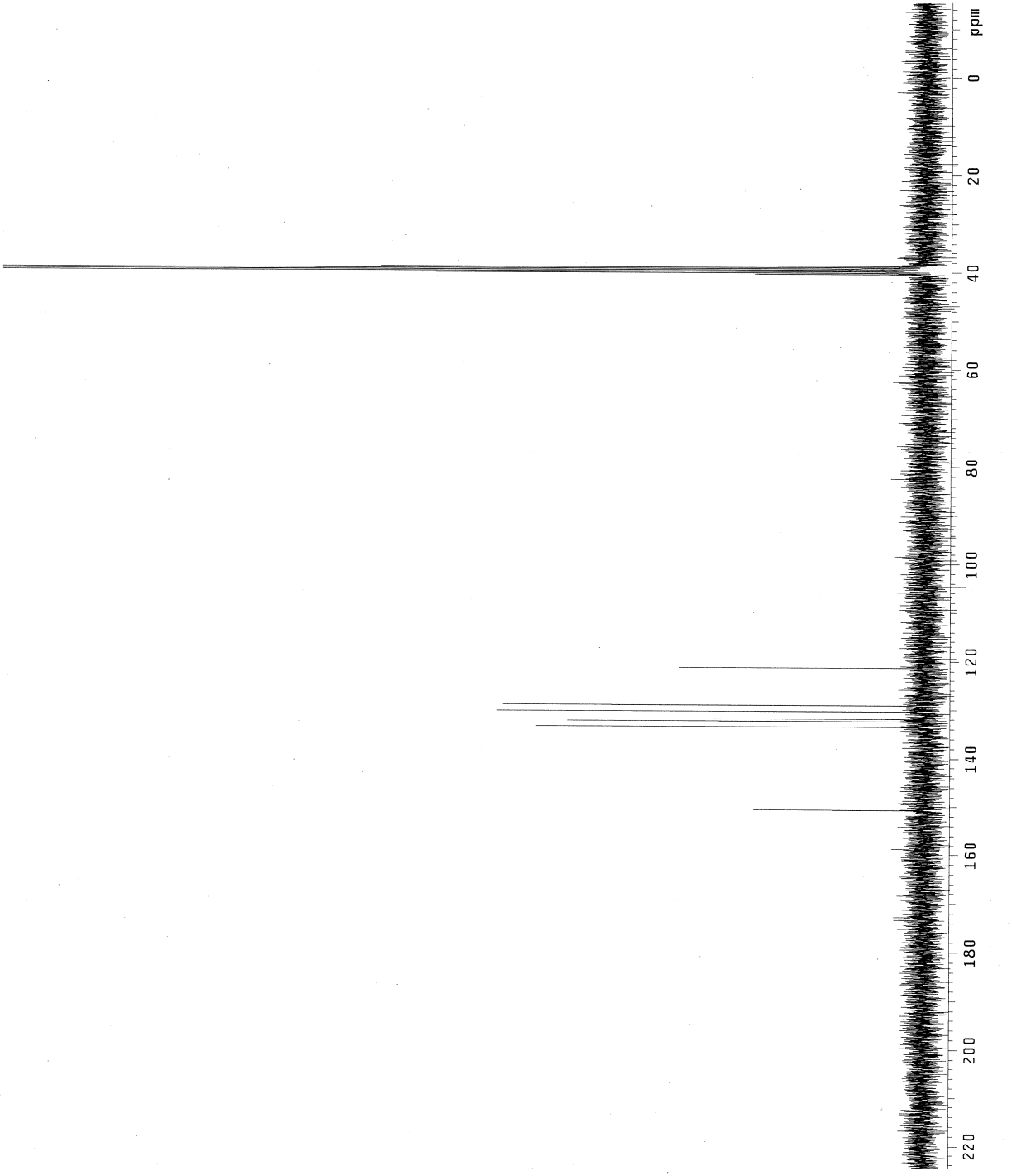
6i



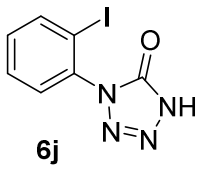
^{13}C NMR FOR 1-(2-BROMOPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6I



6i



LC DATA FOR 1-(2-IODOPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6J



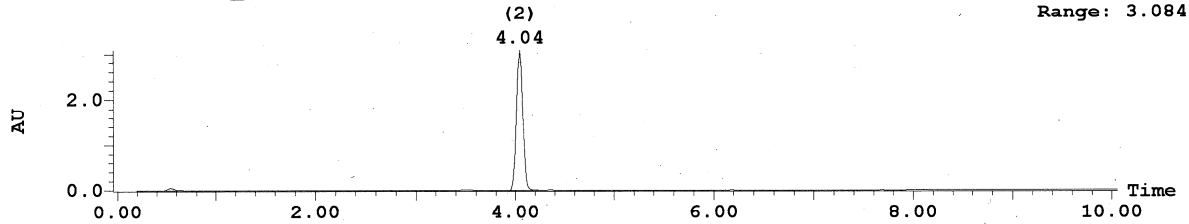
6j

Openlynx Report - Page 1

Vial:1:D,2 File:MD1740-176B Date:08-Aug-2013
Time:14:50:59 Zed: Method:10min

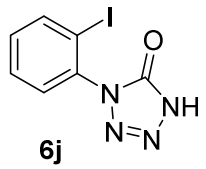
Printed: Thu Aug 08 15:04:10 2013

3: UV Detector: 253_255 Smooth (Mn, 1x1) 3.084
Range: 3.084

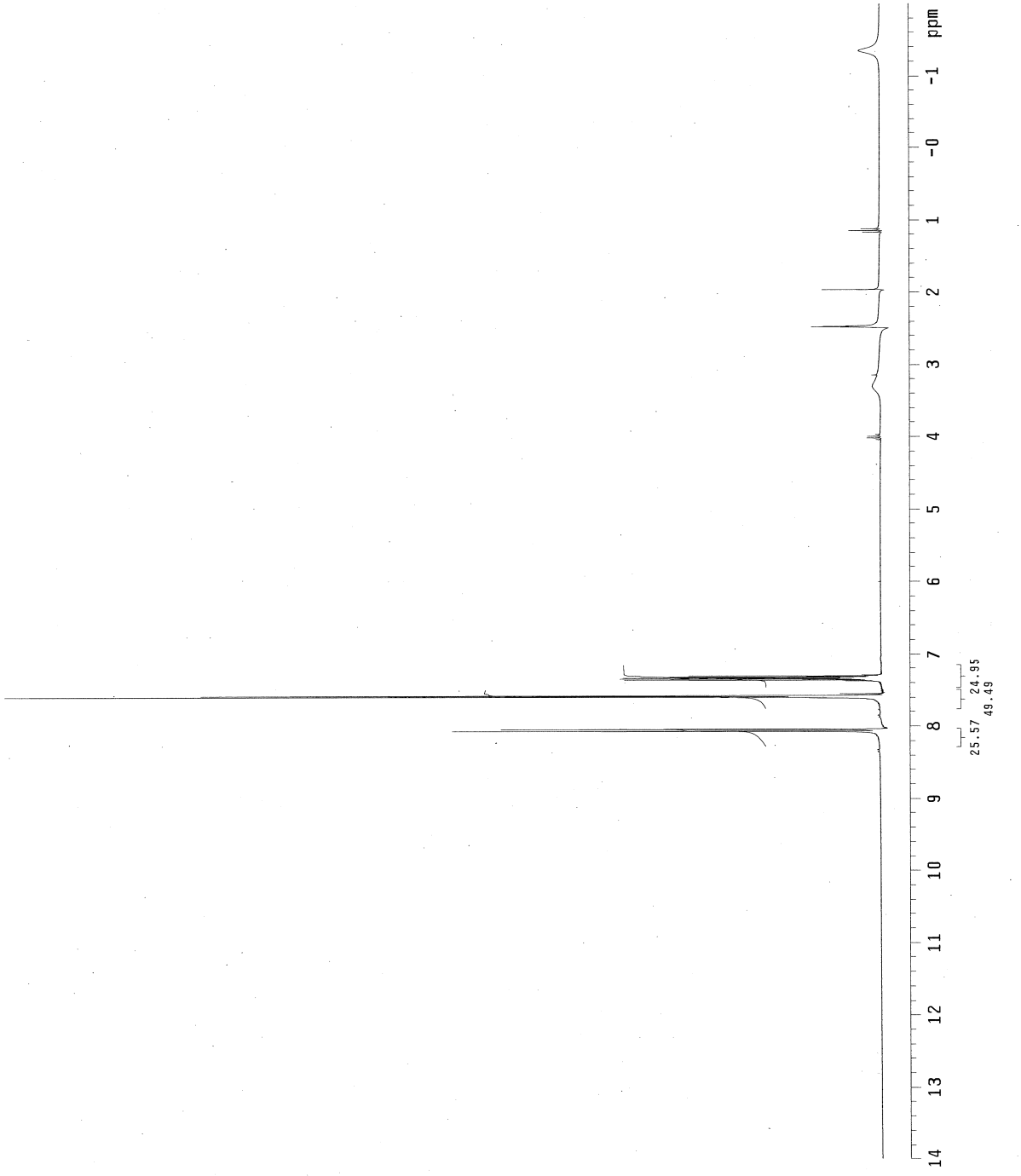


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		0.54	4e+003	1.63	0	5e+004	
2		4.04	2e+005	98.37	0	3e+006	

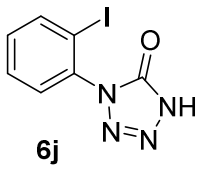
^{1}H NMR FOR 1-(2-IODOPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6J



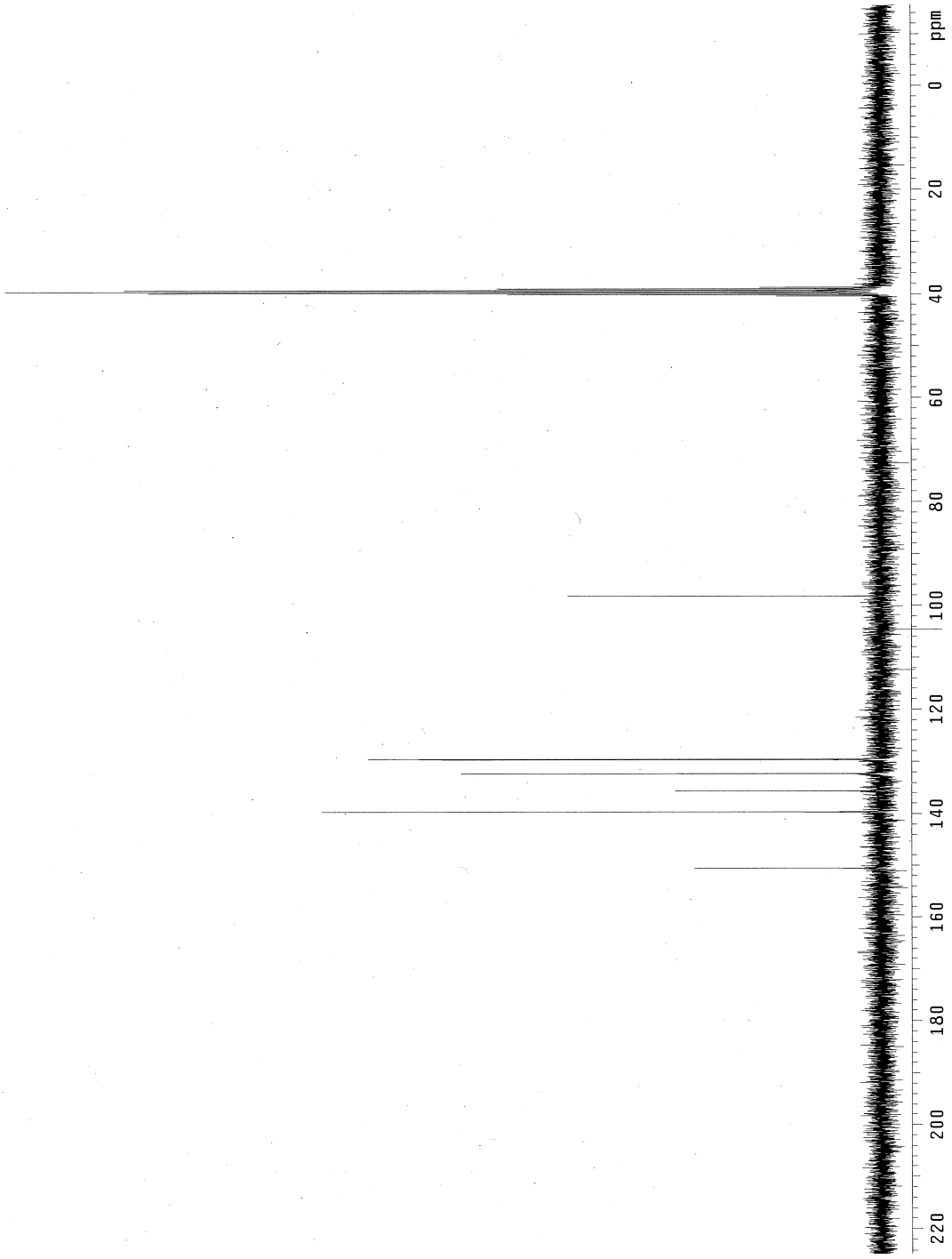
6j



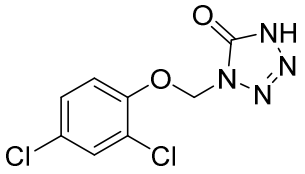
^{13}C NMR FOR 1-(2-IODOPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6J



6j



LC DATA FOR 1-((2,4-DICHLOROPHENOXY)METHYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6K



6k

Openlynx Report - Page 1

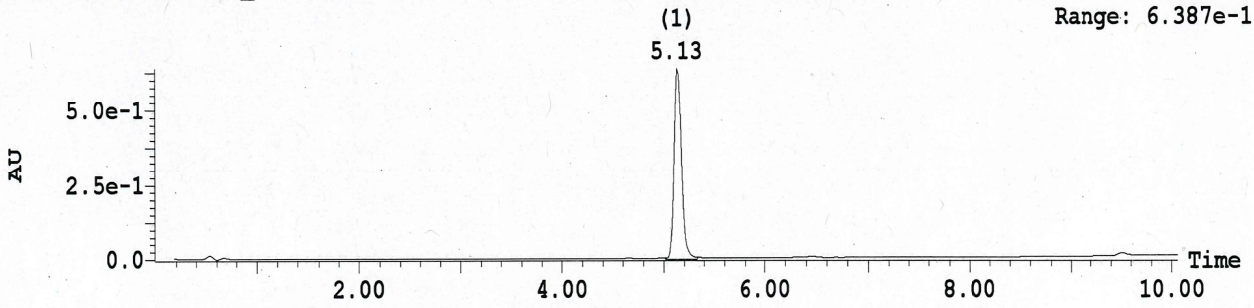
Vial:1:G,12 File:MD1856-127 Date:01-Oct-2014

Time:14:21:19 Zed: Method:10min

Printed: Wed Oct 01 14:34:43 2014

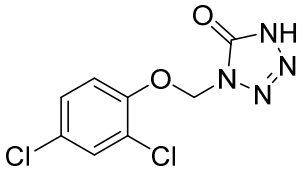
3: UV Detector: 253_255 Smooth (Mn, 1x1) 6.394e-1

Range: 6.387e-1

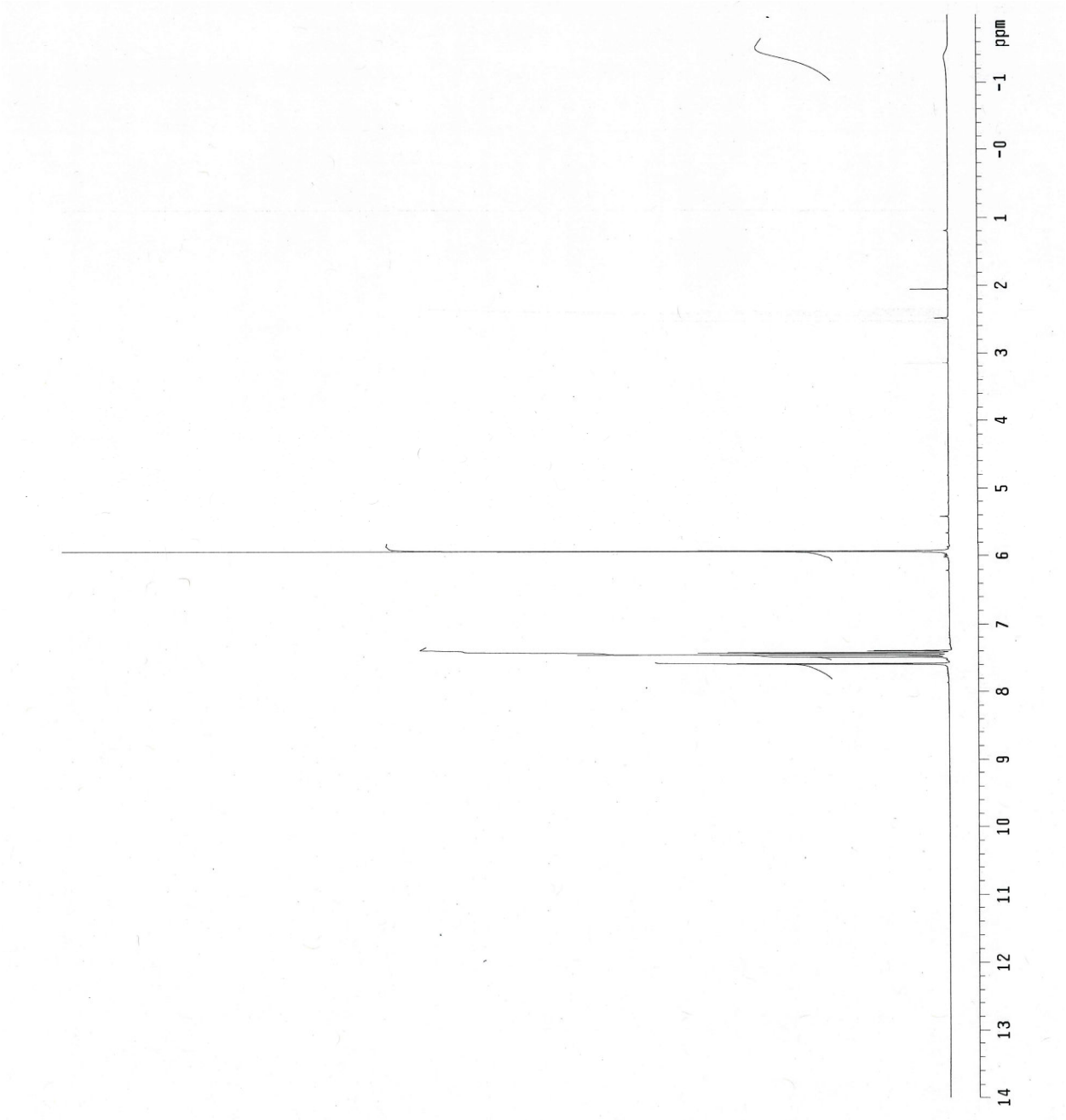


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		5.13	5e+004	100.00	0	6e+005	

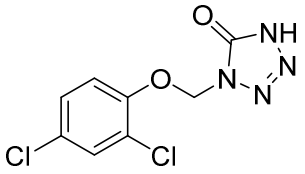
^{1}H NMR FOR 1-((2,4-DICHLOROPHENOXY)METHYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6K



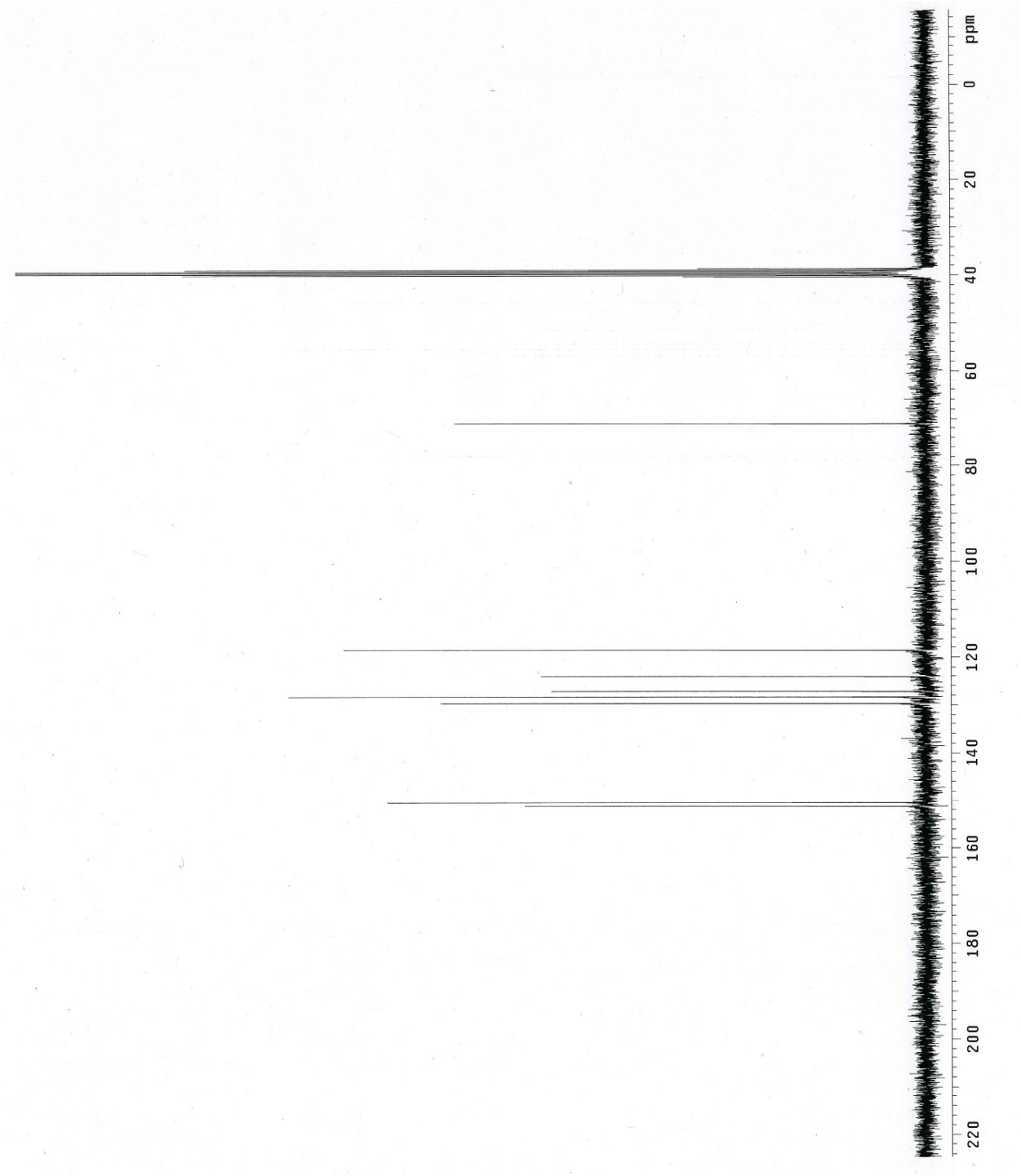
6k



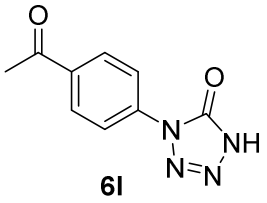
^{13}C NMR FOR 1-((2,4-DICHLOROPHENOXY)METHYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6K



