Supplementary information for

NHC Catalysed direct addition of HMF to diazo compounds: Synthesis of Acyl Hydrazones with antitumor activity

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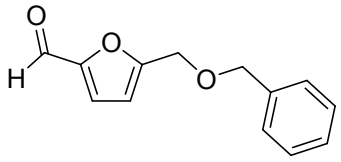
General Remarks

Synthesis

Dichloromethane (DCM), toluene, methanol and acetonitrile were freshly dried and distilled over calcium hydride, while THF was dried from sodium/benzophenone. All reactions were performed in oven-dried glassware under argon atmosphere. N-heterocyclic carbenes (NHCs) were prepared following reported procedures[1-3], with exception of 1-Mesityl-3,4-dimethyl-4H-1,2,4-triazolium tetrafluoroborate and (5*R*,6*S*)-2-Mesityl-5,6-diphenyl-6,8-dihydro-5H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium tetrafluoroborate which were purchased from Aldrich. All bases were acquired from Sigma-Aldrich and used without any previous purification with exception of potassium t-butoxide which was freshly sublimed before use. Diazo compounds were prepared according to procedures described in the literarure[4-9]. HMF[10] and 2,5-furan dicarbaldehyde[11] were prepared according to the literature procedures.
Preparative thin layer chromatography (TLC) plates were prepared with silica gel 60 GF254 MercK (Ref.1.07730.1000). Reaction mixtures were analysed by TLC using ALUGRAM® SIL G/UV254 from MN (Ref. 818133, silica gel 60), and visualisation of TLC spots was effected using ultraviolet (UV) and phosphomolybdic acid solution. Nuclear magnetic resonance (NMR) spectra were recorded in a Bruker AMX 400 and in a Bruker Avance II 300 using $CDCl_3$ and $(CD_3)_2SO$ as solvents and $(CH_3)_4Si$ (^1H) as internal standard. All coupling constants are expressed in Hz. Electrospray ionization (ESI) mass spectra were recorded in a mass spectrometer (Micromass Quattro Micro API, Waters, Ireland) with a Triple Quadrupole (TQ) and with an electrospray ion source operating in positive mode. Elemental analysis was S2 performed in a Flash 2000 CHNS-O analyzer (ThermoScientific, UK).

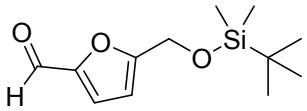
Synthesis of HMF protected derivatives

5-(Benzyloxy)methyl)furan-2-carbaldehyde



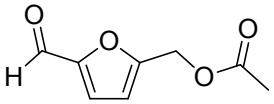
Benzyl bromide (3.8 g, 22.2 mmol) and silver oxide (2.6 g, 11.1 mmol) were successively added to a stirred solution of HMF (1.4 g, 11.1 mmol) dissolved in DMF (15 mL). The mixture was stirred for 50 h at RT. The solution was evaporated under reduced pressure and the residue was chromatographed (silica; hexane-EtOAc, 1:1) to give the desired product (1.2 g, 50 % yield).
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.9 Hz, 3H), 1.27-1.31 (m, 4H), 1.63 (quint, J = 7.4 Hz, 2H), 2.35 (t, J = 7.6, 2H), 5.12 (s, 2H), 6.58 (d, J = 3.55 Hz, 1H), 7.21 (d, J = 3.55 Hz, 1H), 9.63 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 64.2, 73.0, 111.4, 122.0, 128.0, 128.1, 128.6, 137.3, 152.7, 158.5, 177.8.The NMR spectra are in good accordance with the literature.[12]

5-(tert-Butyldimethylsilyl)oxy)methyl)furan-2-carbaldehyde



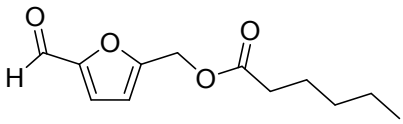
To a solution of HMF (1.6 g, 12.7 mmol) in DMF (3.2 mL) were added imidazole (2.2 g, 31.7 mmol, 2.5 equiv.) and *tert*-butyldimethylsilyl chloride (2.3 g, 15.2 mmol, 1.2 equiv.). The solution was stirred for 22 h. The silylated compound was extracted with hexane (5 x 20 mL). The collected organic layers were washed with brine, dried over Na_2SO_4, and the solvent removed to give the crude product that was distillated (100ºC/0.8 mbar) giving the product (1.9 g, 63 % yield) as a light yellow liquid that solidifies in the freezer (0ºC).
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.89 (s, 9H), 4.71 (s, 2H), 6.45 (d, J = 3.53 Hz, 1H), 7.19 (d, J = 3.53 Hz, 1H), 9.56 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ -5.3, 18.4, 25.8, 57.9, 58.7, 109.5, 122.6, 152.3, 161.5, 175.6.The NMR spectra are in good accordance with the literature.[13]

(5-Formylfuran-2-yl)methyl acetate



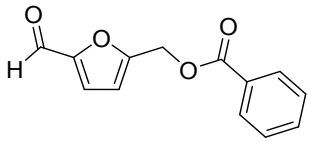
To a flame dried round-bottom flask, HMF (3.5 g, 27.8 mmol), MeCN (50 mL) and acetic anhydride (4.3 mL, 45.6 mmol) were added followed by catalytic amount of pyridine (0.5 mL, 6.2 mmol). The reaction mixture was allowed to stir at room temperature for 22h under argon atmosphere. The solvent was removed and the product purified by column chromatography with silica gel (hexane/ethyl acetate 8:2) to give the product (4.3 g, 93% yield) as a pale yellow oil that crystallized in the freezer (0ºC).
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.11 (s, 3H), 5.12 (s, 2H), 6.58 (d, J = 3.55 Hz, 1H), 7.21 (d, J = 3.55 Hz, 1H), 9.64 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.8, 57.9, 112.7, 121.8, 153.0, 160.8, 155.6, 170.5, 178.0.The NMR spectra are in good accordance with the literature.[12]

(5-Formylfuran-2-yl)methyl hexanoate



To a flame dried round-bottom flask, HMF (0.250 g, 1.98 mmol), MeCN (10 mL) and hexanoic anhydride (0.51 mL, 2.2 mmol, 1.1 equiv.) were added followed by catalytic amount of pyridine (32 µL, 0.4 mmol, 0.2 equiv.). The reaction mixture was allowed to stir at room temperature for 66 h under argon atmosphere. The mixture was quenched with cold water, acidified with HCl 1M and extracted with Et_2O. The combined organic layers were dried over MgSO4, filtered and the solvent removed to give the crude product that was purified by column chromatography with silica gel (hexane/ethyl acetate 8:2) to give the product (0.315 g, 71% yield) as a pale yellow oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.9 Hz, 3H), 1.27-1.31 (m, 4H), 1.63 (quint, J = 7.4 Hz, 2H), 2.35 (t, J = 7.6, 2H), 5.12 (s, 2H), 6.58 (d, J = 3.55 Hz, 1H), 7.21 (d, J = 3.55 Hz, 1H), 9.63 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.0, 22.4, 24.6, 31.3, 34.06, 57.8, 112.6, 121.9, 152.9, 155.8, 173.3, 178.0.The NMR spectra are in good accordance with the literature.[14]

(5-Formylfuran-2-yl)methyl benzoate



To a flame dried round-bottom flask, HMF (1.0 g, 7.9 mmol) and pyridine (4 mL) were added followed by benzoyl chloride (1 mL, 8.7 mmol, 1.1 equiv.). The reaction mixture was allowed to stir at reflux for 1.5 h under argon atmosphere. The mixture was quenched with cold water (50 mL), acidified with HCl 1M and extracted with Et_2O. The combined organic layers were dried over MgSO4, filtered and the solvent removed to give the crude product that was recrystallized from Et_2O/hexane as a pale orange solid (0.86 g, 47% yield).
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (s, 2H), 6.68 (d, J = 3.55 Hz, 1H), 7.24 (d, J = 3.55 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 7.58 (tt, J = 7.45, 1.30 Hz, 1H), 8.06 (m, 2H), 9.65 (s, 1H).The NMR spectra are in good accordance with the literature.[15]

Synthetic procedures

Optimization of the reaction conditions Table 1

NHC precursor (x mol %) and base (x mol %) were dissolved in freshly dry solvent (0.5 mL) inside a round bottom flask under argon. The mixture was stirred for 10 minutes at room temperature. Then a solution of diazo compound (0.24 mmol in 0.5 mL of solvent) was added. Immediately after, HMF (x eq. in 0.5 mL of solvent) was slowly added over the specified amount of time. The mixture was left reacting until most of diazo compound was consumed, usually 16 hours. The final product, N-Acylhydrazone, was isolated by preparative thin layer chromatography (eluent: Hexane/Ethyl acetate).

Substrate scope Table 2 and scheme 2

NHC precursor **4** (20 mol %) and DBU (40 mol %) were dissolved in freshly dry DCM (0.5 mL) inside a round bottom flask under argon. The mixture was stirred for 10 minutes at room temperature. Then a solution of diazo compound (0.24 mmol in 0.5 mL of DCM) was added. Immediately after, HMF (1.2 eq., 40 mg in 0.5 mL of DCM) (or protected HMF) was slowly added over two hours. The mixture was left reacting until most of diazo

compound was consumed, usually 16 hours. The final product, N-Acylhydrazone, was isolated by flash chromatography (eluent: Hexane/Ethyl acetate).

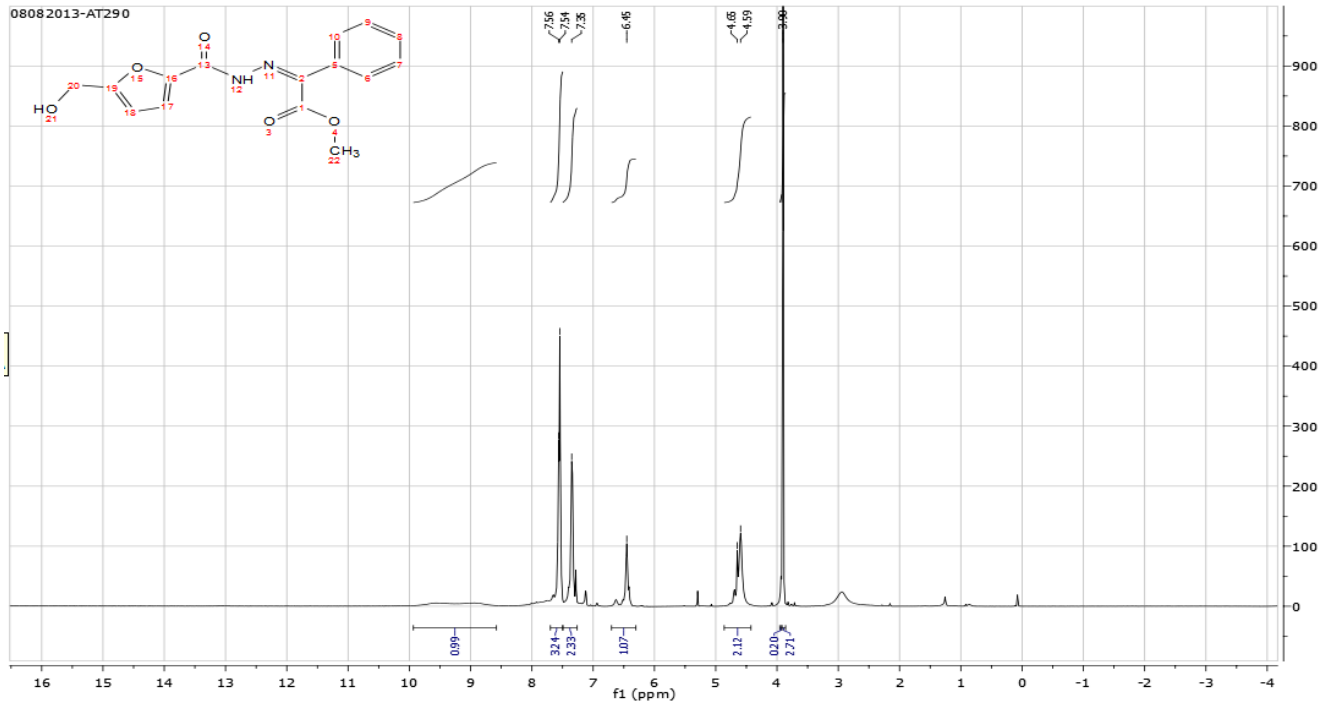
N-acyl hydrazones characterization

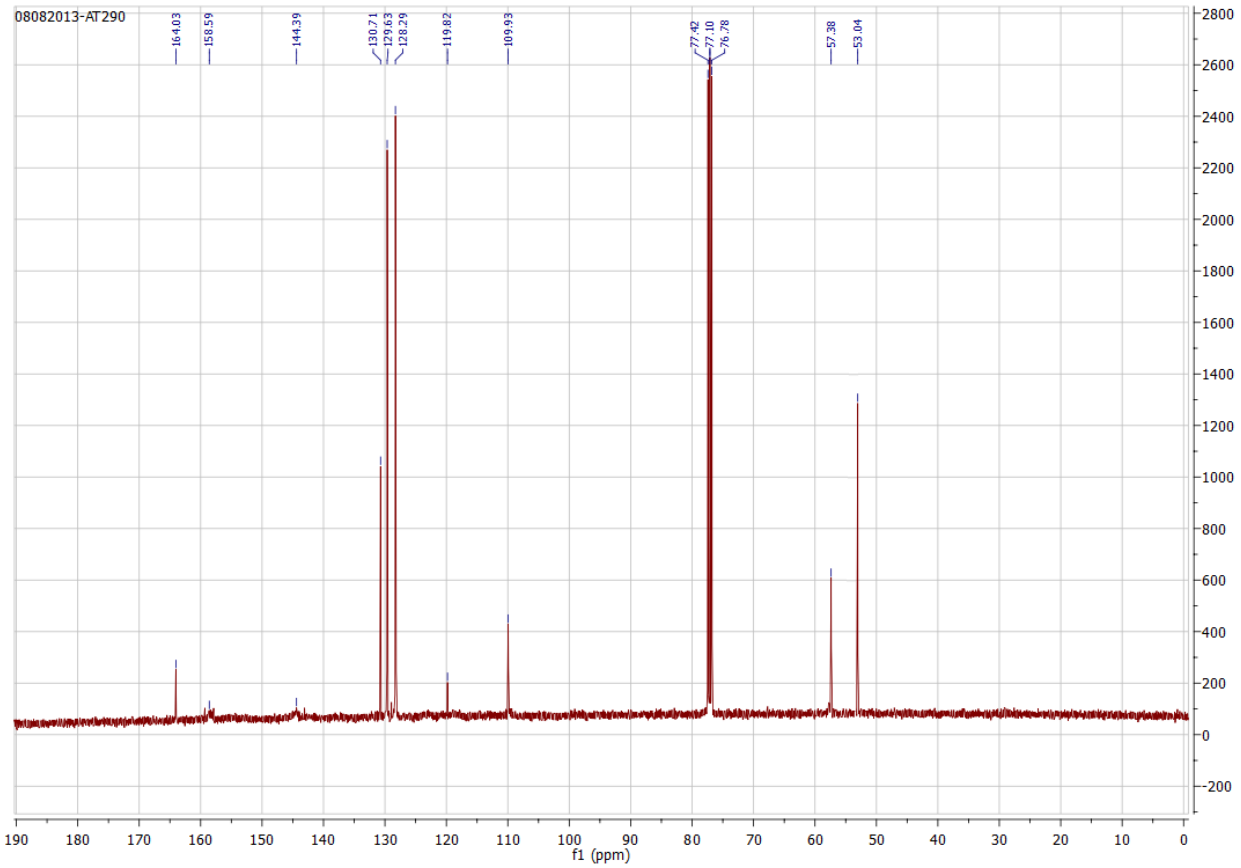
Methyl 2-(2-(5-(hydroxymethyl)furan-2-carbonyl)hydrazono)-2-phenylacetate3

Isolated as a slightly yellow powder (60 mg, 80 % yield), an inseparable mixture of geometric isomersisomer ratio 1/9.The broadening of N-H does not allow the determination which isomer is the major.

^{1}H NMR (400 MHz, $CDCl_3$) δ10.0-8.5 (broad signal, N-H), 7.56-7.34 (6H, m, protons 6-10 and 18), 6.45 (1H, m, proton 17), 4.65-4.59 (2H, m, protons 20), 3.90 (3H, s, protons 22). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.03 (C1), 158.59 (C19), 144.39 (C16), 130.71 (C8), 129.63 (C6 and C10), 128.29 (C7 and C9), 119.82 (C17), 109.93 (C18), 57.38 (C21), 53.04 (C22).

Elementar analysis for $(C_{15}H_{14}N_2O_5)_3H_2O$ calc. %C 58,44; %H 4,79; %N 9,09 found %C 58,41; %H 4,45; %N 8,84.

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130.71
129.63
128.29
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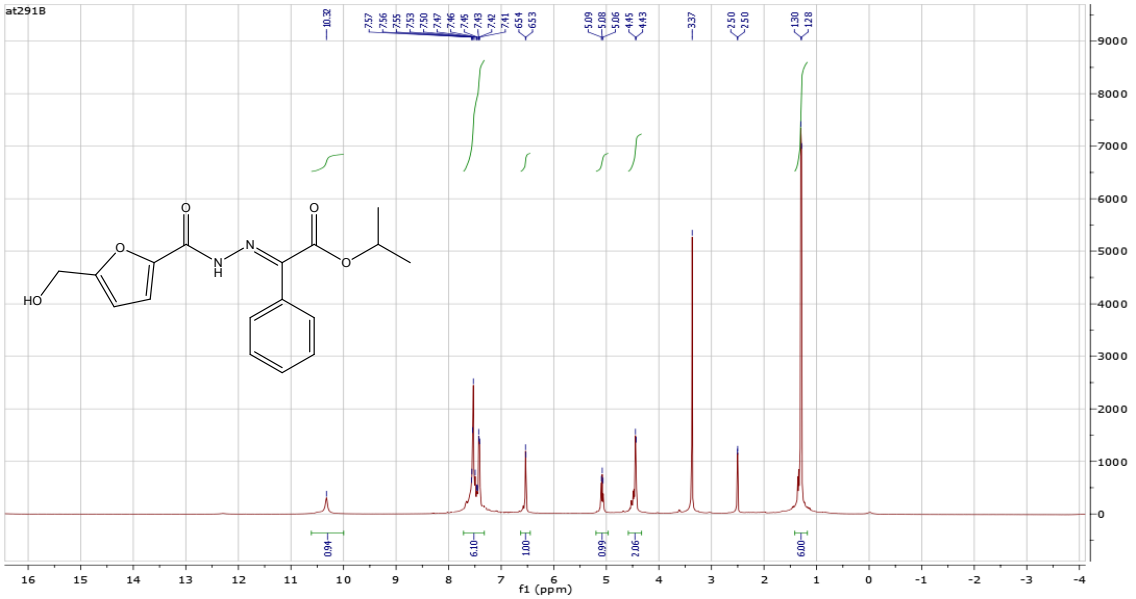
109.93
77.42
77.10
76.78
57.38
53.04
f1 (ppm)

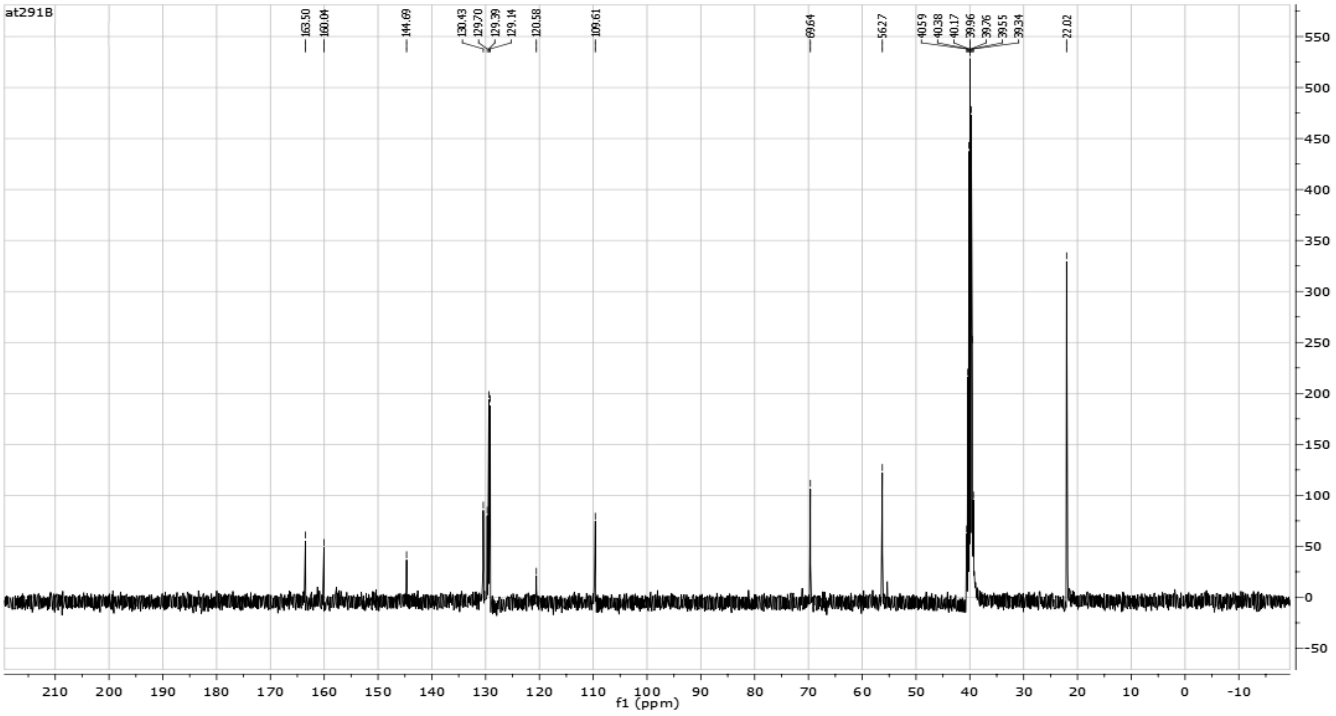
***(E)*-Isopropyl 2-(2-(5-(hydroxymethyl)furan-2-carbonyl)hydrazono)-2-phenylacetate12**

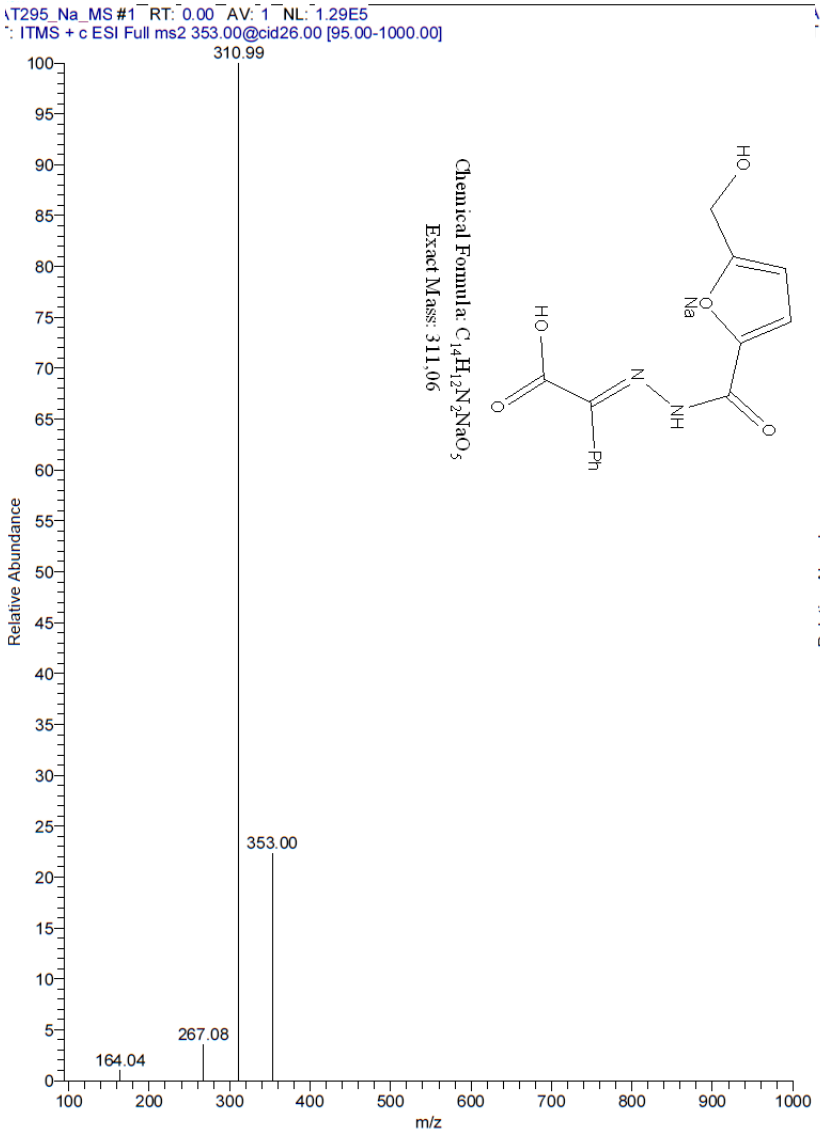
Isolated as a slightly yellow oil (53 mg, 68 % yield), isolated as a single geometric isomerin DMSOwith the structure depicted in ^{13}C spectra, indicating that isomerization occurs in deuterated chloroform.

^{1}H NMR (400 MHz, DMSO) δ 10.31 (1H,bs, N-H), 7.57-7.41 (6H, m, phenyl aromatics + H ortho to carbonyl in furan), 6.54-6.53 (1H, d, H meta to carbonyl in furan), 5.09-5.06 (1H, COOC**H**$(CH_3)_2$), 4.45-4.43 (2H, d, HOC**H$_2$**), 1.30-1.28 (6H, d, COOCH**$(CH_3)_2$**). ^{13}C NMR (101 MHz, DMSO) δ 163.50 (**C**OOCH$(CH_3)_2$), 160.04 (furan quaternary linked to HO**C**H_2), 144.69 (Ph quaternary), 130.43 (Ph), 129.70 (Ph), 129.39 (Ph), 129.14 (Ph), 120.58 (furan C ortho to carbonyl), 109.61 (furan C meta to carbonyl), 69.64 (HO**C**H_2), 56.27 (COO**C**H$(CH_3)_2$), 22.02 (COOCH(**C**$H_3)_2$).

MS (ESI+, M+Na)=353.1; MS (ESI+, 353.1)=311.0 (loss of propylene); MS (ESI+, 311.0)=267.1 (loss of CO_2). HRMS (EI, M+) calc. 331.1294 found 331.1296.



