

Supporting Information

Synthetic strategy and antiviral evaluation of diamide containing heterocycles targeting dengue and yellow fever virus

Milind Saudi^a, Joanna Zmurko^b, Suzanne Kaptein^b, Jef Rozenski^a, Bharat Gadakh^a,
Patrick Chaltin^{c,d}, Arnaud Marchand^c, Johan Neyts^b, Arthur Van Aerschot^{a*,∞}

^a KU Leuven, Medicinal Chemistry, Rega Institute for Medical Research,
Minderbroedersstraat 10, 3000 Leuven, Belgium

^b KU Leuven, Laboratory of Virology and Chemotherapy, Rega Institute for Medical
Research, Minderbroedersstraat 10, 3000 Leuven, Belgium

^c CISTIM Leuven vzw, Gaston Geenslaan 2, 3001 Leuven Belgium

^d Centre for Drug Design and Discovery (CD3), KULeuven Research and
Development, Waaistraat 6, 3000 Leuven, Belgium

List of contents

General Information.....	S2
HRMS, ¹ H and ¹³ C NMR spectra	S3-S69

General Information

Reagents and solvents were purchased from commercial suppliers (Acros, Sigma-Aldrich, Bachem, Novabiochem) and used as provided, unless indicated otherwise. All the solvents were of analytical grade and were stored over 4Å molecular sieves. Reactions were carried out in oven-dried glassware under a nitrogen atmosphere with stirring at 85°C.

¹H and ¹³C NMR spectra of the compounds dissolved in CDCl₃, MeOD or DMSO-d₆ were recorded on a Bruker UltraShield Avance 300 MHz or 500 MHz spectrometer. The chemical shifts are expressed as δ values in parts per million (ppm), using the residual solvent peaks (CDCl₃: ¹H, 7.26 ppm; ¹³C, 77.00 ppm; MeOD: ¹H, 3.31 ppm; ¹³C, 49.00 ppm) as a reference. Coupling constants are given in Hertz (Hz). The peak patterns are indicated by the following abbreviations: bs = broad singlet, d = doublet, m = multiplet, q = quadruplet, s = singlet and t = triplet.

Spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Samples were infused at 3 μL.min⁻¹ and spectra were obtained in positive (or negative) ionization mode with a resolution of 15000 (FWHM) using leucine enkephalin as lock mass.

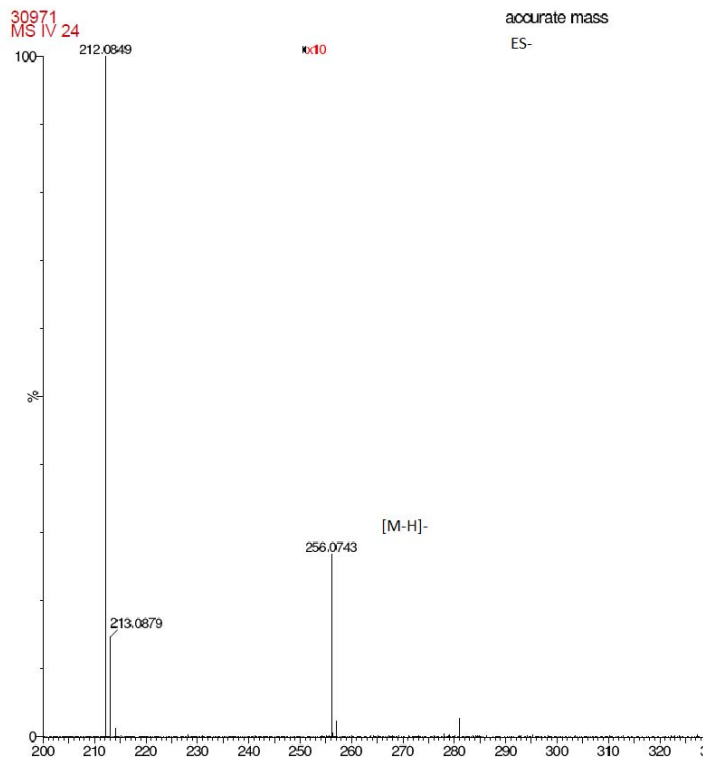
For TLC, precoated aluminium sheets were used (Merck, Silica gel 60 F₂₅₄). The spots were visualized by UV light at 254 nm. Column chromatography was performed on ICN silica gel 60A° 40-60 μM.

This supporting information provides the ¹H and ¹³C NMR and HRMS spectra for all new final compounds with numbering according to the manuscript. NMR spectra were not decoupled for fluorine, and especially carbon spectra are often difficult to interpret with in some cases double signals for rotamers and fluorine coupled carbon signals, leading often to missing signals for quaternary carbons.