6k



LC DATA FOR 1-(4-ACETYLPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6L



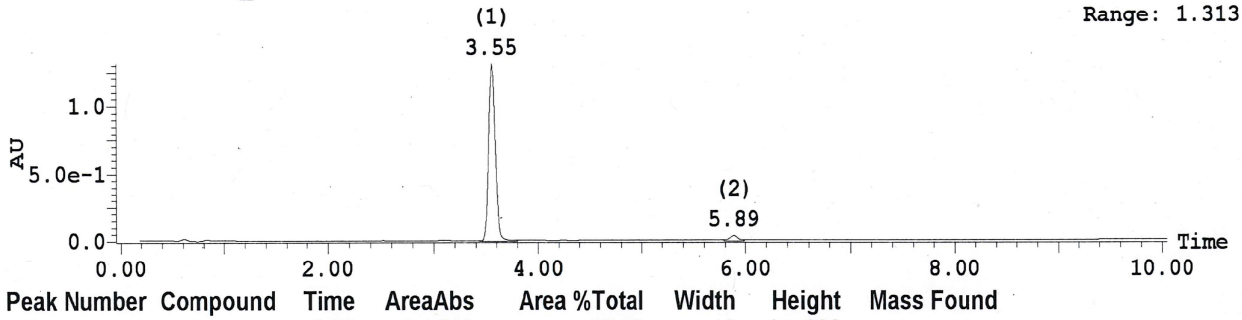
6l

Openlynx Report - Page 1

Vial:1:B,2 File:MD1856-013A Date:05-Nov-2013
Time:17:49:56 Zed: Method:10min

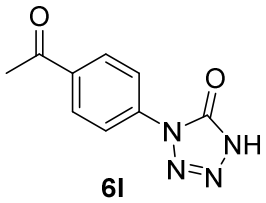
Printed: Tue Nov 05 18:03:03 2013

3: UV Detector: 253_255 Smooth (Mn, 1x1) 1.315
Range: 1.313

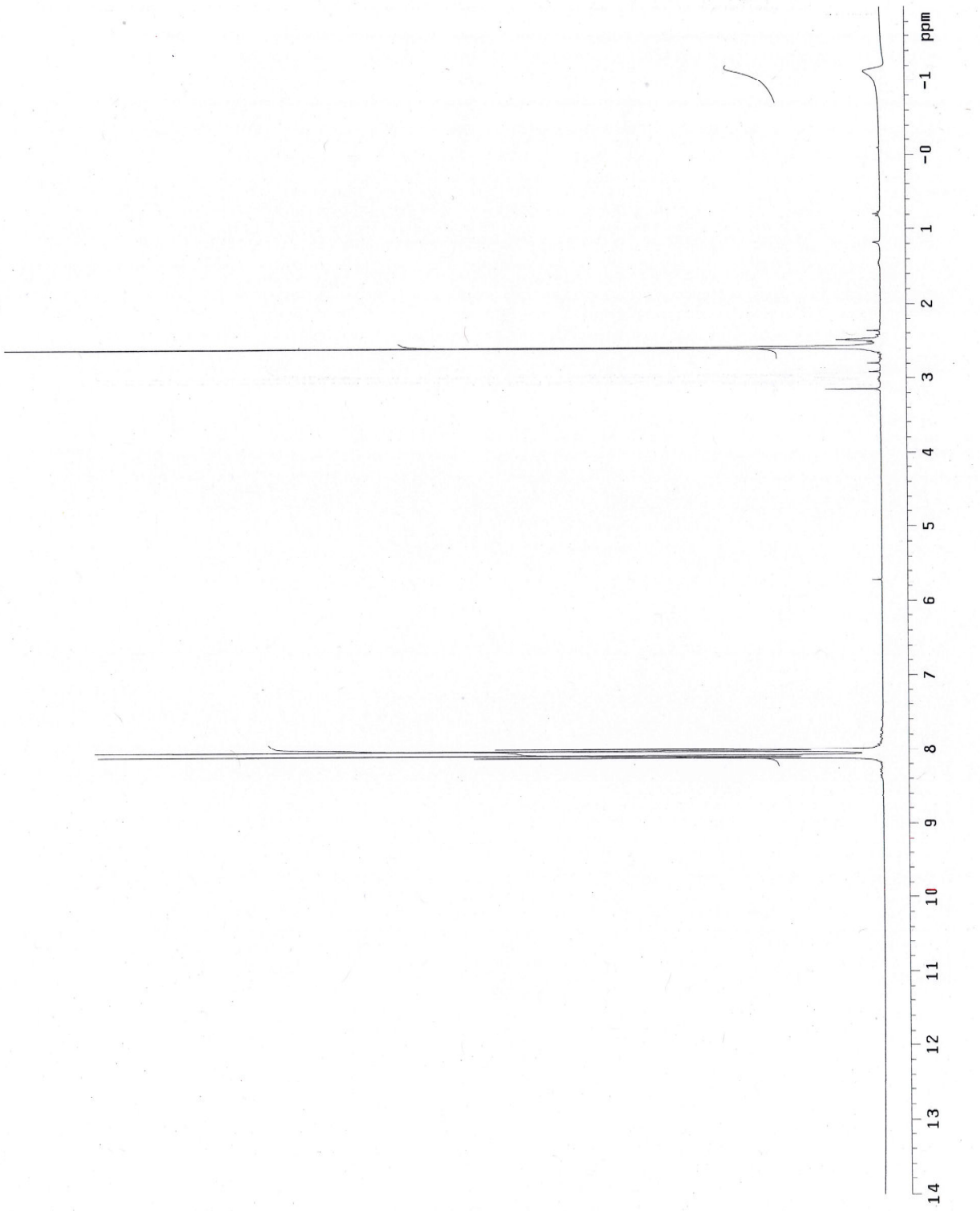


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		3.55	1e+005	97.52	0	1e+006	
2		5.89	2e+003	2.48	0	3e+004	

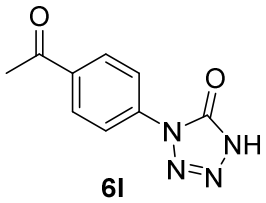
^{1}H NMR FOR 1-(4-ACETYLPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6L



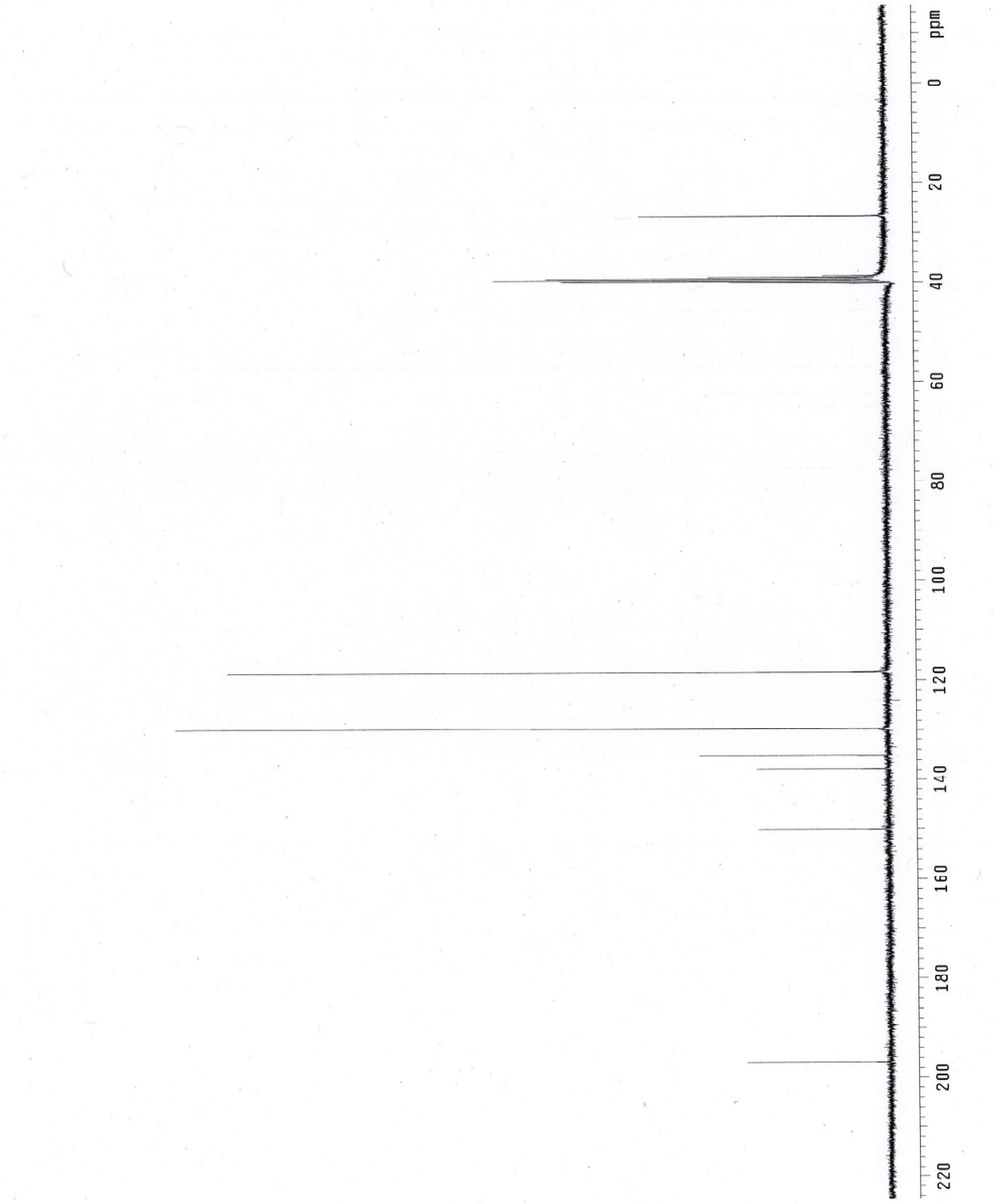
6l



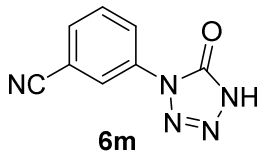
^{13}C NMR FOR 1-(4-ACETYLPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6L



6l



LC DATA FOR 1-(3-CYANOPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6M



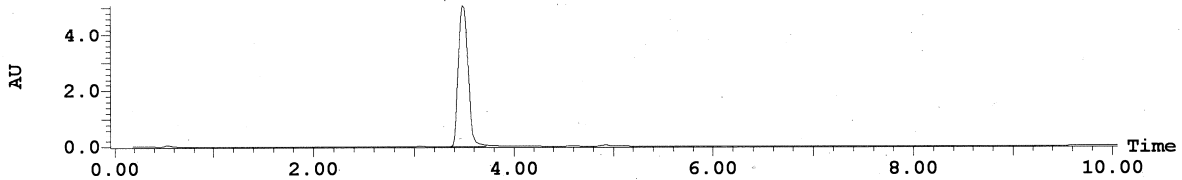
6m

Openlynx Report - Page 1

Vial:1:C,2 File:MD1740-176A Date:08-Aug-2013
Time:14:37:47 Zed: Method:10min

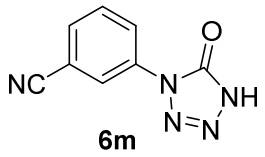
Printed: Thu Aug 08 14:50:57 2013

3: UV Detector: 253_255 Smooth (Mn, 1x1) 5.074
(1) Range: 5.074
3.48

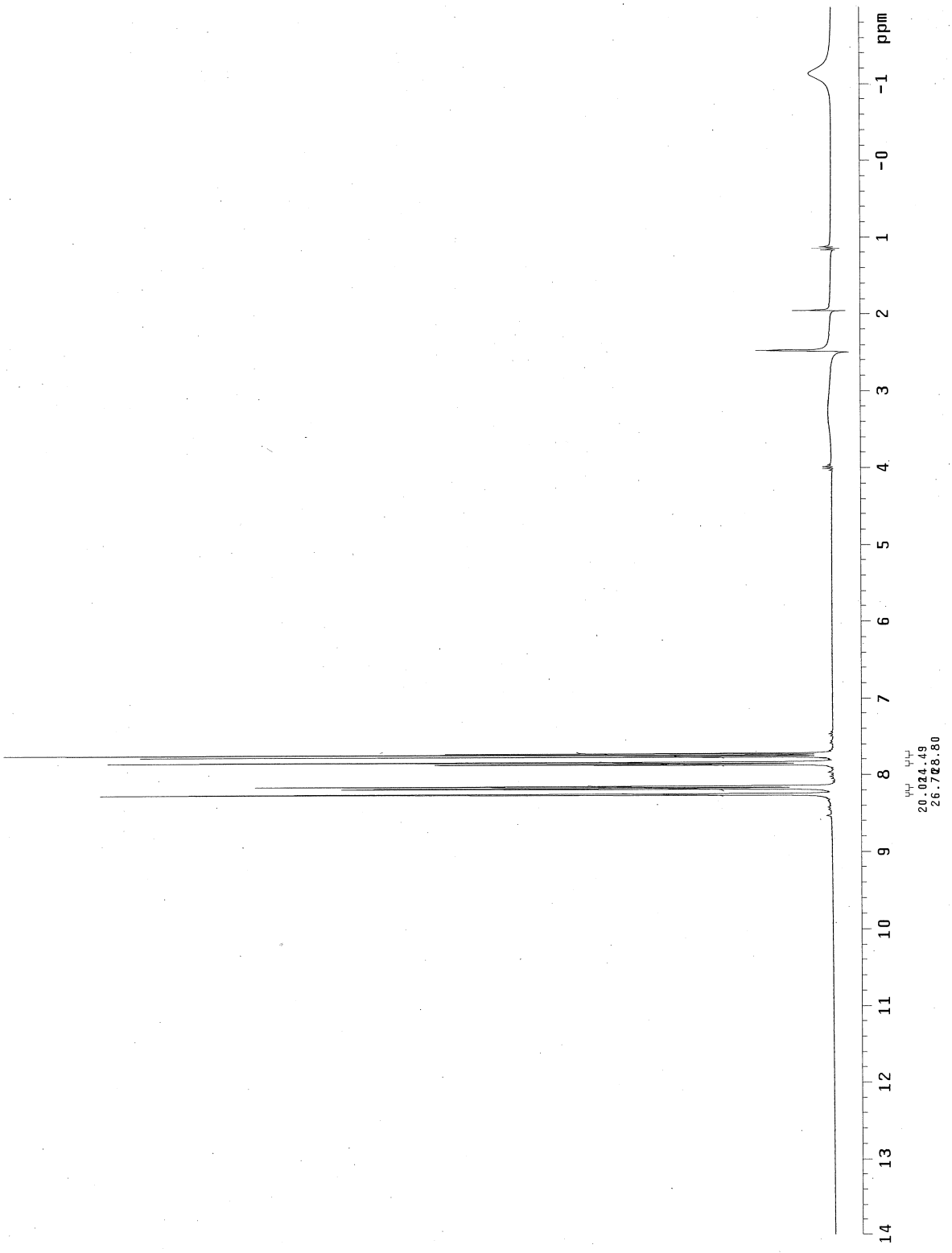


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		3.49	6e+005	100.00	0	5e+006	

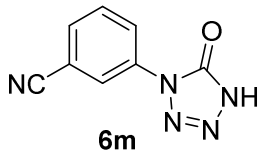
^{1}H NMR FOR 1-(3-CYANOPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6M



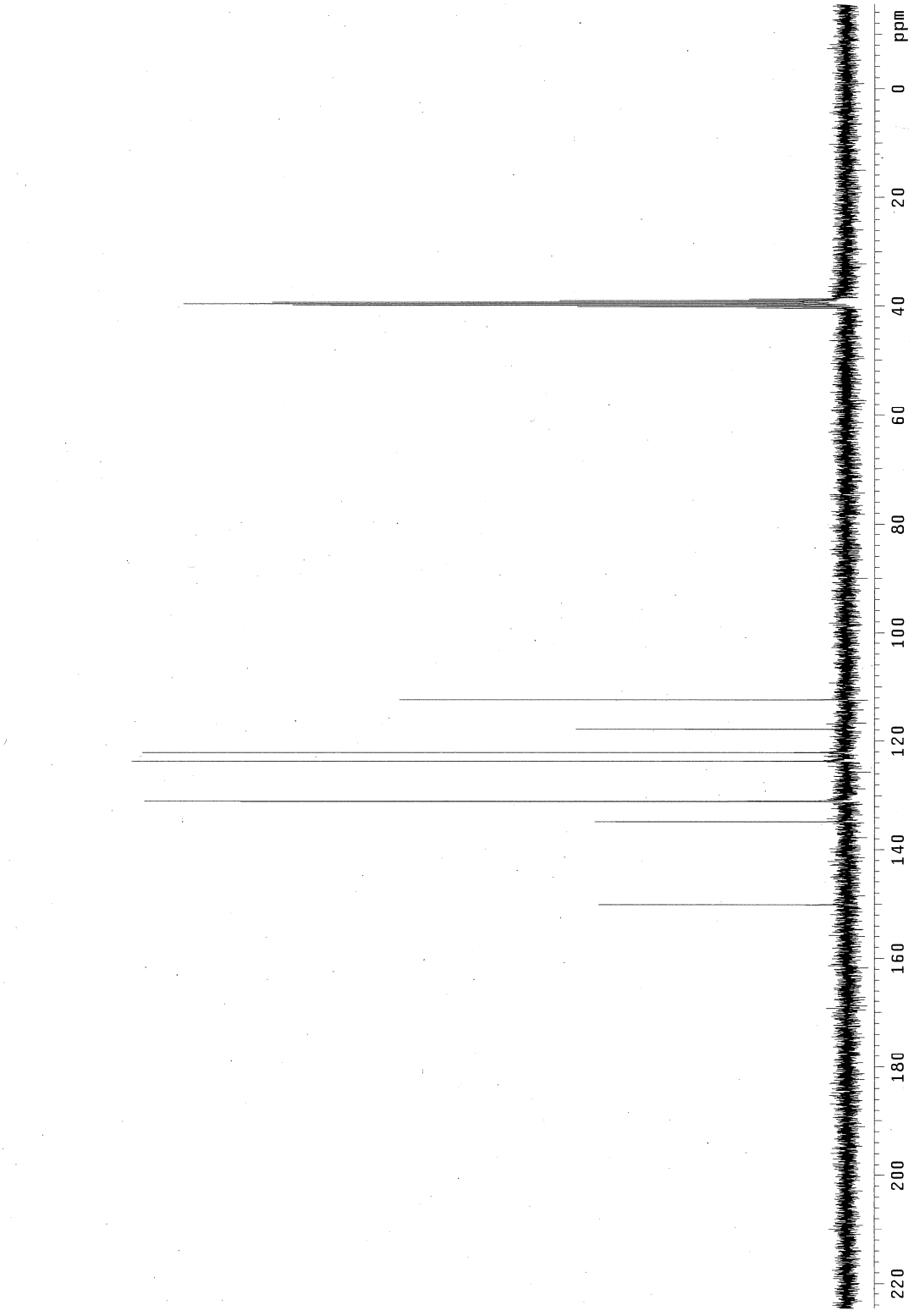
6m



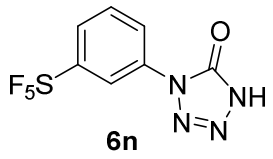
^{13}C NMR FOR 1-(3-CYANOPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6M



6m



LC DATA FOR 1-(3-(PENTAFLUOROSULFANYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6N



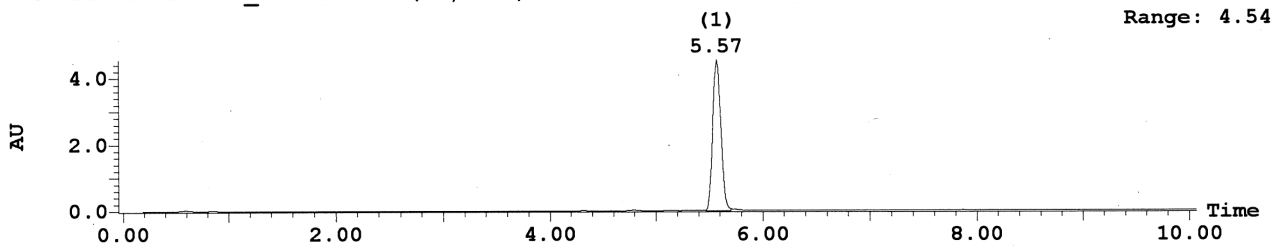
6n

Openlynx Report - Page 1

Vial:1:C,4 File:MD1856-034 Date:14-Jan-2014
Time:17:59:38 Zed: Method:10min

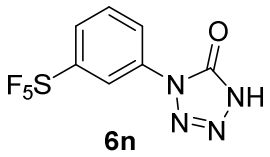
Printed: Tue Jan 14 18:12:56 2014

3: UV Detector: 253_255 Smooth (Mn, 1x1) 4.541
Range: 4.54

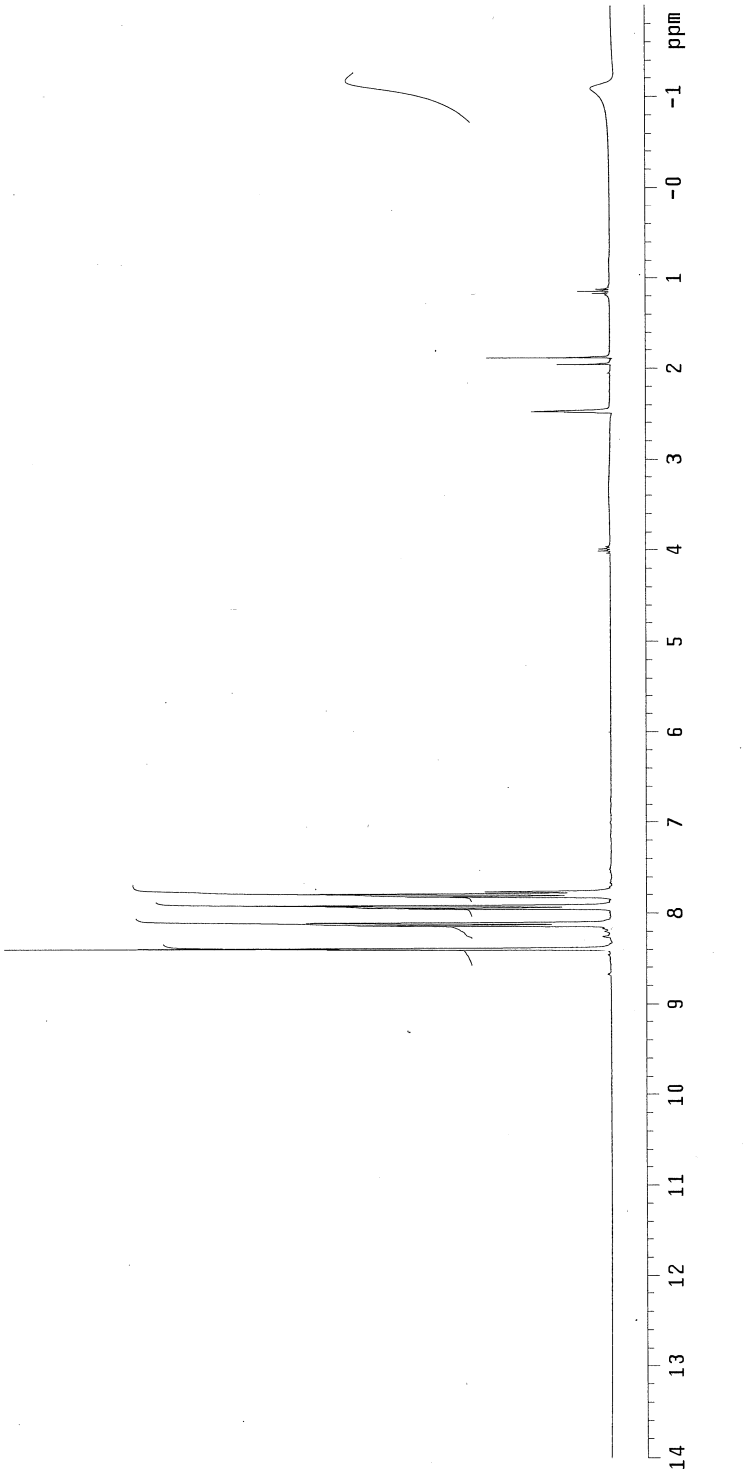


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		5.57	4e+005	100.00	0	5e+006	

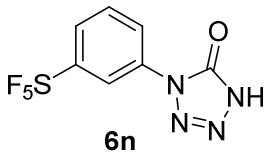
^{1}H NMR FOR 1-(3-(PENTAFLUOROSULFANYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6N