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Exact Mass: 311.06
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HO
Ph
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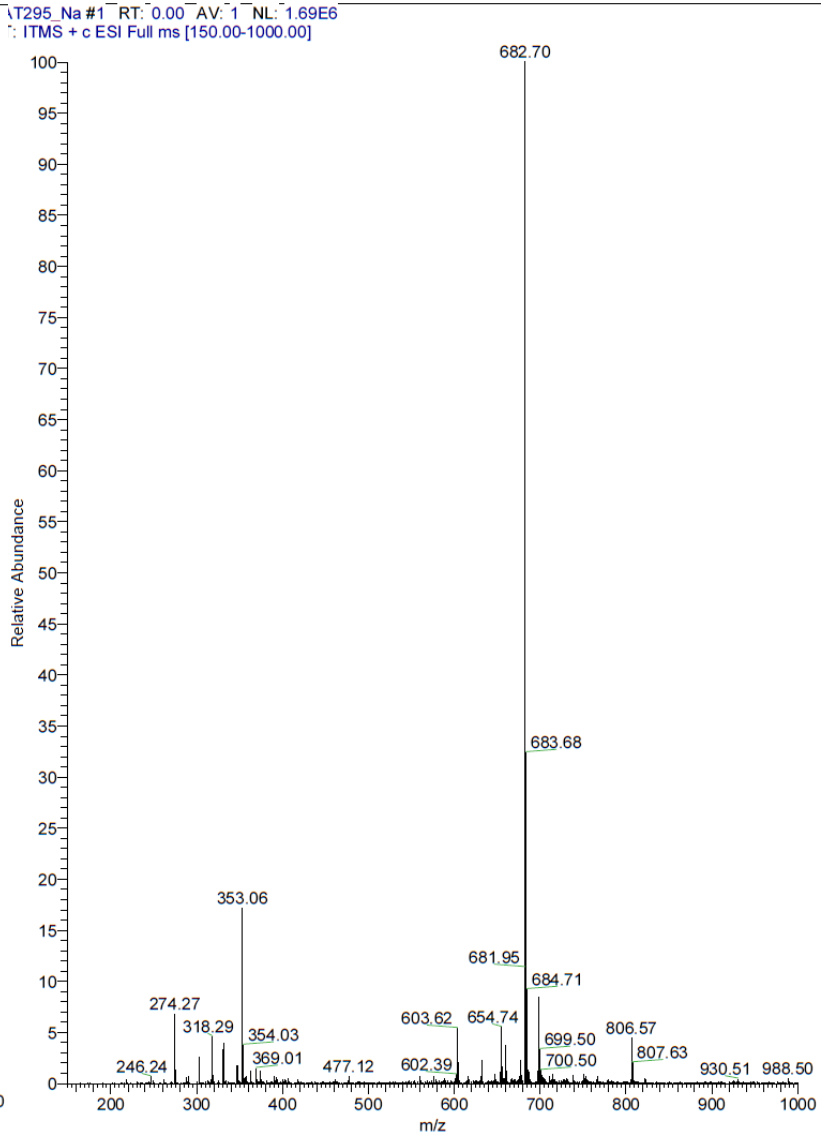
Relative Abundance
m/z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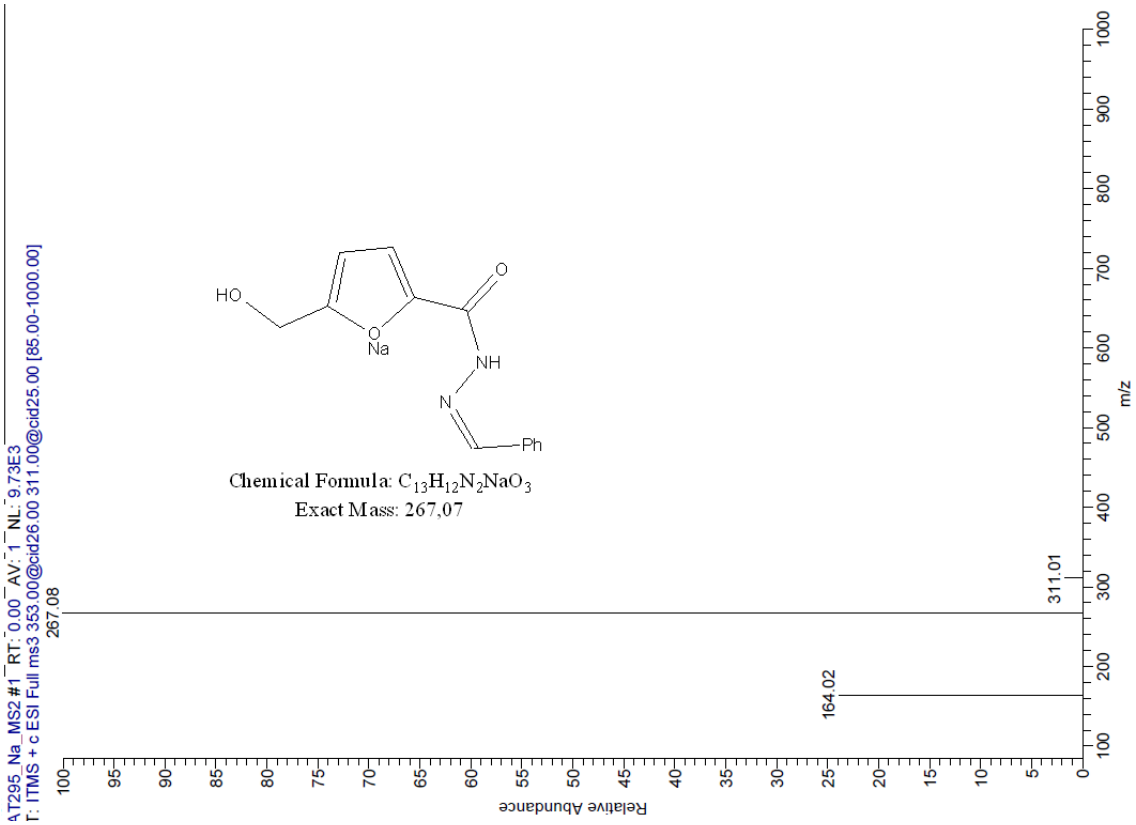
Relative Abundance
m/z



Elemental Composition Report **Page 1**

Multiple Mass Analysis: 46 mass(es) processed - displaying only valid results
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Selected filters: None

Monoisotopic Mass, Odd and Even Electron Ions
49 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
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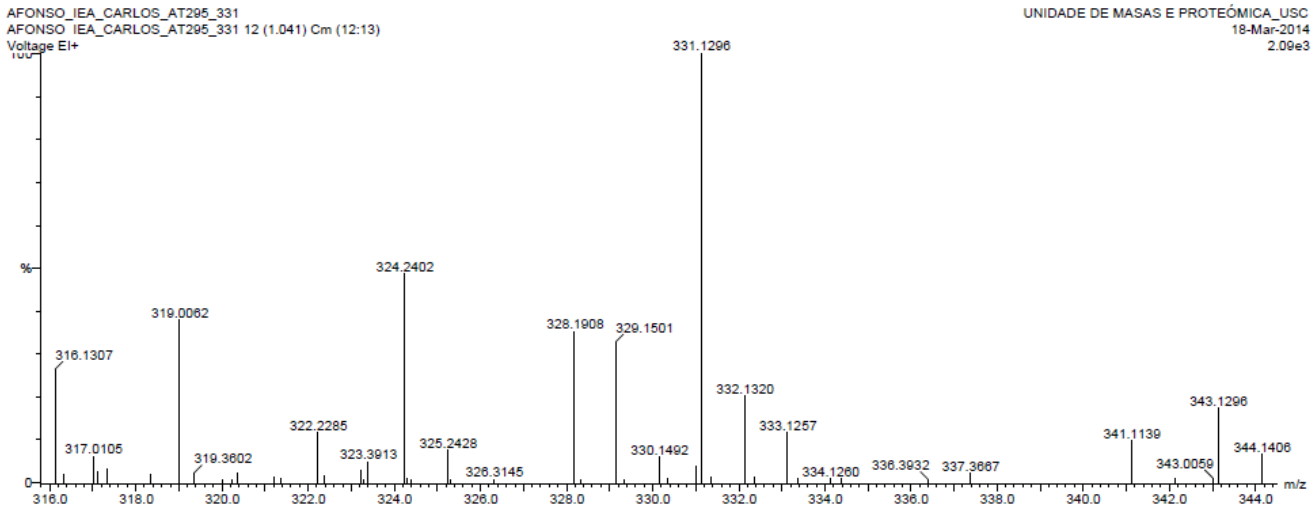

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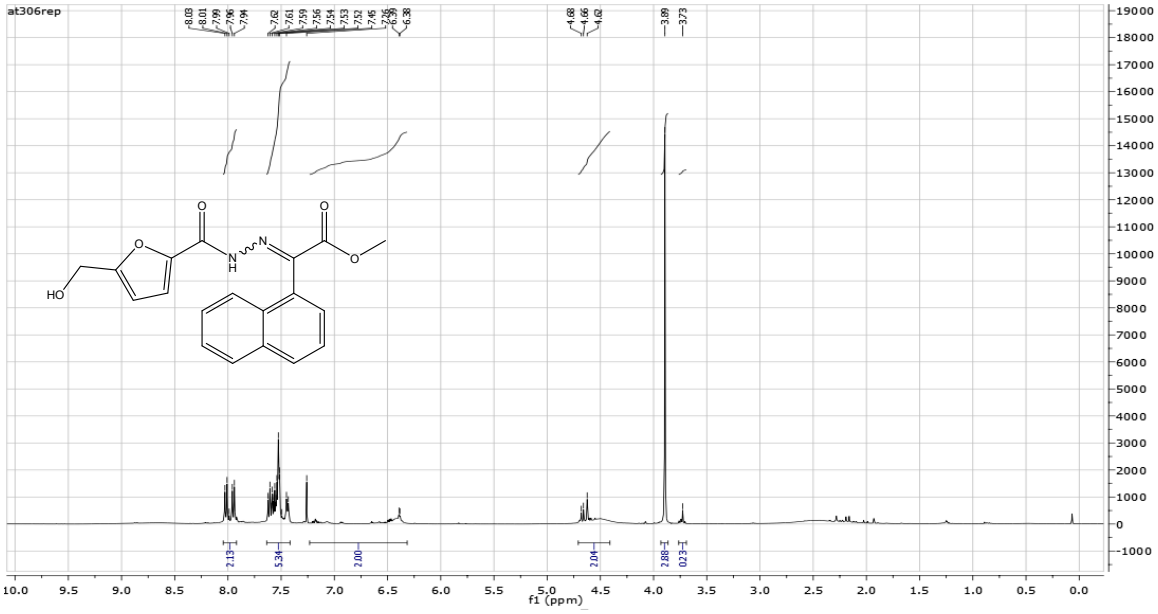
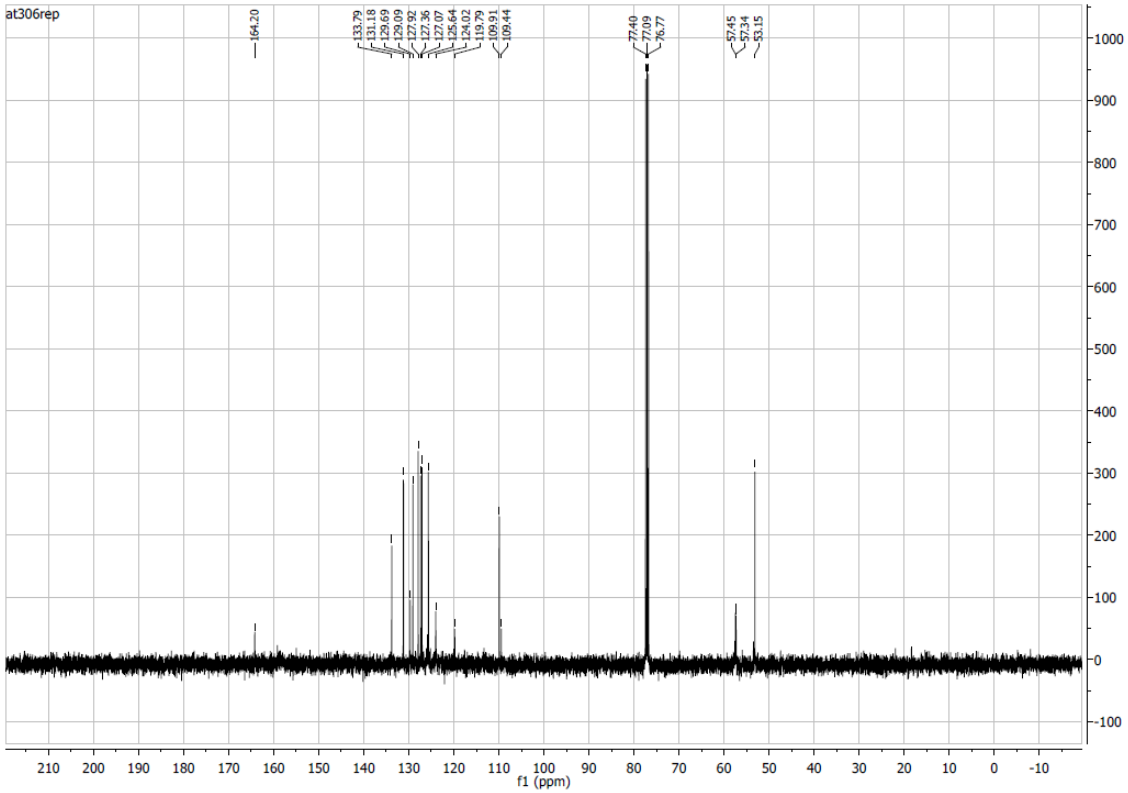
Methyl 2-(2-(5-(hydroxymethyl)furan-2-carbonyl)hydrazono)-2-(naphthalen-1-yl)acetate13
Isolated as a yellow powder (26 mg, 31 % yield), isolated as an inseparable mixture of geometric isomers 1:9. The broadening of N-H does not allow the determination which isomer is the major.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-7.94 (2H, m, naphthalene H2 and H4 position), 7.61-7.52 (5H, m, naphthalene H3, H5, H6, H7 and H8), 7.20-6.42 (2H, m, furan protons), 4.68-4.52 (2H, m, $HOCH_2$) 3.89

(3H, s, OCH_3).^{13}C NMR (101 MHz, $CDCl_3$) δ 164.20(**C**$OOCH_3$), 133.79, 131.18, 129.69, 129.09, 127.92, 127.36, 127.07, 125.64, 124.02, 119.79(furan C ortho to carbonyl), 109.91-109.44 (furan C meta to carbonyl), 57.45-57.34(HO**C**H_2), 53.15 (COO**C**$H(CH_3)$).
MS (ESI+, M+Na)=375.1; MS (ESI+, 375.1)=315.1(loss of 2 formaldeydes). HRMS (ESI-TOF, M+Na) calc. 375.0957 found 375.0955.

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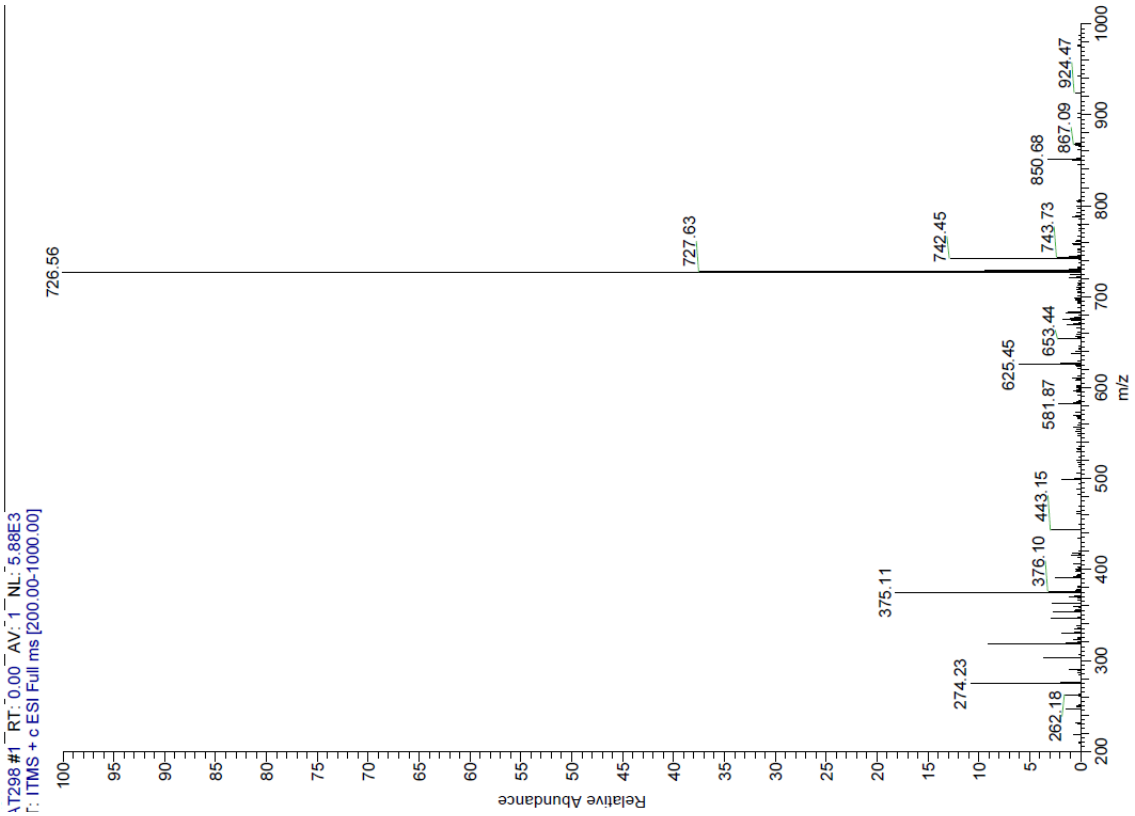
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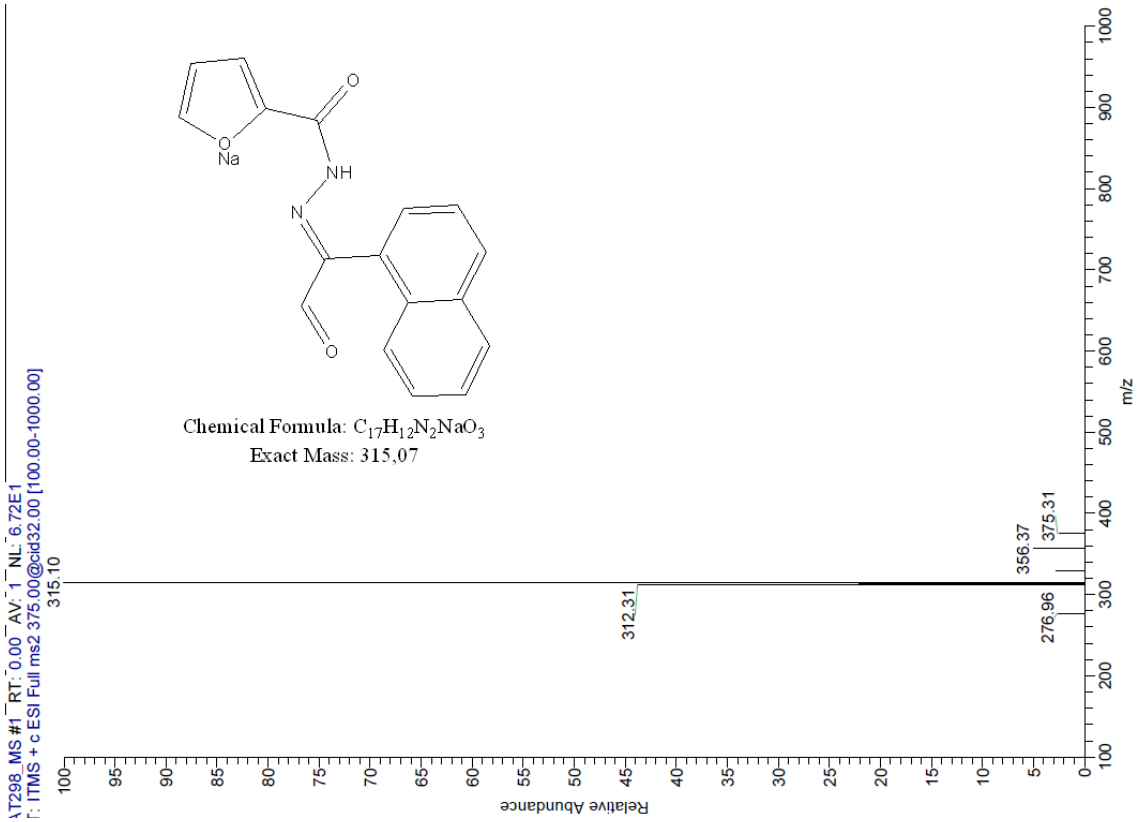
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Relative Abundance
m/z

ESPECTRO ESI-FIA-TOF-Medida de Masas Exactas

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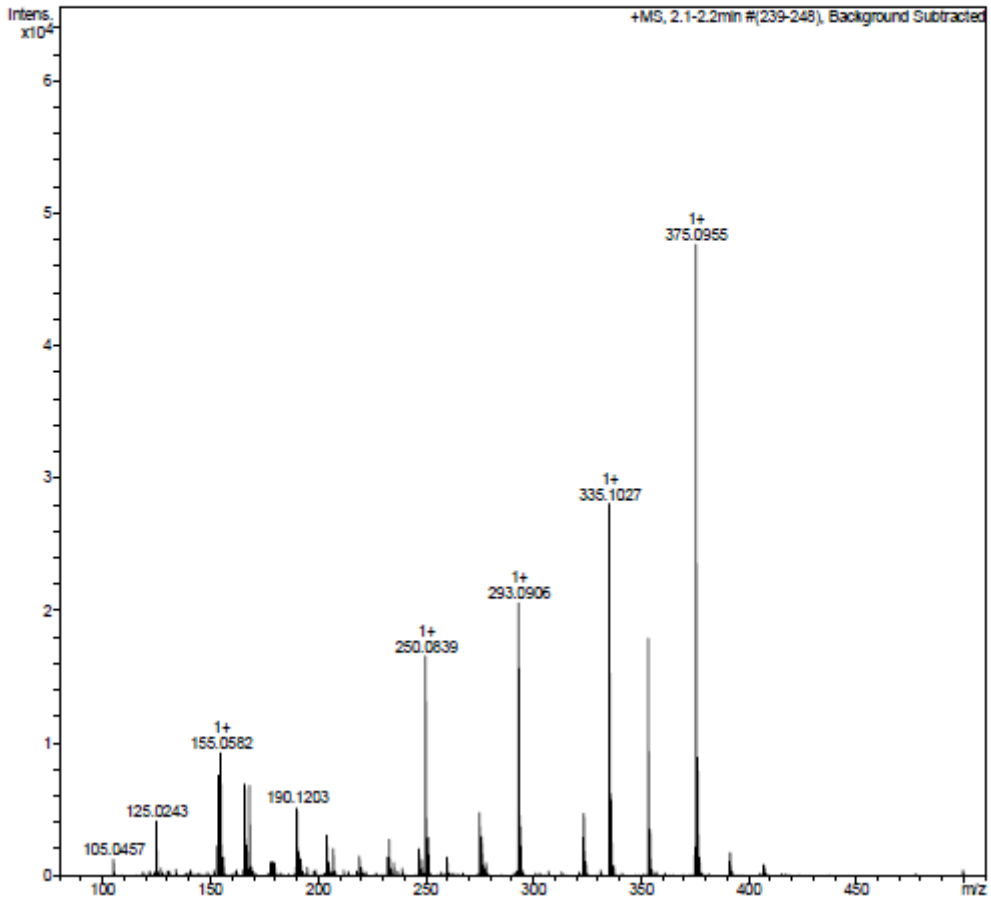
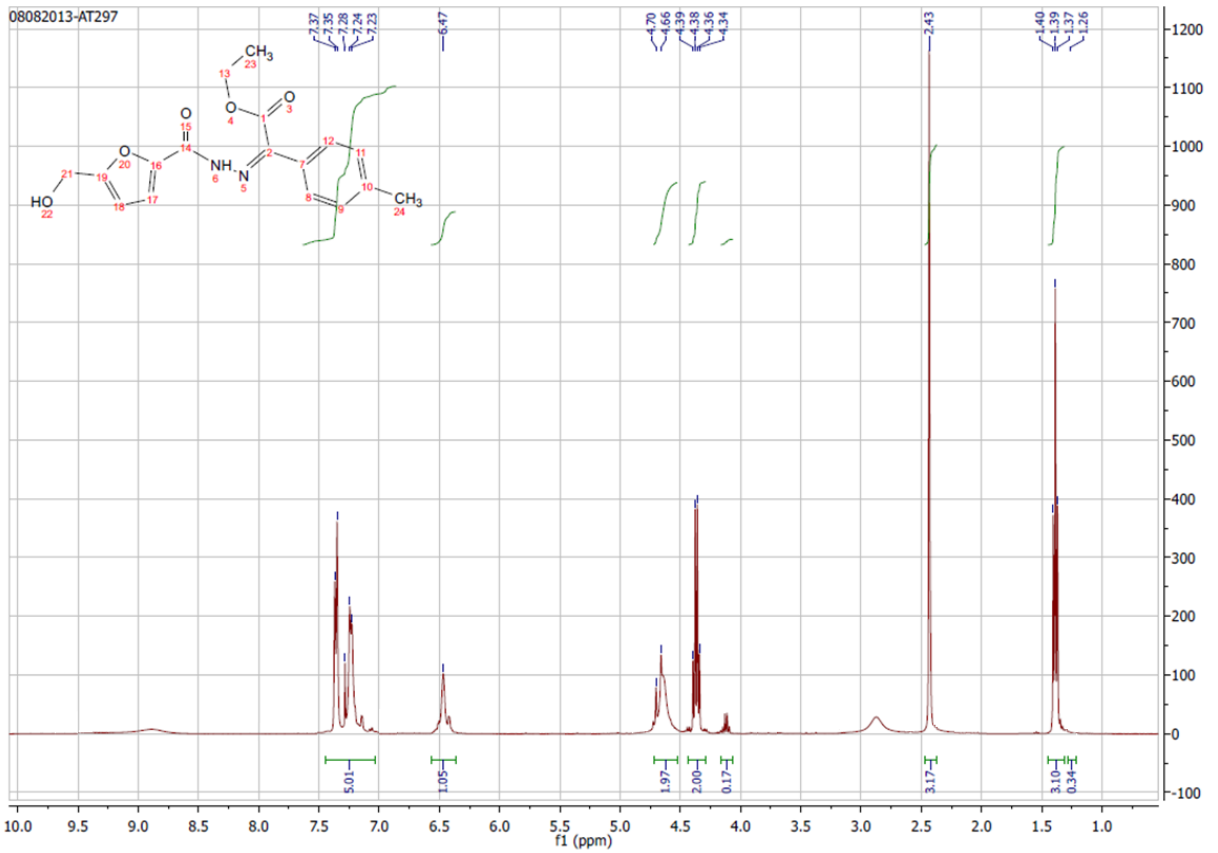


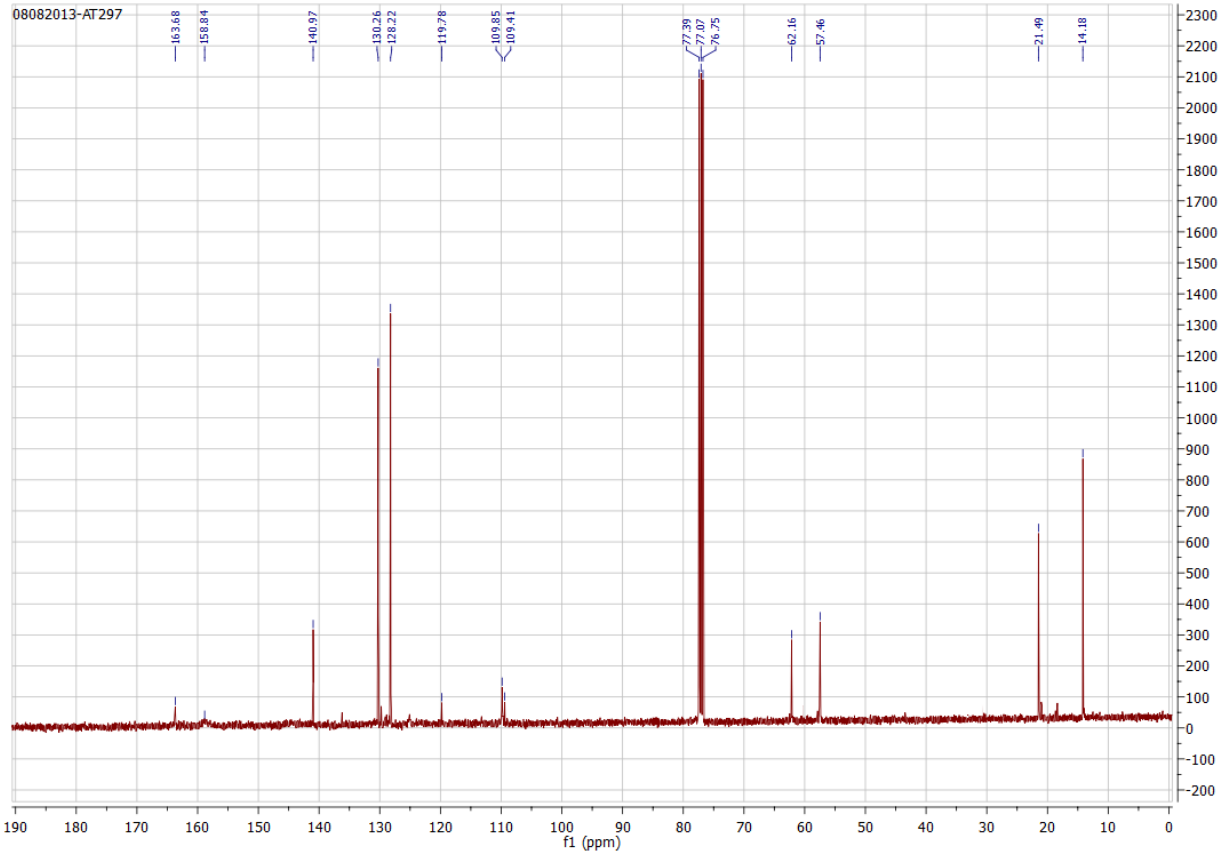
Ethyl 2-(2-(5-(hydroxymethyl)furan-2-carbonyl)hydrazono)-2-(4-tolyl)acetate 14

Isolated as a slightly yellow oil (33 mg, 42 % yield) isolated as an inseparable mixture of geometric isomers 1:9. The broadening of N-H does not allow the determination which isomer is the major.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.23 (5H, m, protons 8,9,11 and 12 and proton 18), 6.47 (1H, m, proton 17), 4.70-4.66 (2H, m, proton 21), 4.39-4.34 (2H, quartet, proton 13), 2.43 (3H, proton 24), 1.40-1.37 (3H, t, proton 23). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.68 (C1), 158.84 (C19), 140.97 (C7), 130.26 (C8+C12), 128.22 (C9+C11), 119.78 (C17), 109.85 (C18), 62.16 (C21), 57.46 (C13), 21.49 (C24), 14.18 (C23). C2, C7, C14 and C16 do not apppear with more accumulation time.

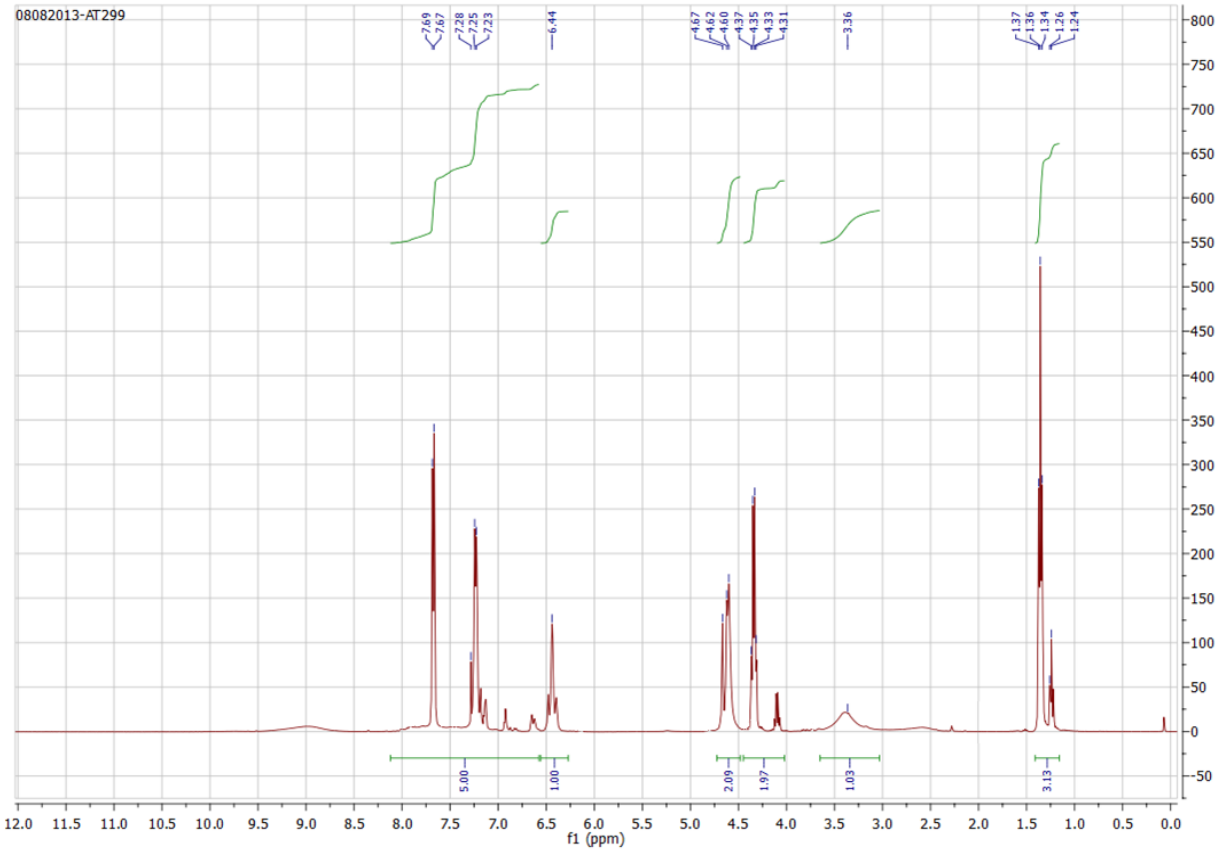
Elementar analysis for $(C_{17}H_{18}N_2O_5)_4H_2O$ calc. %C 60.98; %H 5.57; %N 8.37 found %C 61.24; %H 5.31; %N 7.99.

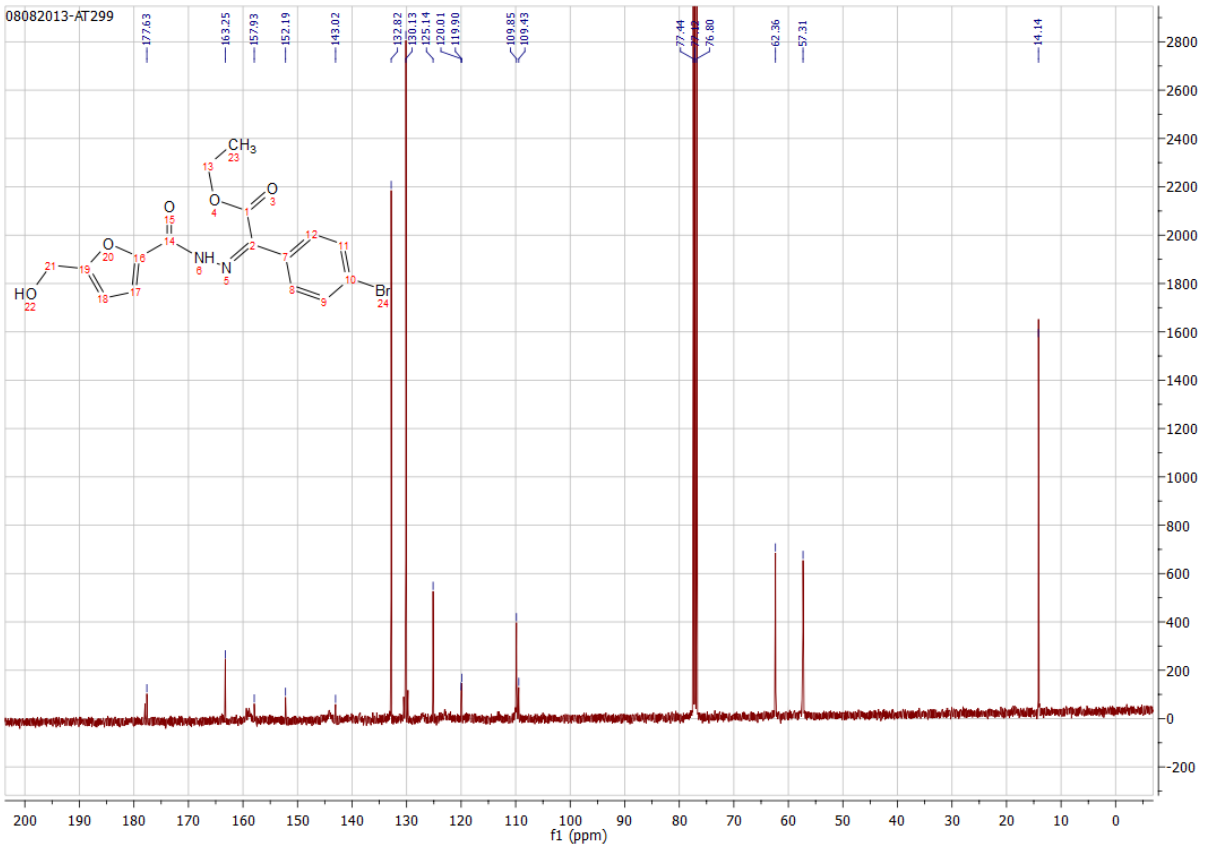




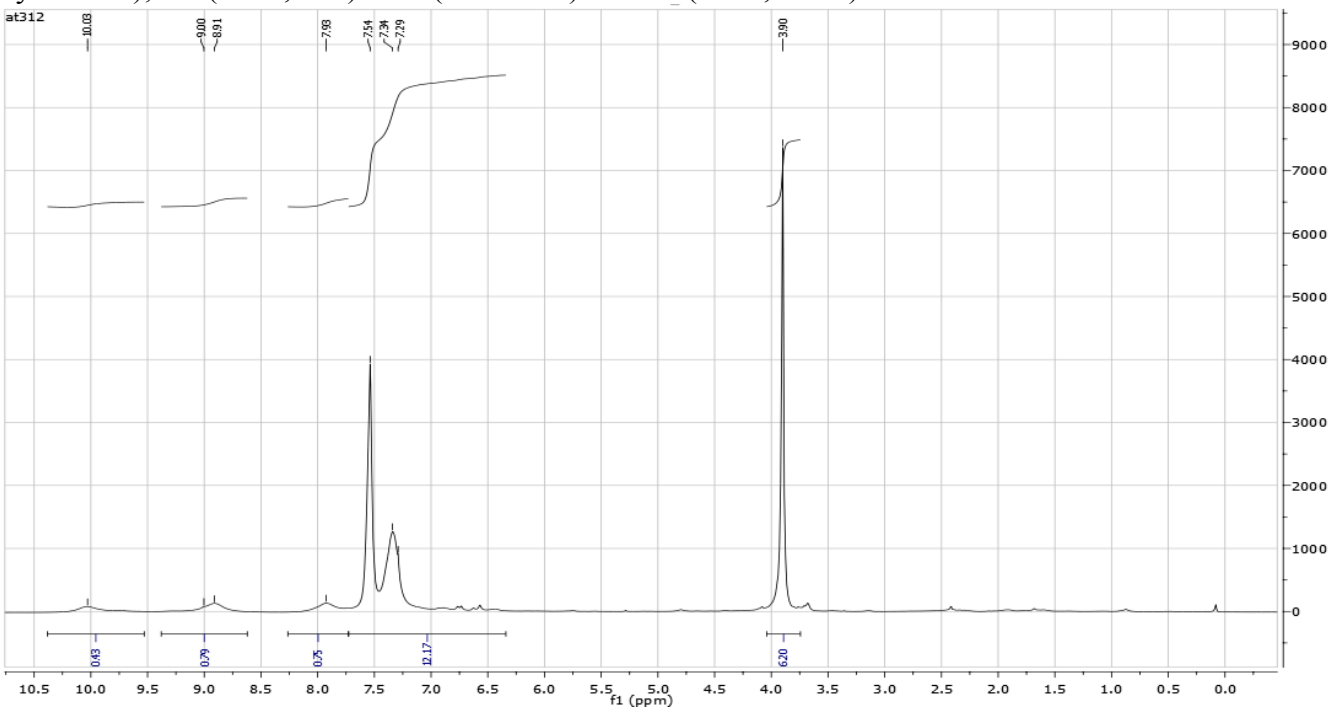
Ethyl 2-(4-bromophenyl)-2-(2-(5-(hydroxymethyl)furan-2-carbonyl)hydrazono)acetate15
Isolated as a slightly yellow powder (58 mg, 64 % yield) isolated as an inseparable mixture of geometric isomers 1:9. The broadening of N-H does not allow the determination which isomer is the major.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.67 (2H, d, protons 9-11), 7-28-7.23 (3H, m, protons 8, 12 and 17), 6.44 (1H, m, proton 18), 4.67-4.60 (2H, m, proton 21), 4.37-4.31 (2H, quartet, proton 13), 3.36 (1H, bs,

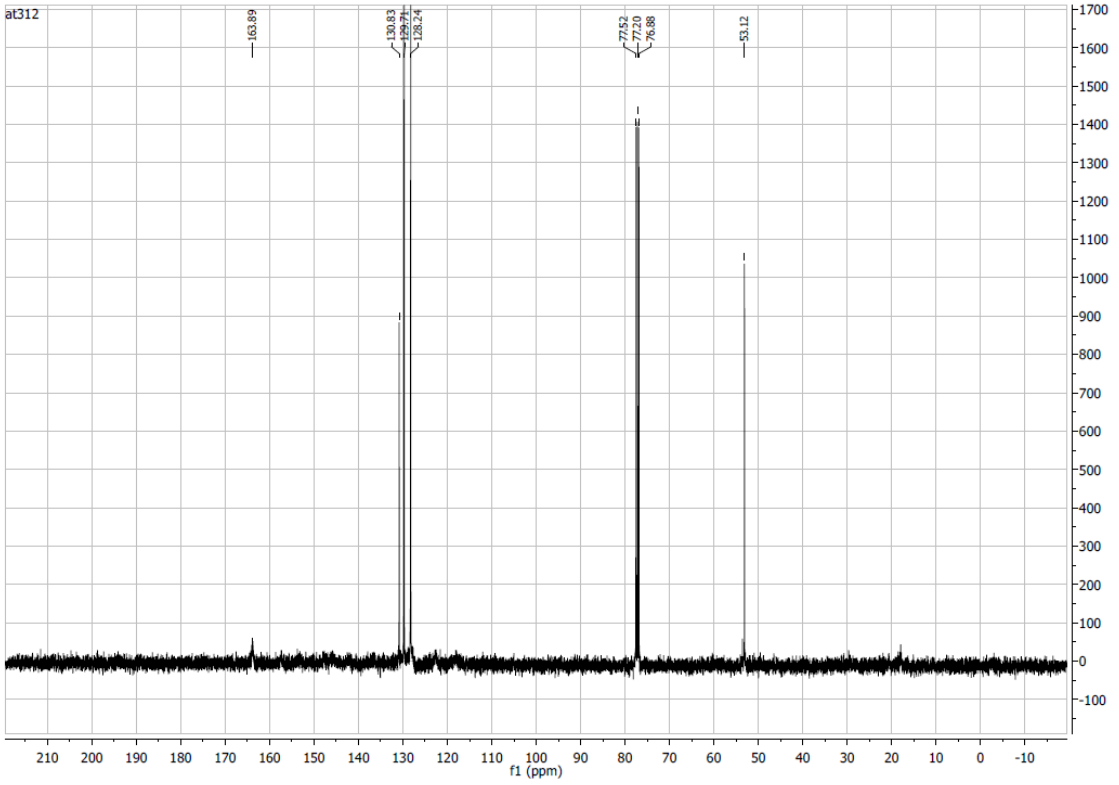
OH), 1.37-1.24 (3H, proton 23). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.63 (C14), 163.25 (C1), 157.93 (C19), 152.19 (C16), 143.02 (C7), 132.82 (C9-C11), 130.13 (C8-C12), 125.14 (C10), 120.01 (C17), 109.85(C18), 62.36 (C21), 57.31 (C13), 14.14 (C23). C2 does not appear with more accumulation time. Elementar analysis for $(C_{16}H_{15}BrN_2O_5)_3H_2O$ calc. %C 47.90; %H 3.94; %N 6.98 found %C 48.05; %H 3.72; %N 6.62.

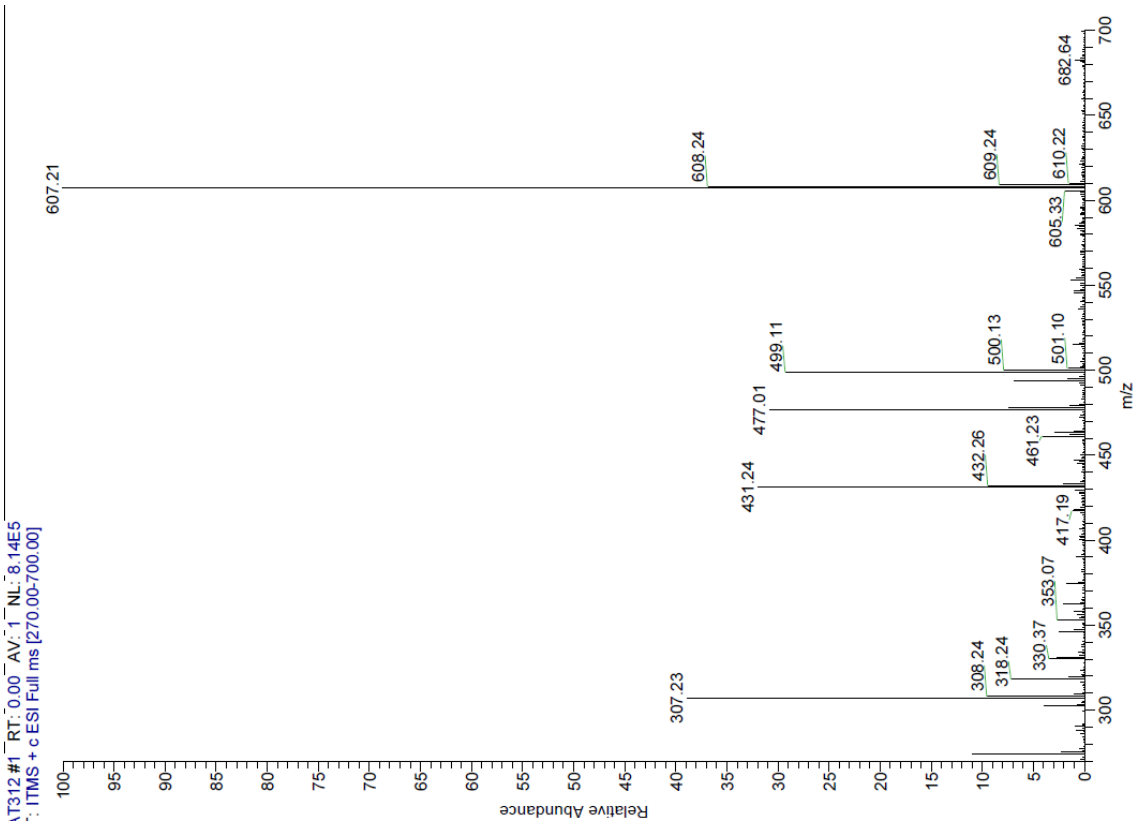




Dimethyl 2,2'-(2,2'-(furan-2,5-dicarbonyl)bis(hydrazin-2-yl-1-ylidene))bis(2-phenylacetate)16
Isolated as a yellow powder (60 mg, 53 % yield) isolated as an inseparable mixture of 3 geometric isomers 4:8:8.
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0-7.93 (2H, three bs, N-H), 7.54-6.50 (12H, m, phenyl + furan ring), 3.90 (6H, s, methyl ester). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.89 (ester carbonyl), 130.83 (Ph para), 129.71 (Ph ortho), 128.24 (Ph meta), 53.12 (methyl ester).
MS (ESI+, M+H)=477.1; MS(ESI+, 477.1)=417 (loss of 2 formaldehyde); MS(ESI+, 417)=270 (loss 1 hydrazone); MS(ESI+, 270)=213 (loss 2 CO). HRMS(ESI+, M+H) calc. 477.1410 found.477.1404




at312
163.89
130.83
129.71
128.24
77.52
77.20
76.88
53.12
f1 (ppm)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: ITMS + c ESI Full ms [270.00-700.00]
Relative Abundance
m/z
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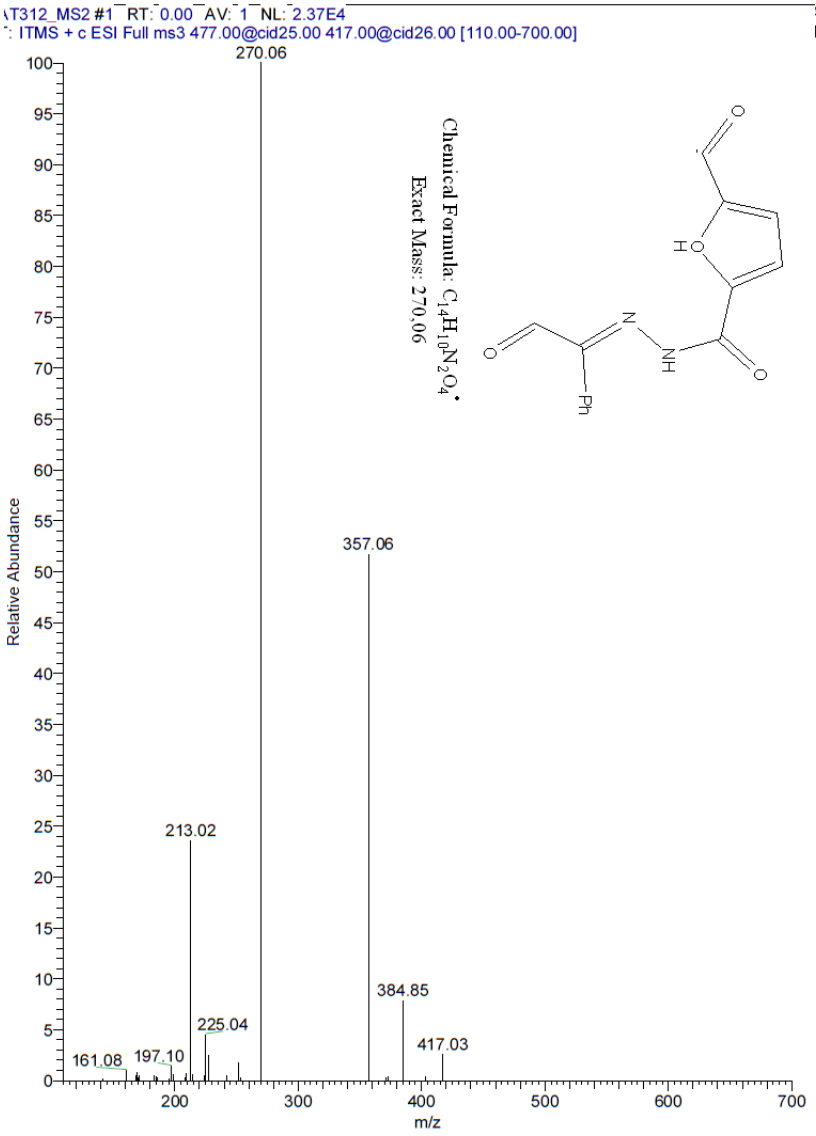
608.24
609.24
610.22
682.64
605.33
499.11
500.13
501.10
477.01
461.23
432.26
431.24
417.19
353.07
330.37
318.24
308.24
307.23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Chemical Formula: C14H10N2O4
Exact Mass: 270.06
Relative Abundance
m/z
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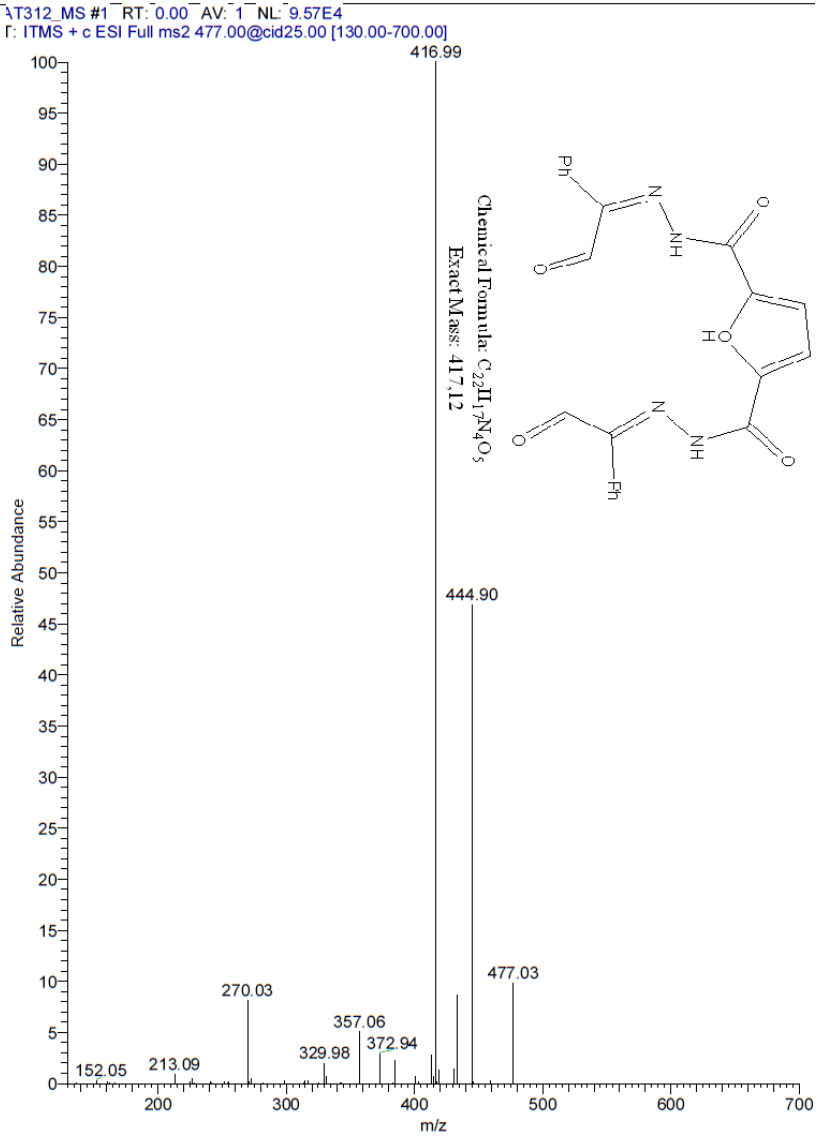
357.06
213.02
384.85
225.04
417.03
161.08
197.10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Exact Mass: 417.12
Relative Abundance
m/z
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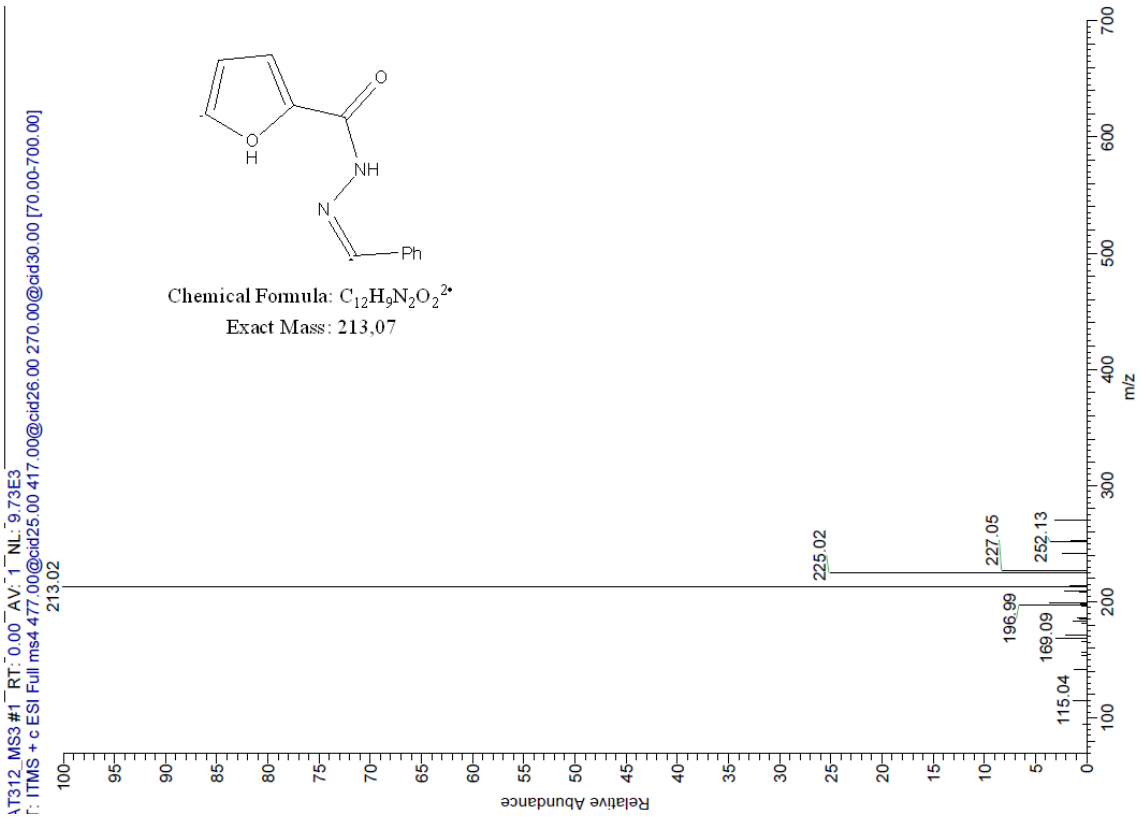
477.03
270.03
357.06
372.94
329.98
213.09
152.05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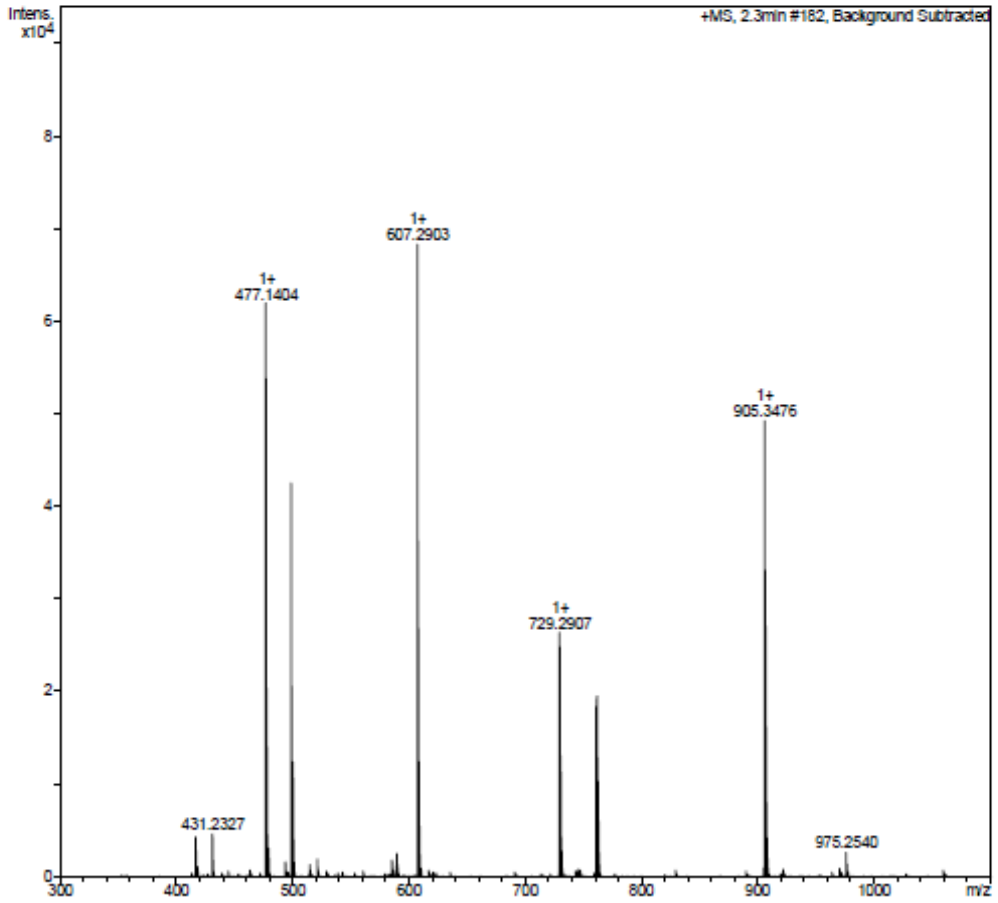
T: ITMS + c ESI Full ms4 477.00@cid25.00 417.00@cid26.00 270.00@id30.00 [70.00-700.00]
O
O
H
NH
N
Ph
Chemical Formula: C12H9N2O2•
Exact Mass: 213,07
213.02
225.02
227.05
252.13
196.99
169.09
115.04
Relative Abundance
m/z

ESPECTRO ESI-FIA-TOF-Medida de Masas Exactas

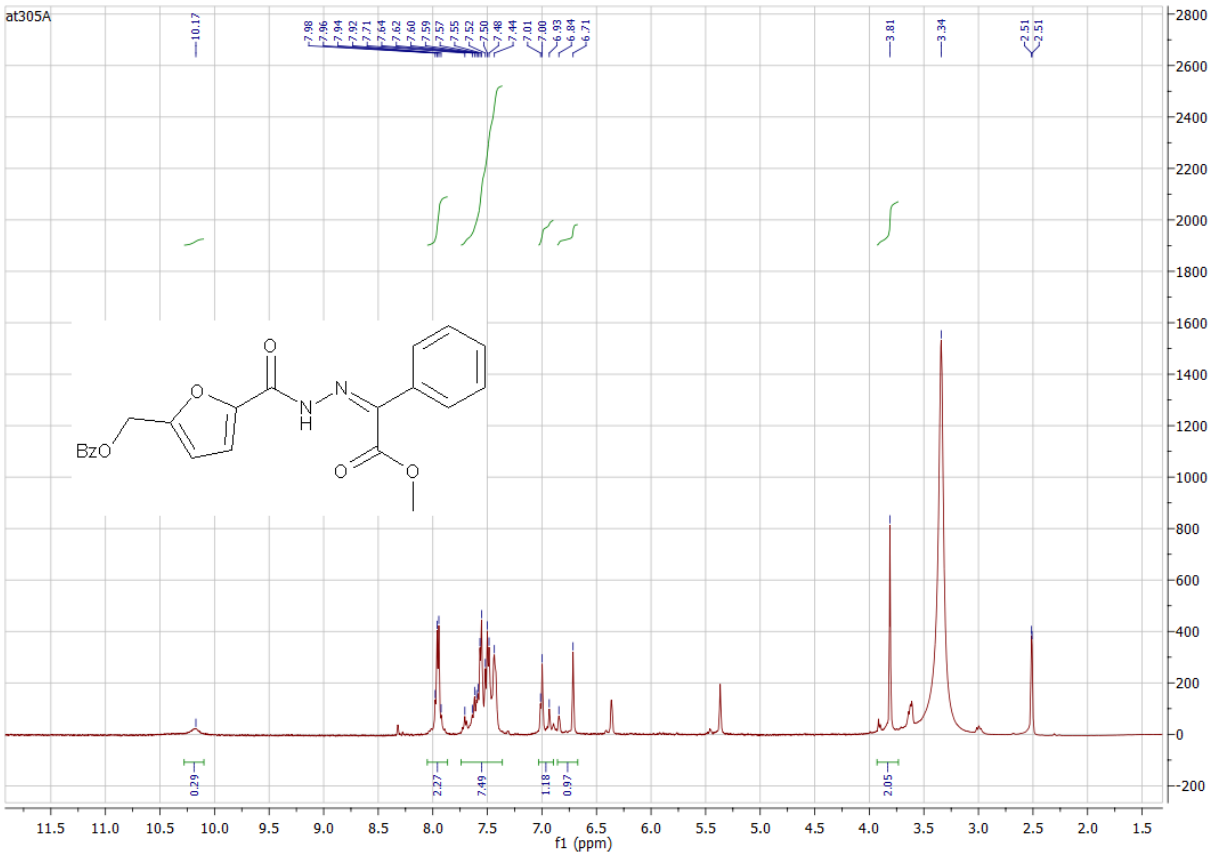
Analysis Info

Sample Name	AT312_476_1-B,2_01_13144.d	Acquisition Date	3/12/2014 2:22:01 PM
Method	fia_pos_medio_350-1500_egf.m	Instrument	micrOTOF