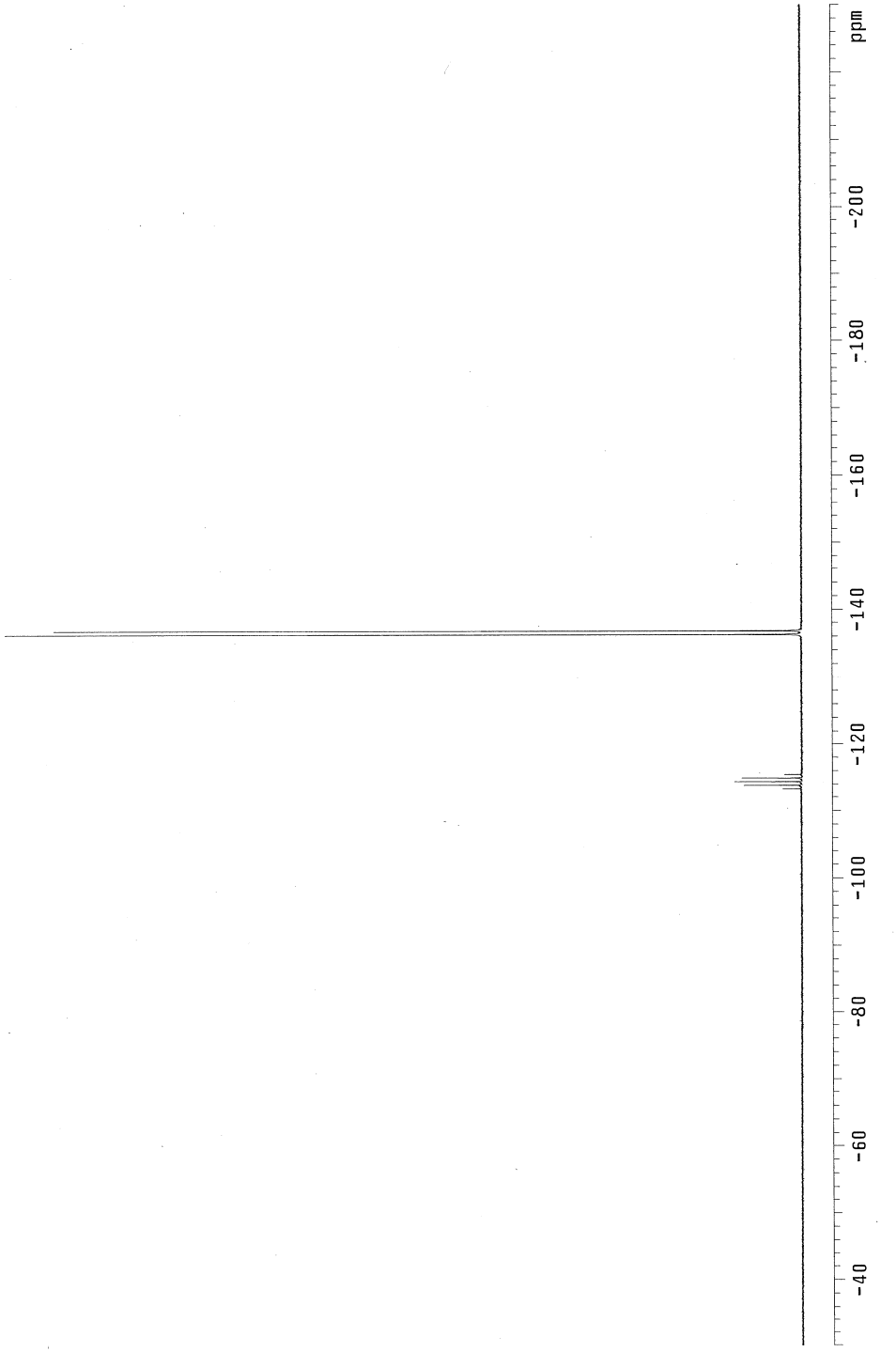
6n



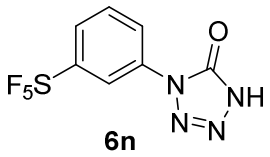
^{19}F NMR FOR 1-(3-(PENTAFLUOROSULFANYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6N



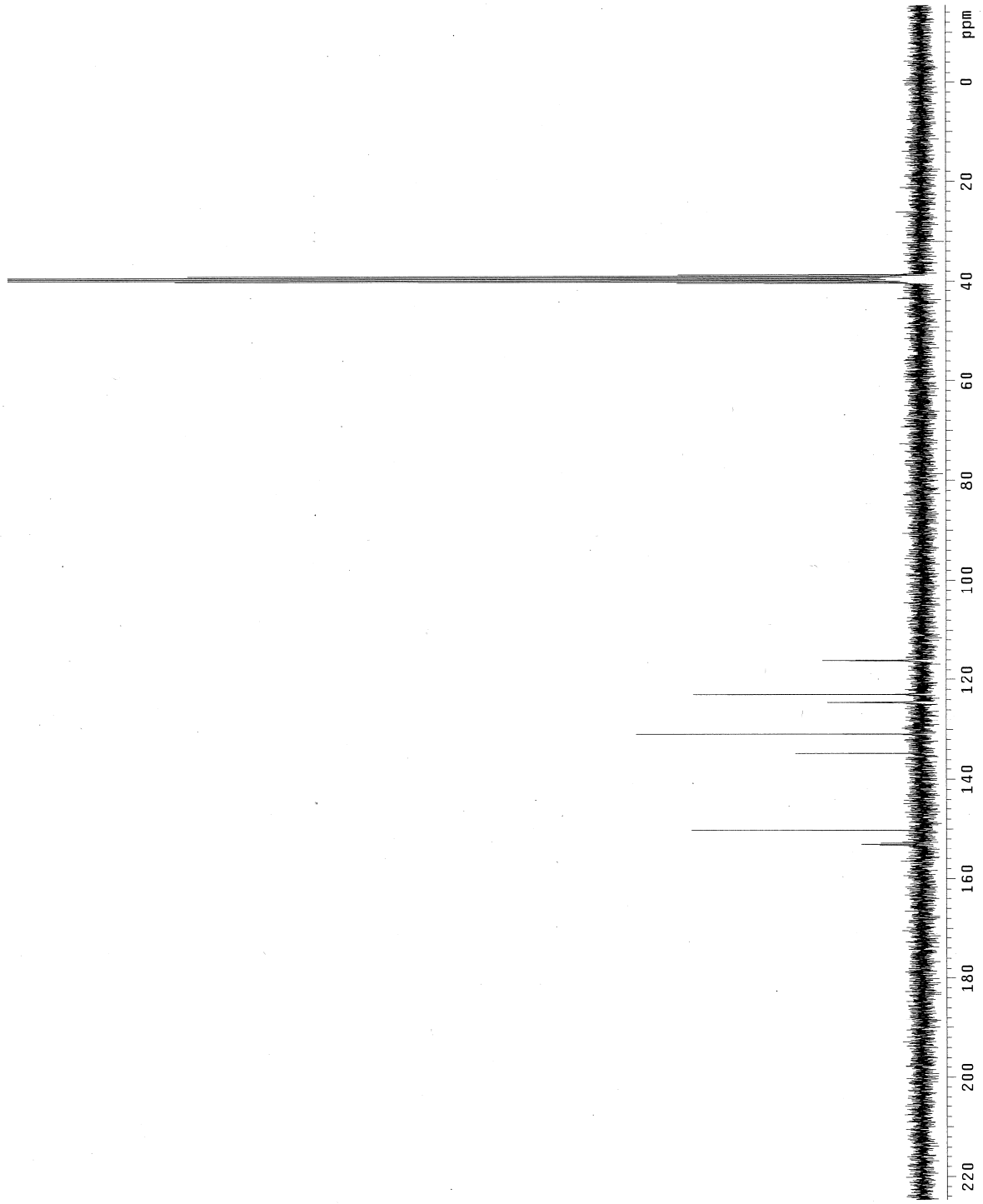
6n



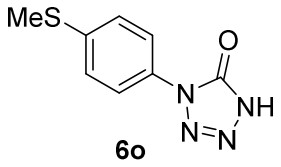
^{13}C NMR FOR 1-(3-(PENTAFLUOROSULFANYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6N



6n



LC DATA FOR 1-(4-(THIOMETHYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6O



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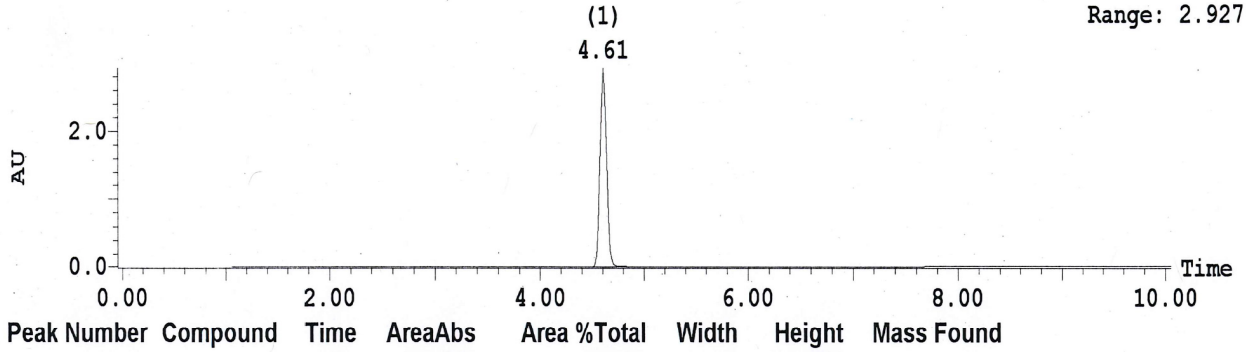
Openlynx Report - Page 1

Vial:2:D,1 File:MD1856-013B Date:04-Nov-2013
Time:15:01:53 Zed: Method:10min

Printed: Mon Nov 04 15:14:55 2013

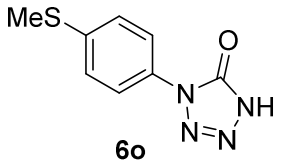
3: UV Detector: 253_255 Smooth (Mn, 1x1) 2.927

Range: 2.927

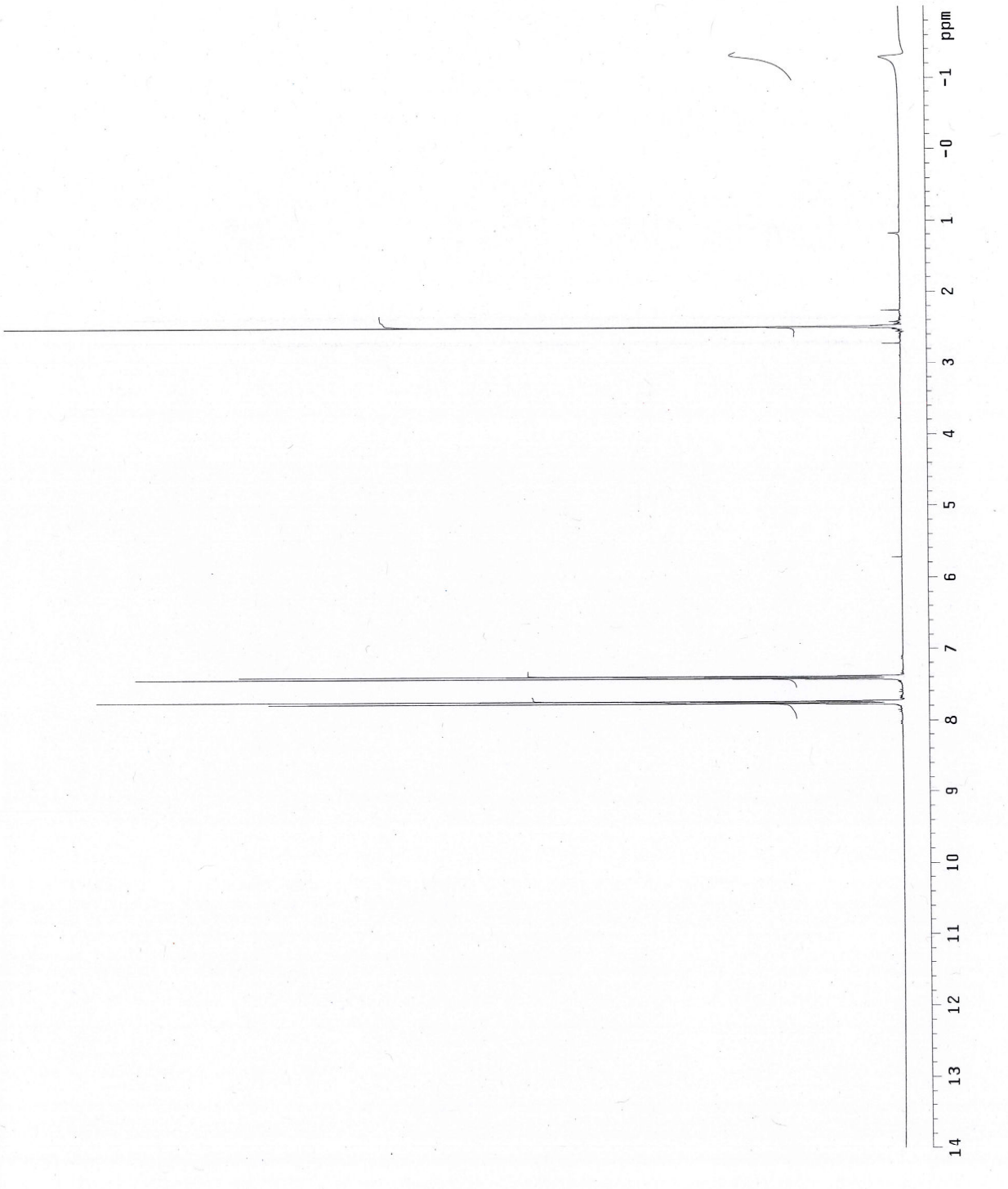


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		4.61	2e+005	100.00	0	3e+006	

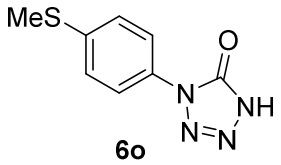
^{1}H NMR FOR 1-(4-(THIOMETHYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6O



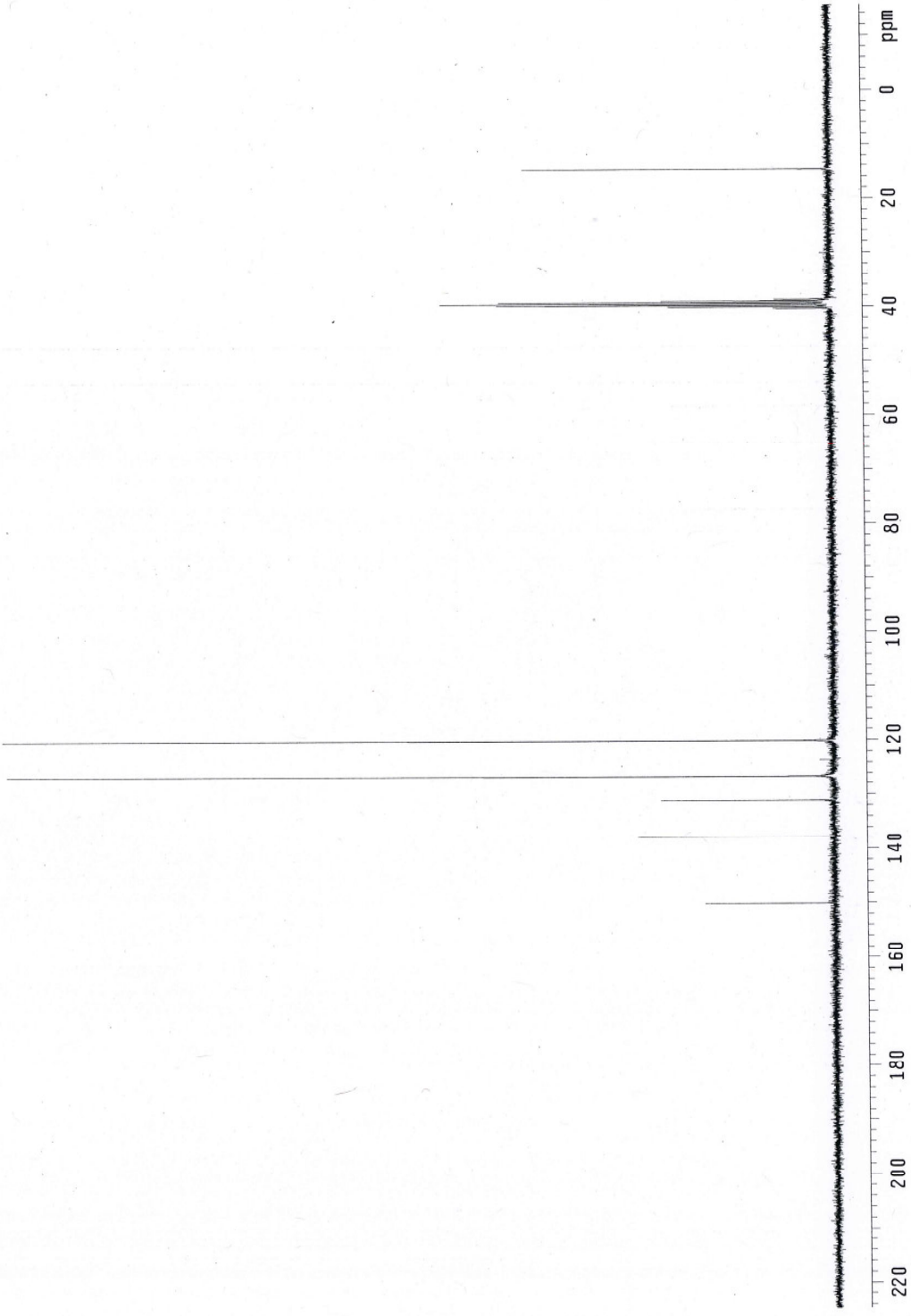
6o



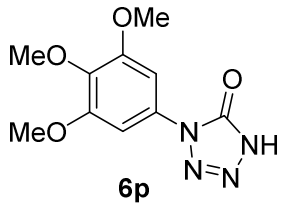
^{13}C NMR FOR 1-(4-(THIOMETHYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6O



6o



LC DATA FOR 1-(3,4,5-TRIMETHOXTPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6P

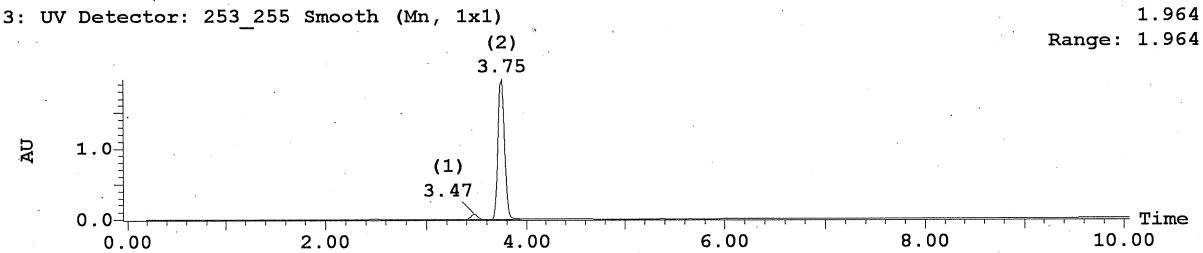


6p

Openlynx Report - Page 1

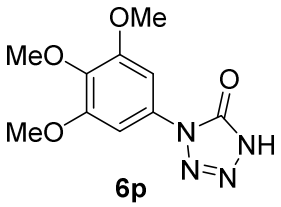
Vial:1:G,7 File:MD1740-176D Date:21-Aug-2013
Time:14:23:30 Zed: Method:10min

Printed: Wed Aug 21 14:34:48 2013

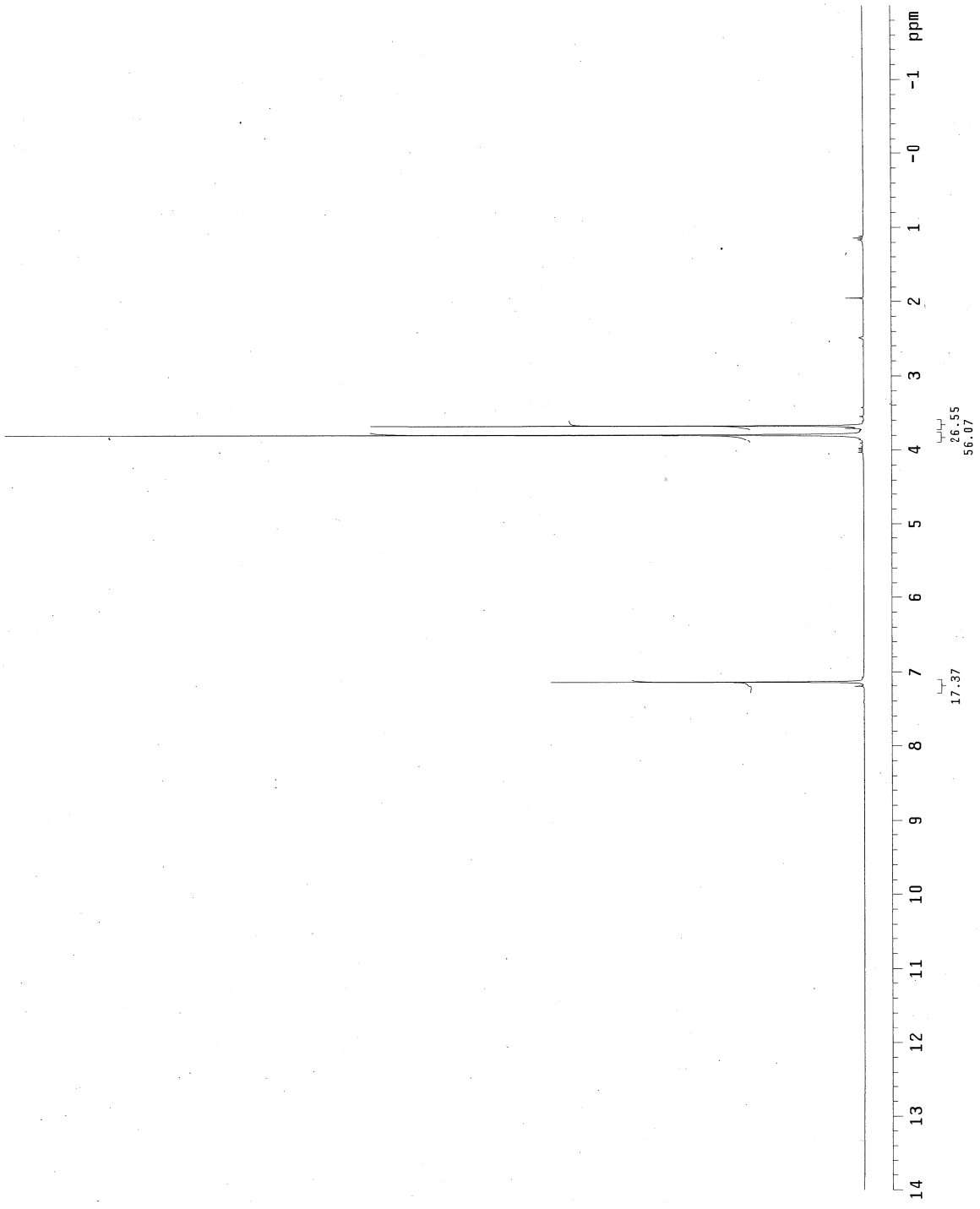


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		3.47	5e+003	3.49	0	7e+004	
2		3.75	1e+005	96.51	0	2e+006	

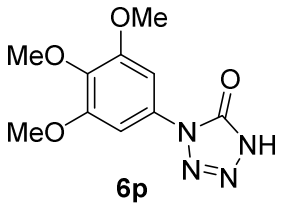
^{1}H NMR FOR 1-(3,4,5-TRIMETHOXTPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6P



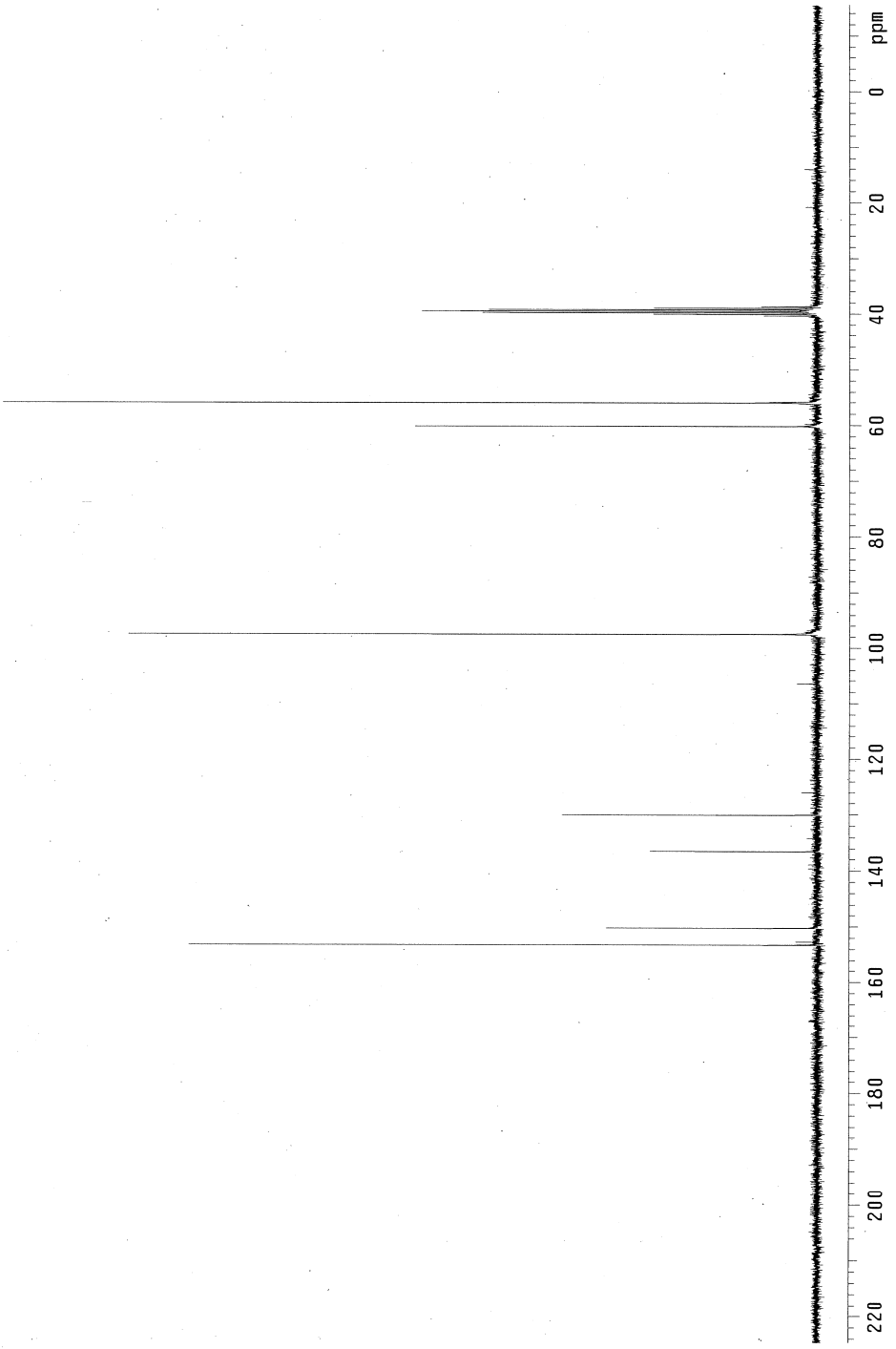
6p



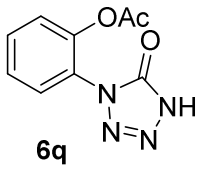
^{13}C NMR FOR 1-(3,4,5-TRIMETHOXTPHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6P