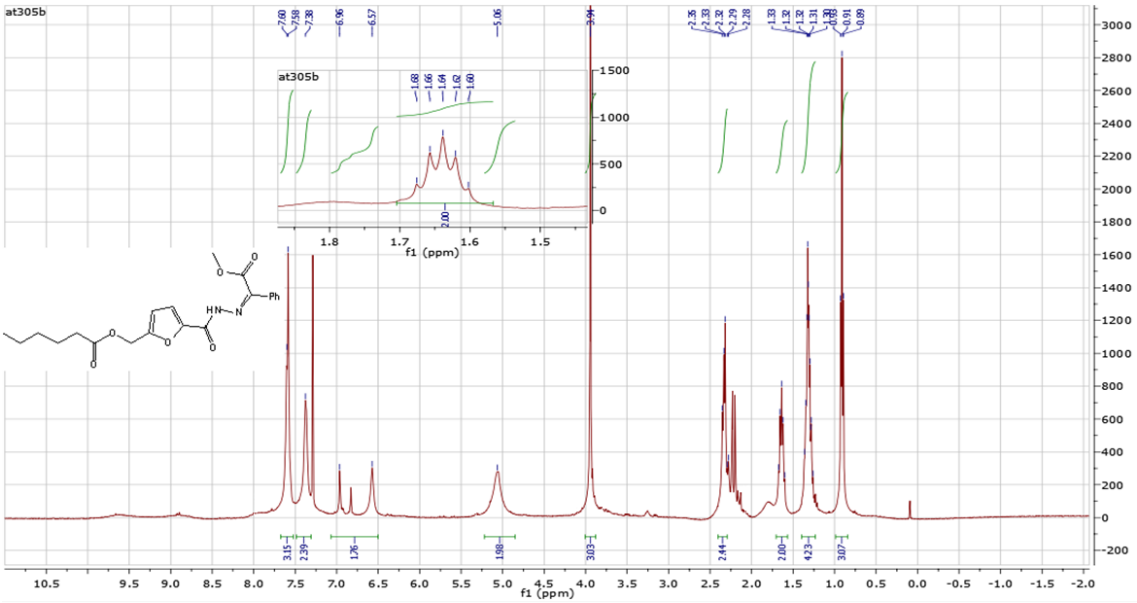


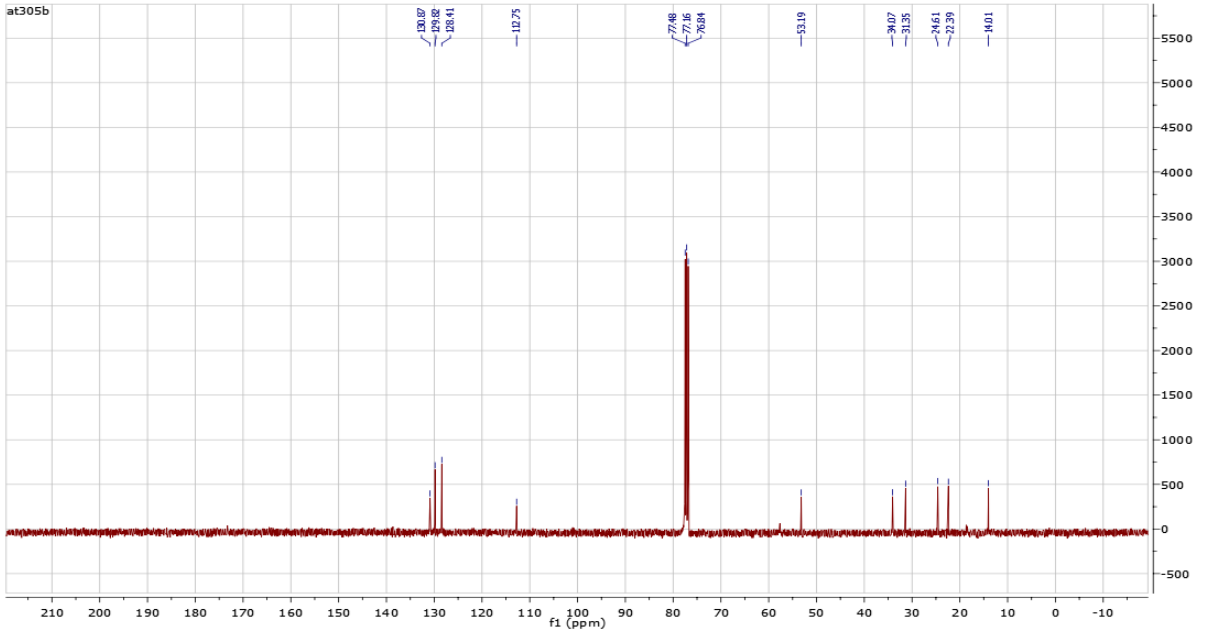
(E)-(5-(2-(2-methoxy-2-oxo-1-phenylethylidene)hydrazinecarbonyl)furan-2-yl)methyl benzoate17

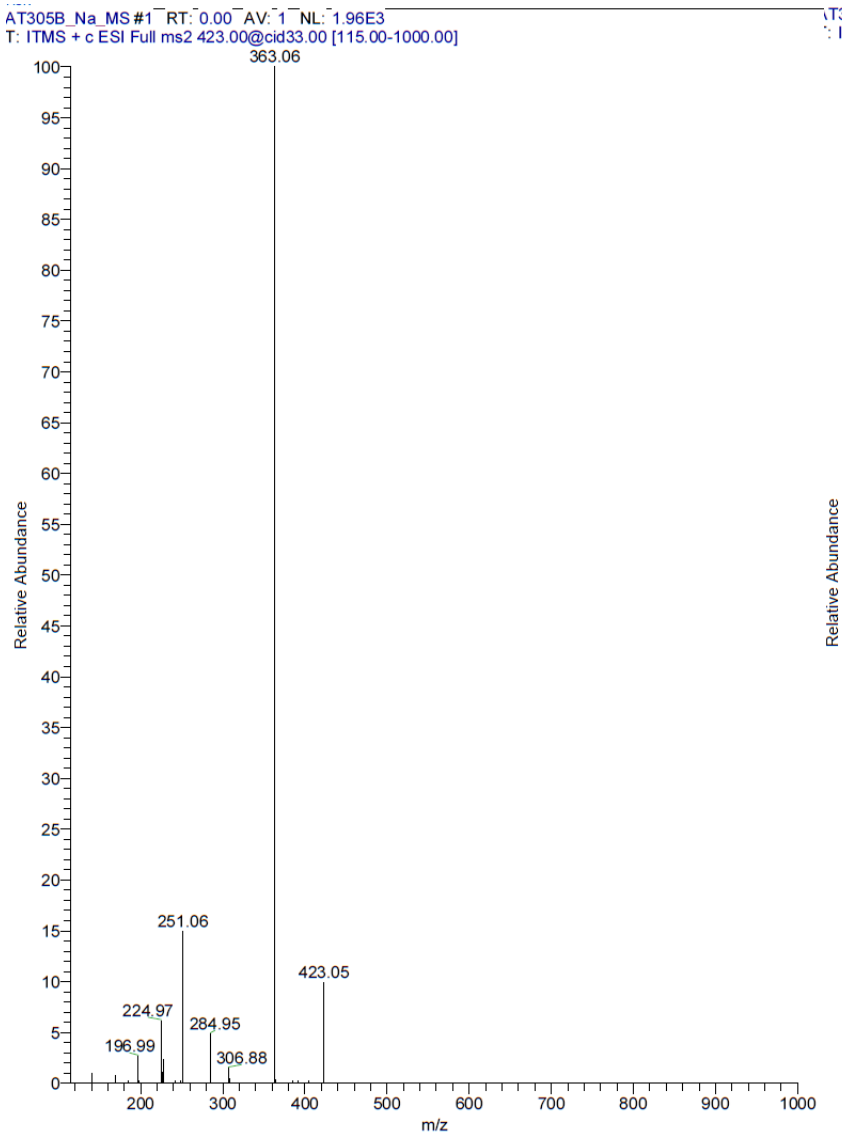
Isolated as a slightly yellow oil (2 mg, 3 % yield) as a single isomer.
^{1}H NMR (400 MHz, DMSO) δ 10.17 (bs, NH), 7.98-7.92 (2H, m, ortho H benzoyl group), 7.71-7.44 (8H,m, remaining H from Ph and Bz), 7.01-6.93 (1H, m, furan ring H ortho to carbonyl), 6.84-6.36 (1H, m, furan ring H meta to carbonyl), 3.81 (2H, m, methylene Hs).
Was not possible to recover the compound from DMSO for further characterizations in pure form.



5-(2-(2-methoxy-2-oxo-1-phenylethylidene)hydrazinecarbonyl)furan-2-ylmethyl hexanoate18
Isolated as a yellow powder (12 mg, 13 % yield) as a single isomer.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.58(3H, m, Ph ortho + para), 7.38(2H, bs, Ph meta), 6.96-6.57(2H, m, furan ring), 5.06 (2H, bs, HxOC**H$_2$**), 3.94 (3H, s, COOC**H$_3$**), 2.35-2.28 (2H, t, C**H$_2$**CO), 1.68-1.60 (2H, quintet, C**H$_2$**CH_2CO), 1.36-1.26 (4H, m, C**H$_2$**C**H$_2$**CH_3), 0.93-0.89 (3H, t, CH_2C**H$_3$**).^{13}C NMR (101 MHz, $CDCl_3$) δ 130.87 (Ph), 129.82 (Ph), 128.41 (Ph), 112.75 (furan C meta to carbonyl), 53.19 (HxO**C**H_2), 34.07 (CH_2**C**H_2CO), 31.35 (**C**H_2CH_2CO), 24.61 (**C**$H_2CH_2CH_3$), 22.39 (**C**H_2CH_3), 14.01 (CH_2**C**H_3).
MS (ESI+, M+M+Na)=822.7; MS (ESI+, M+Na)=423.2; MS (ESI+, 423)=363.1; MS (ESI+, 363.1)=225.0; MS (ESI+, 225.0)=141.0. The fragmentation pattern sugest the gradual loss of the molecule functional groups, however rearrangements may take place. HRMS(M+Na) calc. 423.1532 found. 423.1516


at305b
f1 (ppm)


at305b
f1 (ppm)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Relative Abundance
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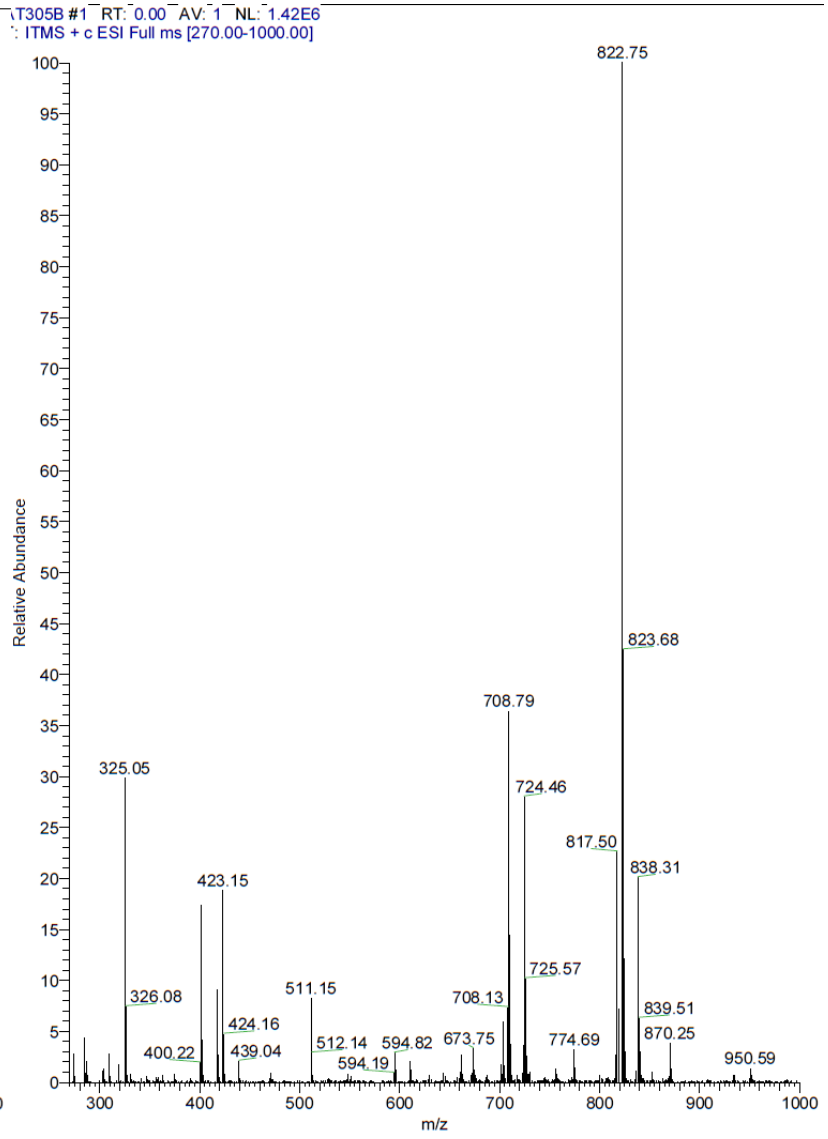
251.06
423.05
224.97
284.95
196.99
306.88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: ITMS + c ESI Full ms [270.00-1000.00]
Relative Abundance
m/z
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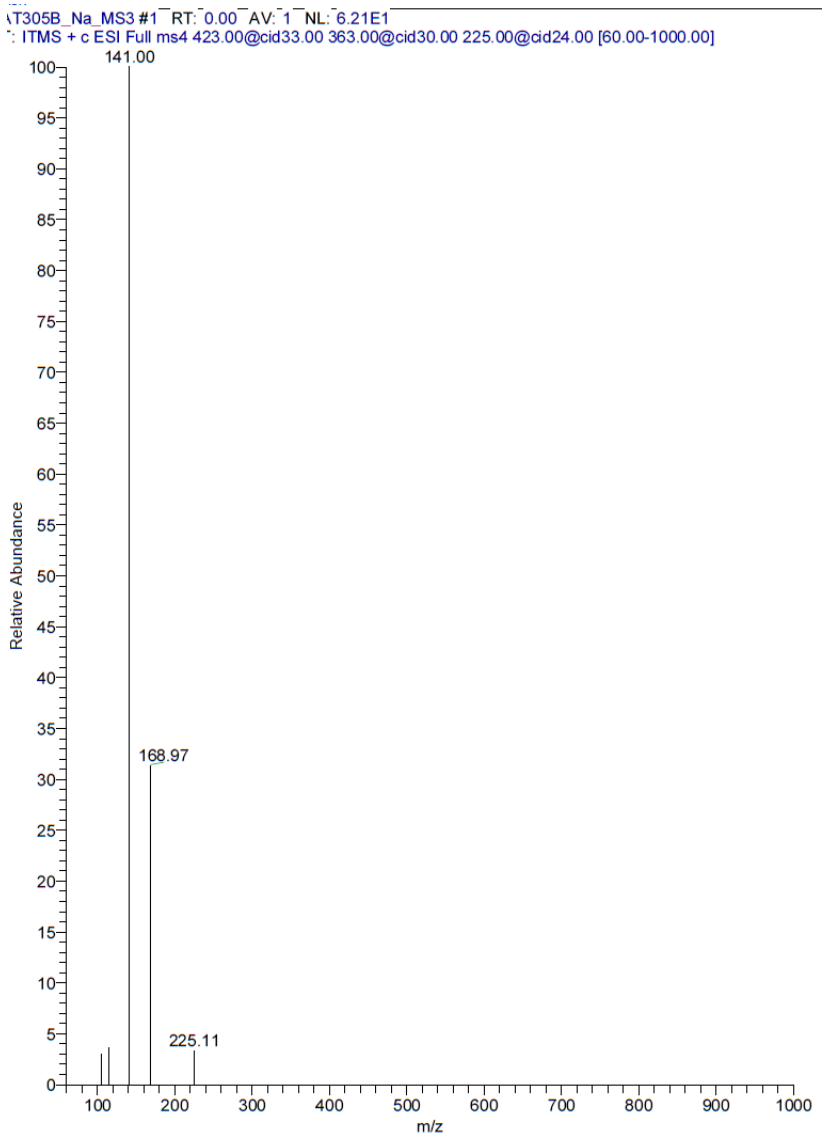
708.79
325.05
724.46
817.50
838.31
423.15
725.57
326.08
511.15
708.13
839.51
424.16
870.25
400.22
439.04
512.14
594.82
673.75
774.69
594.19
950.59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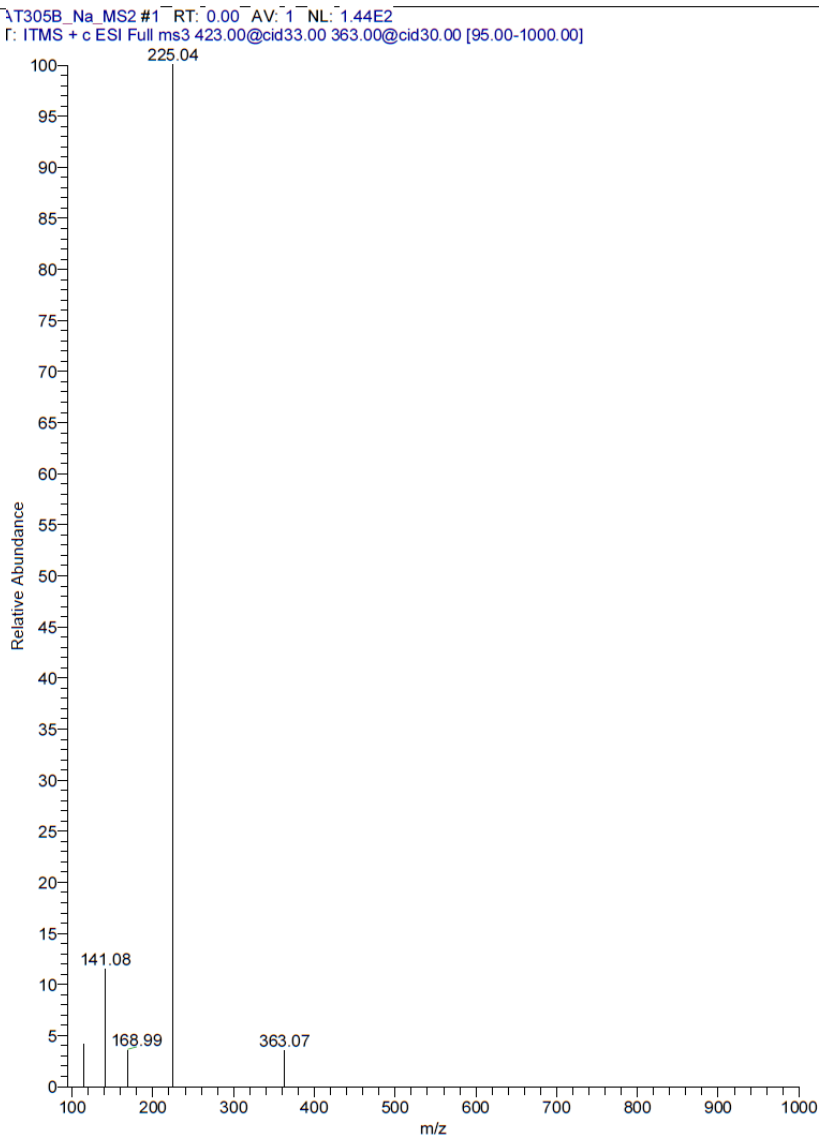
141.00
168.97
225.11
Relative Abundance
m/z


AT305B_Na_MS2 #1 RT: 0.00 AV: 1 NL: 1.44E2
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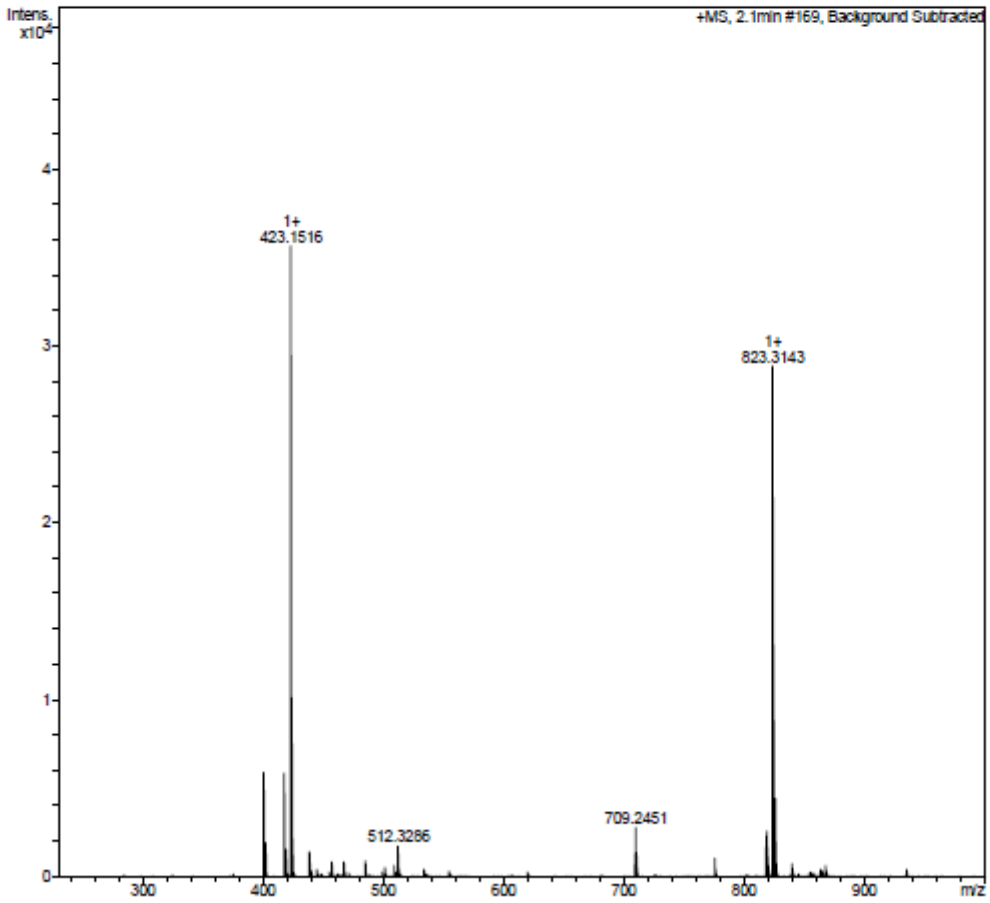
225.04
141.08
168.99
363.07
Relative Abundance
m/z

ESPECTRO ESI-FIA-TOF-Medida de Masas Exactas

Analysis Info

Sample Name	AT305B_400_1-A,12_01_13140.d	Acquisition Date	3/12/2014 1:44:48 PM
Method	fia_pos_medio_350-1500_egf.m	Instrument	micrOTOF

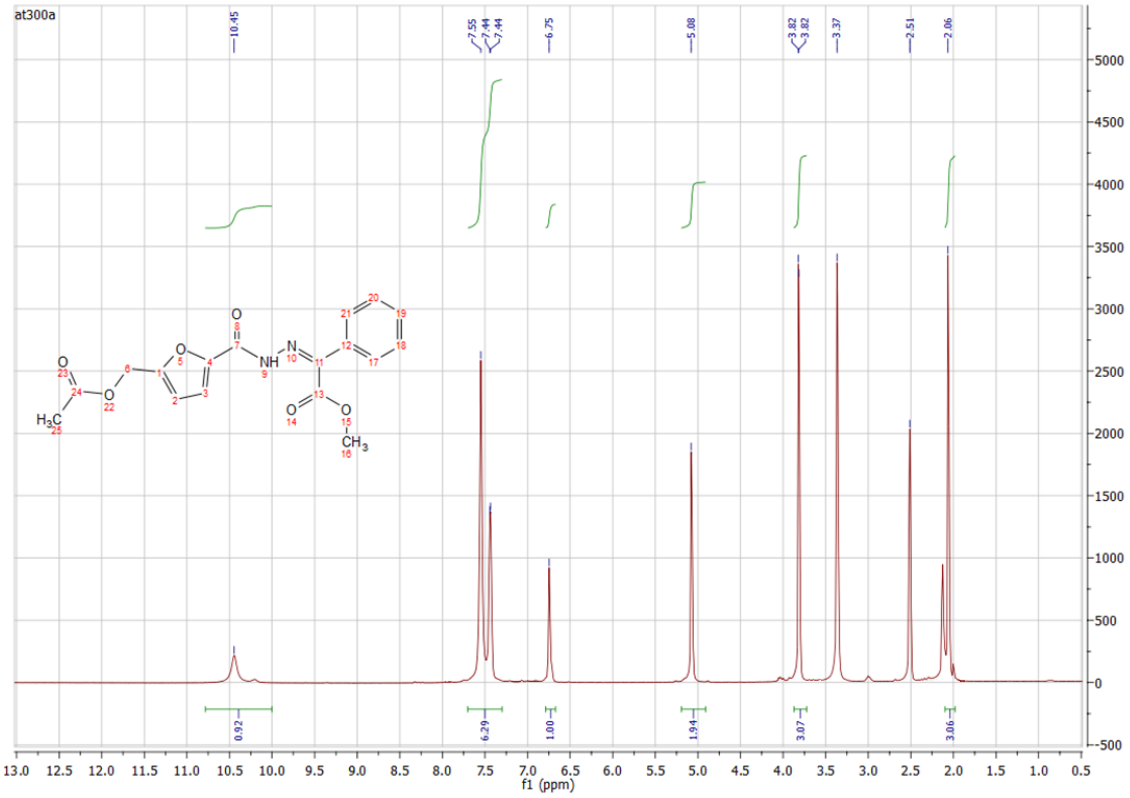


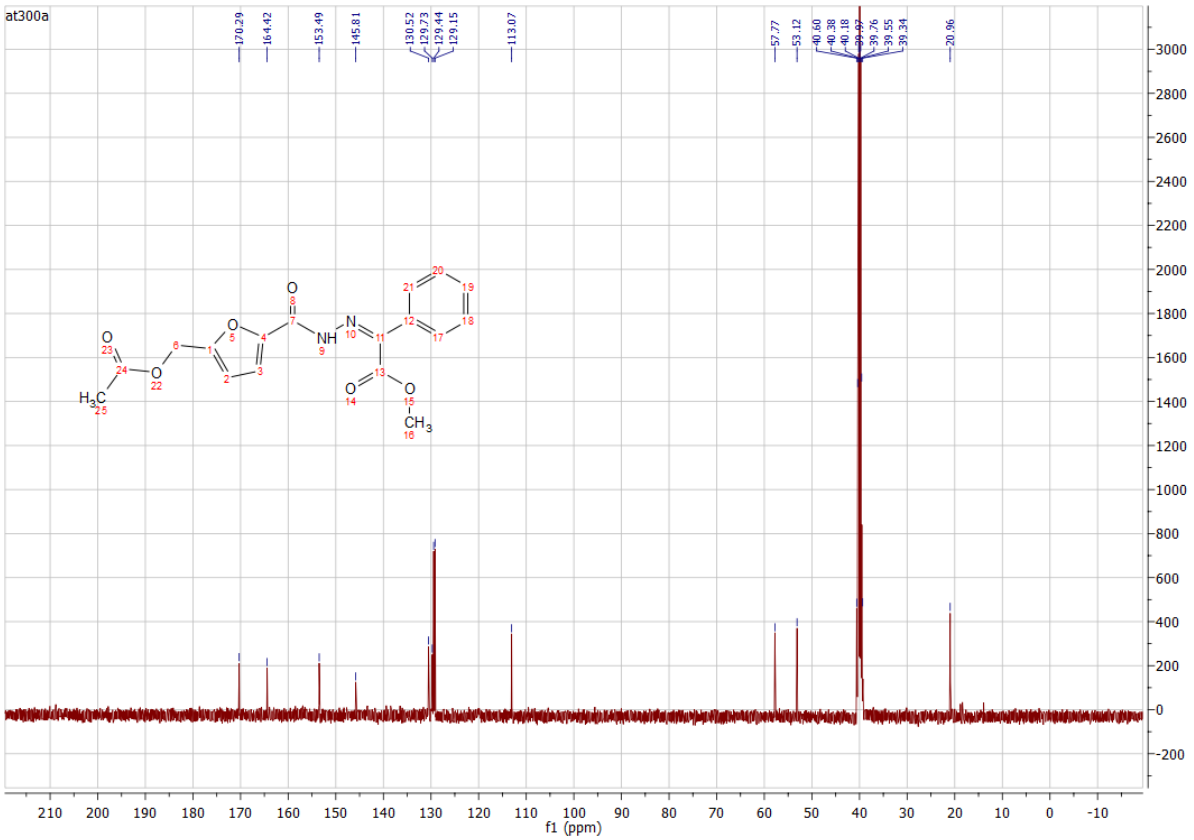
(E)-methyl 2-(2-(5-(acetoxymethyl)furan-2-carbonyl)hydrazono)-2-phenylacetate 19

Isolated as a slightly yellow oil (28 mg, 34 % yield) as a single isomer.

^{1}H NMR (400 MHz, DMSO) δ 10.45 (1H, bs), 7.55-7.44 (6H, m, Ph + furan ring), 6.75 (1H, bs, furan ring), 5.08 (2H, s, AcOC**H$_2$**), 3.82 (3H, s, COO**CH$_3$**), 2.06 (3H, s, Acetyl CH_3). ^{13}C NMR (101 MHz, DMSO) δ 170.29 (C24), 164.42 (C13), 153.49 (C1), 145.81 (C4), 130.52 (C12), 129.73 (C19), 129.44 (C18+C20), 129.15 (C21+C17), 113.07 (C2), 57.77 (C5), 53.12 (C16), 20.96 (C25).