6p



LC DATA FOR 2-(5-OXO-4,5-DIHYDRO-1*H*-TETRAZOL-1-YL)PHENYL ACETATE 6Q



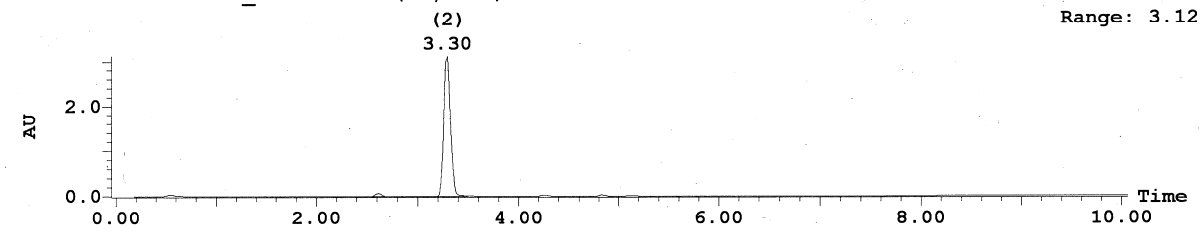
6q

Openlynx Report - Page 1

Vial:1:E,7 File:MD1740-178C Date:08-Aug-2013
Time:16:10:22 Zed: Method:10min

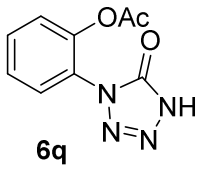
Printed: Thu Aug 08 16:23:32 2013

3: UV Detector: 253_255 Smooth (Mn, 1x1) 3.12
Range: 3.12

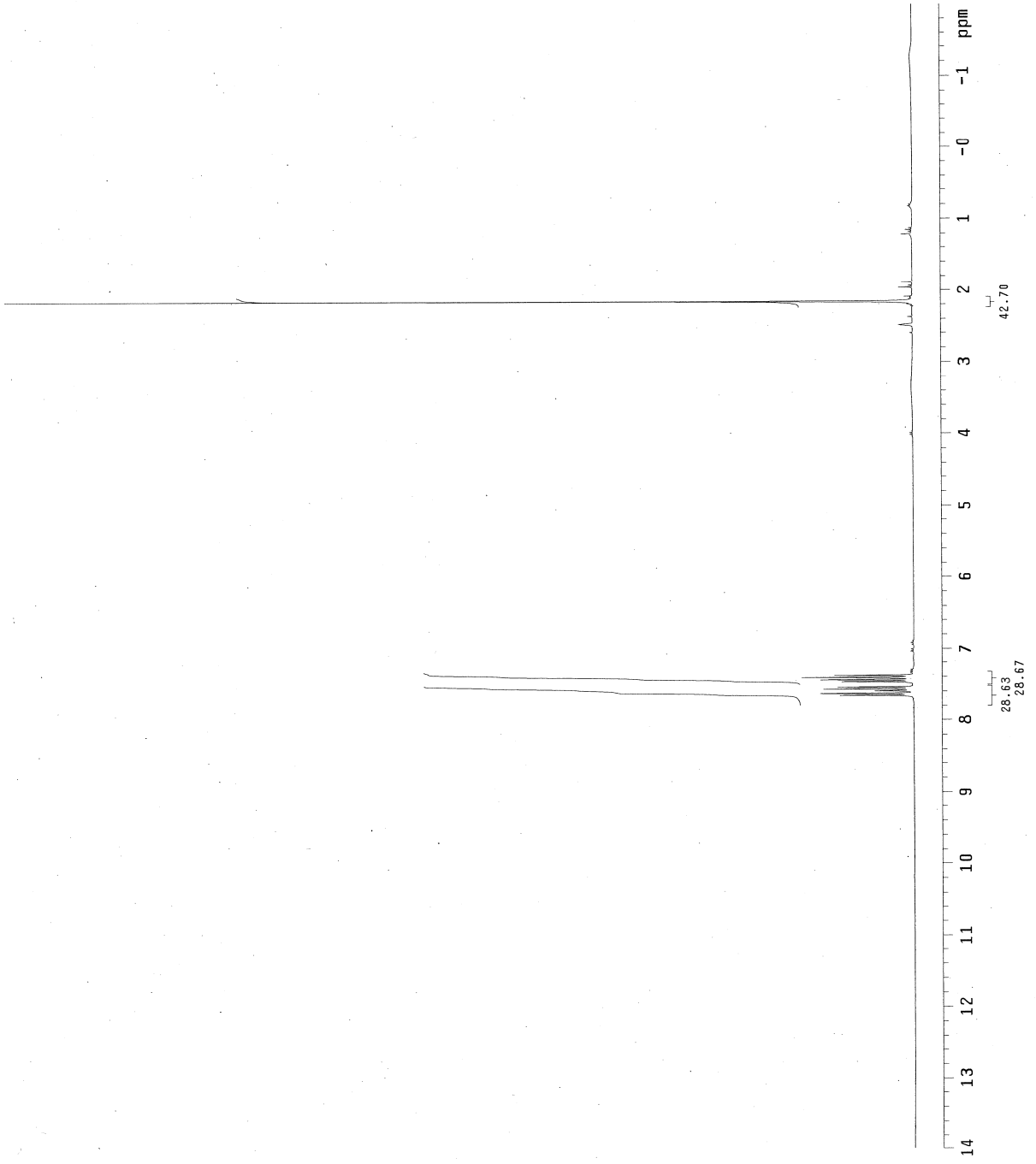


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		2.61	5e+003	2.01	0	7e+004	
2		3.30	2e+005	97.99	0	3e+006	

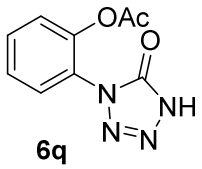
^{1}H NMR FOR 2-(5-OXO-4,5-DIHYDRO-1*H*-TETRAZOL-1-YL)PHENYL ACETATE 6Q



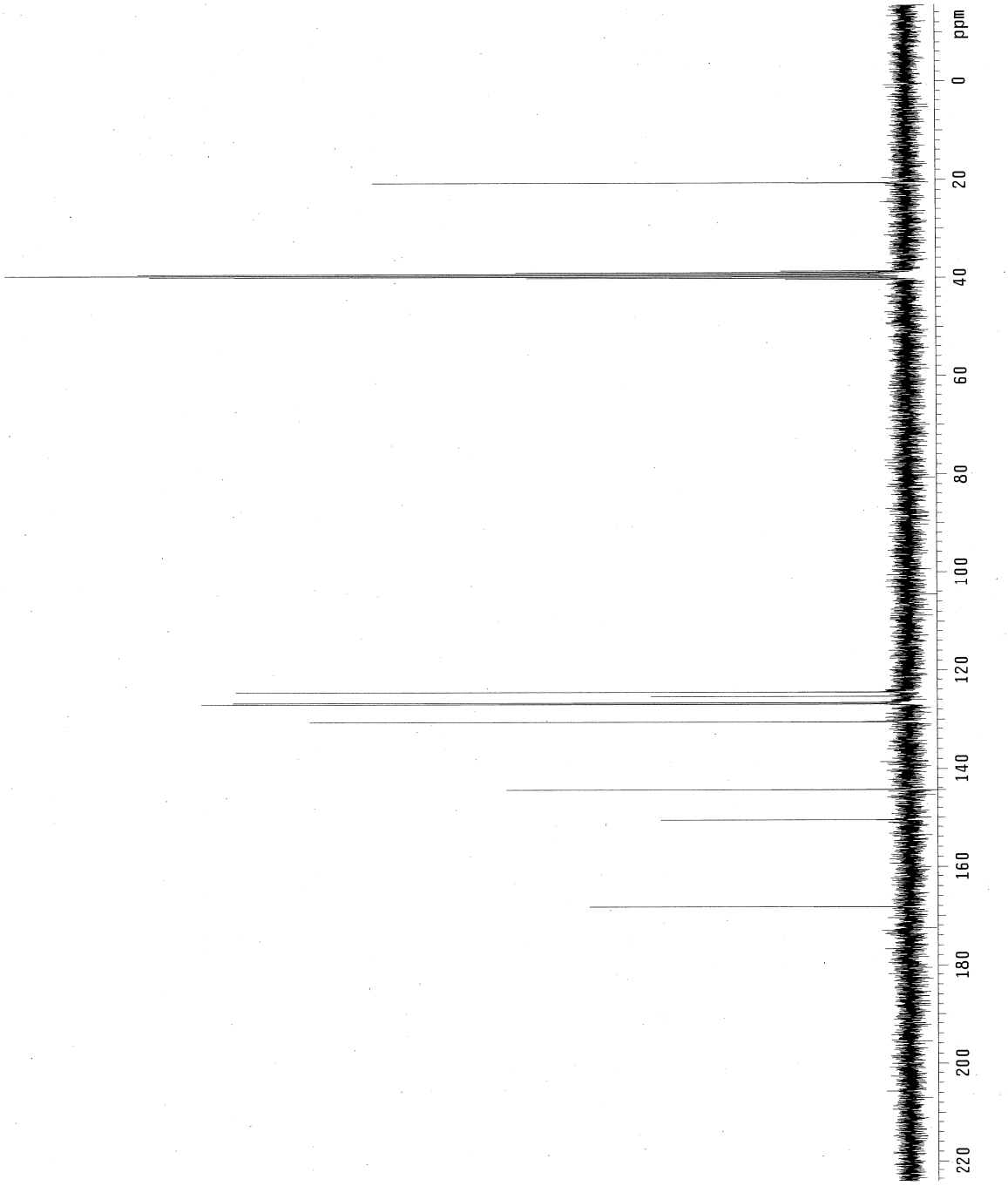
6q



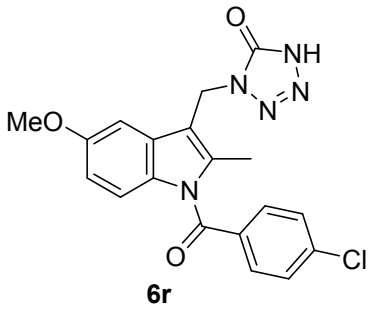
^{13}C NMR FOR 2-(5-OXO-4,5-DIHYDRO-1*H*-TETRAZOL-1-YL)PHENYL ACETATE 6Q



6q



LC DATA FOR 1-((1-(4-CHLOROBENZOYL)-5-METHOXY-1*H*-INDOL-3-YL)METHYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6R



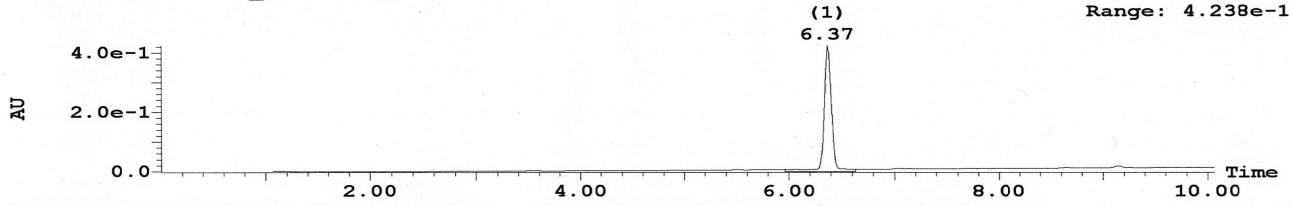
6r

Openlynx Report - Page 1

Vial:1:E,6 File:MD1856-108 Date:26-Jun-2014
Time:15:19:22 Zed: Method:10min

Printed: Thu Jun 26 15:30:40 2014

3: UV Detector: 253_255 Smooth (Mn, 1x1) 4.238e-1
Range: 4.238e-1



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		6.37	3e+004	100.00	1	4e+005	

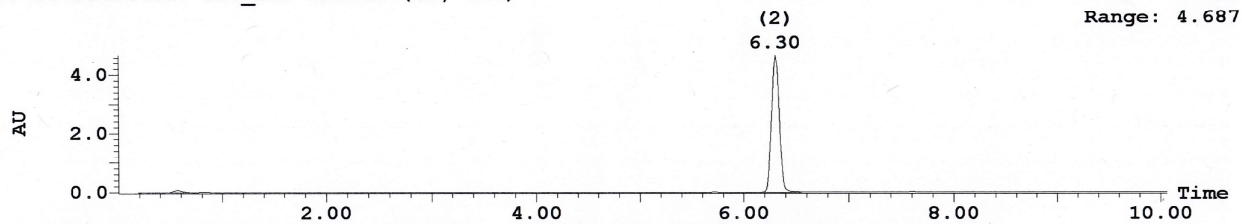
LC DATA FOR COMMERCIAL INDOMETHACIN (AS A COMPARISON TO COMPOUND 6R ABOVE)

Openlynx Report - Page 1

Vial:2:C,3 File:MD18560-114 Date:26-Jun-2014
Time:16:39:46 Zed: Method:10min

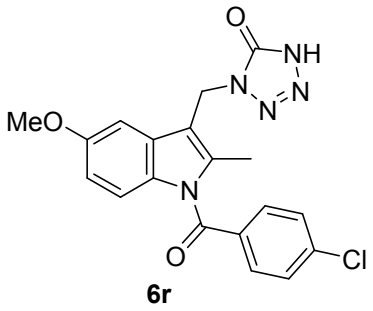
Printed: Thu Jun 26 16:53:05 2014

3: UV Detector: 253_255 Smooth (Mn, 1x1) 4.687
Range: 4.687

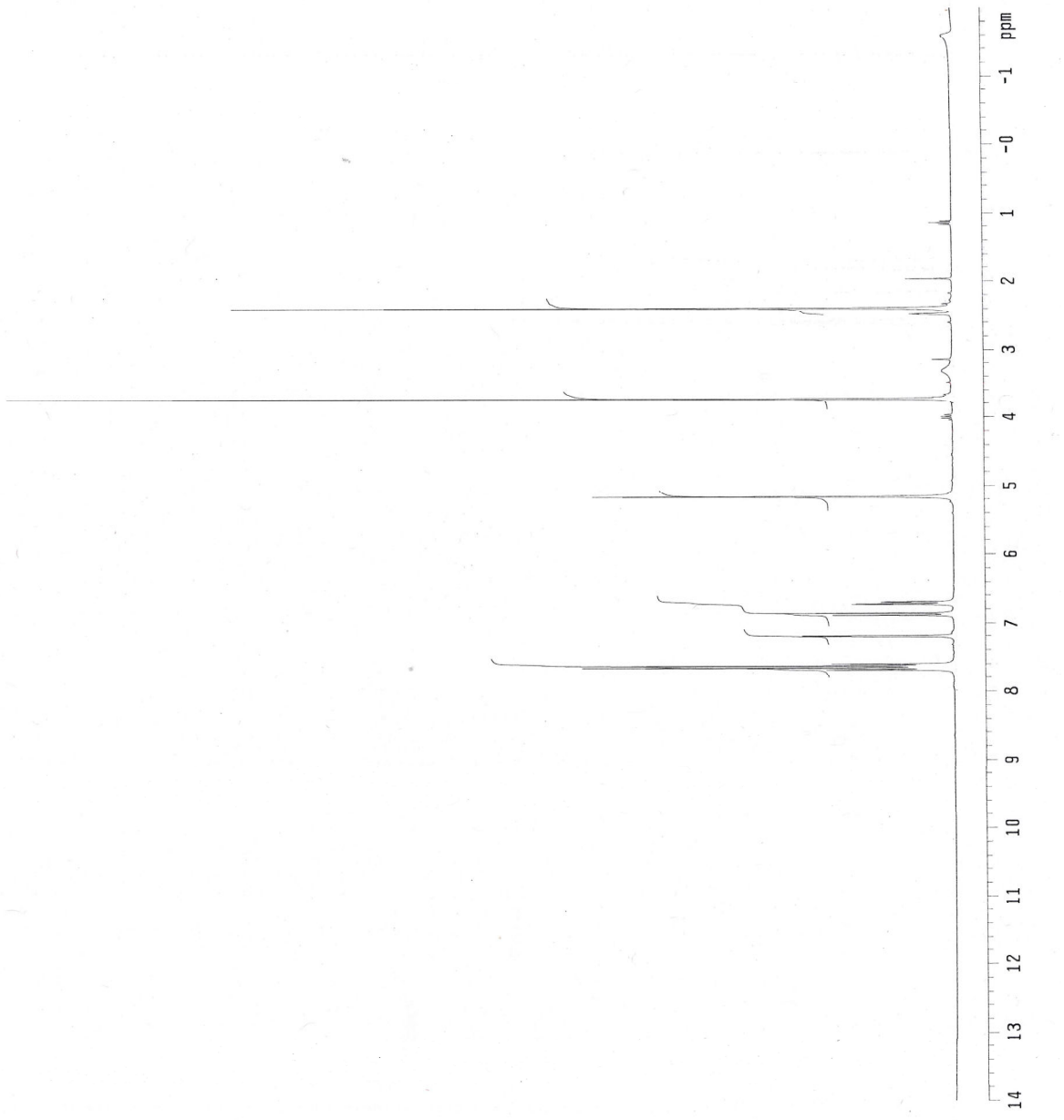


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		0.57	7e+003	1.65	0	7e+004	
2		6.30	4e+005	98.35	0	5e+006	

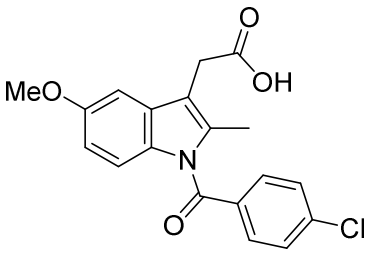
^{1}H NMR FOR 1-((1-(4-CHLOROBENZOYL)-5-METHOXY-1*H*-INDOL-3-YL)METHYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6R



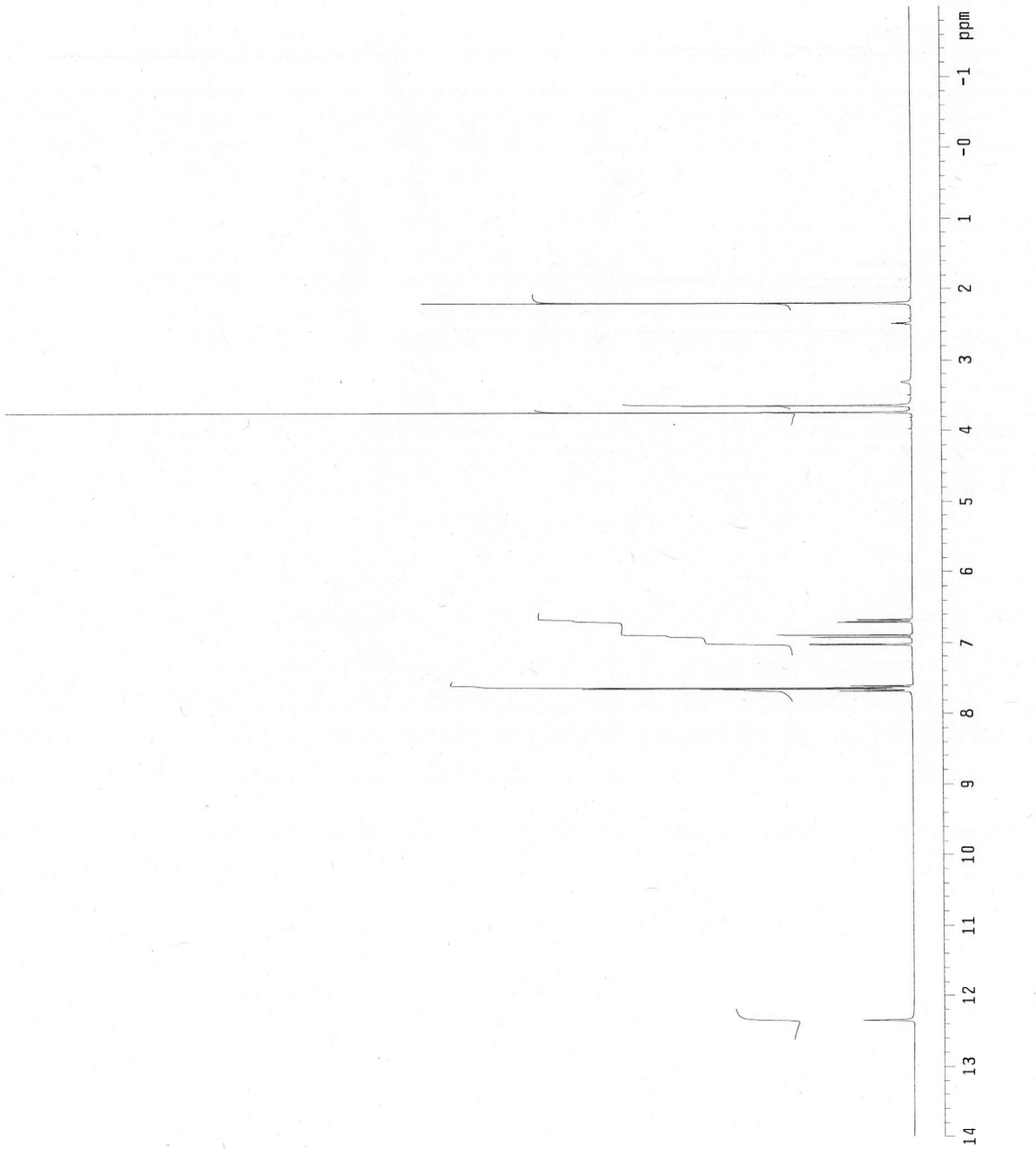
6r



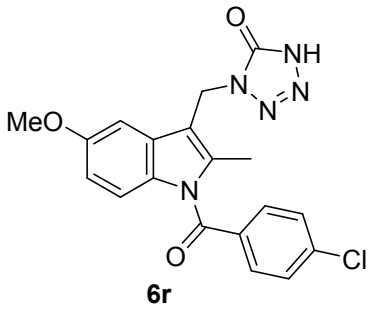
^{1}H NMR FOR COMMERCIAL INDOMETHACIN (AS A COMPARISON TO COMPOUND 6R ABOVE)



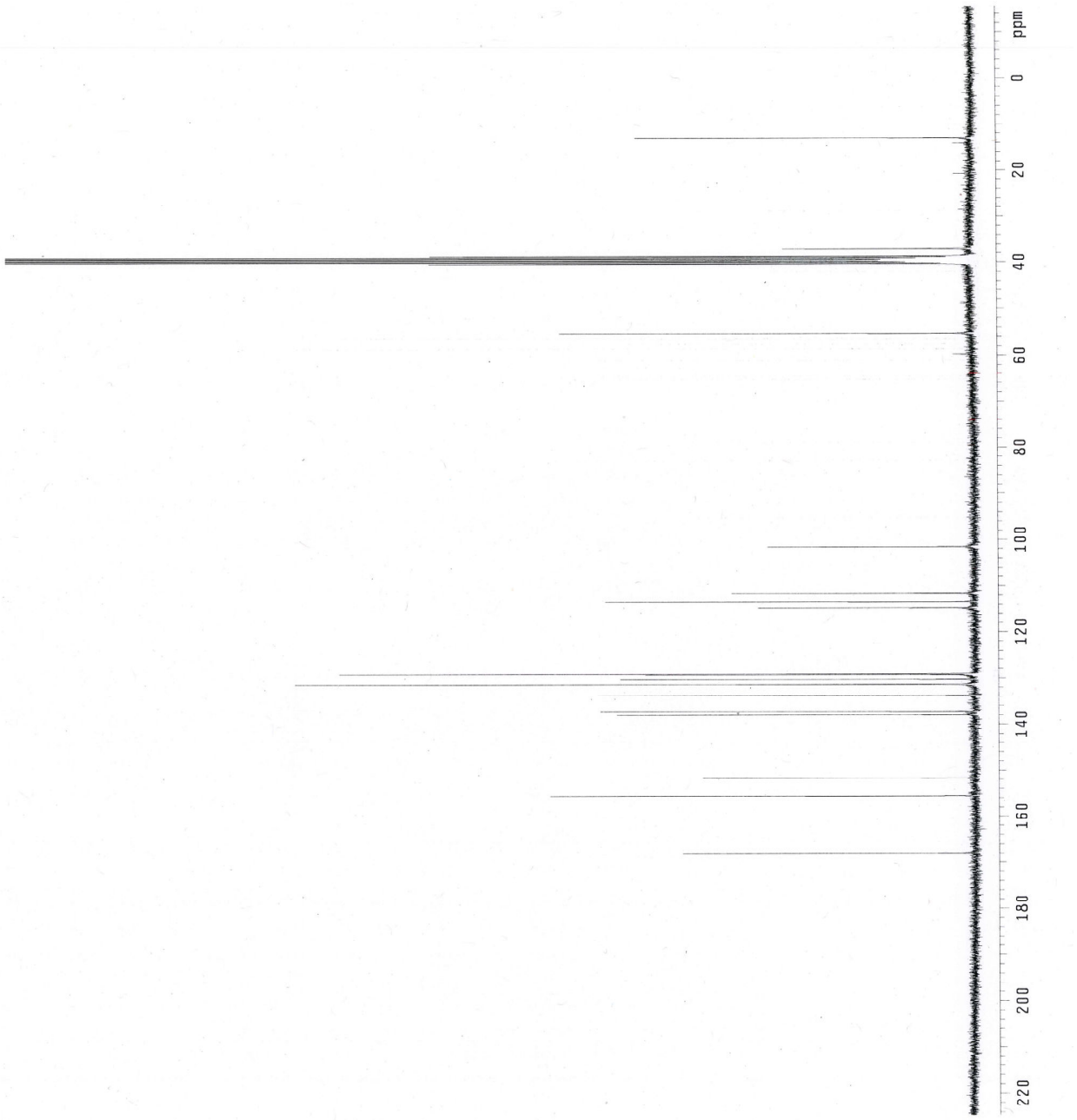
Indomethacin



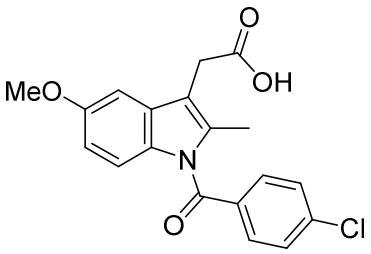
^{13}C NMR FOR 1-((1-(4-CHLOROBENZOYL)-5-METHOXY-1*H*-INDOL-3-YL)METHYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6R



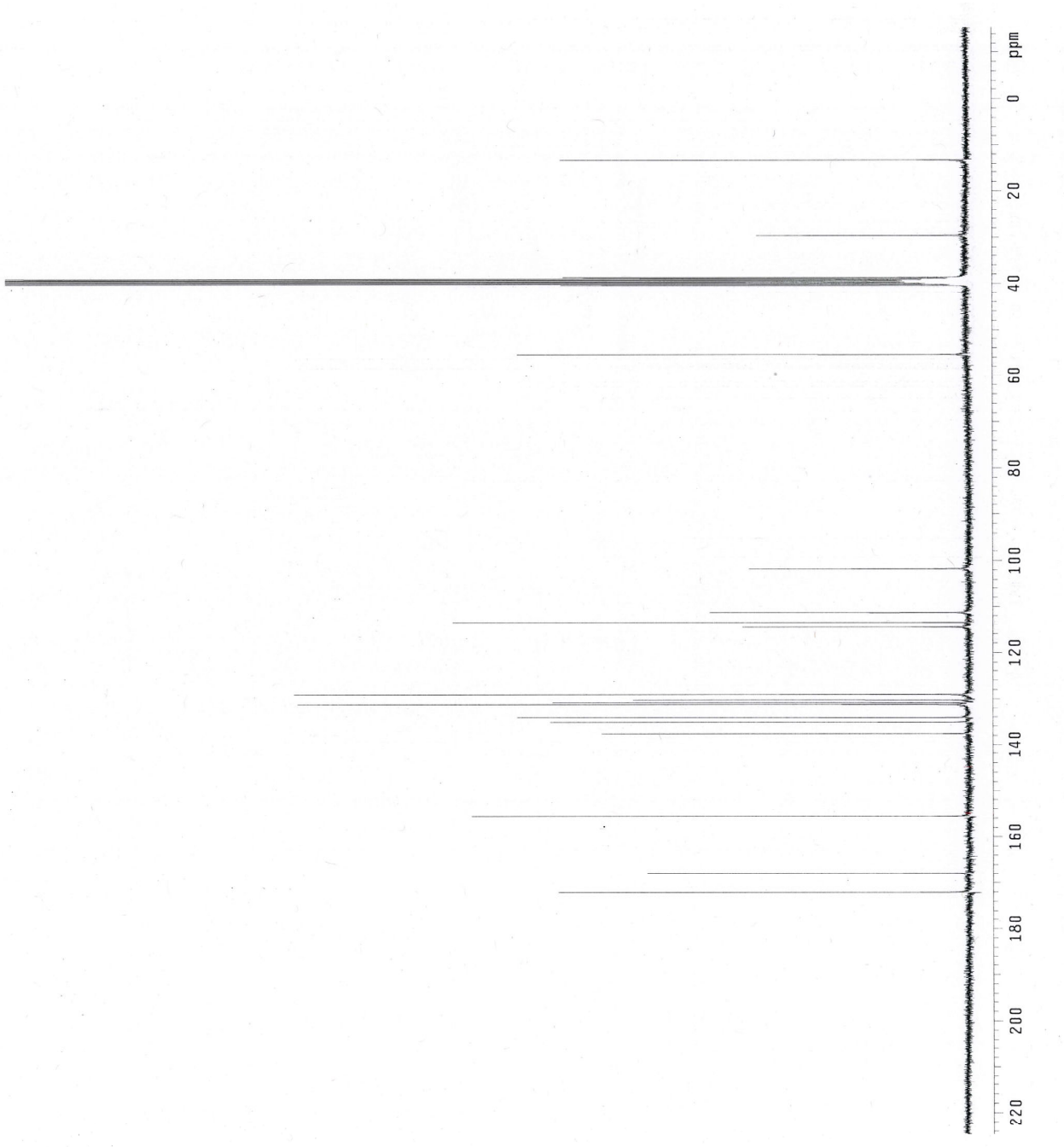
6r



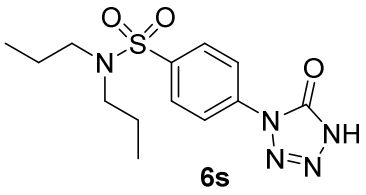
^{13}C NMR FOR COMMERCIAL INDOMETHACIN (AS A COMPARISON TO COMPOUND 6R ABOVE)



Indomethacin



LC DATA FOR 4-(5-OXO-4,5-DIHYDRO-1*H*-TETRAZOL-1-YL)DIPROPYLBENEZENESULFONAMIDE 6S



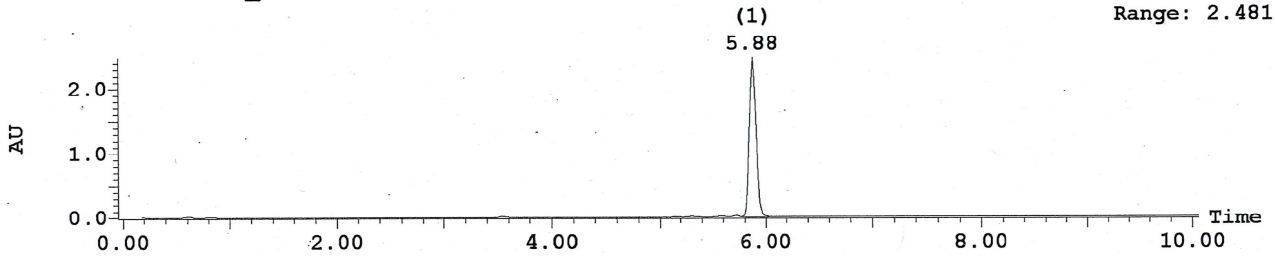
6s

Openlynx Report -

Vial:1:G,11 File:MD1856-013C Date:30-Oct-2013
Time:18:52:58 Zed: Method:10min

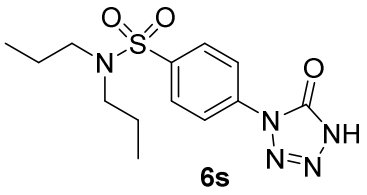
Printed: Wed Oct 30 19:06:00 2013

3: UV Detector: 253_255 Smooth (Mn, 1x1) 2.481
Range: 2.481

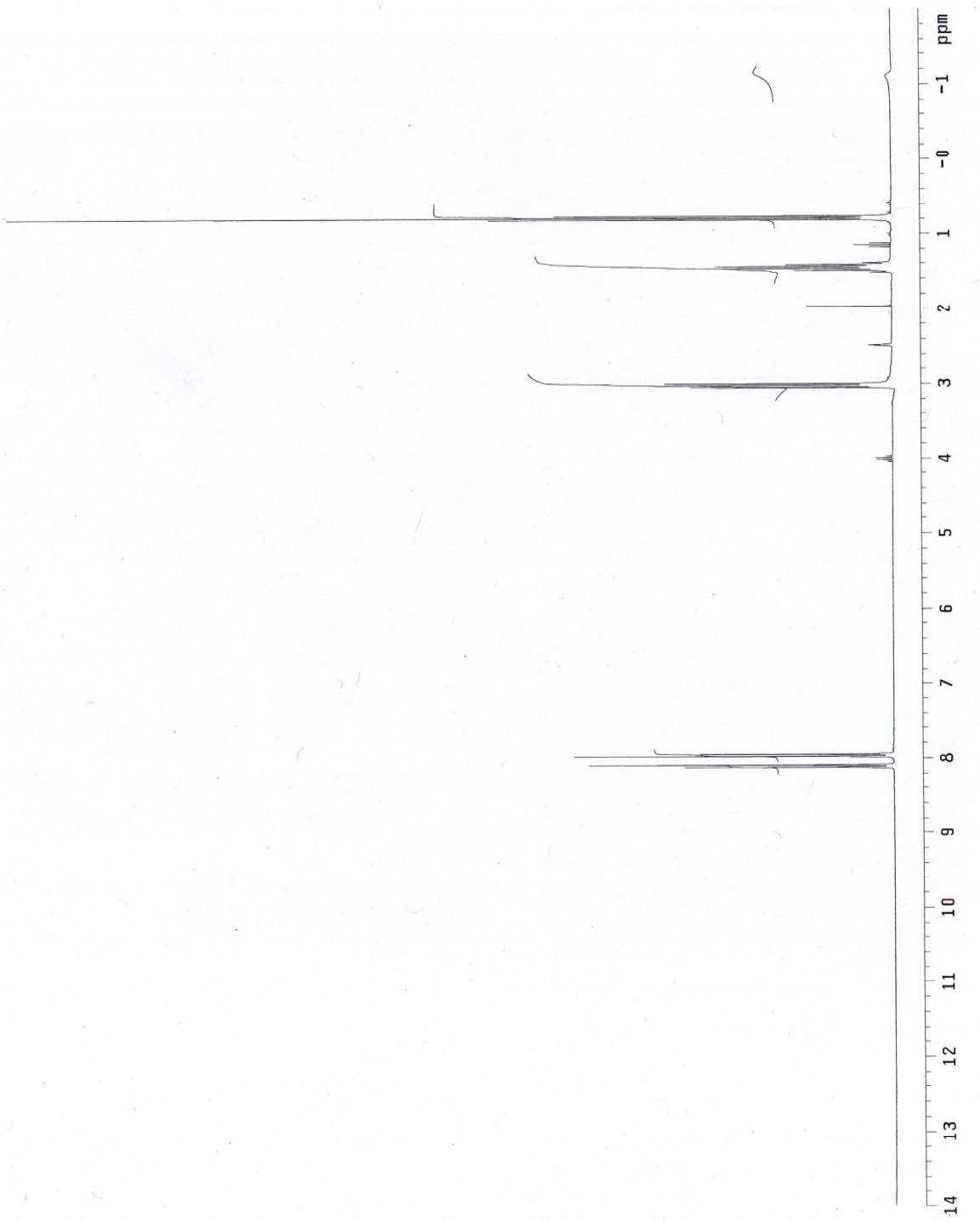


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		5.88	2e+005	100.00	0	2e+006	

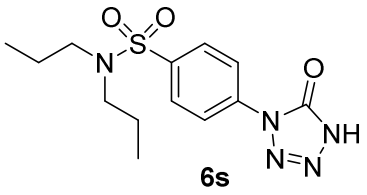
^{1}H NMR FOR 4-(5-OXO-4,5-DIHYDRO-1*H*-TETRAZOL-1-YL)DIPROPYLBENEZENESULFONAMIDE 6S



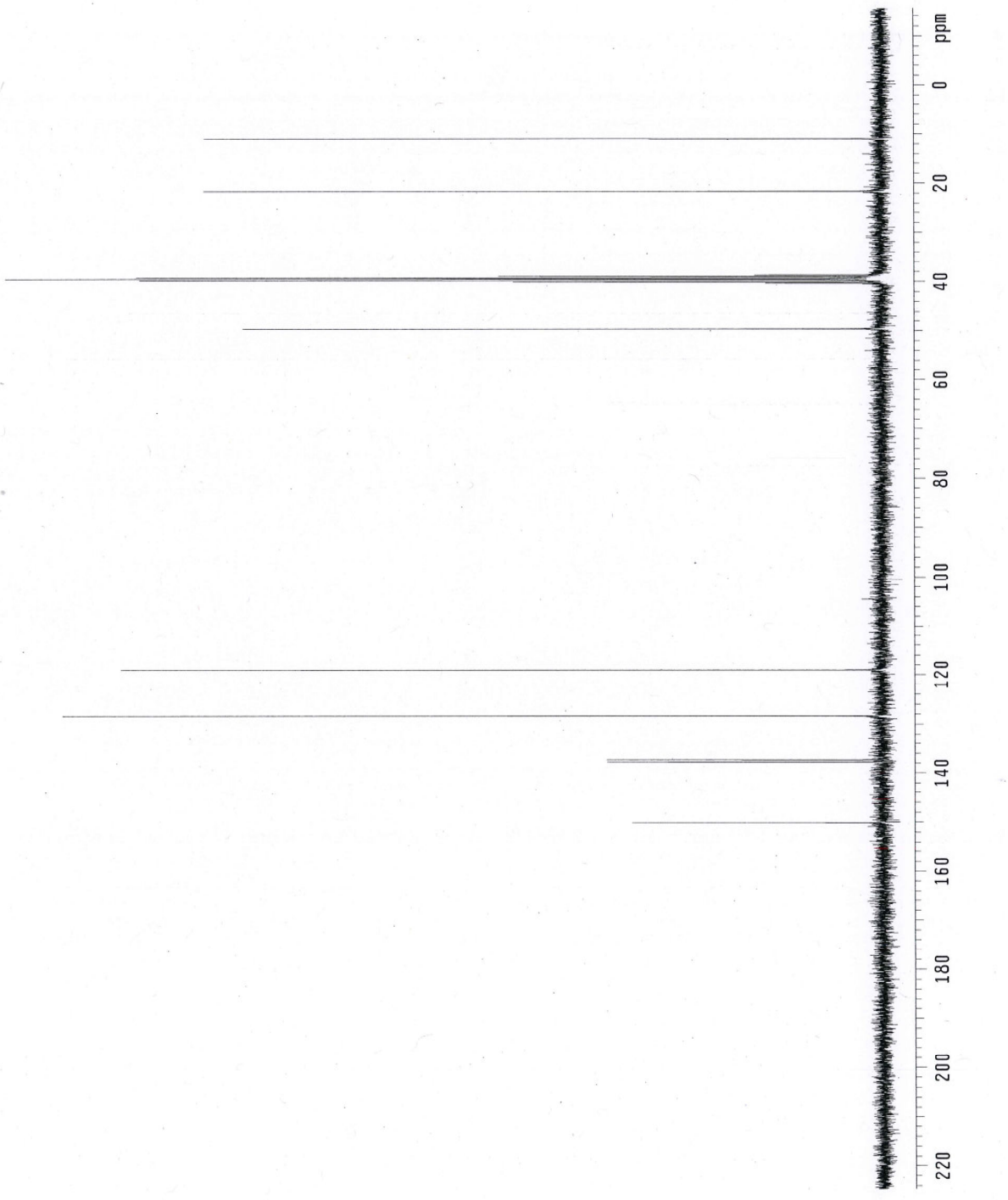
6s



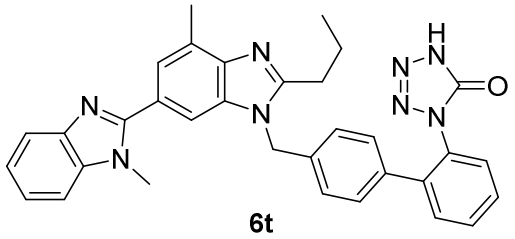
^{13}C NMR FOR 4-(5-OXO-4,5-DIHYDRO-1*H*-TETRAZOL-1-YL)DIPROPYLBENEZENESULFONAMIDE 6S



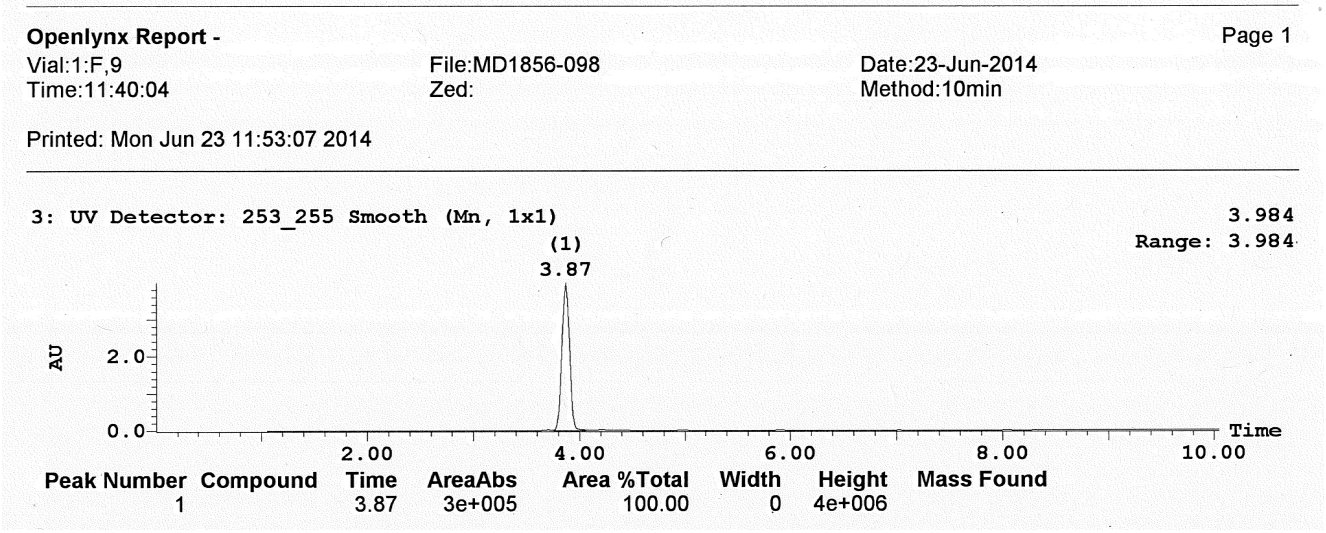
6s



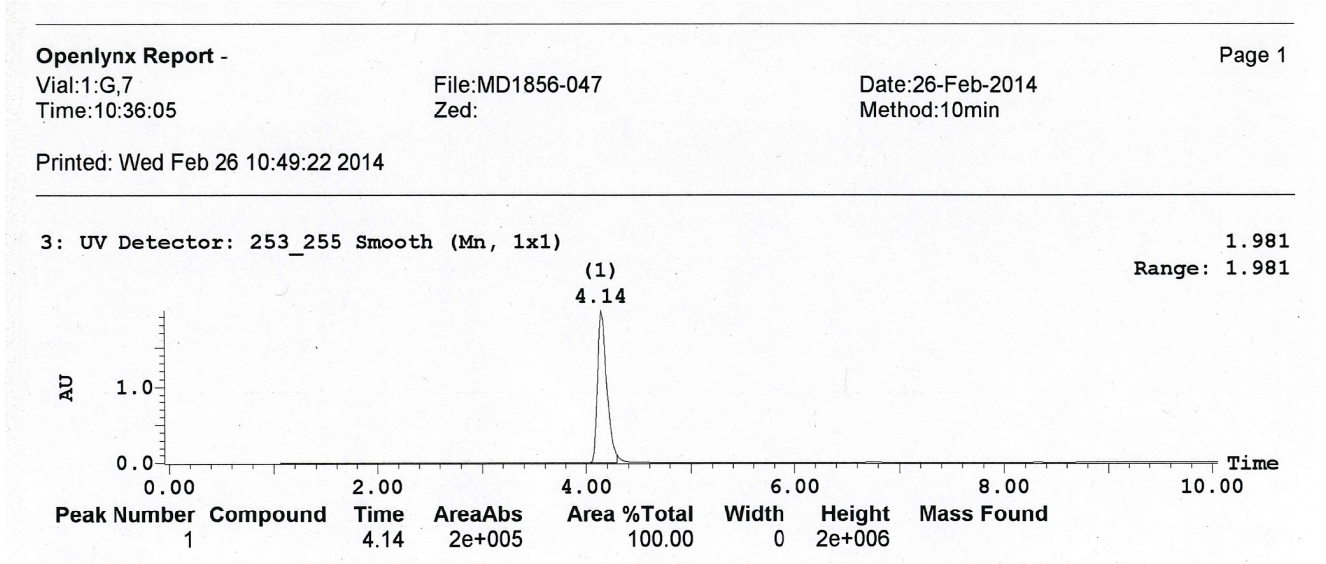
LC DATA FOR 1-(4'-((1,7-DIMETHYL-2'-PROPYL-1*H*,3'*H*-[2,5'-DIBENZO[*D*]IMIDAZOL]-3'-YL)METHYL-[1,1'-BIPHENYL-2-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6T



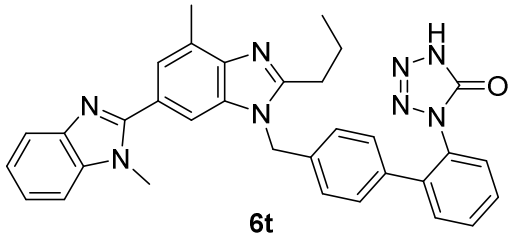
6t



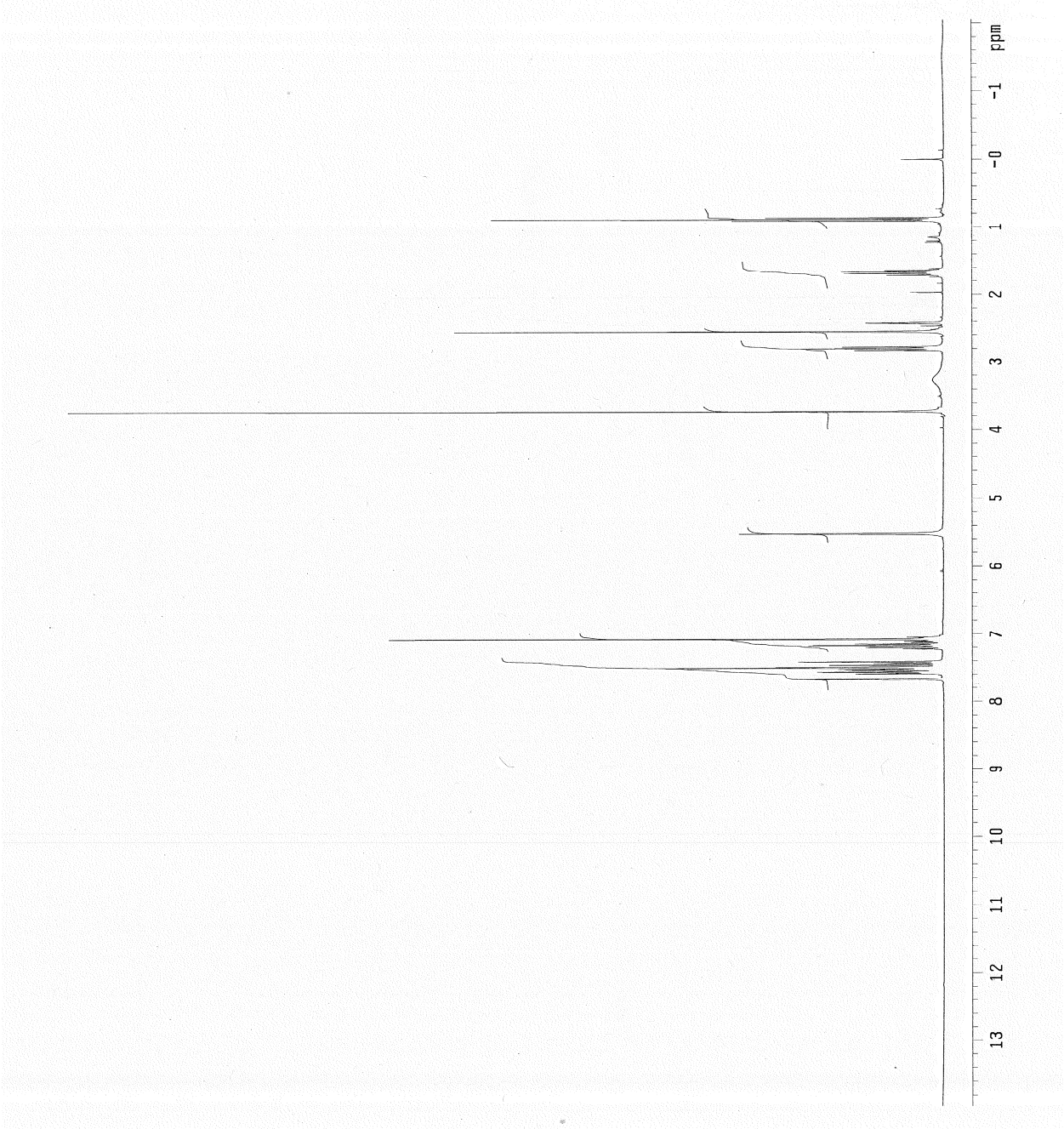
LC DATA FOR COMMERCIAL TELMISARTAN (AS A COMPARISON TO COMPOUND 6T ABOVE)