Elementar analysis for $C_{17}H_{16}N_2O_6$ calc. %C 59.30; %H 4.68; %N 8.14 found %C 59.68; %H 5.10; %N 8.02.



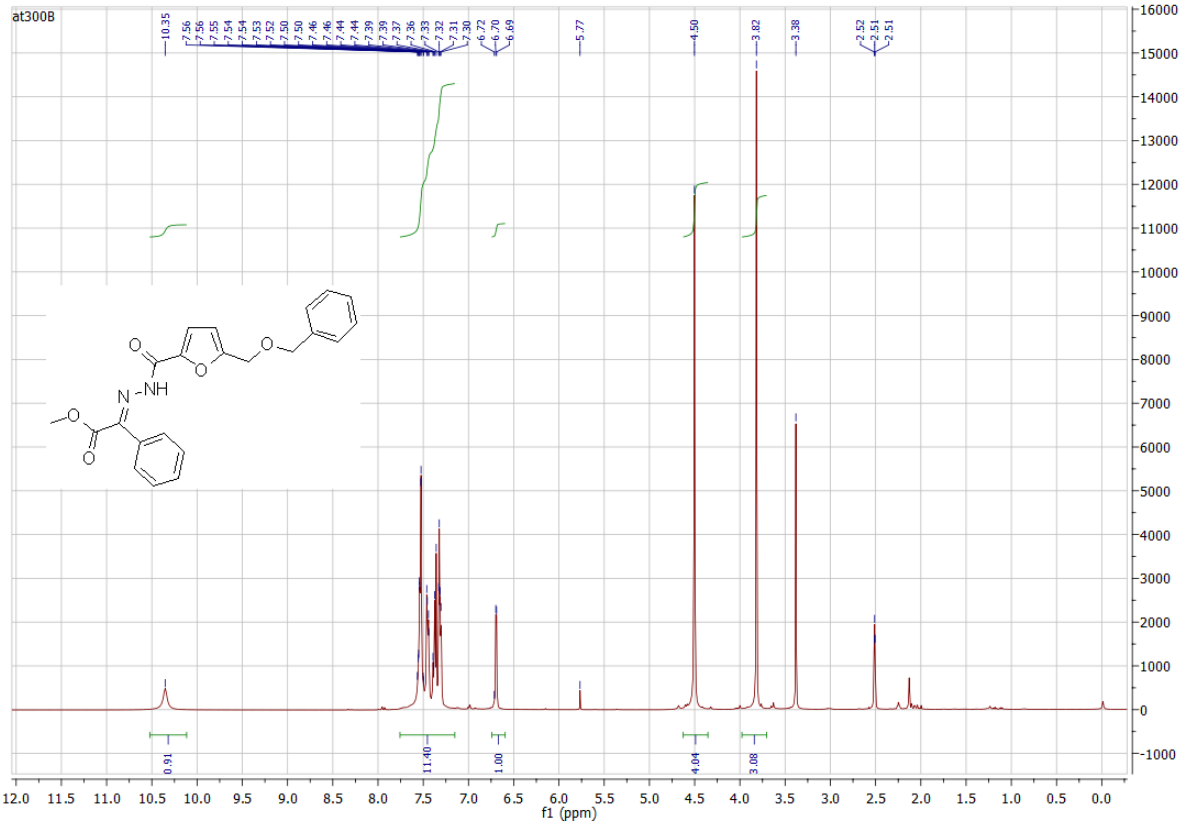


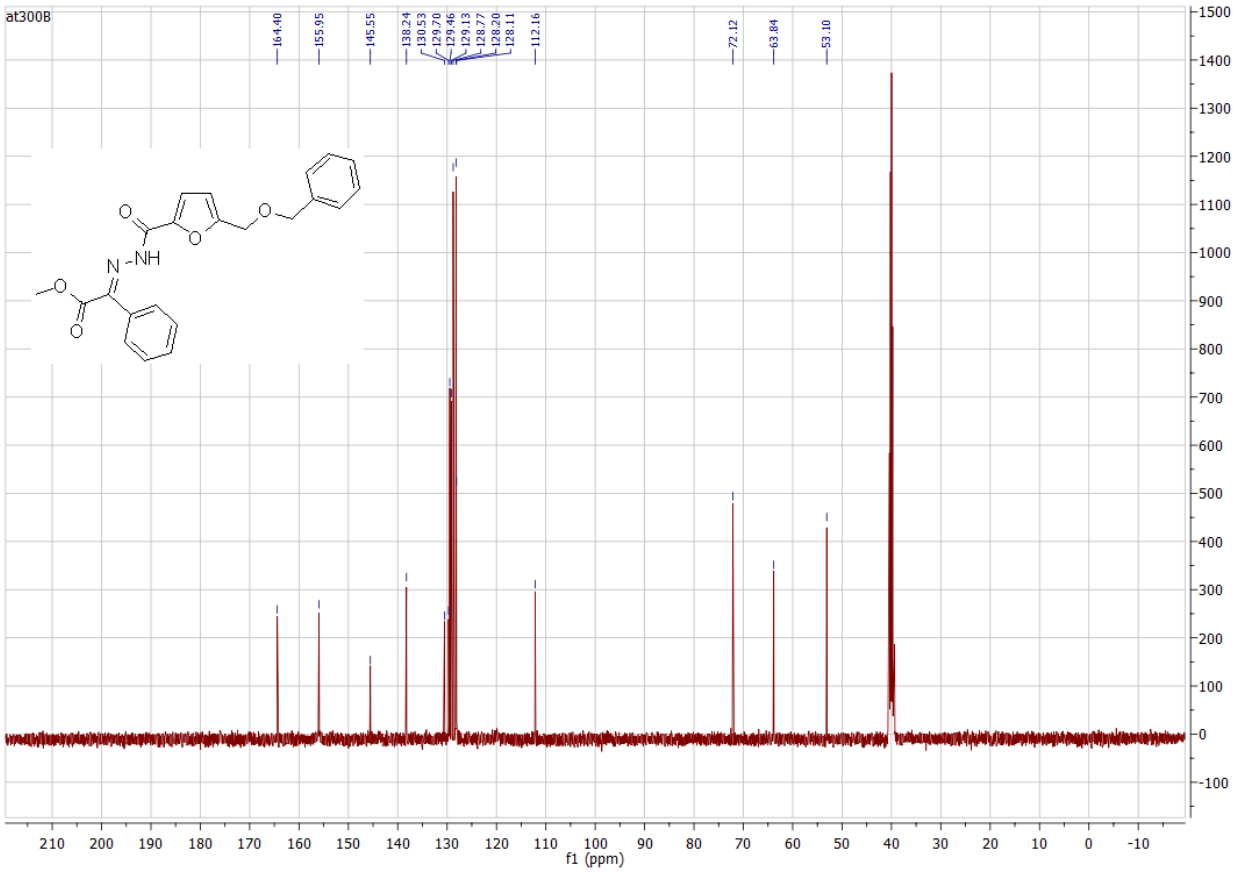
(E)-methyl 2-(2-(5-((benzyloxy)methyl)furan-2-carbonyl)hydrazono)-2-phenylacetate20

Isolated as a slightly yellow oil (83 mg, 89 % yield) as a single isomer.

^{1}H NMR (400 MHz, DMSO) δ 10.35 (1H, bs, N-H), 7.56-7.30 (11H, m, Phenyl groups + H ortho to carbonyl in furan), 6.70-6.69 (1H, d, H meta to carbonyl in furan), 4.50 (4H, bs, C**H$_2$**OC**H$_2$**), 3.82 (3H, s, COO**CH$_3$**). ^{13}C NMR (101 MHz, DMSO) δ 164.40 (**C**OOCH$_3$), 155.95 (furan quaternary linked to

HO**C**H_2), 145.55 (furan quaternary linked to carbonyl), 138.24 (Ph), 130.53 (Ph), 129.70 (Ph), 129.46 (Ph), 129.13 (Ph), 128.77 (Ph), 128.20 (Ph), 128.11 (Ph), 112.16 (furan C meta to carbonyl), 72.12 (**C**H_2OCH_2Ph), 63.84 (CH_2O**C**H_2Ph), 53.10 (COO**C**$\mathbf{H_3}$).
Elementar analysis for $C_{22}H_{20}N_2O_5$ calc. %C 67.34; %H 5.14; %N 7.14 found %C 67.32; %H 5.17; %N 7.15.



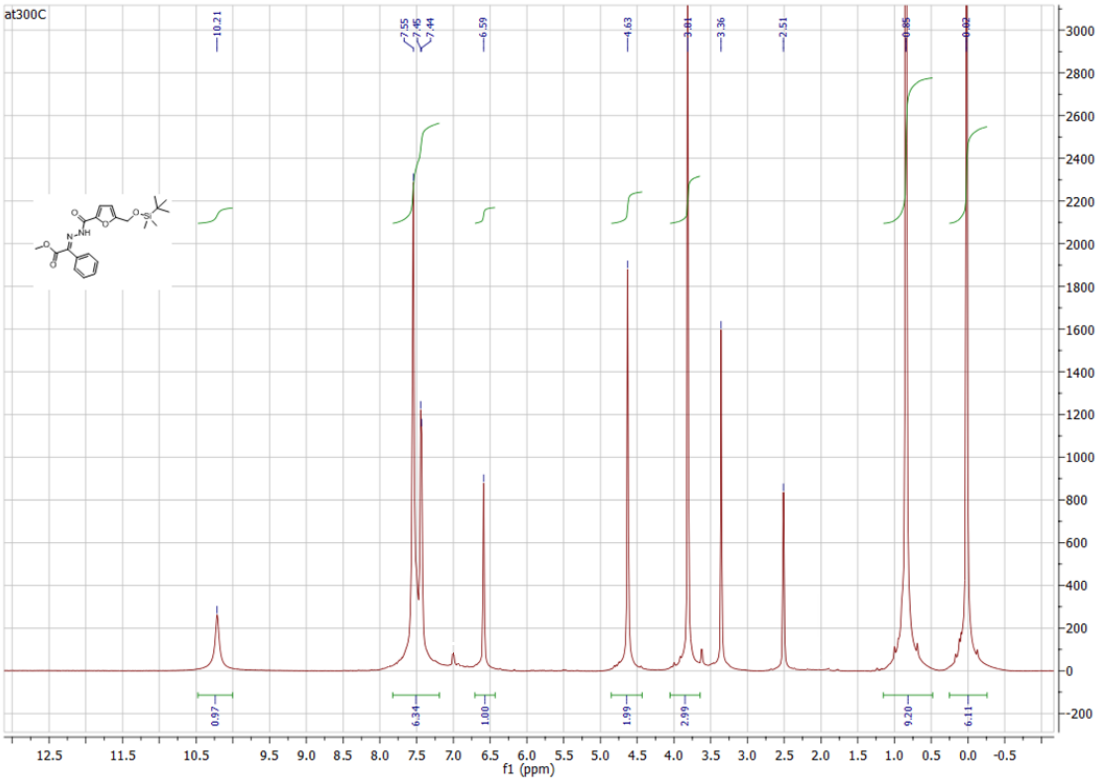


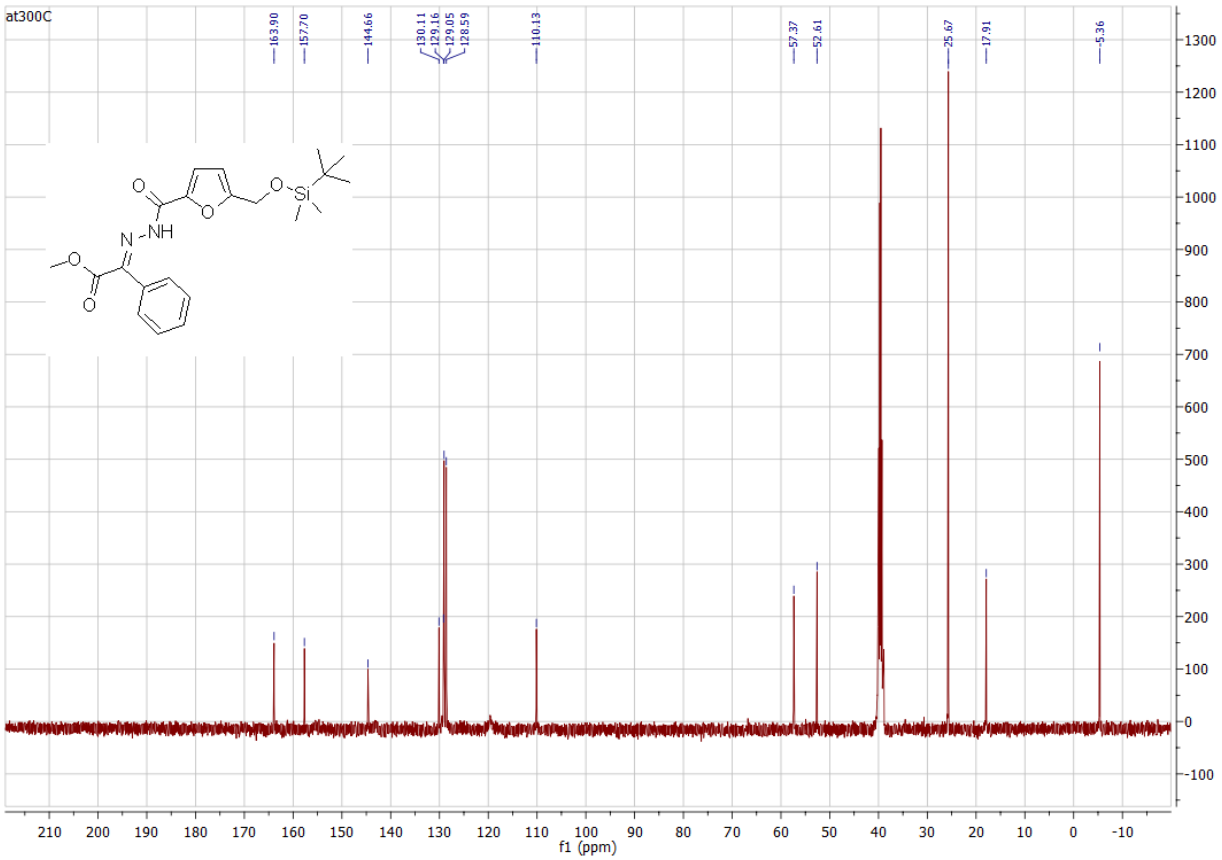
(*E*)-methyl 2-(2-(5-(((tert-butyldimethylsilyl)oxy)methyl) furan-2-carbonyl)hydrazono)-2-(phenyl) acetate21

Isolated as a slightly yellow oil (98 mg, >99 % yield) as a single isomer.

^{1}H NMR (400 MHz, DMSO) δ 10.21 (1H, s, N-H), 7.55- 7.44 (6H, m, phenyl aromatics + H ortho to carbonyl in furan), 6.59 (1H, bs, H meta to carbonyl in furan), 4.63 (2H, s, OC**H$_2$**), 3.81 (3H, s, COO**CH$_3$**), 0.85 (9H, s, t-butyl TBDMS), 0.02 (6H, s, methyl TBDMS). ^{13}C NMR (101 MHz, DMSO) δ 163.90 (**C**OOCH$_3$), 157.70 (furan quaternary linked to HO**C**H$_2$), 144.66 (furan quaternary linked to carbonyl), 130.11 (Ph), 129.16 (Ph), 129.05 (Ph), 128.59 (Ph), 110.13 (furan C meta to carbonyl), 57.37 ((TBDMSO**C**H$_2$)), 52.61 (COO**C**H$_3$), 25.67 (methyl carbon TBDMS), 17.91 (t-butyl carbons), -5.36 (Quaternary from TBDMS).

Elementar analysis for $C_{21}H_{28}N_2O_5Si$ calc. %C 60.55; %H 6.78; %N 6.73 found %C 60.42; %H 6.56; %N 6.70.



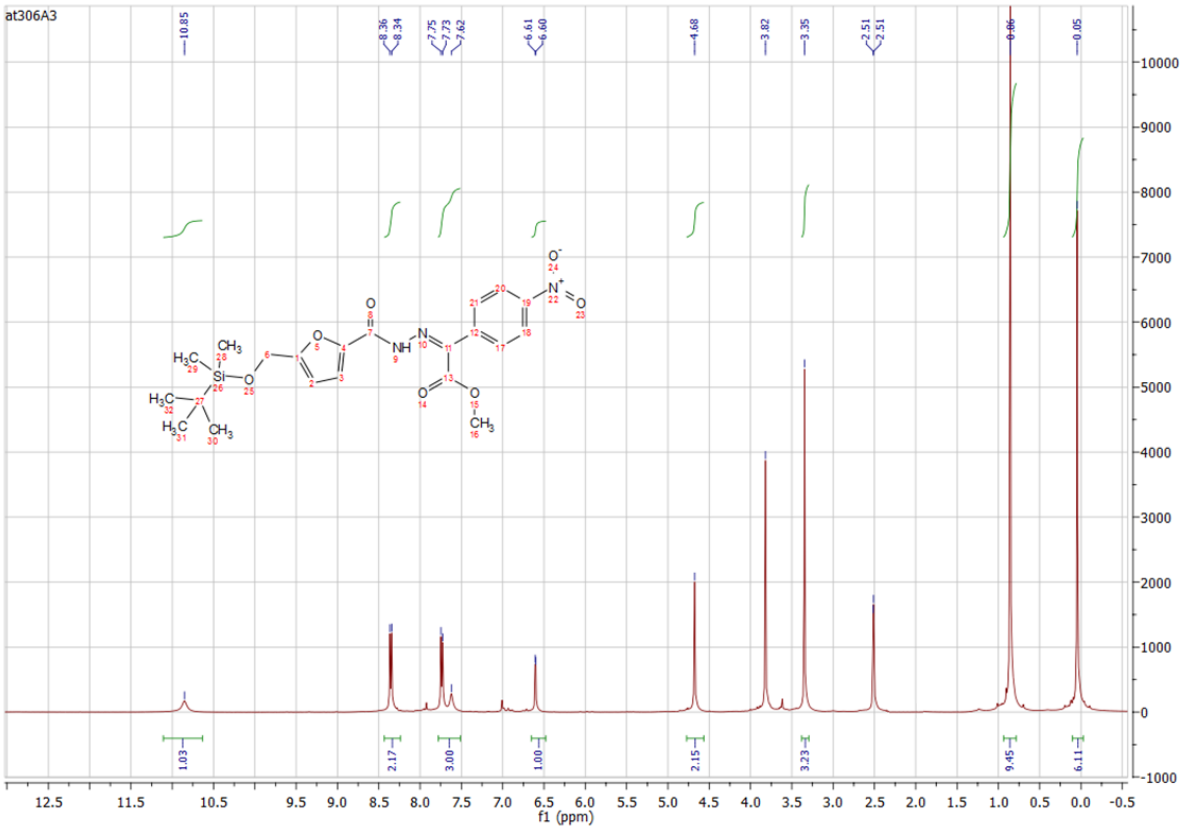


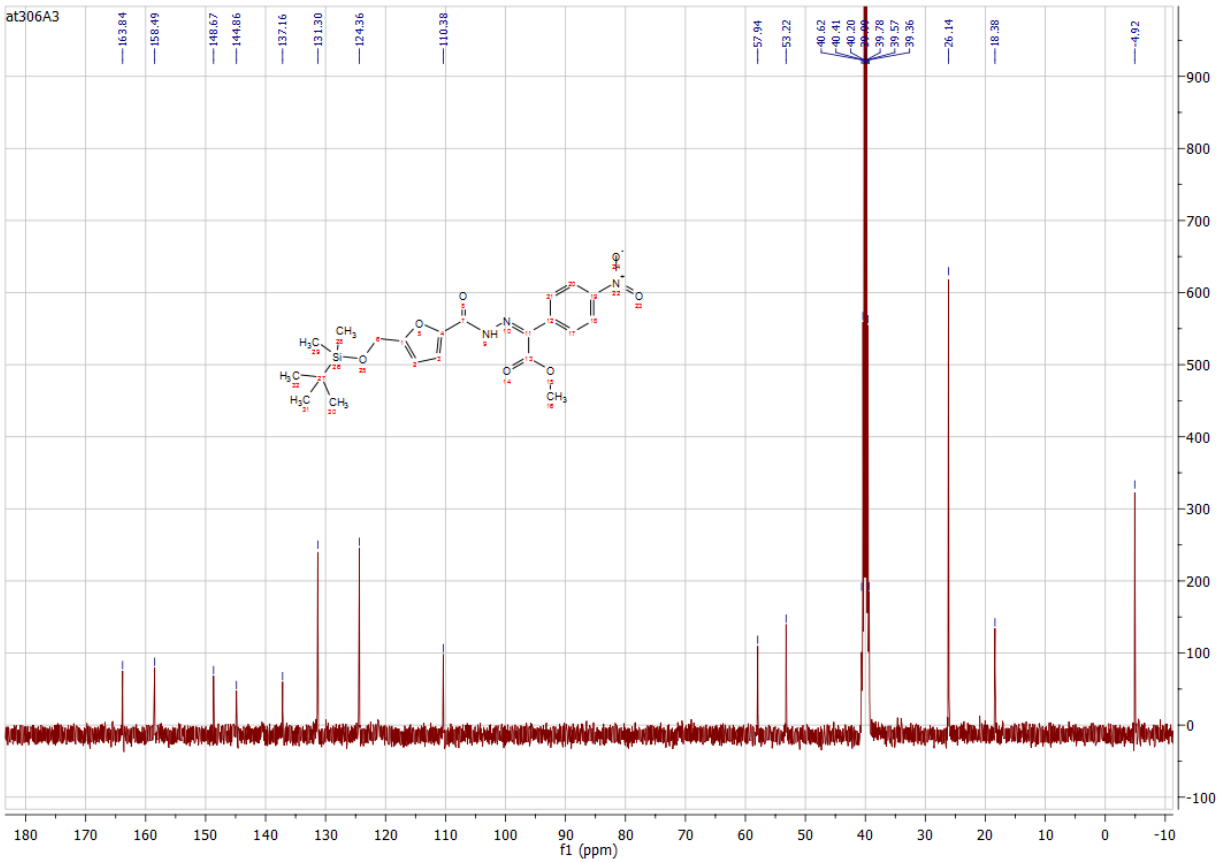
(E)-methyl 2-(2-(5-(((tert-butyldimethylsilyl)oxy)methyl)furan-2-carbonyl)hydrazono)-2-(4-nitrophenyl)acetate22

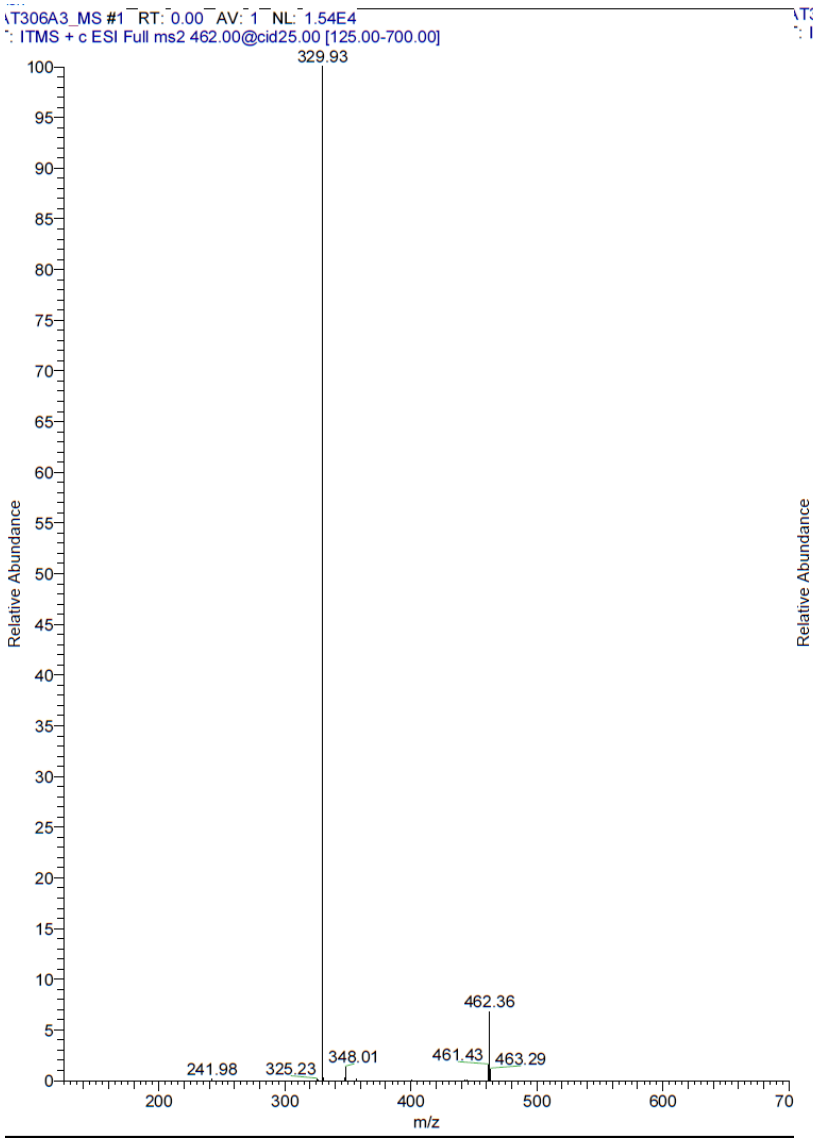
Isolated as a yellow powder (30 mg, 27 % yield) as a single isomer.

^{1}H NMR (400 MHz, DMSO) δ 10.85 (1H, bs, N-H), 8.36-8.34 (2H, d, H18+H20), 7.75-7.62 (3H, m, H17+H21+H3), 6.61-6.60 (1H, d, H2), 4.68 (2H, s, H6), 3.35 (3H, s, H16), 0.86 (9H, s, t-butyl TBDMS), 0.05 (6H, s, methyl TBDMS). ^{13}C NMR (101 MHz, DMSO) δ 163.84 (**C**OOCH$_3$), 158.49 (furan quaternary linked to HO**C**H$_2$), 148.67 (Ph quaternary nitro), 144.86 (furan quaternary linked to

carbonyl), 137.16 (Ph quaternary hydrazone), 131.30 (C18+C20), 124.36 (C17+C21), 110.38 (furan C meta to carbonyl), 57.94 (TBDMSO**C**H_2), 53.22 (COO**C**H_3), 26.14 (methyl carbon TBDMS), 18.38 (t-butyl carbons), -4.92 (Quaternary from TBDMS).
MS (ESI+, M+H)=461.8; MS (ESI+, 461.8)=330.0; MS (ESI+, 330.0)=242.0; MS (ESI+, 242.0)=214.0. The fragmentation pattern suggests the sequencial loss of functional groups from the molecule, however rearrangements may take place. HRMS (ESI-TOF, M+Na) calc. 484.1516 found 484.1516