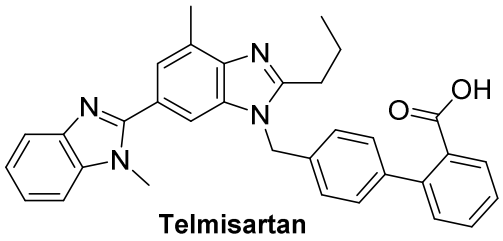
^{1}H NMR FOR 1-(4'-((1,7-DIMETHYL-2'-PROPYL-1*H*,3'*H*-[2,5'-DIBENZO[*D*]IMIDAZOL]-3'-YL)METHYL-[1,1'-BIPHENYL-2-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6T



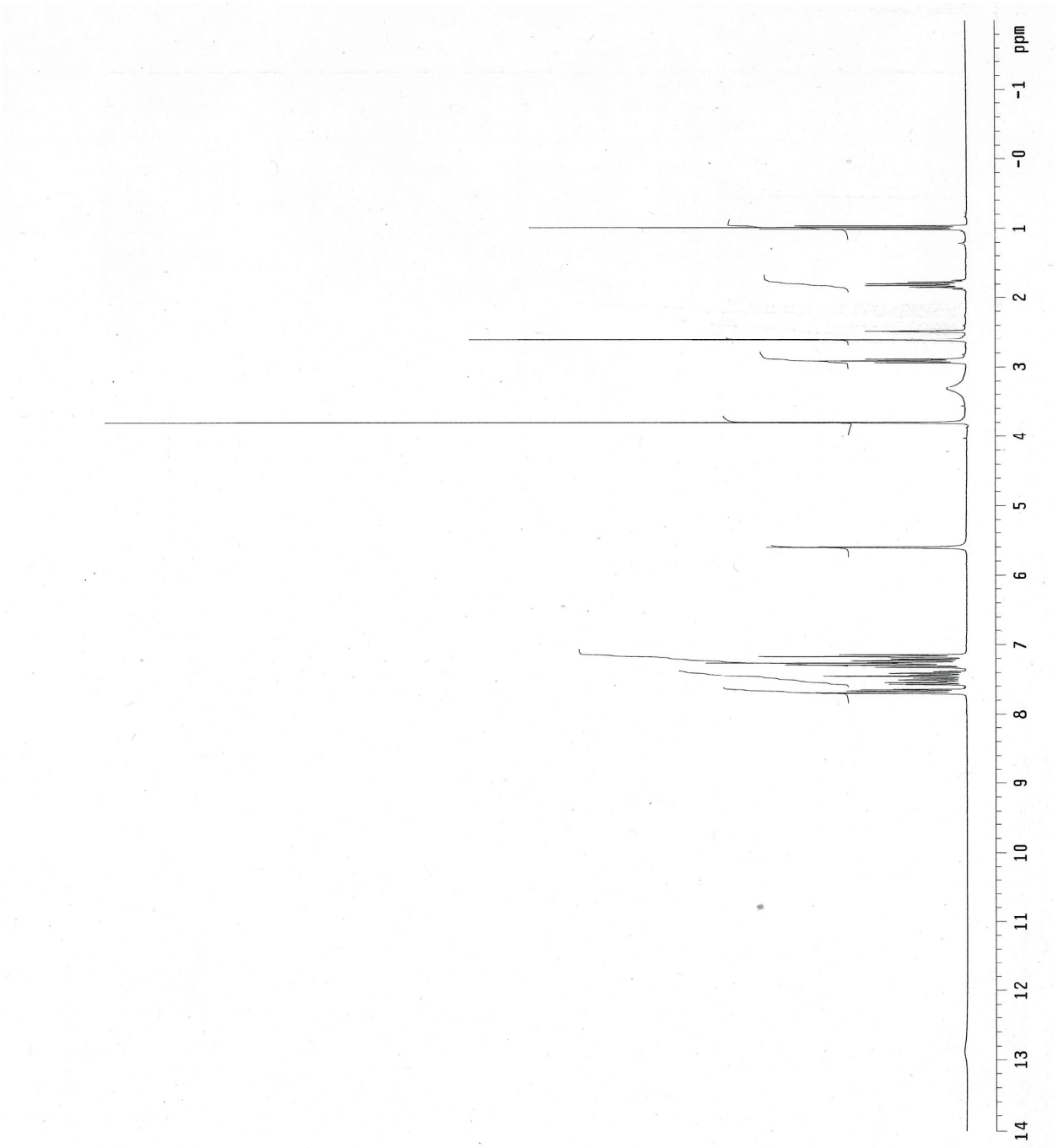
6t



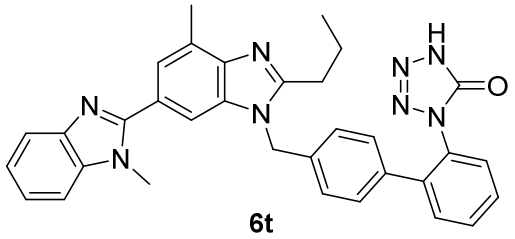
^{1}H NMR FOR COMMERCIAL TELMISARTAN (AS A COMPARISON TO COMPOUND 6T ABOVE)



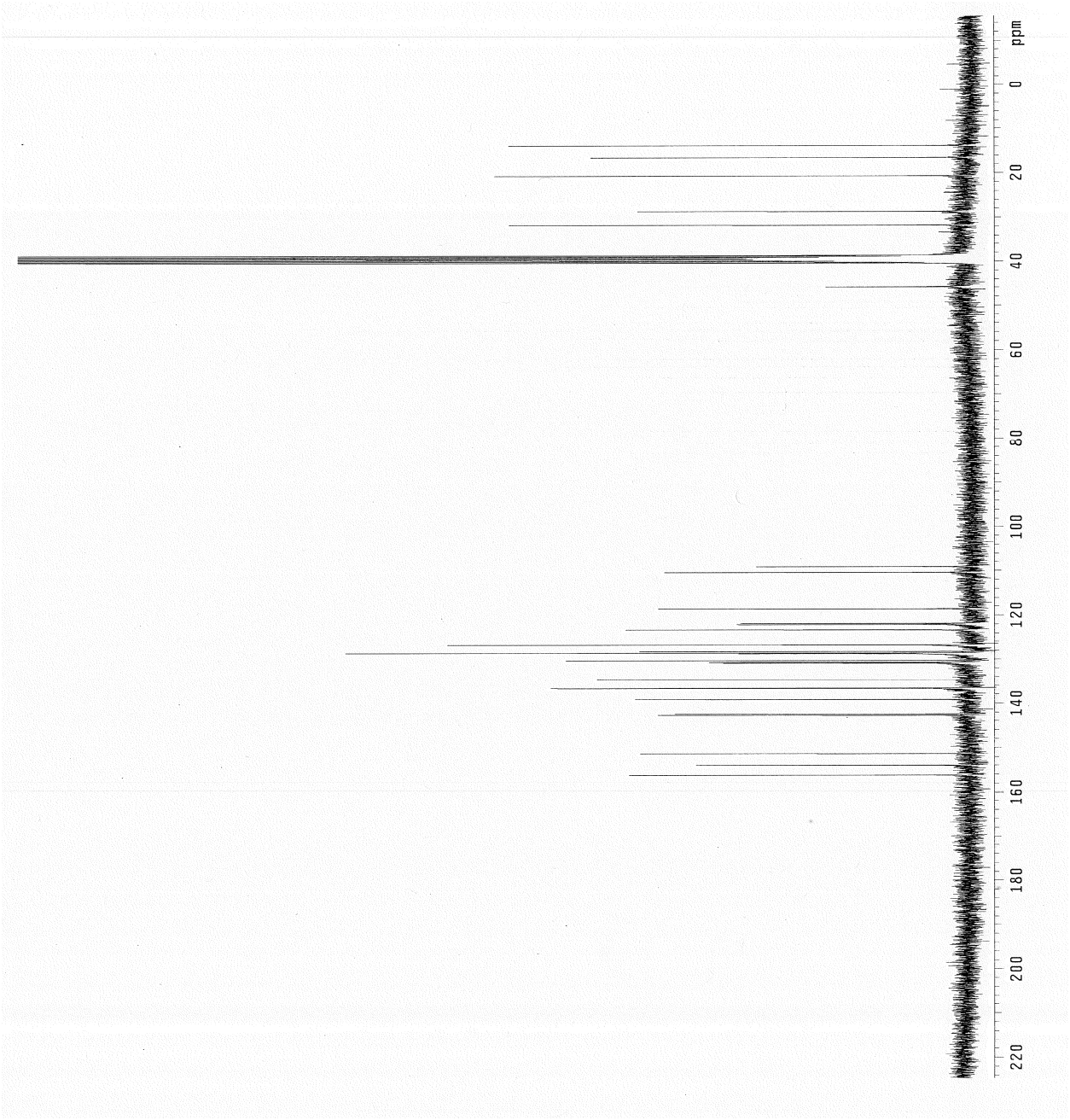
Telmisartan



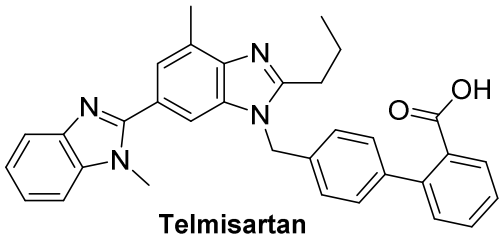
^{13}C NMR FOR 1-(4'-((1,7-DIMETHYL-2'-PROPYL-1*H*,3'*H*-[2,5'-DIBENZO[*D*]IMIDAZOL]-3'-YL)METHYL-[1,1'-BIPHENYL-2-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6T



6t

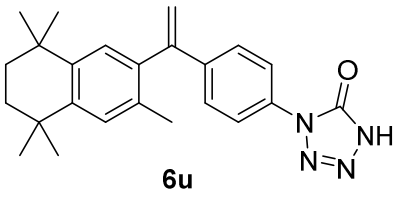


^{13}C NMR FOR COMMERCIAL TELMISARTAN (AS A COMPARISON TO COMPOUND 6T ABOVE)



Telmisartan

LC DATA FOR 1-(4-(1-(3,5,5,8,8-PENTAMETHYL-5,6,7,8-TETRAHYDRONAPHTHALEN-2-YL)VINYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6U



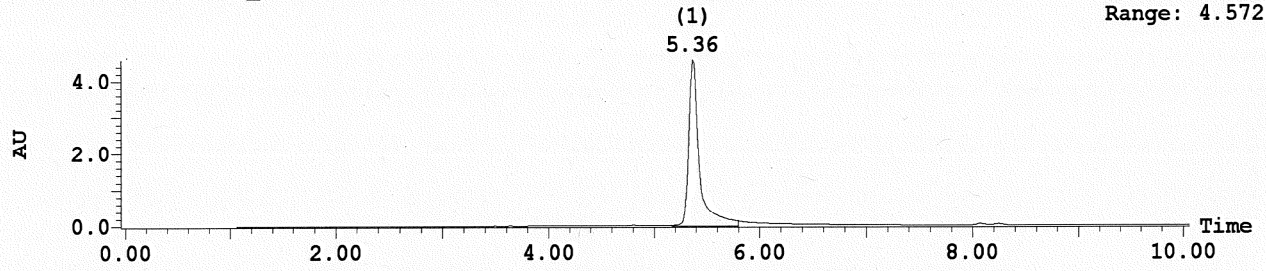
6u

Openlynx Report - Page 1

Vial:2:A,2 File:MD1856-097 Date:02-Jun-2014
Time:15:38:35 Zed: Method:10min_fast

Printed: Mon Jun 02 15:51:36 2014

3: UV Detector: 253_255 Smooth (Mn, 1x1) 4.573
Range: 4.572



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		5.36	5e+005	100.00	1	5e+006	

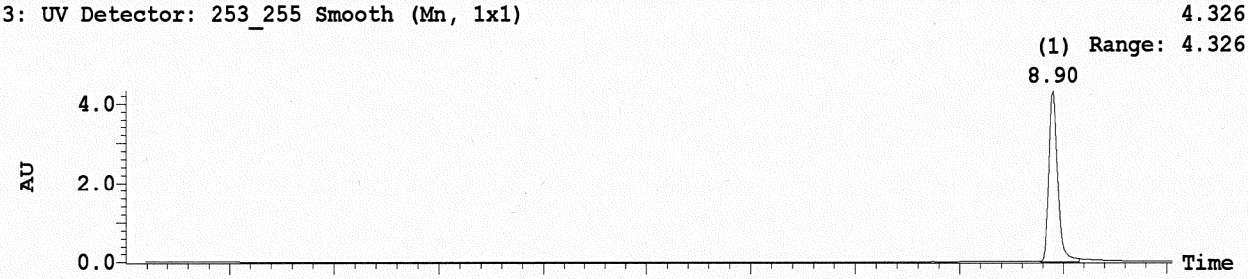
LC DATA FOR COMMERCIAL BEXAROTENE (AS A COMPARISON TO COMPOUND 6U ABOVE)

Openlynx Report - Page 1

Vial:2:B,3 File:MD1856-104 Bexarotene Date:13-Jun-2014
Time:15:42:16 Zed: Method:10min

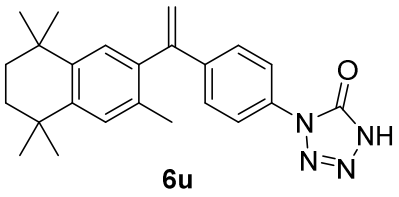
Printed: Fri Jun 13 15:55:34 2014

3: UV Detector: 253_255 Smooth (Mn, 1x1) 4.326
(1) Range: 4.326

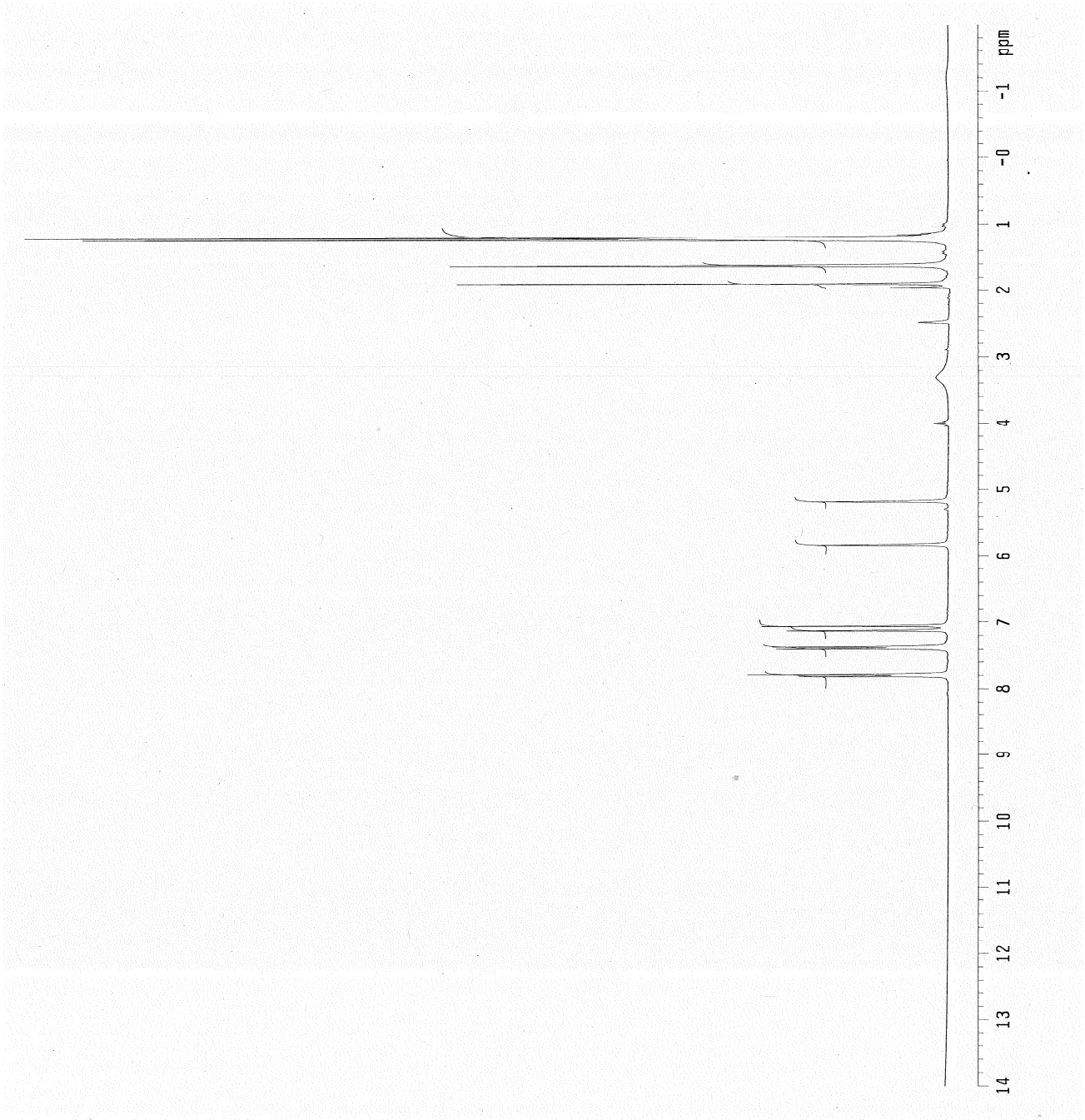


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		8.91	4e+005	100.00	0	4e+006	

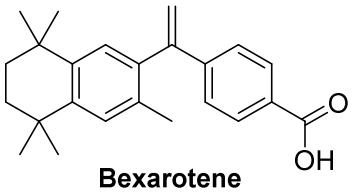
^{1}H NMR FOR 1-(4-(1-(3,5,5,8,8-PENTAMETHYL-5,6,7,8-TETRAHYDRONAPHTHALEN-2-YL)VINYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6U



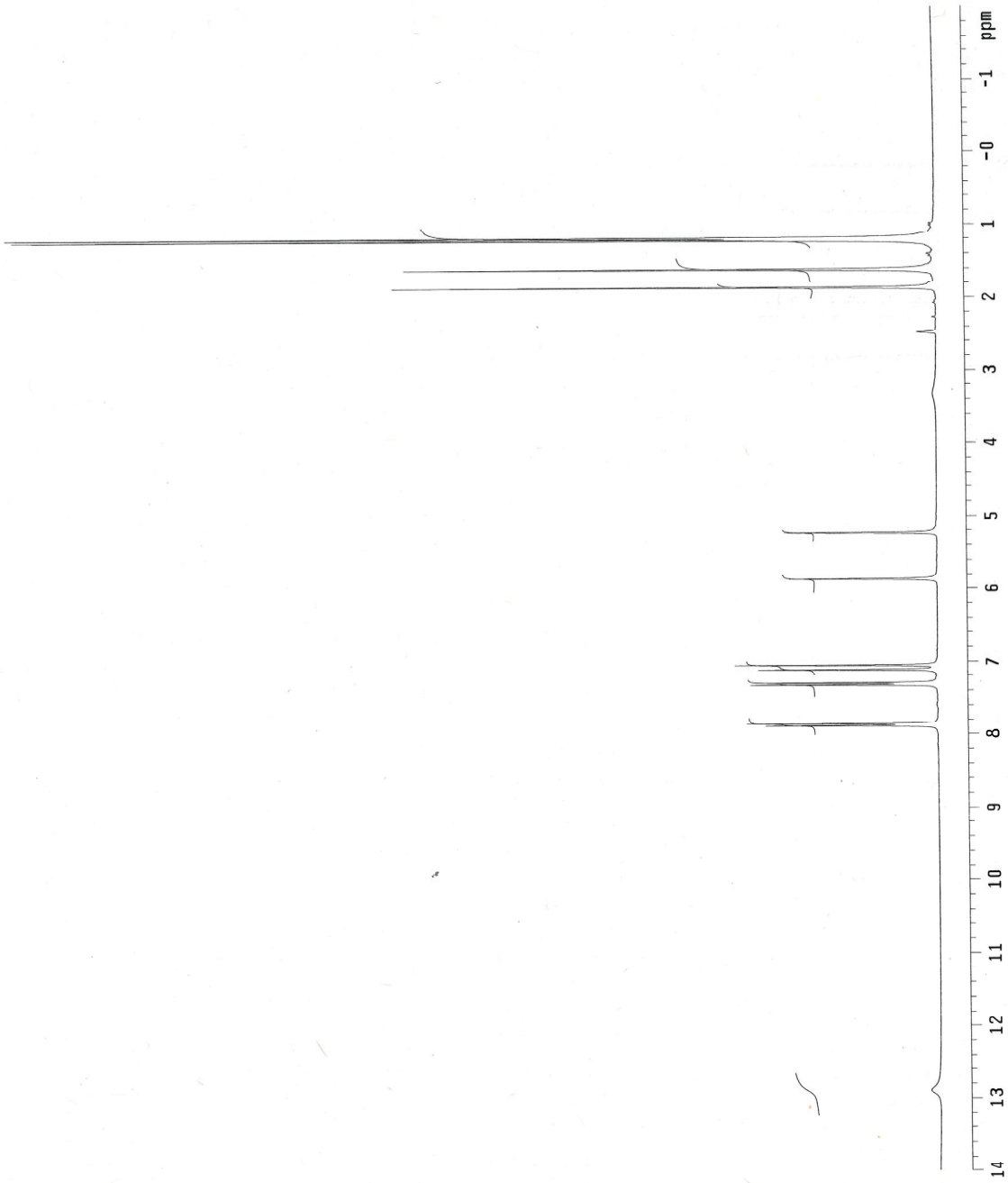
6u



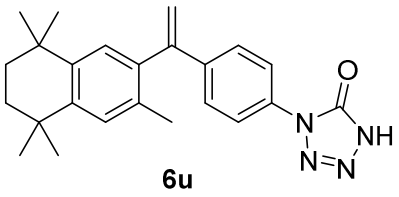
^{1}H NMR FOR COMMERCIAL BEXAROTENE (AS A COMPARISON TO COMPOUND 6U ABOVE)



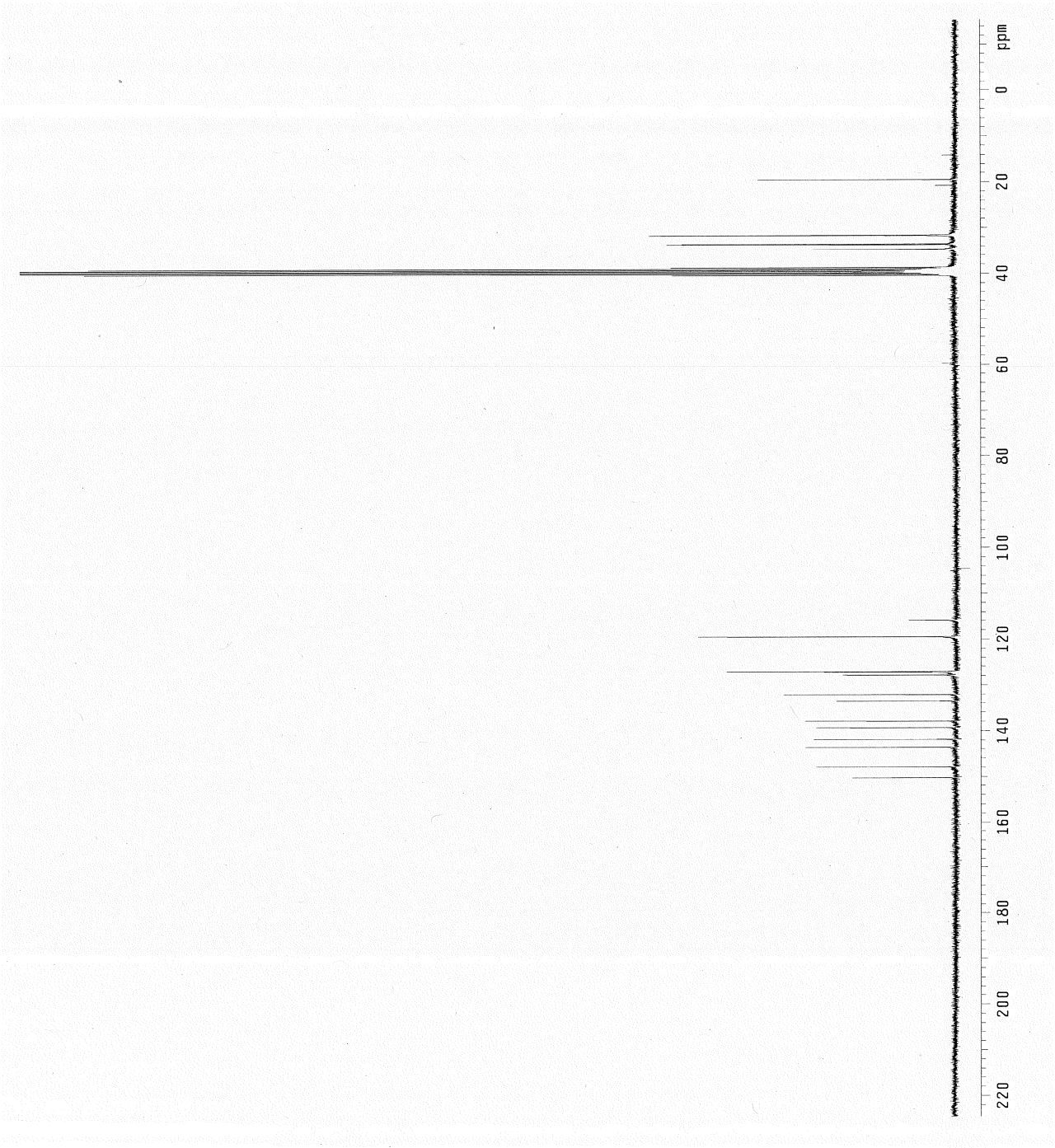
Bexarotene



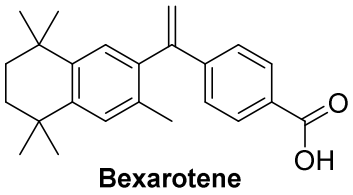
^{13}C NMR FOR 1-(4-(1-(3,5,5,8,8-PENTAMETHYL-5,6,7,8-TETRAHYDRONAPHTHALEN-2-YL)VINYL)PHENYL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6U



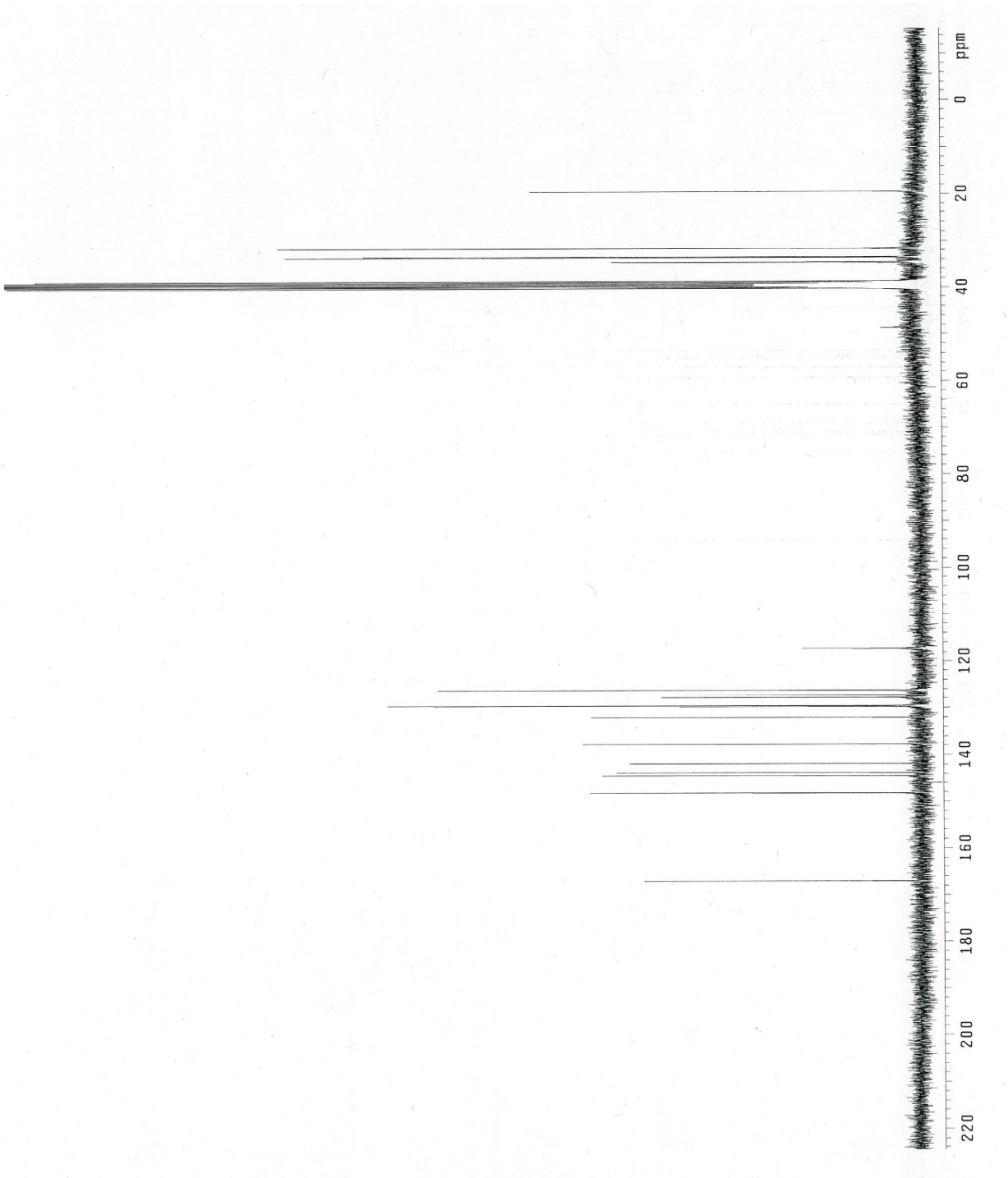
6u



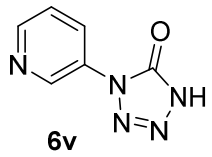
^{13}C NMR FOR COMMERCIAL BEXAROTENE (AS A COMPARISON TO COMPOUND 6U ABOVE)



Bexarotene



LC DATA FOR 1-(PYRIDIN-3-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6V



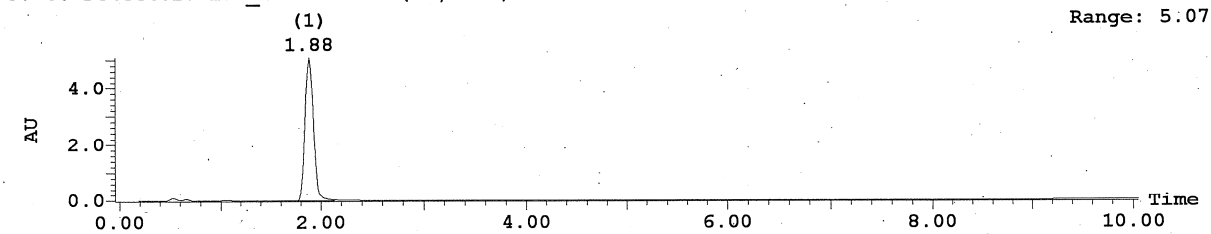
6v

Openlynx Report - Page 1

Vial:1:G,7 File:MD1740-172D Date:14-Aug-2013
Time:15:29:53 Zed: Method:10min

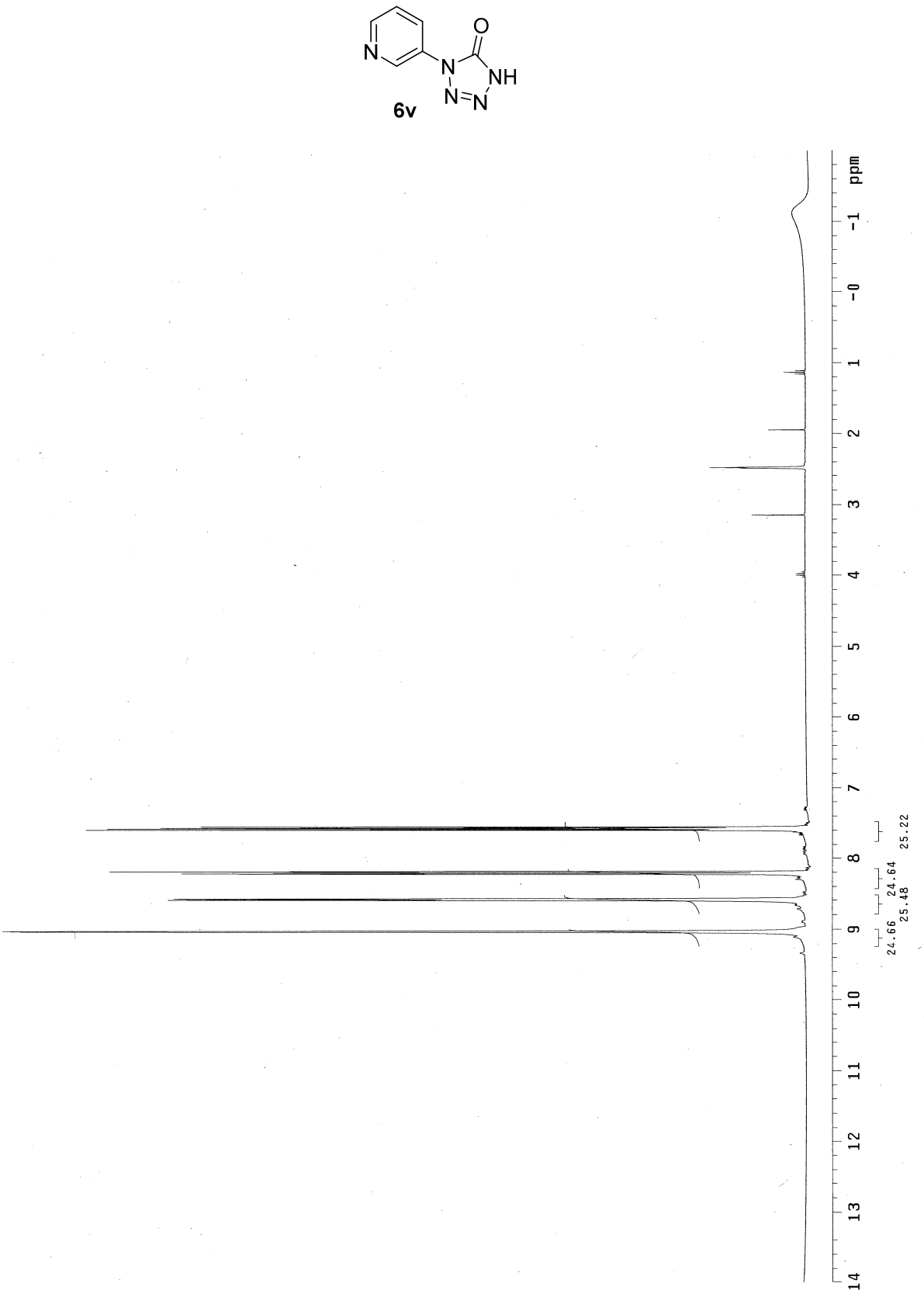
Printed: Wed Aug 14 15:41:16 2013

3: UV Detector: 253_255 Smooth (Mn, 1x1) 5.07
Range: 5.07

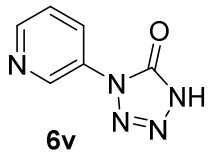


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		1.89	5e+005	100.00	0	5e+006	

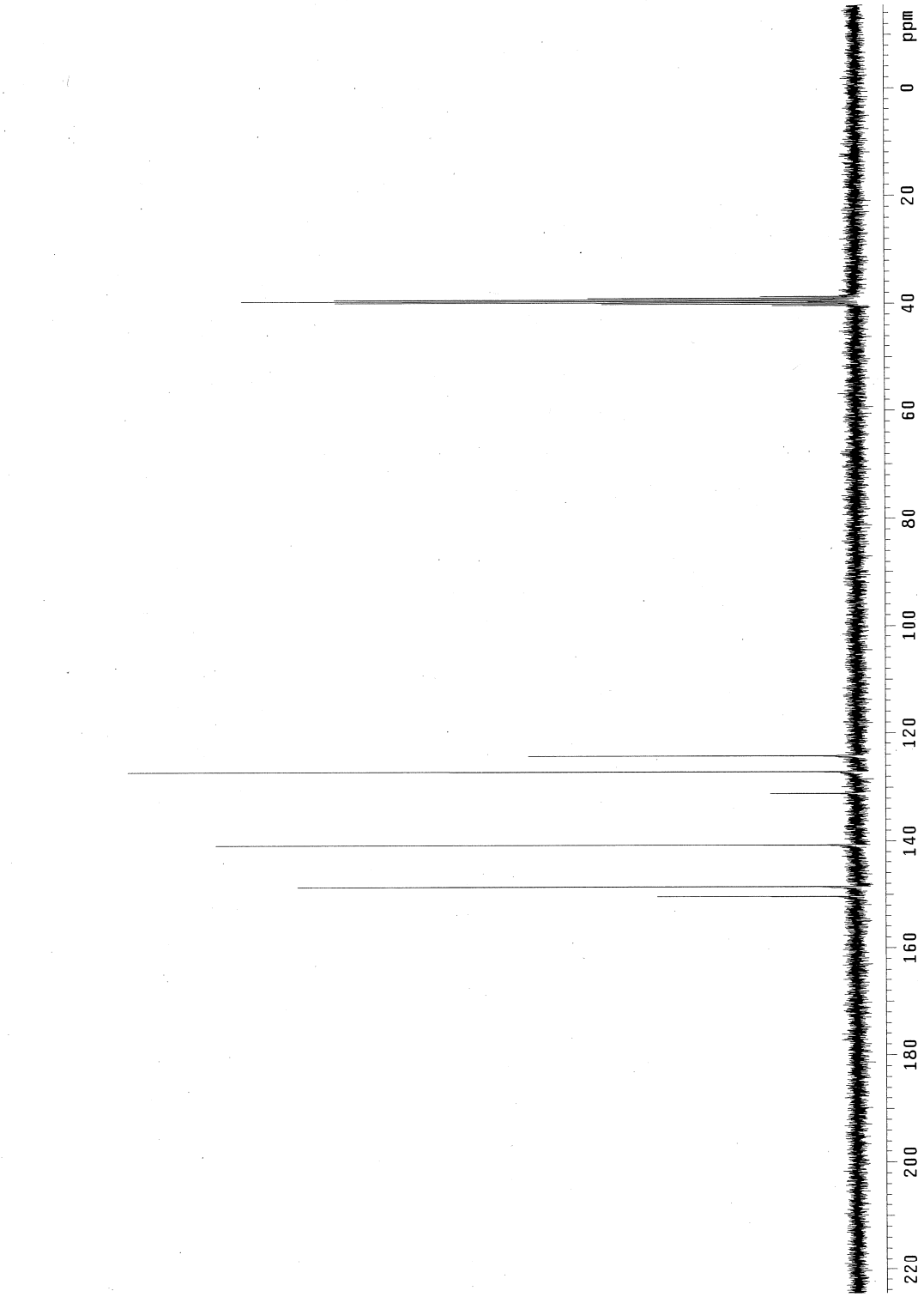
^{1}H NMR FOR 1-(PYRIDIN-3-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6V



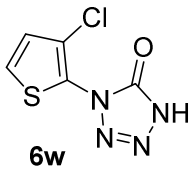
^{13}C NMR FOR 1-(PYRIDIN-3-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6V



6v



LC DATA FOR 1-(3-CHLOROTHIOPHEN-2-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6W

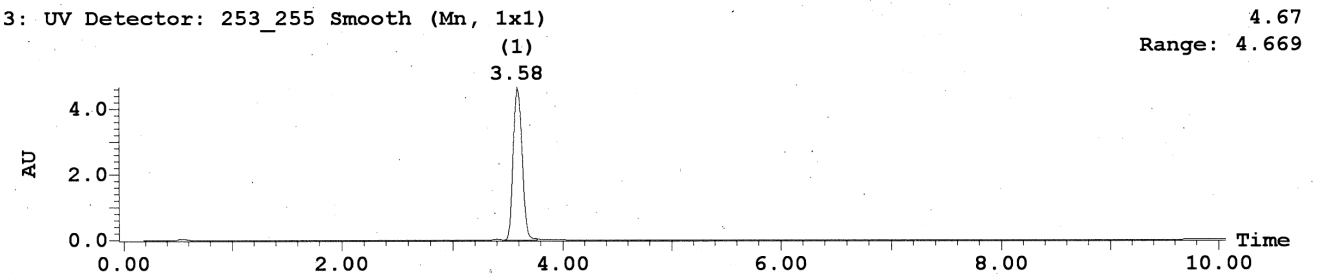


6w

Openlynx Report - Page 1

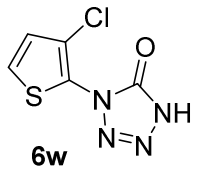
Vial:1:C,7 File:MD1740-177C Date:08-Aug-2013
Time:15:45:07 Zed: Method:10min

Printed: Thu Aug 08 15:57:13 2013

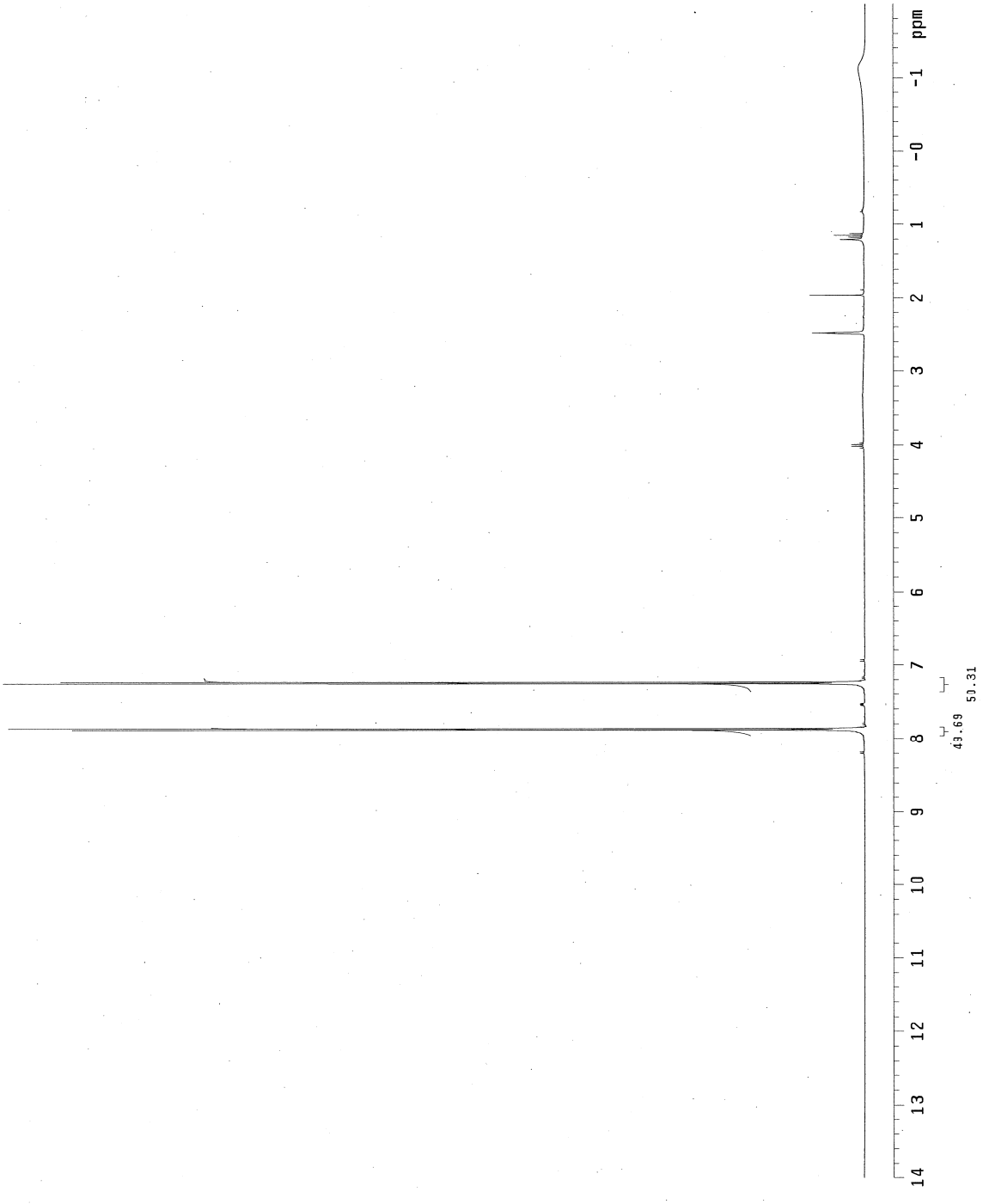


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		3.58	4e+005	100.00	0	5e+006	

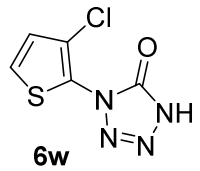
^{1}H NMR FOR 1-(3-CHLOROTHIOPHEN-2-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6W



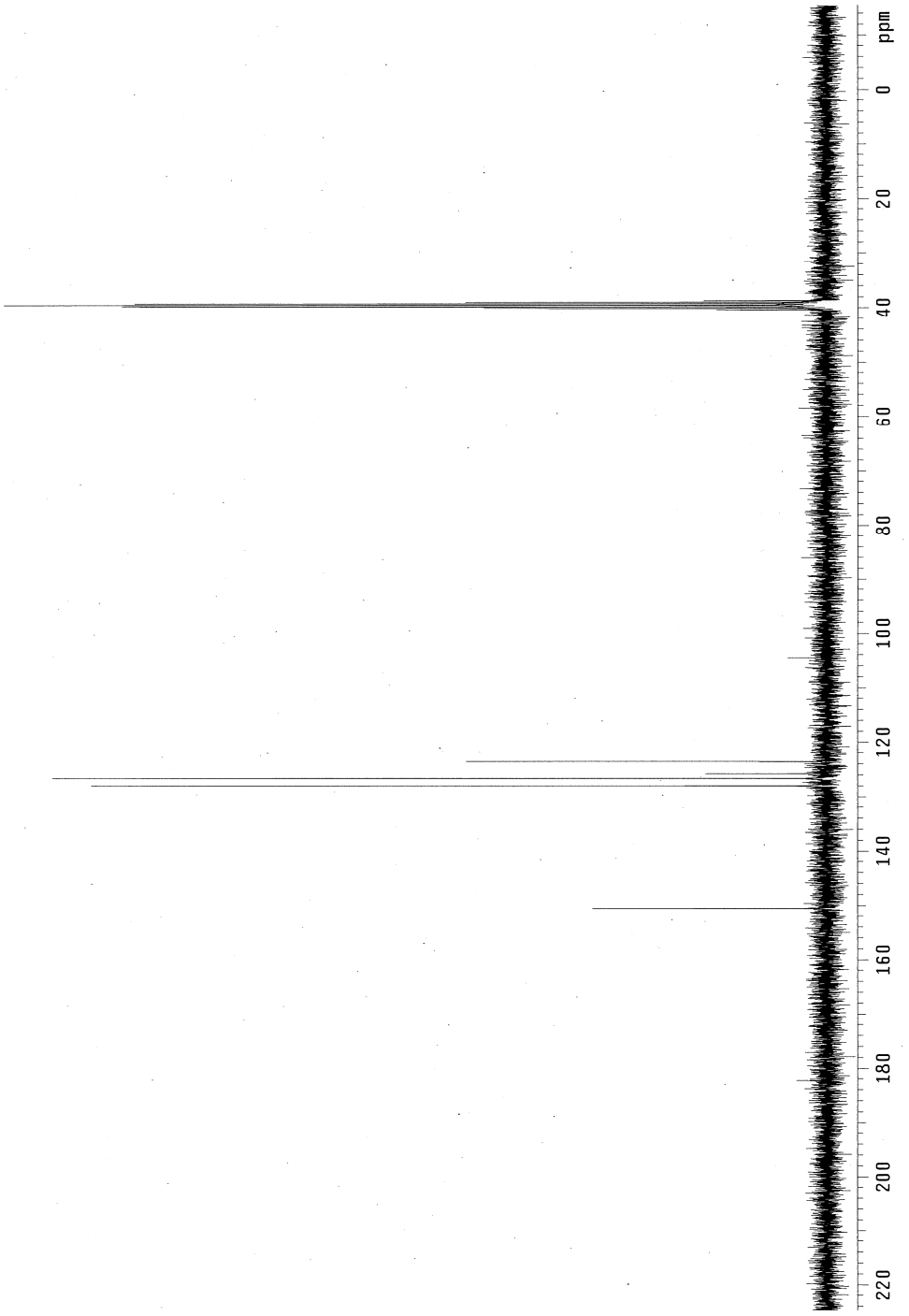
6w



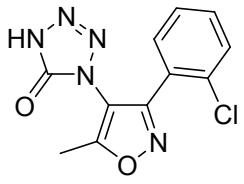
^{13}C NMR FOR 1-(3-CHLOROTHIOPHEN-2-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6W