at306A3
163.84
158.49
148.67
144.86
137.16
131.30
124.36
110.38
57.94
53.22
40.62
40.41
40.20
39.99
39.78
39.57
39.36
26.14
18.38
-4.92
f1 (ppm)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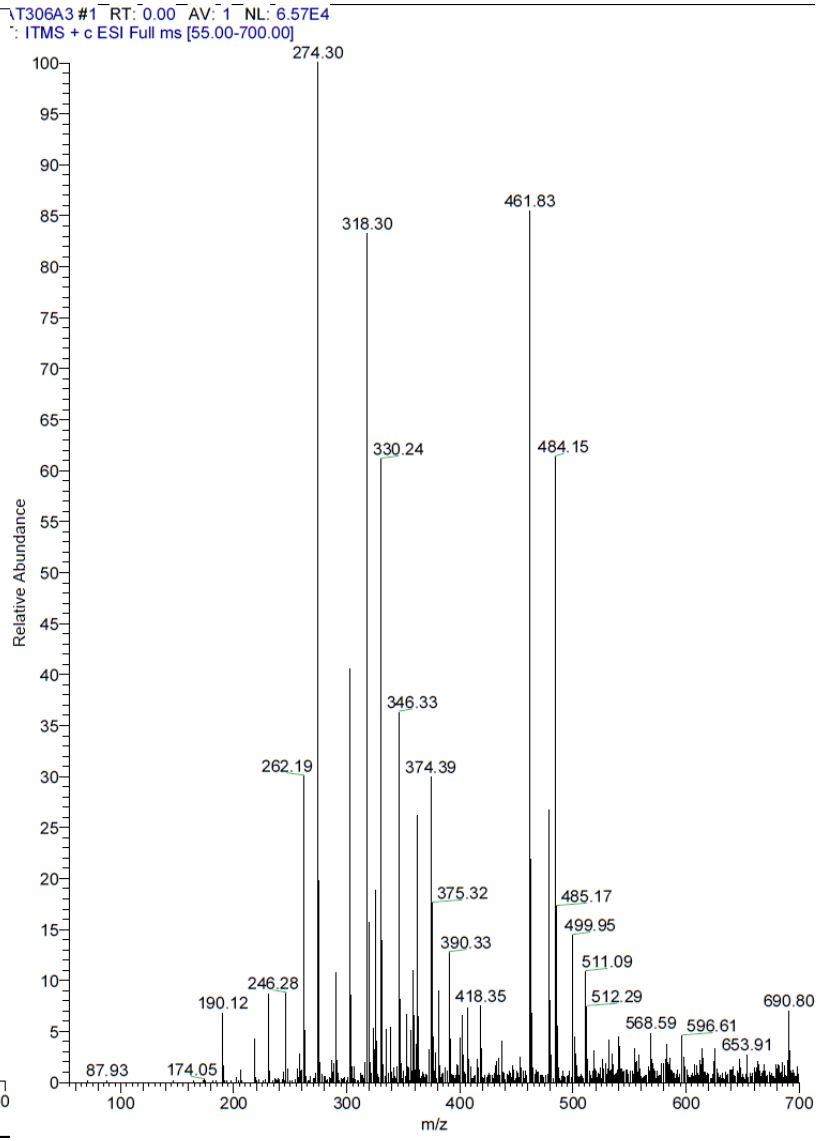
348.01
461.43
463.29
Relative Abundance
m/z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: ITMS + c ESI Full ms [55.00-700.00]
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461.83
318.30
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262.19
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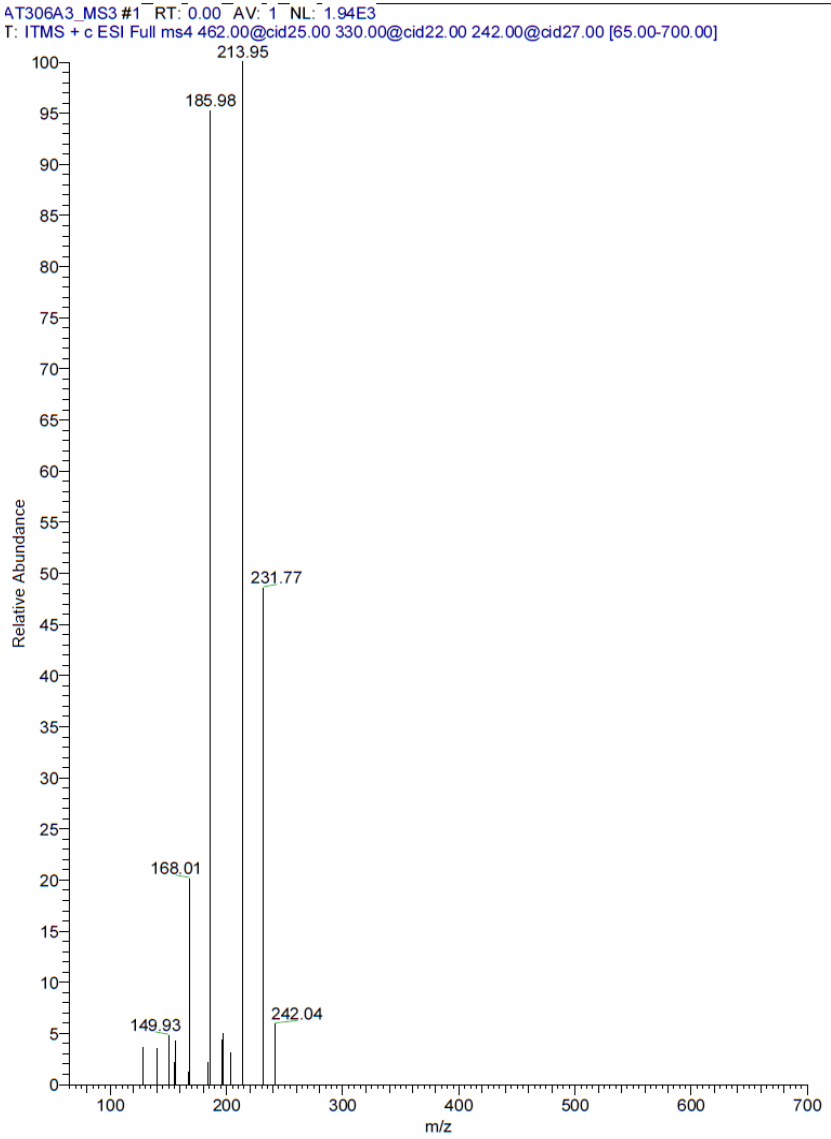
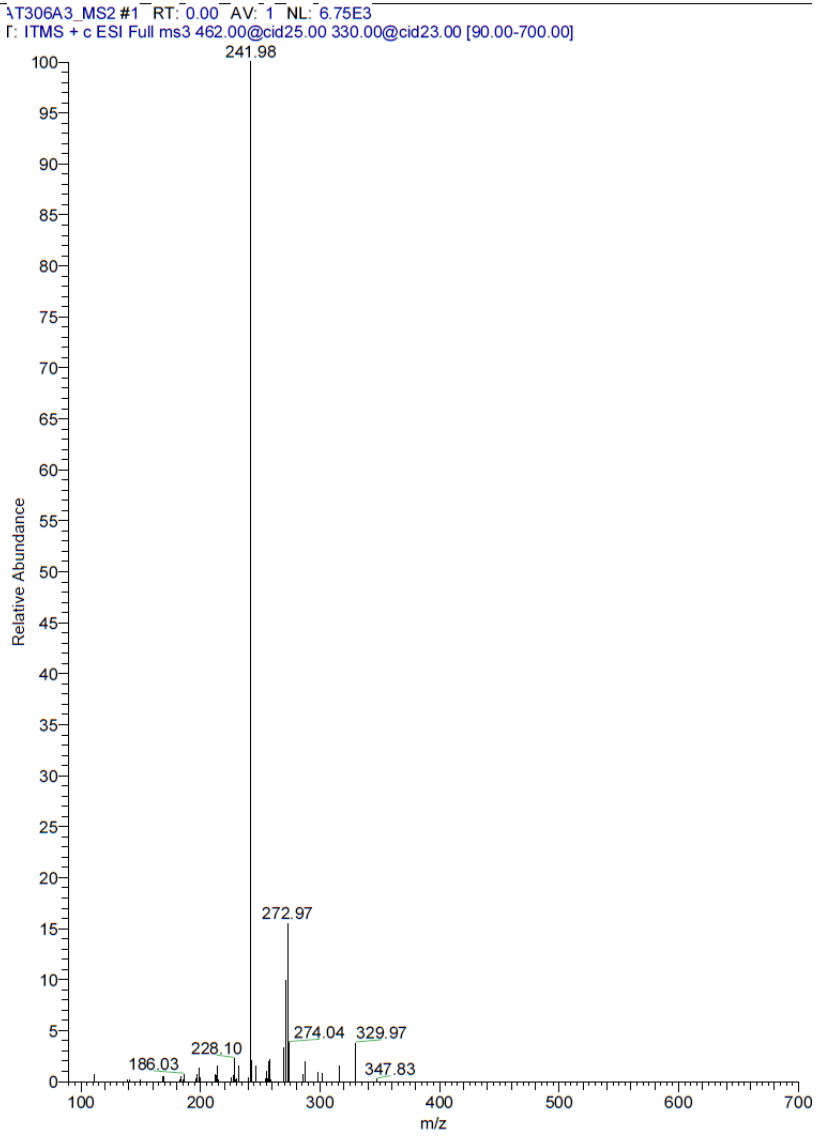
499.95
390.33
511.09
246.28
418.35
512.29
190.12
690.80
568.59
596.61
653.91
87.93
174.05
Relative Abundance
m/z

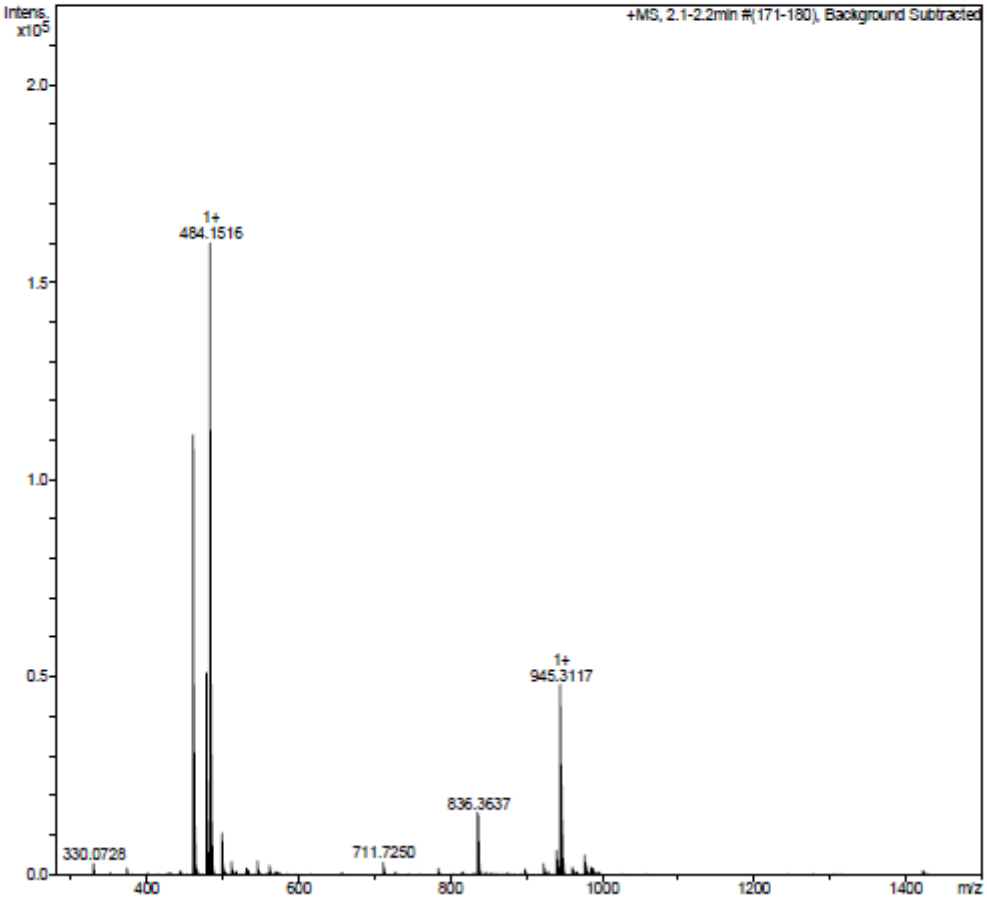

AT306A3_MS3 #1 RT: 0.00 AV: 1 NL: 1.94E3
T: ITMS + c ESI Full ms4 462.00@cid25.00 330.00@cid22.00 242.00@cid27.00 [65.00-700.00]
213.95
185.98
231.77
168.01
149.93
242.04
Relative Abundance
m/z


AT306A3_MS2 #1 RT: 0.00 AV: 1 NL: 6.75E3
T: ITMS + c ESI Full ms3 462.00@cid25.00 330.00@cid23.00 [90.00-700.00]
241.98
272.97
274.04
329.97
228.10
186.03
347.83
Relative Abundance
m/z

ESPECTRO ESI-FIA-TOF-Medida de Masas Exactas

Analysis Info

Sample Name	AT306A3_461_1-C,9_01_13192.d	Acquisition Date	3/18/2014 11:48:02 AM
Method	fia_pos_medio_350-1500_egf.m	Instrument	micrOTOF

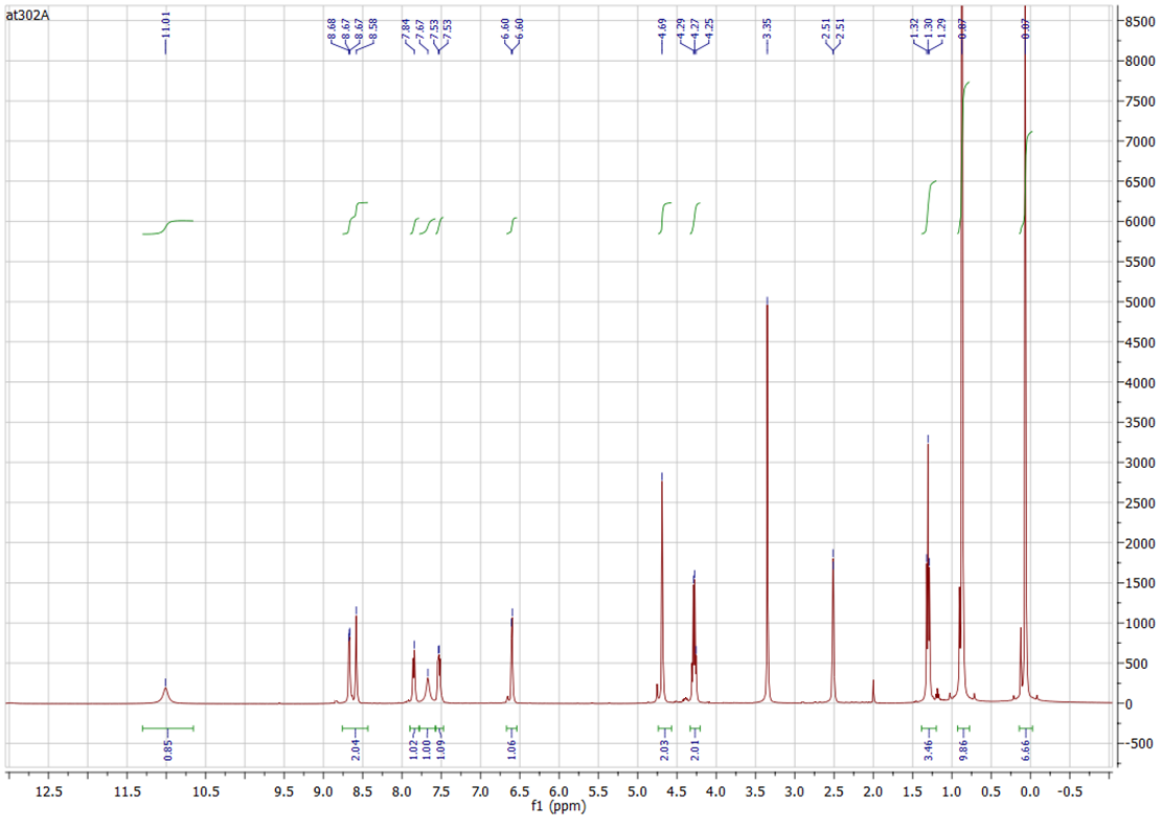


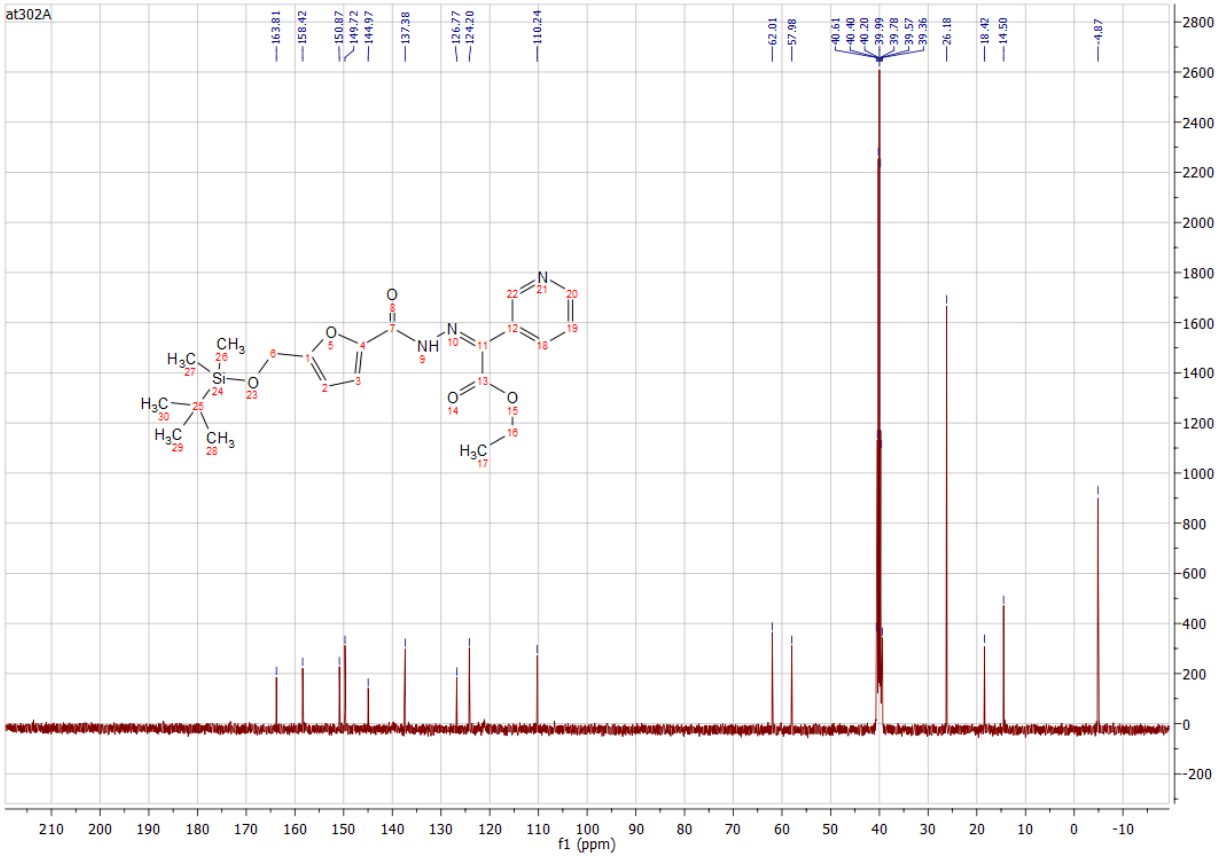
(E)-ethyl 2-(2-(5-(((tert-butyldimethylsilyl)oxy)methyl)furan-2-carbonyl)hydrazono)-2-(pyridin-3-yl)acetate23

Isolated as a yellow oil (81 mg, 80 % yield) as a single isomer.

^{1}H NMR (400 MHz, DMSO) δ 11.01 (1H, bs, N-H), 8.68-8.58 (2H, m, H22+H18), 7.84 (1H, d, H20), 7.67 (1H, bs, H3), 7.53 (1H, d, H19), 6.60 (1H, d, H2), 4.69 (2H, s, H6), 4.29-4.25 (2H, quartet, H16), 1.32-1.29 (3H, t, H17), 0.87 (9H, s, t-butyl TBDMS), 0.07 (6H, s, methyl TBDMS). ^{13}C NMR (101 MHz, DMSO) δ 163.81 (**C**OOCH$_3$), 158.42 (furan quaternary linked to HO**C**H$_2$), 150.87 (C20), 149.72 (C22), 144.97 (C4), 137.38 (C18), 126.77 (C12), 124.20 (C19), 110.24 (furan C meta to carbonyl), 62.01 (TBDMSO**C**H$_2$), 57.98 (**C**H$_2$CH$_3$), 26.18 (methyl carbon TBDMS), 18.42 (t-butyl carbons), 14.50 (CH$_2$**C**H$_3$), -4.87 (Quaternary from TBDMS).

Elementar analysis for $C_{21}H_{29}N_3O_5Si$ calc. %C 58.45; %H 6.77; %N 9.74 found %C 58.55; %H 6.73; %N 9.53.



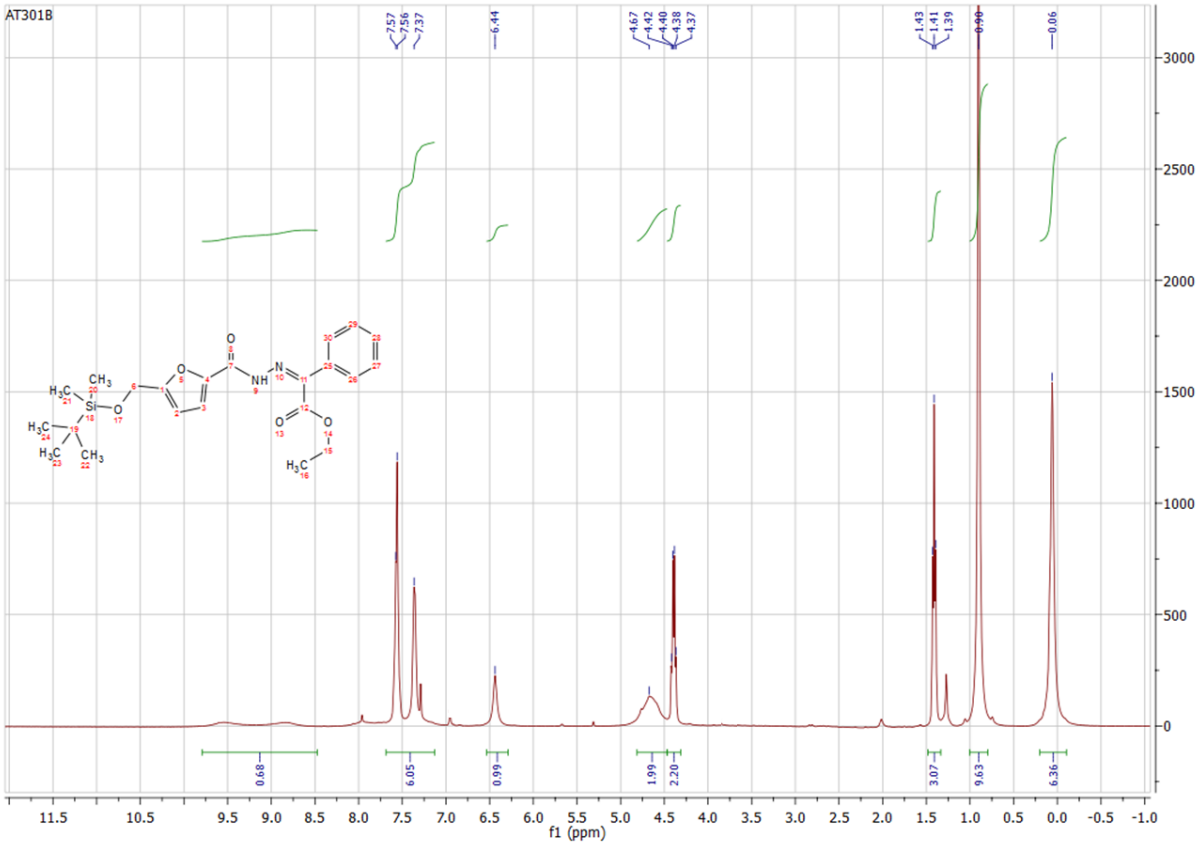


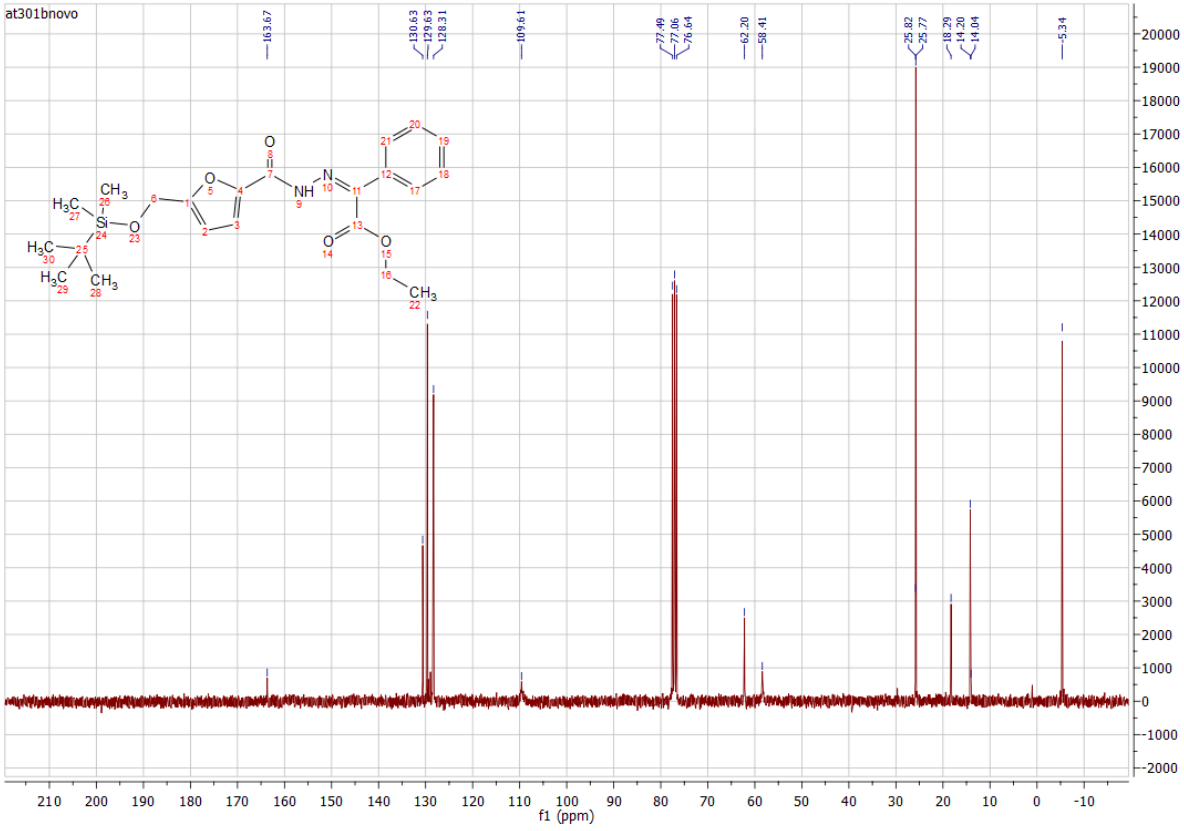
(E)-ethyl 2-(2-(5-(((tert-butyldimethylsilyl)oxy)methyl) furan-2-carbonyl)hydrazono)-2-phenylacetate24

Isolated as a slightly yellow oil (74 mg, 73 % yield) as a single isomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.37 (6H, m, Ph + furan H near to carbonyl), 6.44 (1H, bs, furan H β to carbonyl), 4.67 (2H, bm, O**C**$\mathbf{H}_2$), 4.42-4.37 (2H, quartet, H15), 1.43-1.39 (3H, t, H16), 0.90 (9H, s, t-

butyl TBDMS), 0.06 (6H, s, methyl TBDMS). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.67 (**C**$OOCH_3$), 130.63 (Ph), 129.63 (Ph), 128.31 (Ph), 109.61 (C2), 62.20 (C4), 58.41 (C15), 25.77 (methyl carbon TBDMS), 18.29 (t-butyl carbons), 14.20 (C16), -5.34 (Quaternary from TBDMS).
Elementar analysis for $C_{22}H_{30}N_2O_5Si$ calc. %C 61.37; %H 7.02; %N 6.51 found %C 61.10; %H 6.96; %N 6.30.



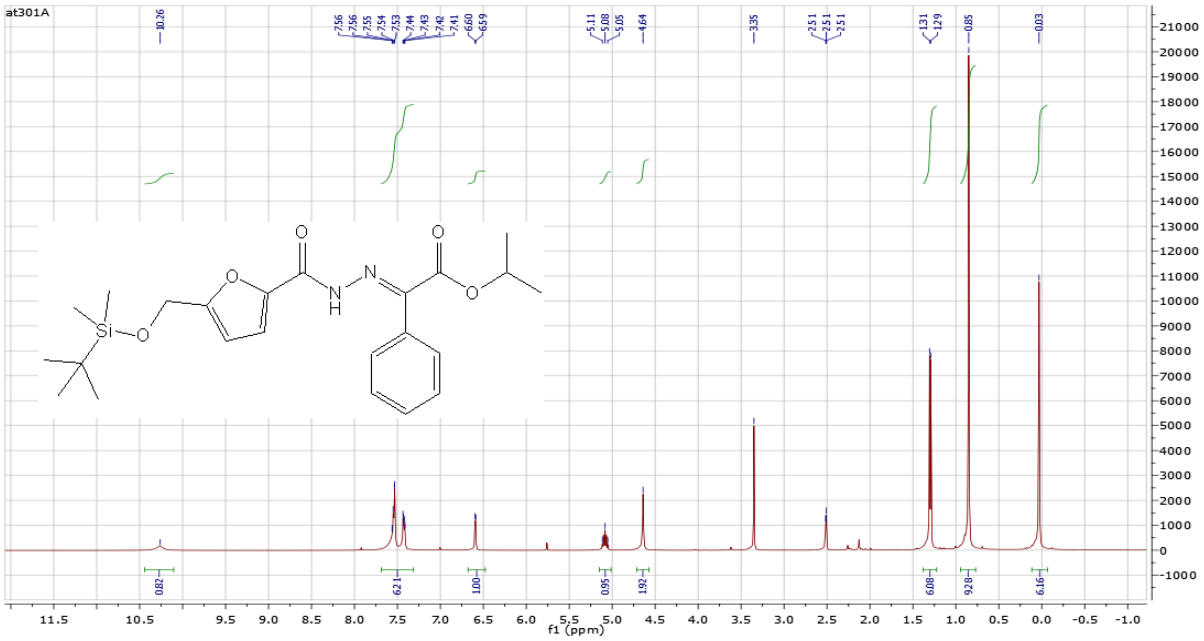


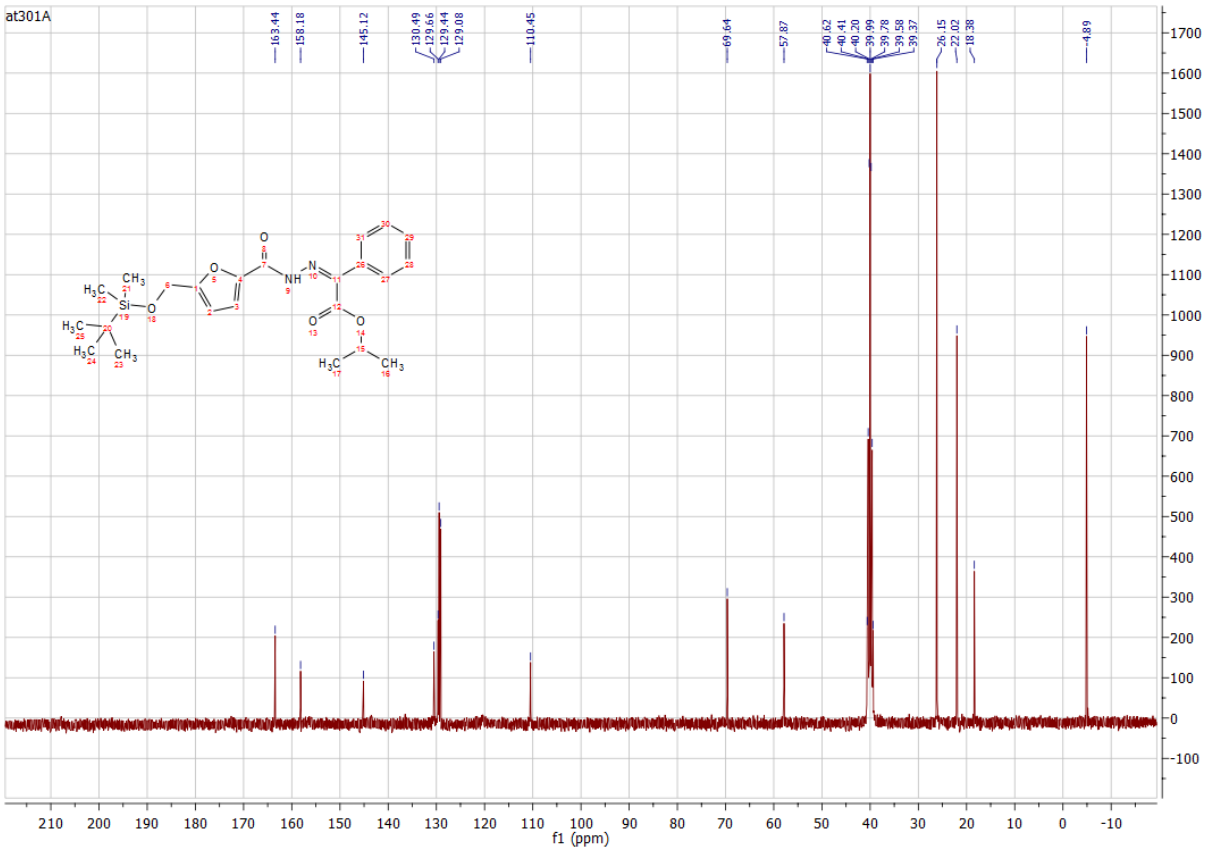
(E)-isopropyl 2-(2-(5-((tert-butyldimethylsilyl)oxy)methyl)furan-2-carbonyl)hydrazono)-2-phenylacetate25

Isolated as a slightly yellow oil (77 mg, 73 % yield) as a single isomer.