6w



LC DATA FOR 1-(3-(2-CHLOROPHENYL)5-METHYLISOXAZOL-4-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6X

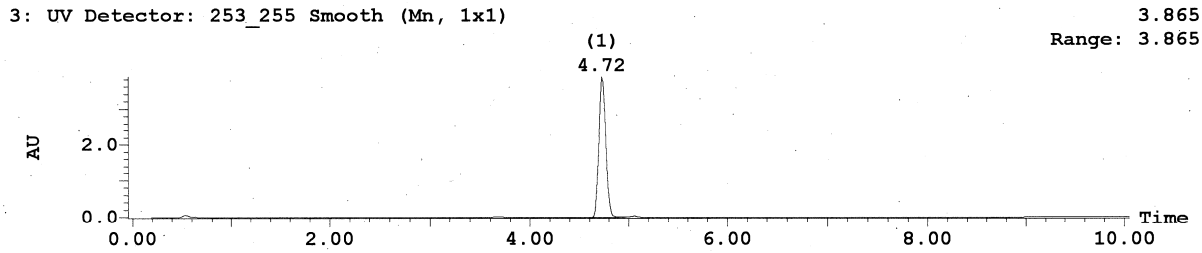


6x

Openlynx Report - Page 1

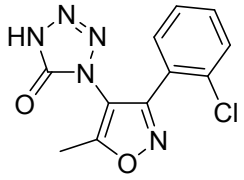
Vial:1:C,4 File:MD1740-177A Date:08-Aug-2013
Time:15:30:41 Zed: Method:10min

Printed: Thu Aug 08 15:43:46 2013

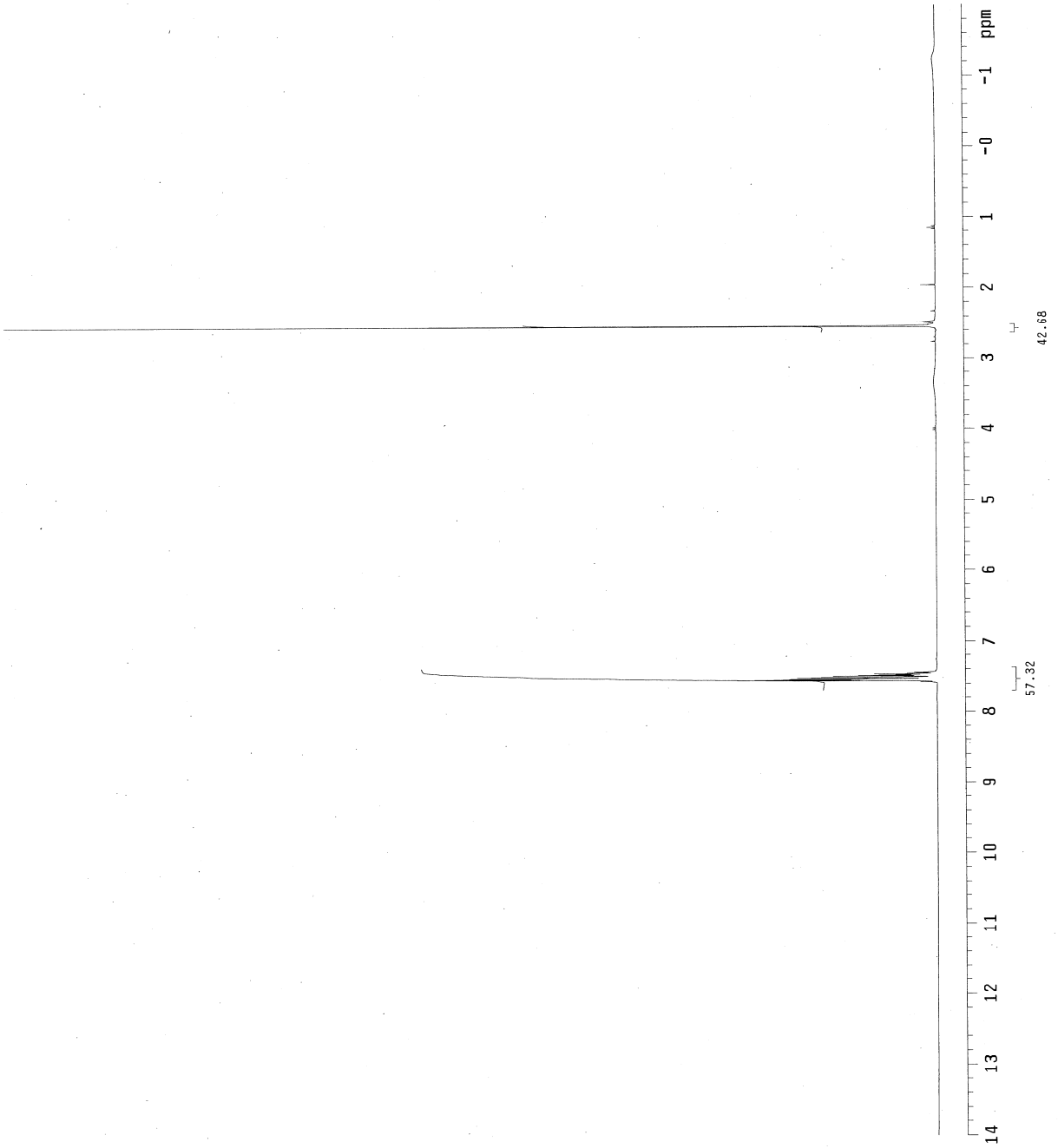


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		4.72	3e+005	100.00	0	4e+006	

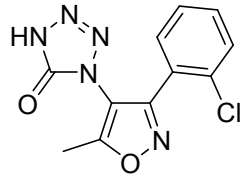
^{1}H NMR FOR 1-(3-(2-CHLOROPHENYL)5-METHYLISOXAZOL-4-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6X



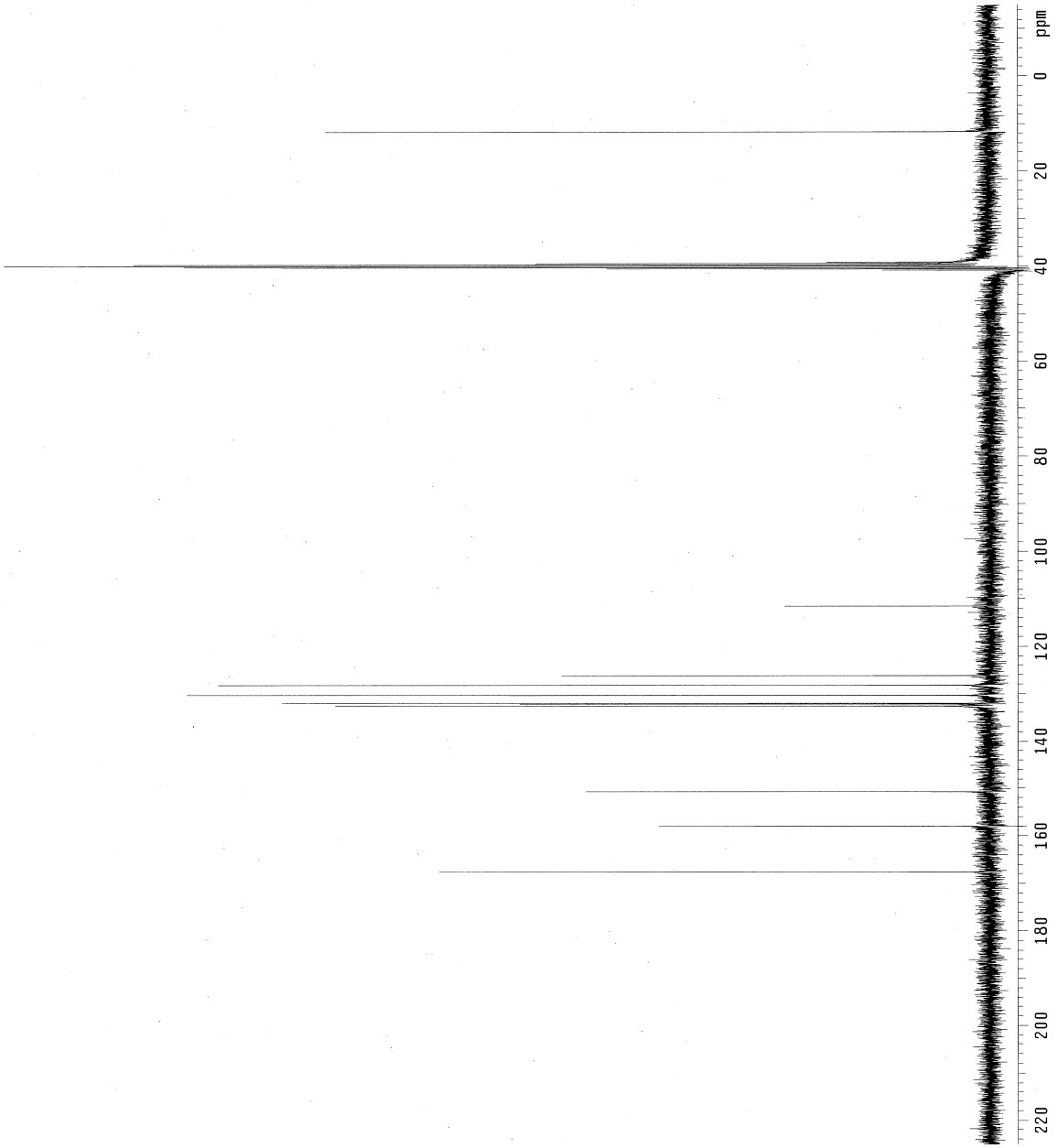
6x



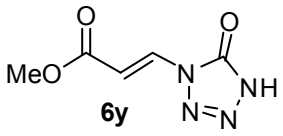
^{13}C NMR FOR 1-(3-(2-CHLOROPHENYL)5-METHYLISOXAZOL-4-YL)-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6X



6x



LC DATA FOR METHYL (*E*)-3-(5-OXO-4,5-DIHYDRO-1*H*-TETRAZOL-1-YL)ACRYLATE 6Y

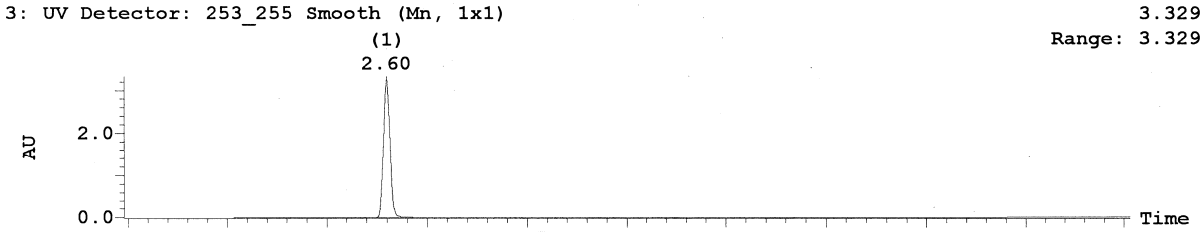


6y

Openlynx Report -

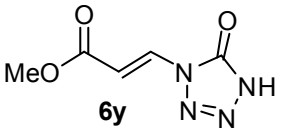
Vial:2:F,1 File:MD1856-017B Date:04-Nov-2013
Time:15:28:10 Zed: Method:10min

Printed: Mon Nov 04 15:41:14 2013

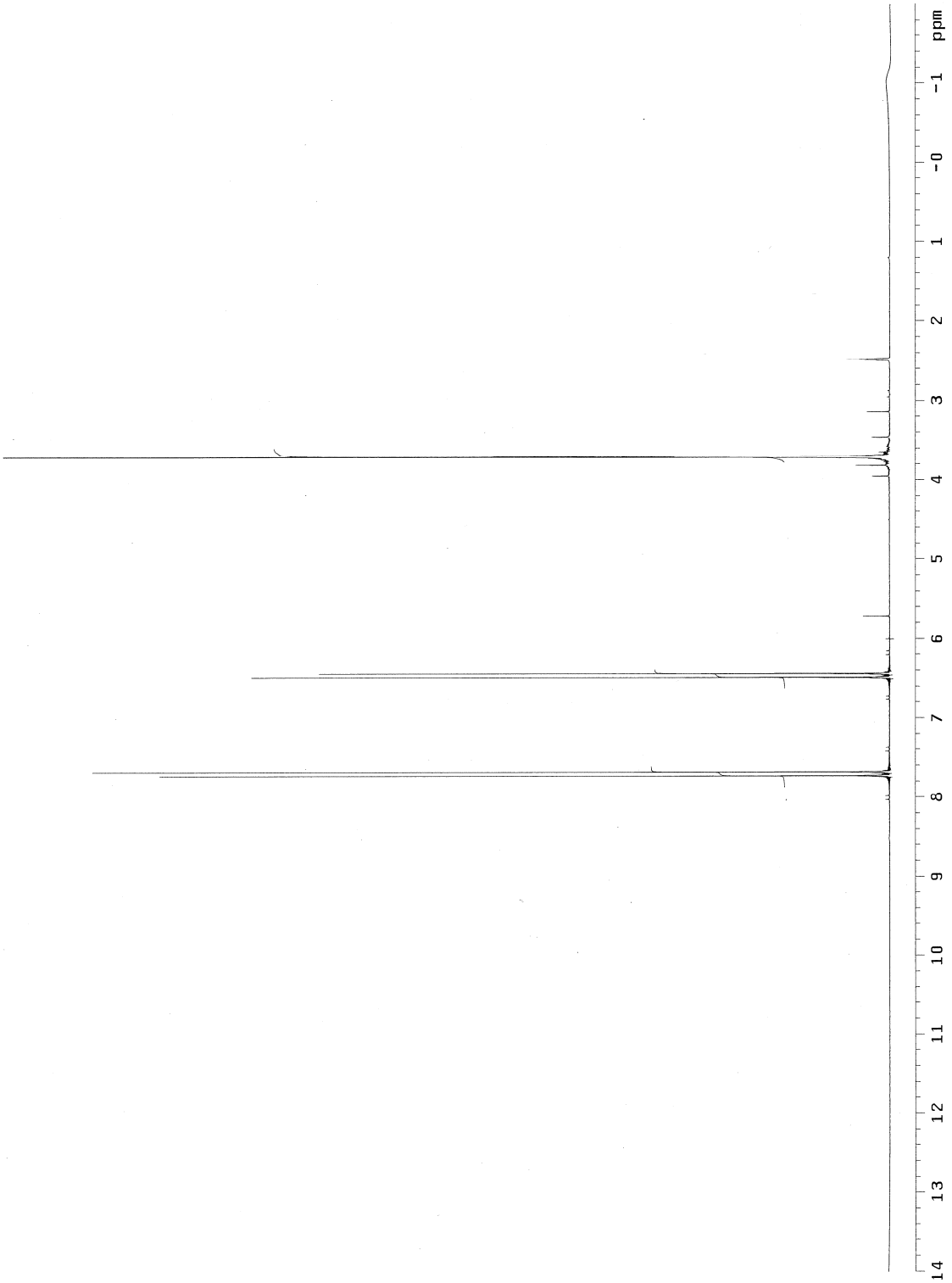


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		2.60	2e+005	100.00	0	3e+006	

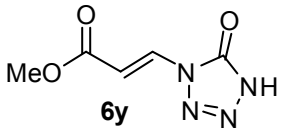
^{1}H NMR FOR METHYL (*E*)-3-(5-OXO-4,5-DIHYDRO-1*H*-TETRAZOL-1-YL)ACRYLATE 6W



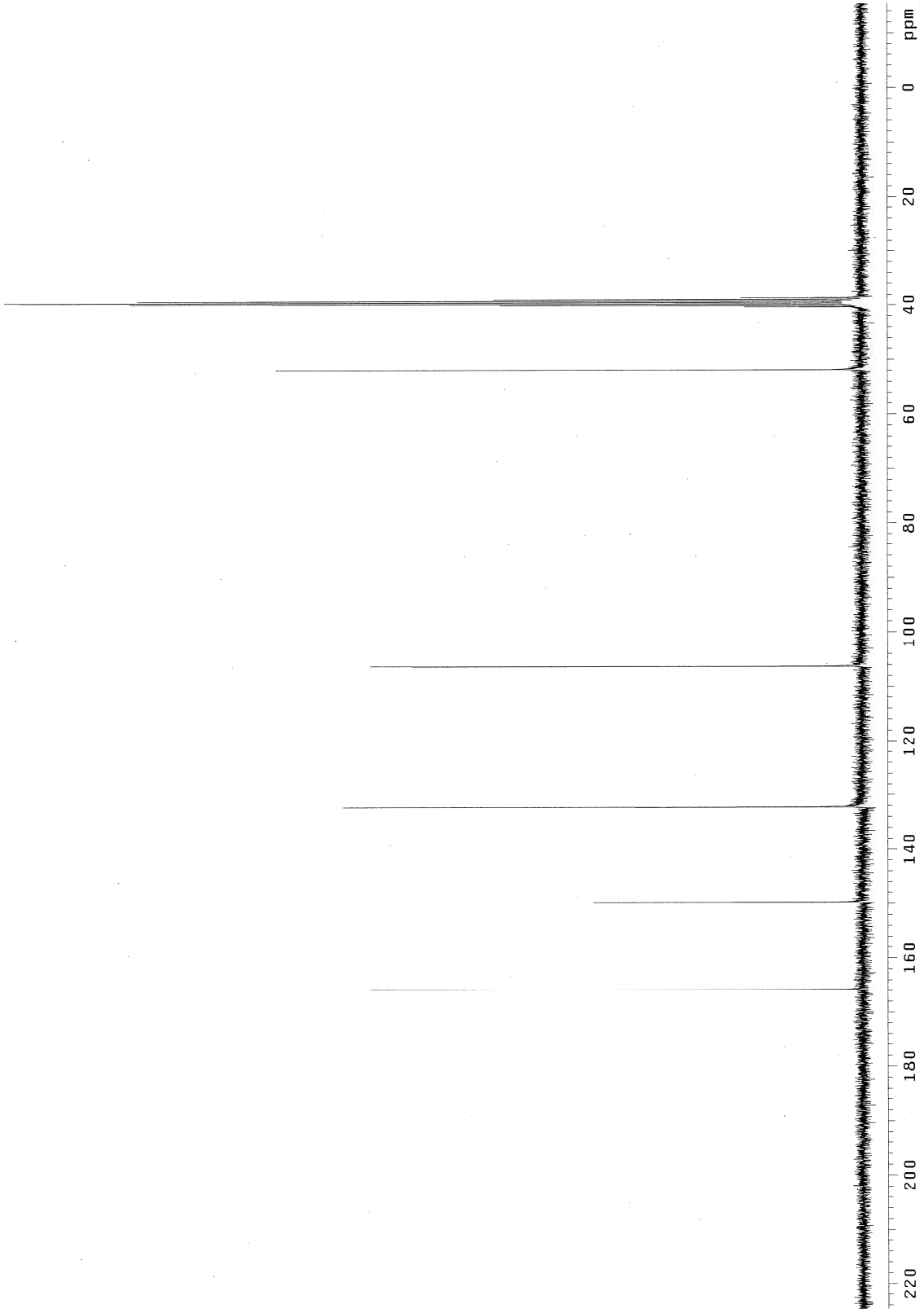
6y



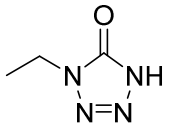
^{13}C NMR FOR METHYL (*E*)-3-(5-OXO-4,5-DIHYDRO-1*H*-TETRAZOL-1-YL)ACRYLATE 6W



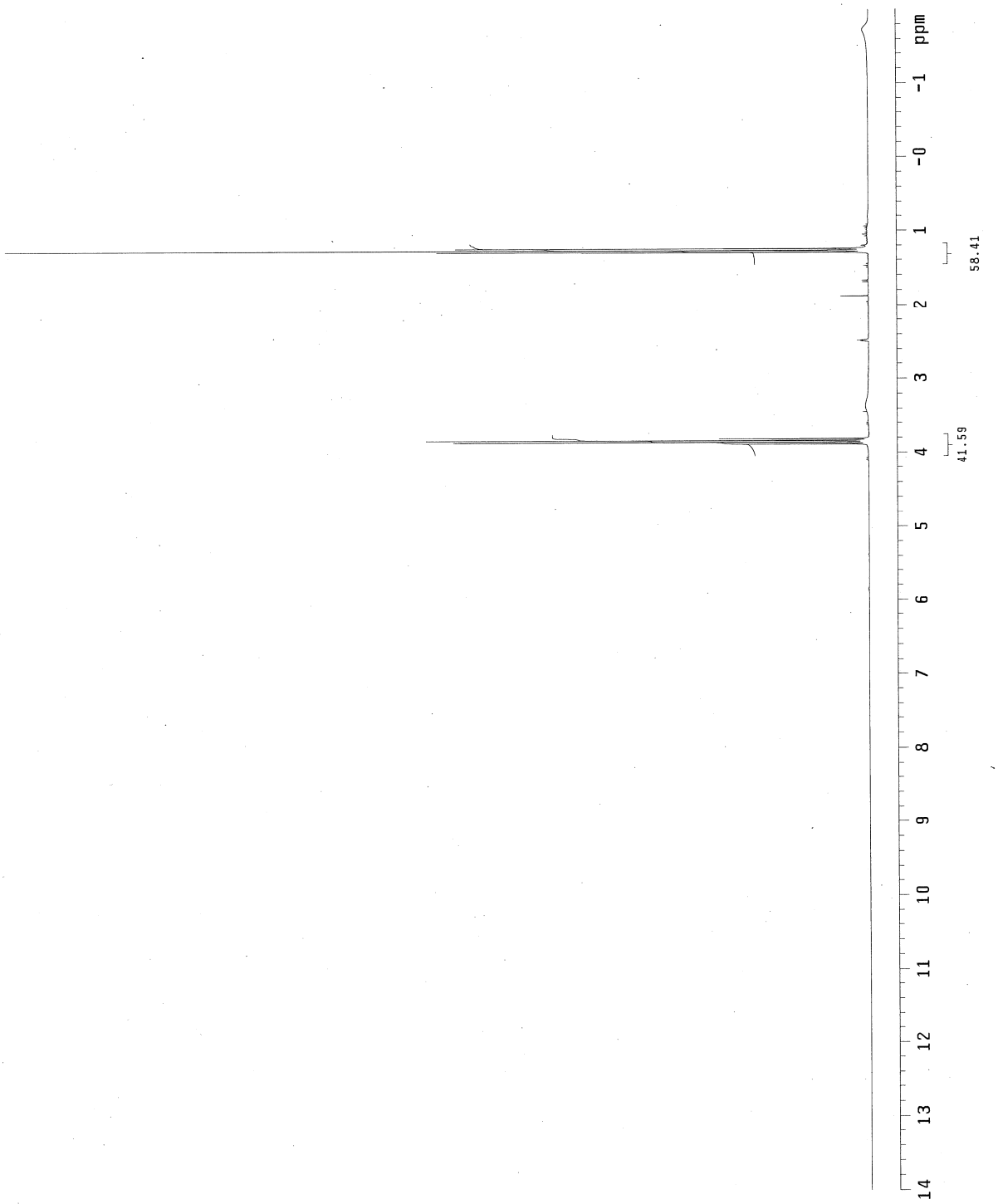
6y



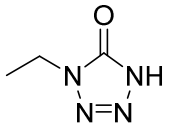
^{1}H NMR FOR 1-ETHYL-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6Z



6z



^{13}C NMR FOR 1-ETHYL-1,4-DIHYDRO-5*H*-TETRAZOL-5-ONE 6Z



6z