^{1}H NMR (400 MHz, DMSO) δ 10.26 (1H, bs, N-H), 7.56-7.41 (6H, m, Ph + furan H near to carbonyl), 6.60-6.59 (1H, d, furan H near to hydroxymethylene), 5.11-5.05 (1H, m, C**H**$(CH_3)_2$), 4.64 (2H, s, O**CH$_2$**), 1.31-1.29 (6H, d, CH(**CH$_3$)$_2$**), 0.85 (9H, s, t-butyl TBDMS), 0.03 (6H, s, methyl TBDMS). ^{13}C NMR (101 MHz, DMSO) δ 163.44 (**C**OOCH_3), 158.18 (quater. C furan at hydroxymethyl), 145.12 (quater. C furan at carbonyl), 130.49 (Ph), 129.66 (Ph), 129.44 (Ph), 129.08 (Ph), 110.45 (furan C near to hydroxymethyl), 69.64 (O**CH$_2$**), 57.87 (C**H**$(CH_3)_2$), 26.15 (methyl carbon TBDMS), 22.02 (CH(**CH$_3$)$_2$**), 18.38 (t-butyl carbons), -4.89 (Quaternary from TBDMS).

Elementar analysis for $C_{23}H_{32}N_2O_5Si$ calc. %C 62.13; %H 7.25; %N 6.30 found %C 62.51; %H 7.19; %N 6.43.



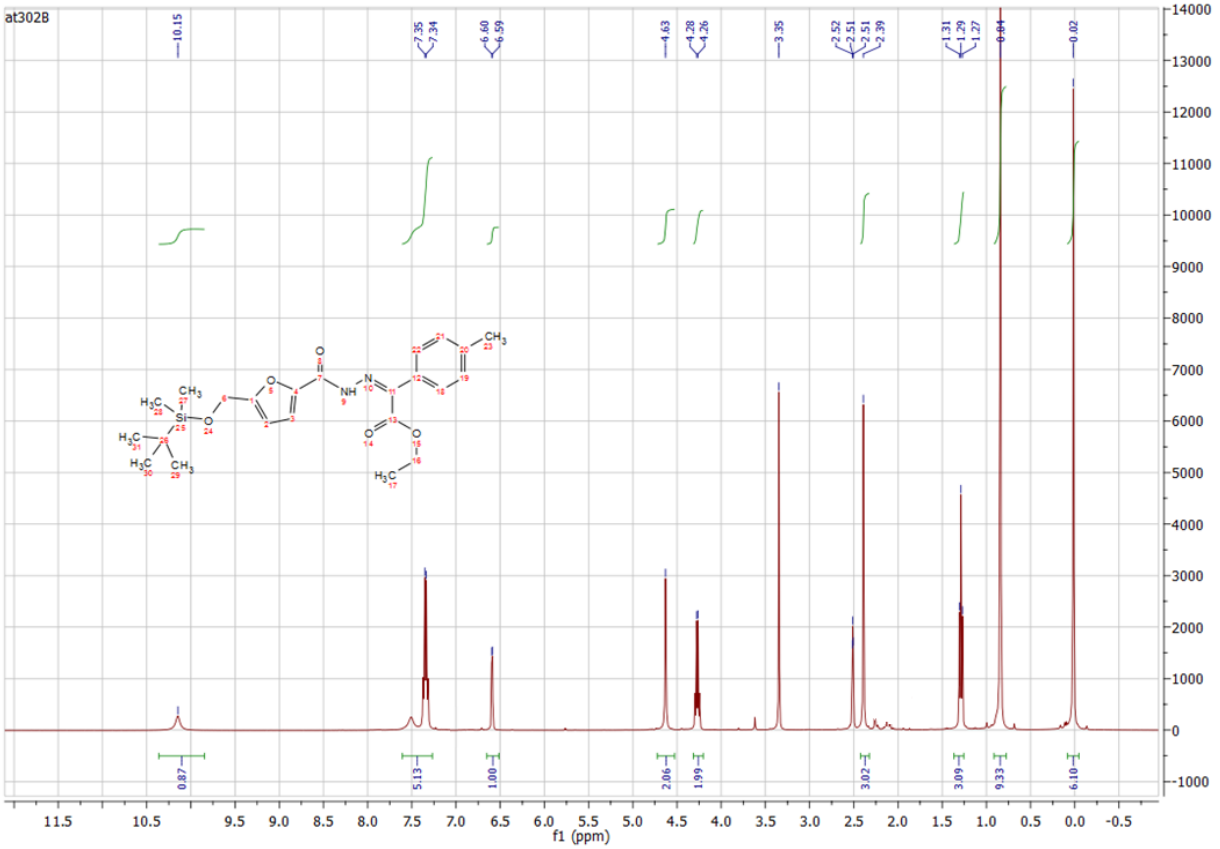


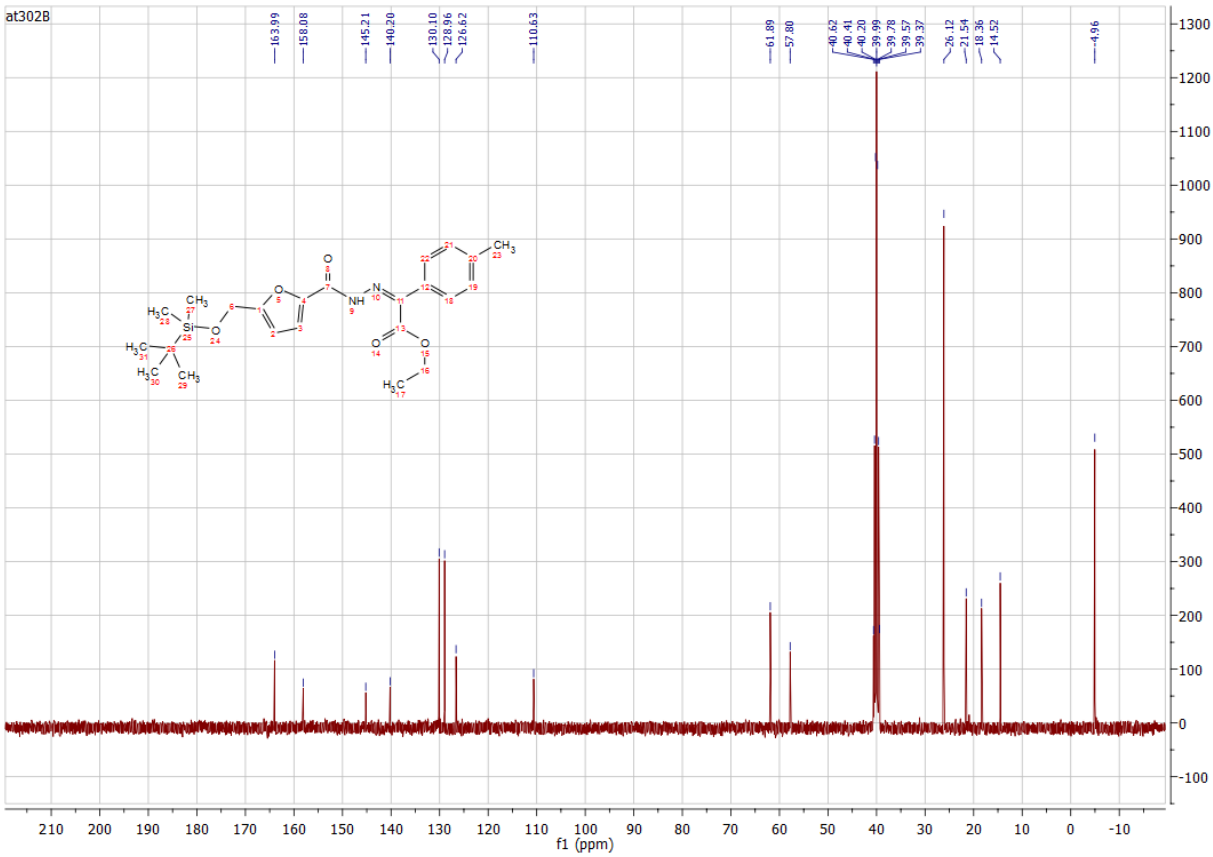
(E)-ethyl 2-(2-(5-(((tert-butyldimethylsilyl)oxy)methyl)furan-2-carbonyl)hydrazono)-2-(p-tolyl)acetate26

Isolated as a slightly yellow oil (81 mg, 77 % yield) as a single isomer.

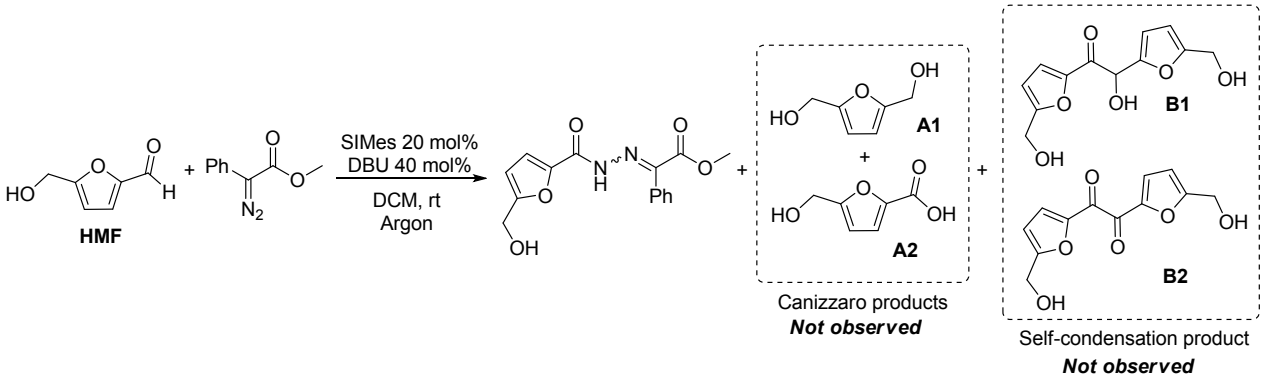
^{1}H NMR (400 MHz, DMSO) δ 10.15 (1H, s, N-H), 7.35 (5H, m, Ph + furan H near to carbonyl), 6.60-6.59 (1H, d, furan H near to hydroxymethylene), 4.63 (2H, s, O**CH$_2$**), 4.28 (2H, quartet, **CH$_2$**CH$_3$), 2.39 (3H, s, CH$_2$**CH$_3$**), 1.31-1.27 (3H, s, methyl at phenyl), 0.84 (9H, s, t-butyl TBDMS), 0.02 (6H, s, methyl TBDMS). ^{13}C NMR (101 MHz, DMSO) δ 163.99 (**C**OOCH$_3$), 158.08 (quater. C furan at hydroxymethyl), 145.21 (quater. C furan at carbonyl), 140.20 (Ph), 130.10 (Ph), 128.96 (Ph), 126.62 (Ph), 110.63 (furan C near to hydroxymethyl), 61.89 (O**CH$_2$**), 57.80 (**CH$_2$**CH$_3$), 26.12 (methyl carbon TBDMS), 21.54 (methyl at phenyl), 18.36 (t-butyl carbons), 14.52 (CH$_2$**CH$_3$**), -4.96 (Quaternary from TBDMS).

Elementar analysis for $C_{23}H_{32}N_2O_5Si$ calc. %C 62.13; %H 7.25; %N 6.30 found %C 62.35; %H 7.16; %N 6.42.


at302B
10.15
7.35
7.34
6.60
6.59
4.63
4.28
4.26
3.35
2.52
2.51
2.51
2.39
1.31
1.29
1.27
0.84
0.02
0.87
5.13
1.00
2.06
1.99
3.02
3.09
9.33
6.10
f1 (ppm)


at302B
163.99
158.08
145.21
140.20
130.10
128.96
126.62
110.63
61.89
57.80
40.62
40.41
40.20
39.99
39.78
39.57
39.37
26.12
21.54
18.36
14.52
-4.96
f1 (ppm)

Selectivity studies of reaction 1 table 2.



Products **A1**, **B1** and **B2** were not observed in the crude reaction mixture analysis by HPLC.

Canizzaro products **A1** and **A2** were prepared accordingly to Subbiah *et al.* [1]. HPLC result of acid A2 is not shown.

Self-condensation products B1 and B2 were prepared using NHC catalysis as following: SIMes (10 mol %) and DBU (20 mol %) were dissolved in freshly dry DCM (0.5 mL) inside a round bottom flask under argon. The mixture was stirred for 15 minutes at room temperature. Then a solution of aldehyde (1 eq. in 0.5 mL of DCM) was added and the mixture was left reacting during four hours. The final product precipitates from the reaction medium. The reaction mixture is filtered off via canola and the crude analyzed by HPLC and ^{1}H NMR.

B1 - ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.50 (d, J = 3.6 Hz, 1H), 6.51 (d, J = 3.6 Hz, 1H), 6.35 (d, J = 3.2 Hz, 1H), 6.22 (d, J = 3.2 Hz, 1H), 5.74 (s, 1H), 4.46 (s, 2H), 4.31 (s, 2H). [2]

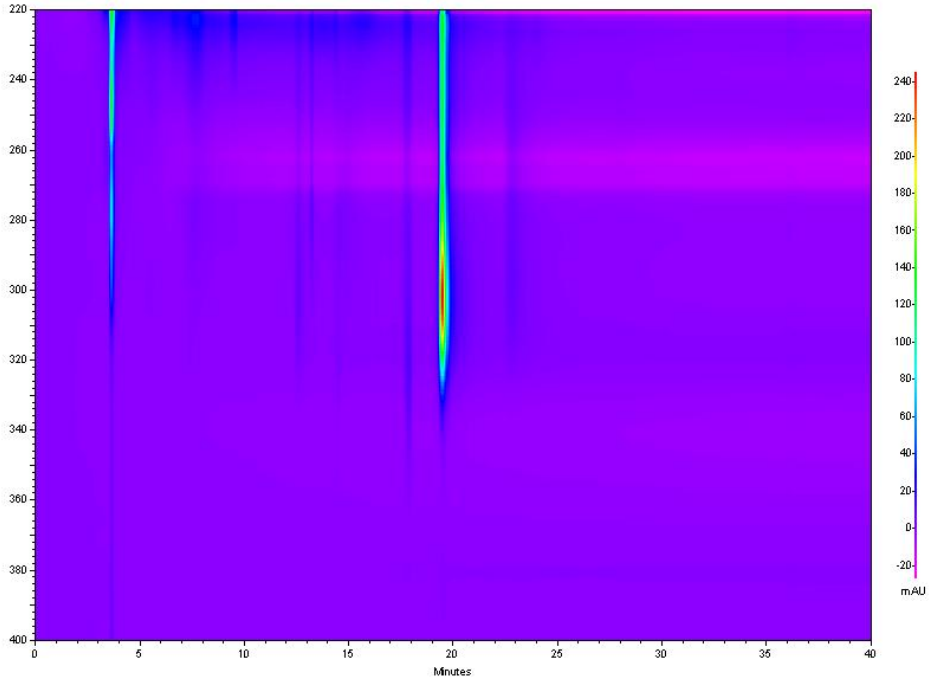
B2 - ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.57 (d, J = 3.7 Hz, 1H), 6.65 (d, J = 3.7 Hz, 1H), 4.54 (s, 2H).

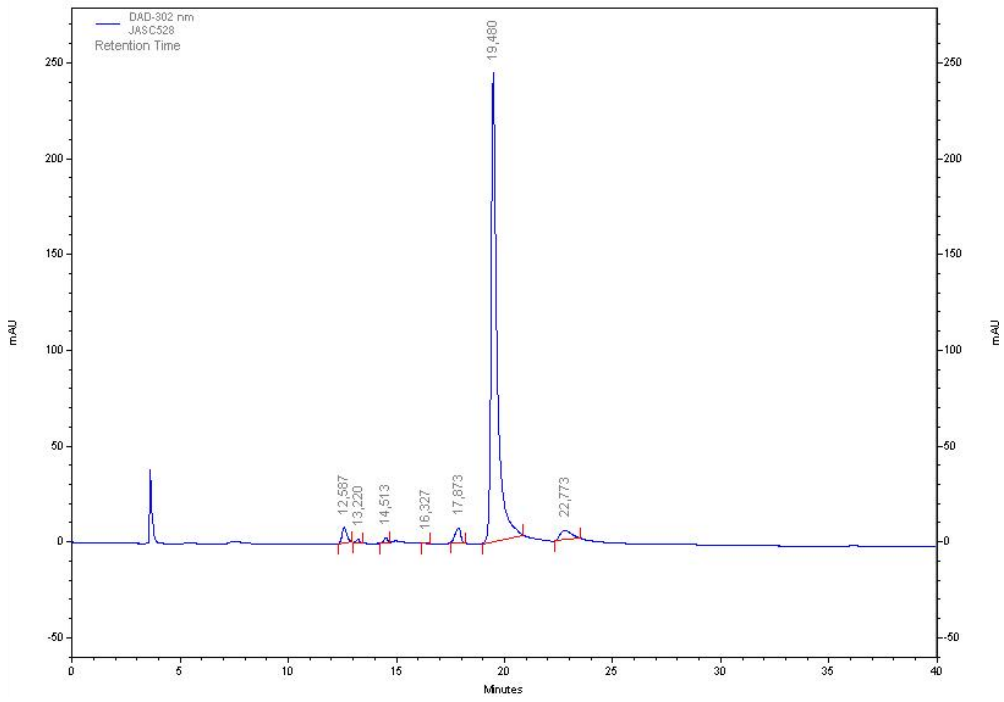
HPLC analysis was performed in a VWR Hitachi machine with a diode array detector L-2455 coupled to a pump L-2130 and using a KROMASIL 100 SIL 5.0 column, eluent: 99:1 to 80:20 (n-hexane/2-propanol) in 10 min then 80:20 (*n*-hexane/2-propanol) for the period showed in the chromatograms.

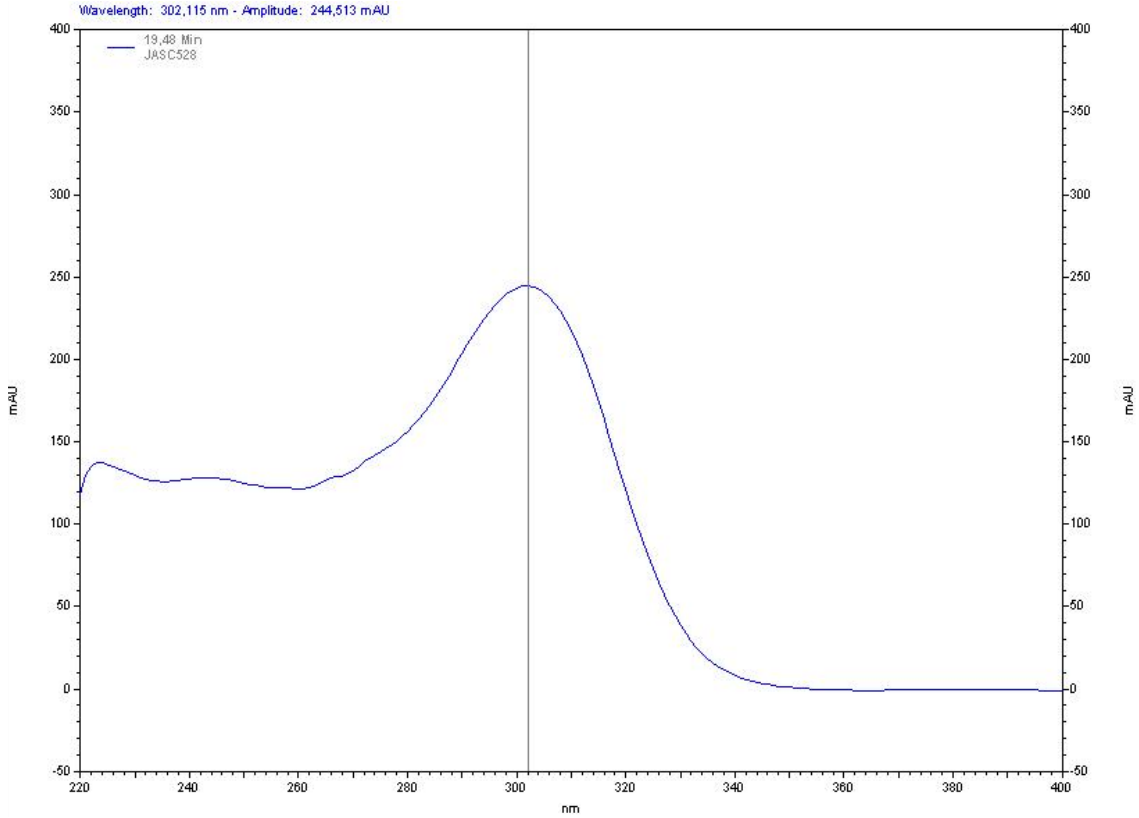
[1] Sowmiah Subbiah, Svilen P. Simeonov, José M. S. S. Esperança,Luís Paulo N. Rebelo, Carlos A. M. Afonso, *Green Chem.*, **2013**, 15, 2849-2853.

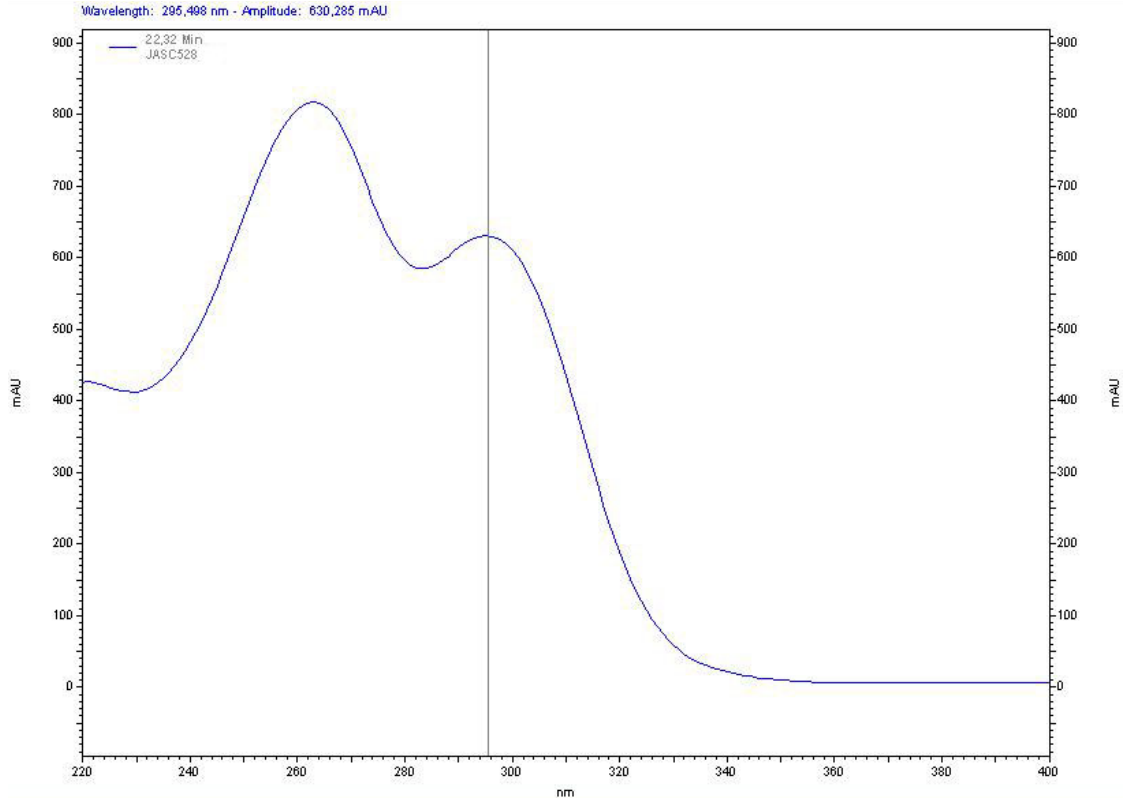
[2] NMR analysis is according to literature: Dajiang (D. J.) Liu and Eugene Y.-X. Chen, *ACS Catal.*, **2014**, 4, 1302–1310.

HPLC of reaction mixture (reaction conditions accordingly to Table 1, entry 1)

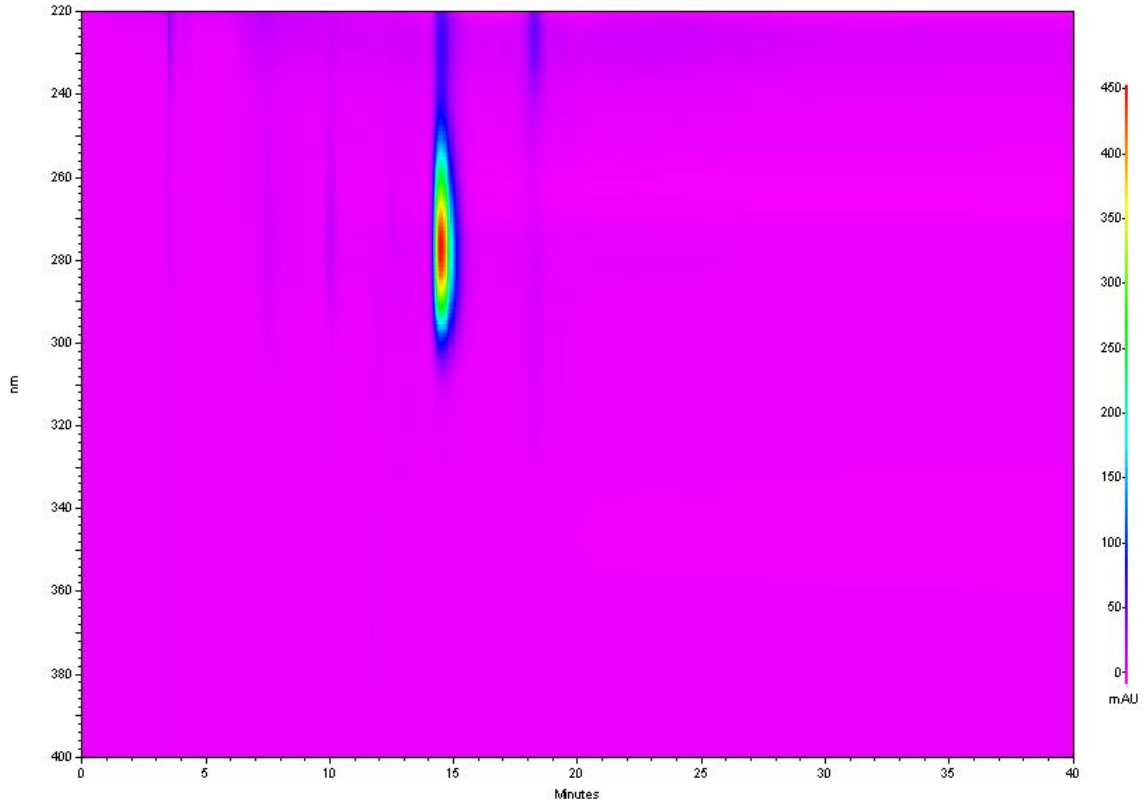

220
240
260
280
300
320
340
360
380
400
0
5
10
15
20
25
30
35
40
Minutes
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
mAU

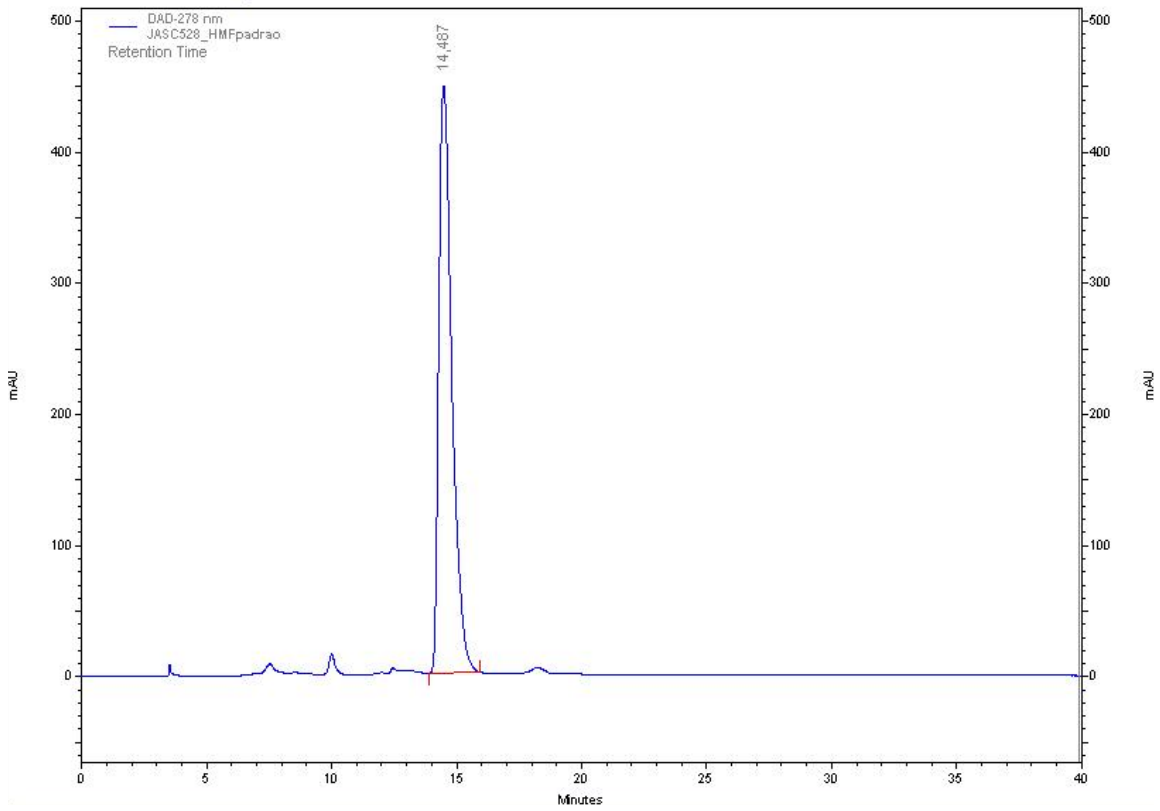

DAD-302 nm
JASC528
Retention Time
19,480
12,587
13,220
14,513
16,327
17,873
22,773
mAU
250
200
150
100
50
0
-50
0
5
10
15
20
25
30
35
40
Minutes

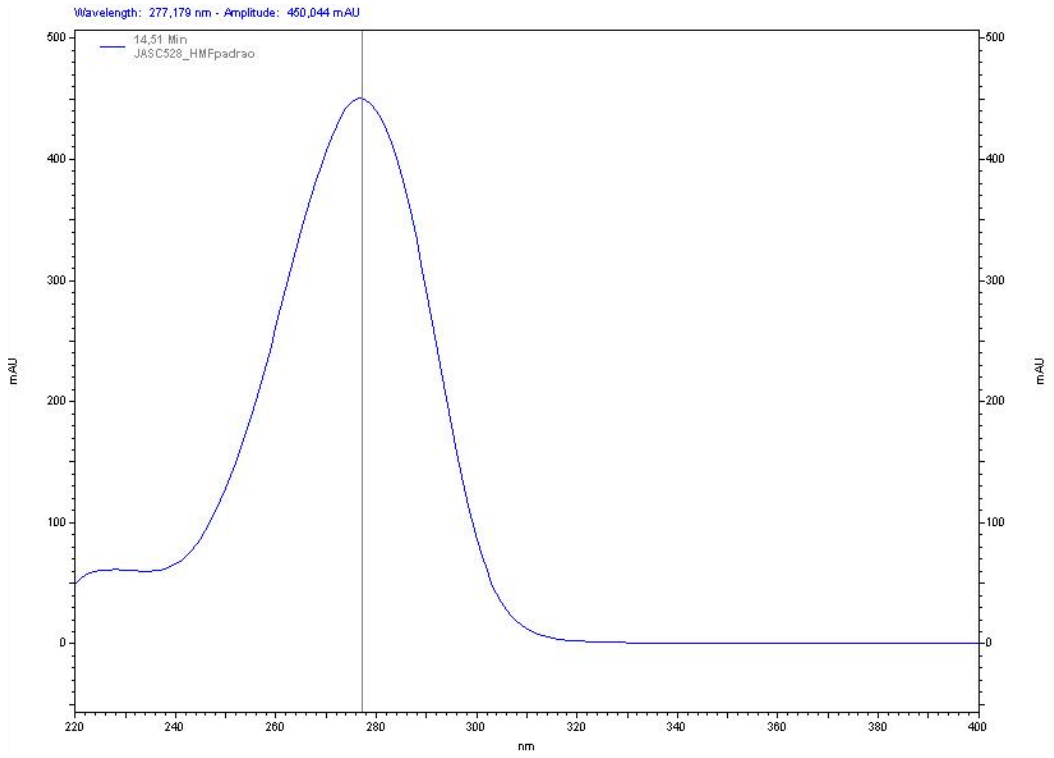

Wavelength: 302,115 nm - Amplitude: 244,513 mAU
19,48 Min
JASC528
mAU
nm


Wavelength: 295,498 nm - Amplitude: 630,285 mAU
22,32 Min
JASC528
mAU
nm

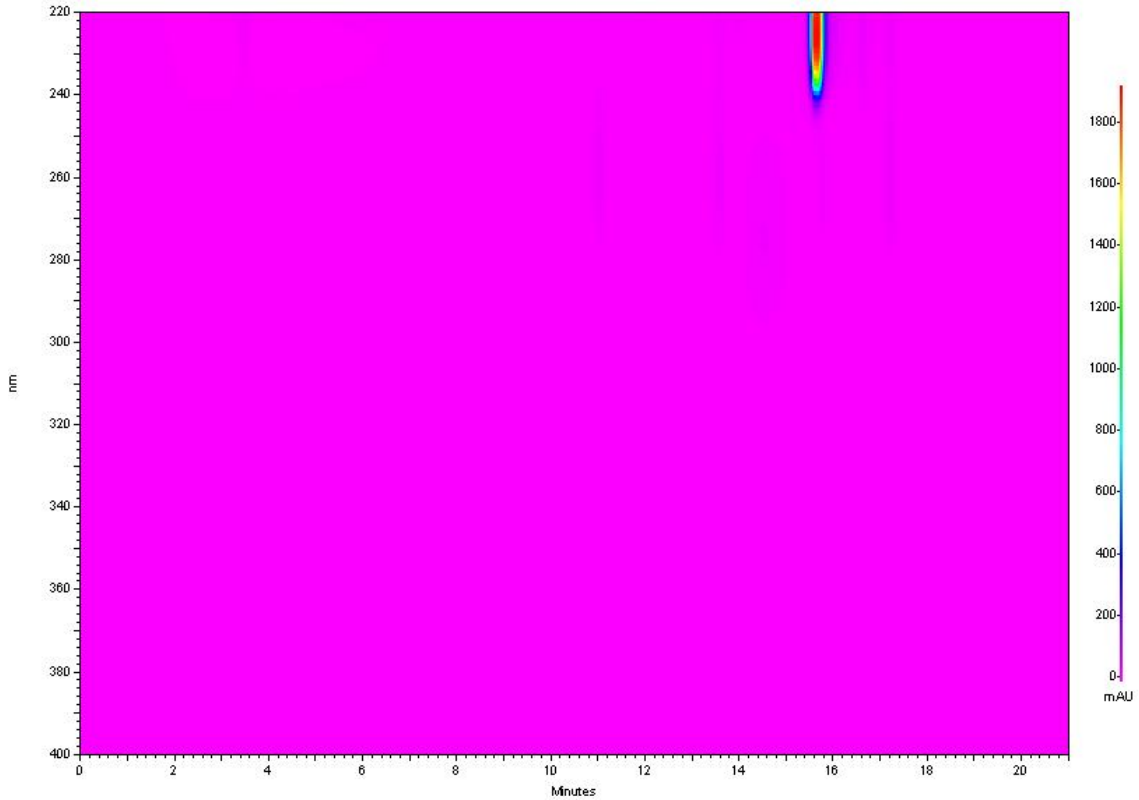
HPLC of **HMF**

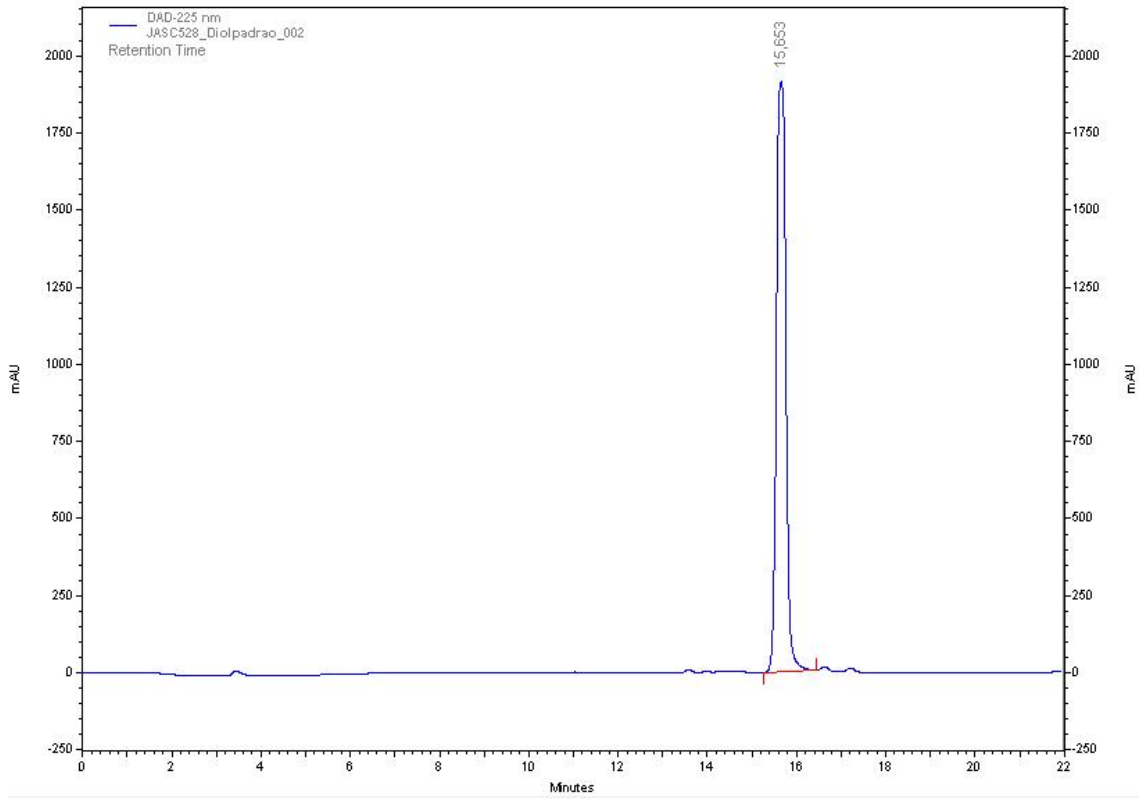

nm
Minutes
mAU

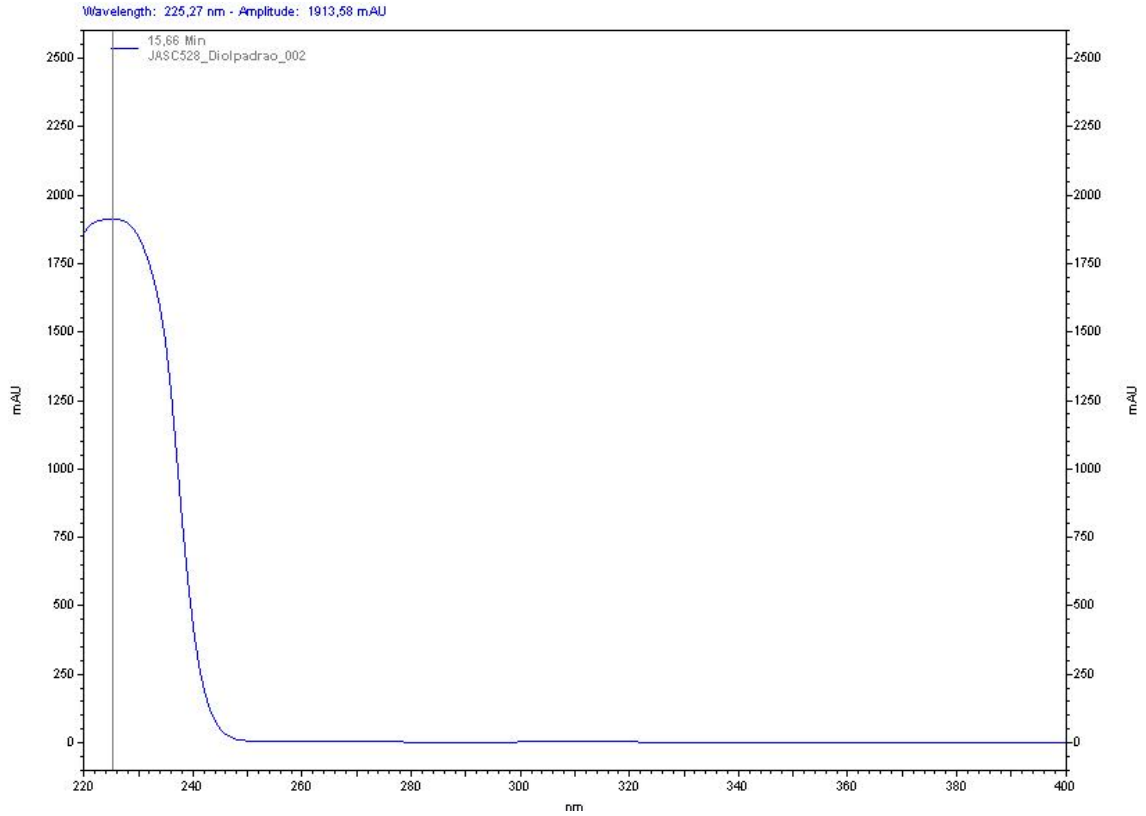

DAD-278 nm
JASC528_HMFpadrao
Retention Time
14,487
mAU
Minutes



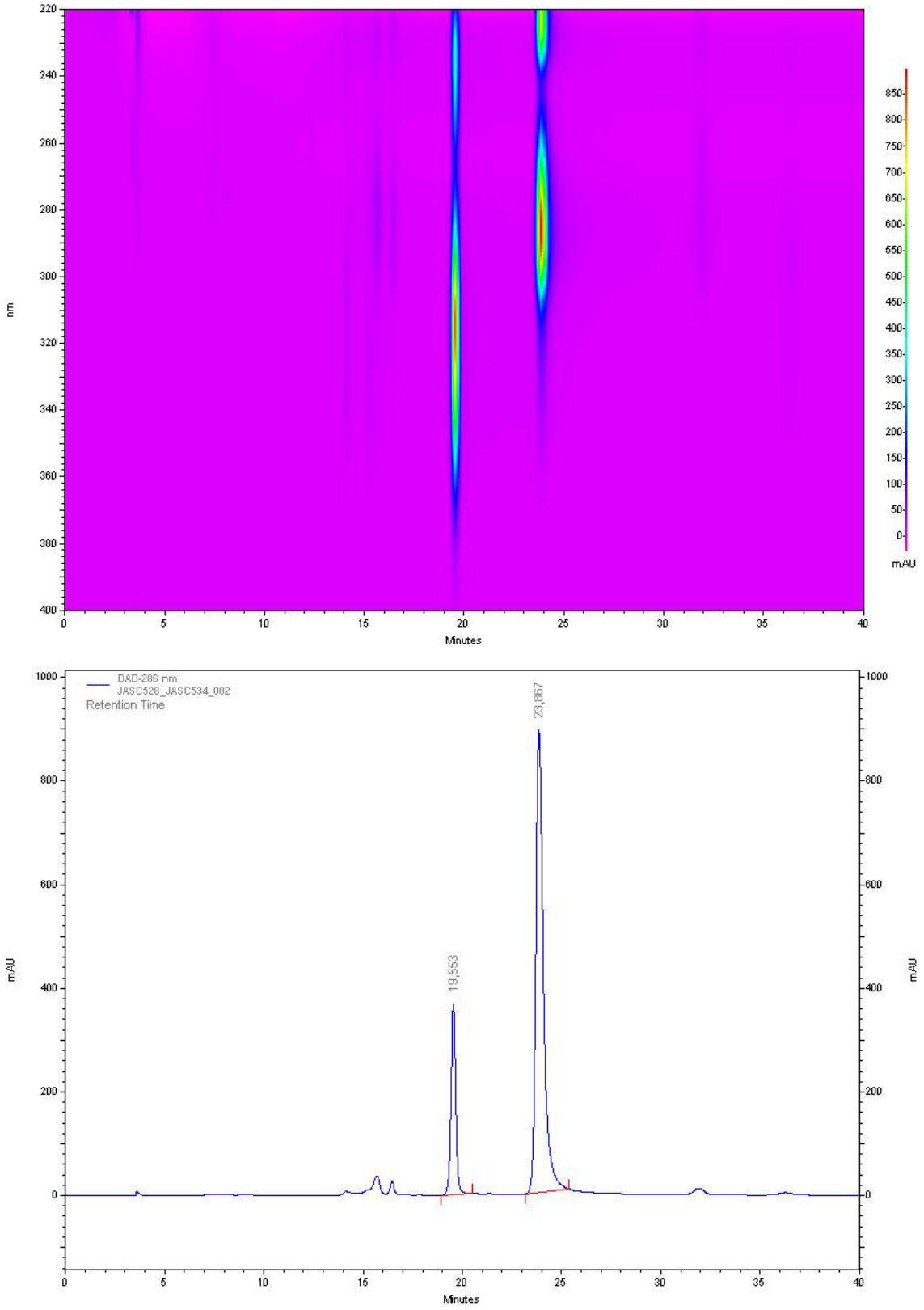
HPLC of canizzaro product **A1**

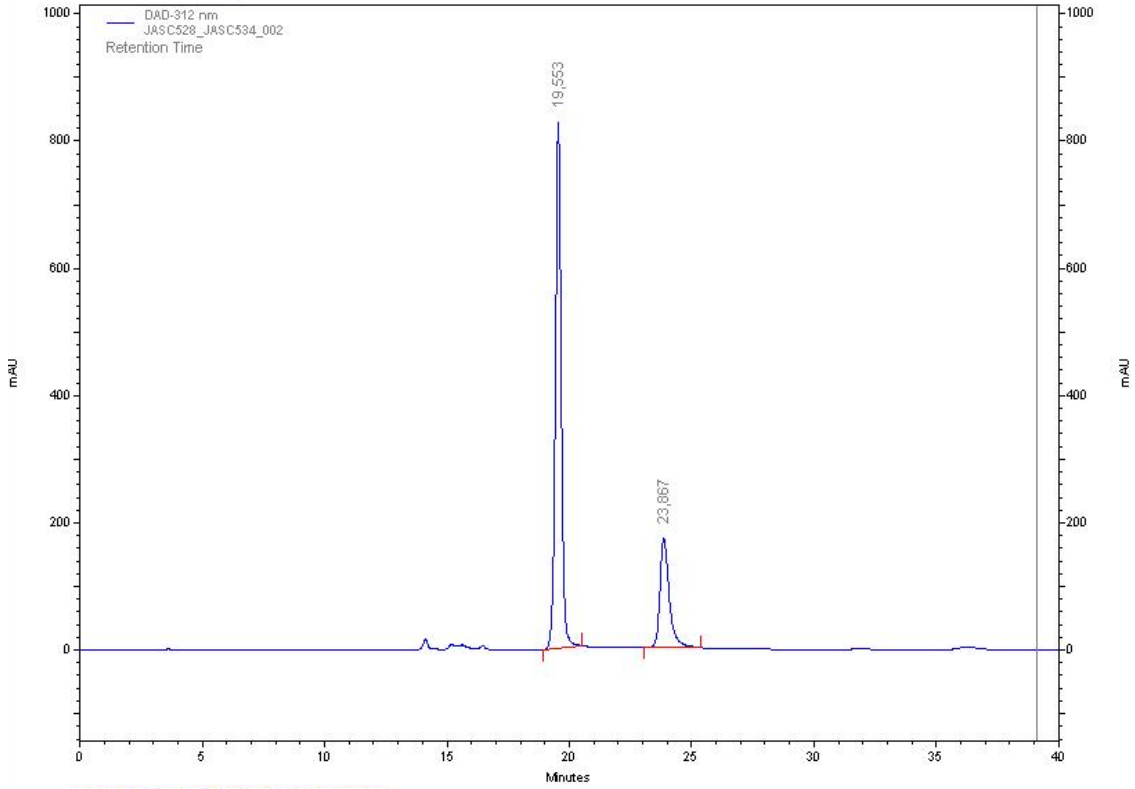



DAD-225 nm
JASC528_Diolpadrao_002
Retention Time
15,653
mAU
Minutes

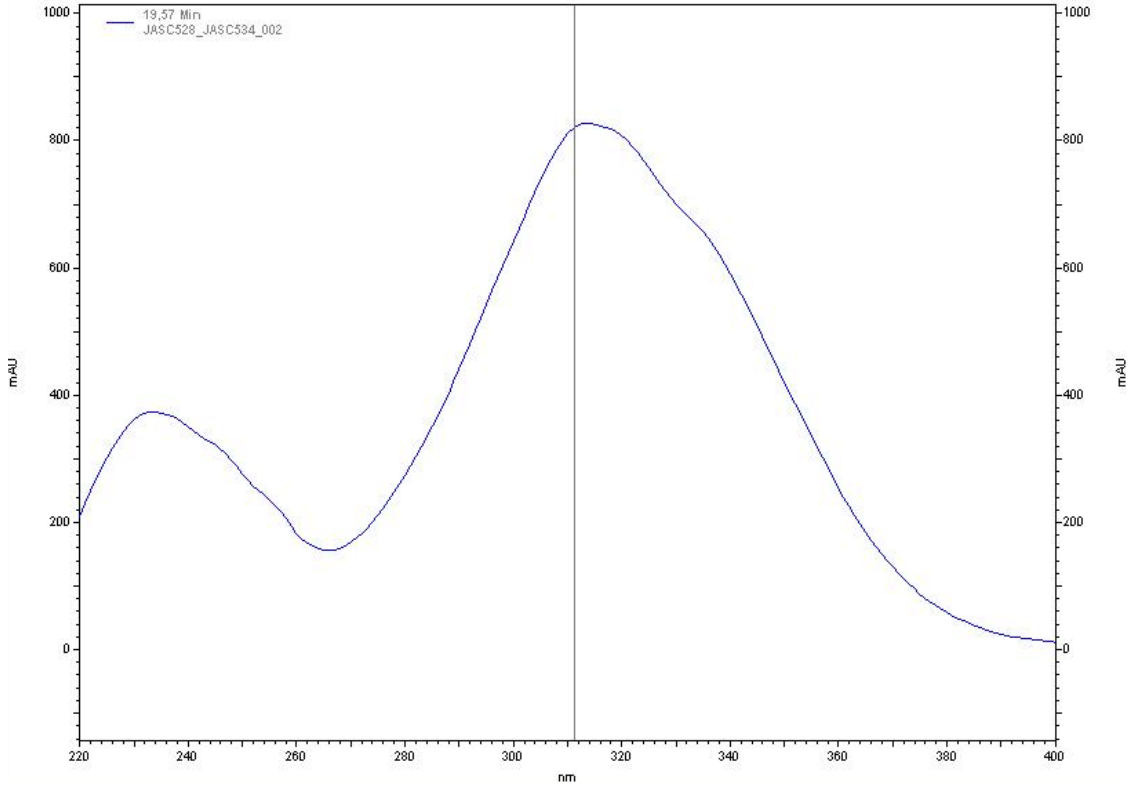

Wavelength: 225,27 nm - Amplitude: 1913,58 mAU
15,66 Min
JASC528_Diolpadrao_002
mAU
nm

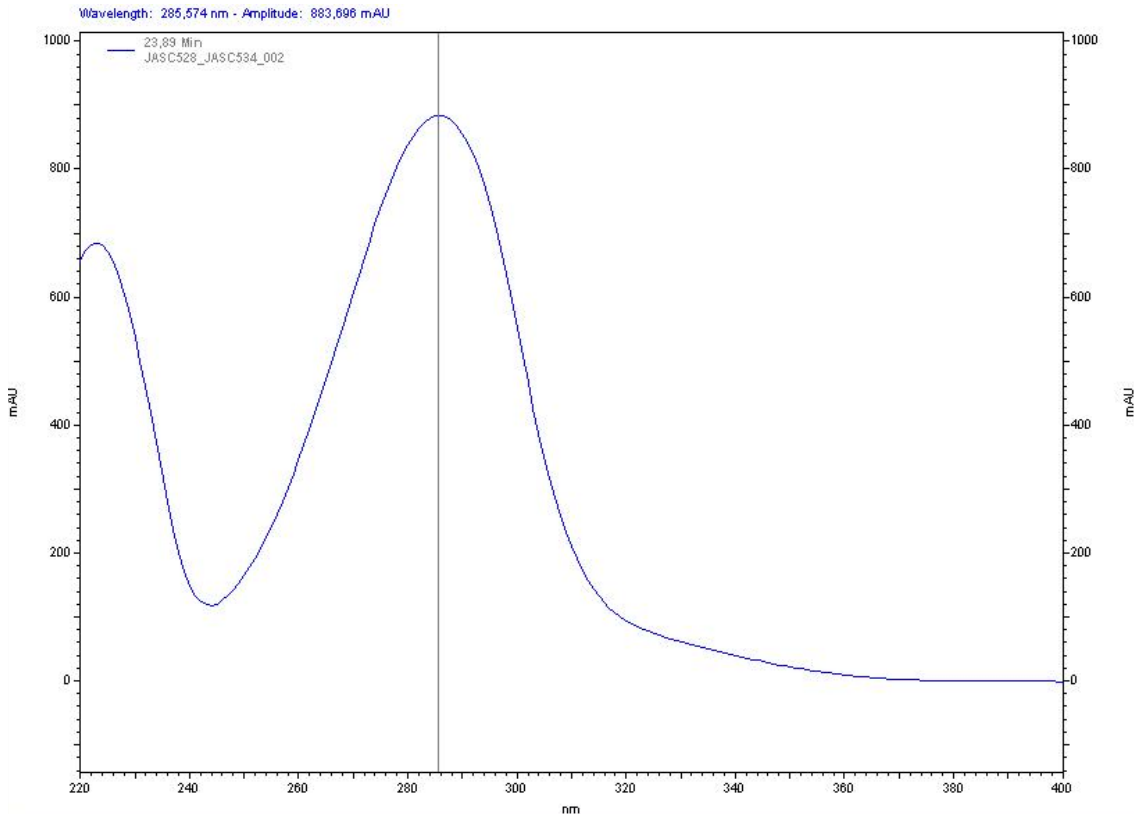
HPLC of self-condensation products **B1** (R_T = 23.867 min) and **B2** (R_T = 19.553 min)





Wavelength: 311,269 nm - Amplitude: 819,392 mAU




Wavelength: 285,574 nm - Amplitude: 883,696 mAU
23,89 Min
JASC528_JASC534_002
mAU
nm
1000
800
600
400
200
0
220
240
260
280
300
320
340
360
380
400

Biological Evaluation

Cell Culture

Human colon adenocarcinoma (CaCo-2 and HT-29), lung cancer (NCI-H460) and breast cancer (MCF-7) cell lines from ATCC were cultivated in RPMI-1640 media supplemented with L- glutamine, 10% fetal bovine serum (FBS) and antibiotic antimycotic solution (A5955, Sigma) and were grown in an incubator with a 5% CO_2 humidified atmosphere and at 37ºC.

Anti-proliferative assay

Each cell line was plated in 96-well plates with a density of approximately $5x10^4$ (NCI-H460), $1x10^5$ (HT-29) and $1{,}5x10^5$ (MCF-7) cells/mL. Plates were incubated overnight and treated the next day with the samples to be tested. Compounds were pre-dissolved in DMSO to make a 5mM stock solution and then diluted with the cell culture media with only 0.5% FBS. The percentage of organic solvent is <1% (v/v) and at this concentrations organic solvent was seen not to affect the viability of these cell models. Concentrations used in the assay were in the range [0-15] μM. Cells were incubated for 24 hours before assessment of the viability. Media was removed and cells were washed with phosphate buffer saline (PBS) after 24 hours incubation. 0.5% FBS fresh cell culture media containing 50μg/ml neutral red was added to the plate. After 3 hours, cell monolayers were washed with PBS and the amount of neutral red retained by the cells extracted and dissolved with an organic solution (19.96 ml distilled water, 20 ml ethanol and 400 μl glacial acetic acid). Plate was gently shake and read at 540 nm in a plate reader. Viability was determined by the ratio of absorbance of treated cells and non-treated cells (control). For each experimental condition, 4 repliques were done and the average points were used to construct a fitting curve in excel. From these fitting curves, IC_{50} was determined. Selectivity index was determined and defined as the IC_{50} obtained for the differentiated CaCo-2 cell line, which is the studied model closest to human normal tissue, divided by the IC_{50} determined for the cancer cell line used in the anti-proliferative assay (HT-29, MCF-7, NCI-H460).

Toxicity assay with CaCo-2 monolayer

Cells were plated in 96-well plates and cultivated more 3-days after reaching total confluency. Differentiated monolayer was incubated with the tested compounds pre-dissolved in DMSO and diluted in the cell culture media with only 0.5% FBS. The percentage of organic solvent is 1% (v/v) and at this concentration viability was seen not to be affected. Cells were incubated with 10, 20 and 50 μM of each compound. Media was removed and cells were washed with phosphate buffer saline (PBS) after 24 hours incubation. Viability was determined likewise described previously, with the exception that, in this case, the neutral red solution was only incubated with the cells for 15 minutes in order to avoid absorbance values above 1. For each experimental condition, 4 repliques were done and the average points were used to construct a fitting curve in excel. From these fitting curves, IC_{50} was determined.

Toxicity curves of the most active compound

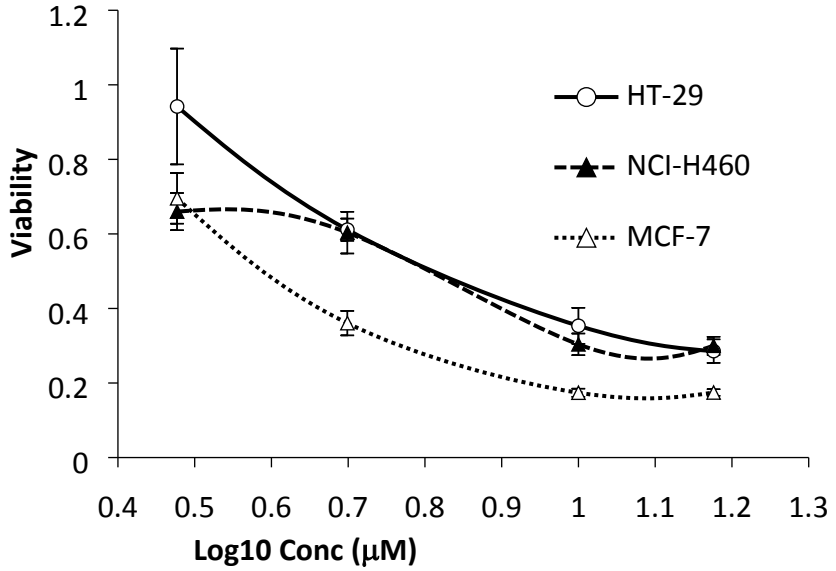


Figure 1: Cells lines were incubated with several concentrations of compound **23** for 24 hours before measurement of the viability with neutral red. Experimental points are an average of 4 repliques and error bars are ± standard deviation.

References

1. Arduengo III, A. J.; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M., *Tetrahedron* **1999**, 55, 14523-14534.
2. Hutt, J. T.; Aron, Z. D., *Org. Let.*. **2011**, 13, 5256-5259.
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