HRMS, ¹H and ¹³C NMR Spectra

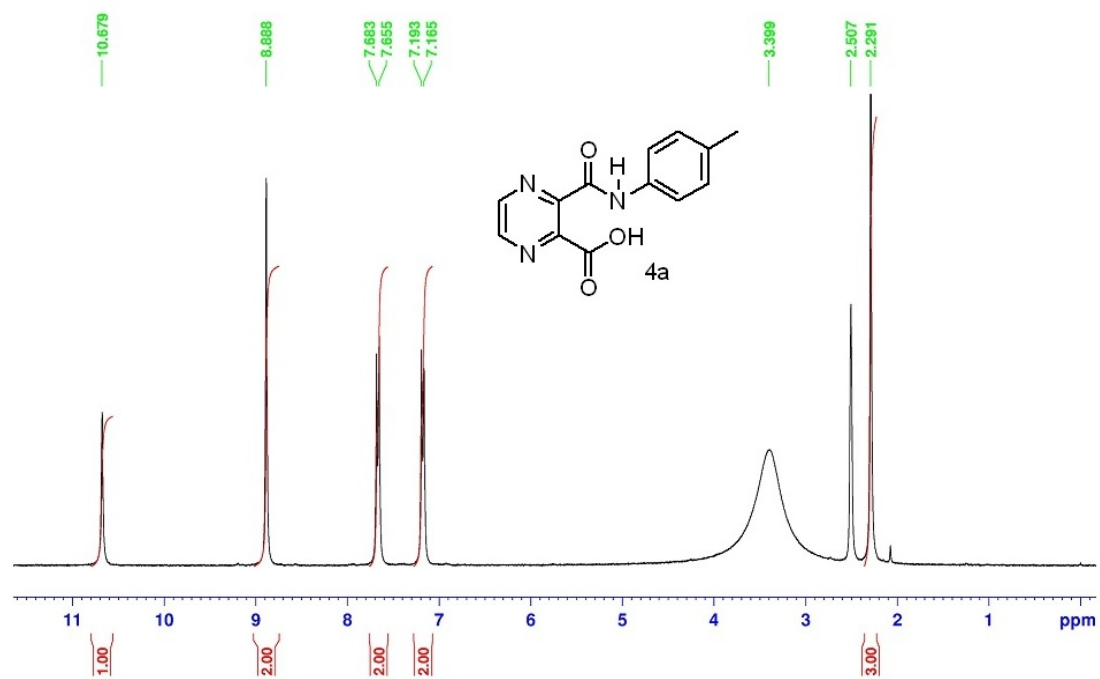
3-(p-tolylcarbamoyl)pyrazine-2-carboxylic acid (4a)

HRMS



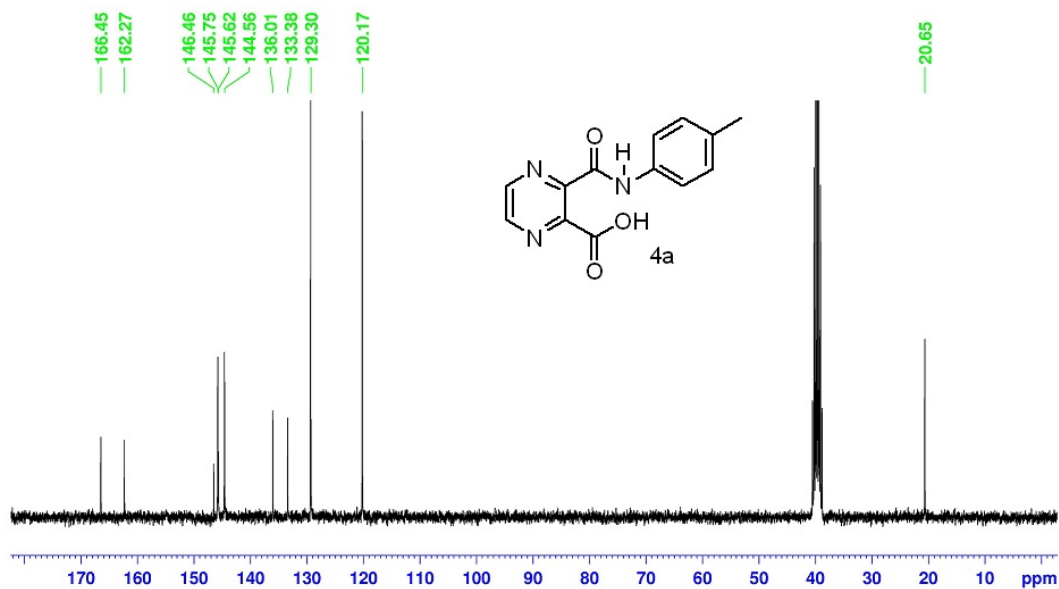
¹H NMR (300 MHz, DMSO)

MS-IV-24 in DMSO
02/11/2011



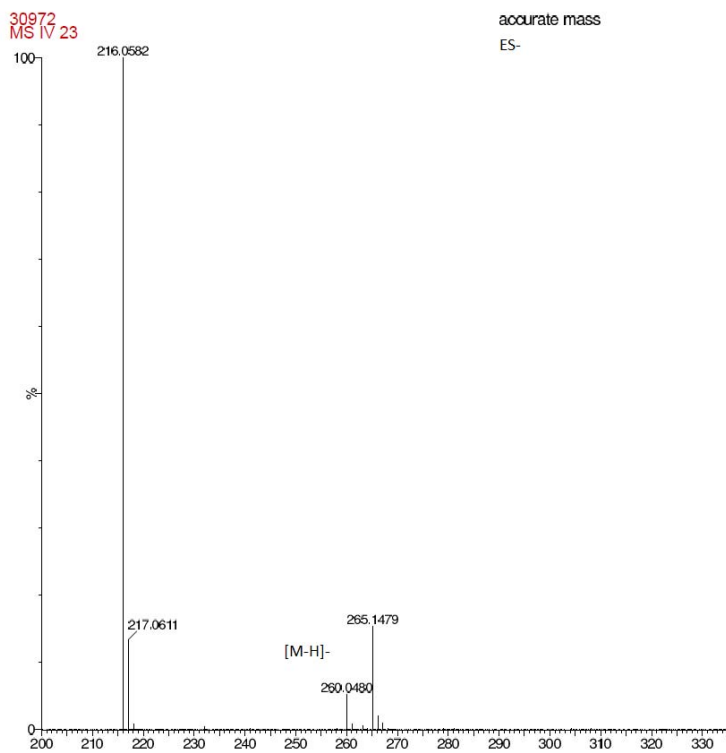
^{13}C NMR (75 MHz, DMSO)

MS-IV-24 C13 in DMSO
02/11/2011



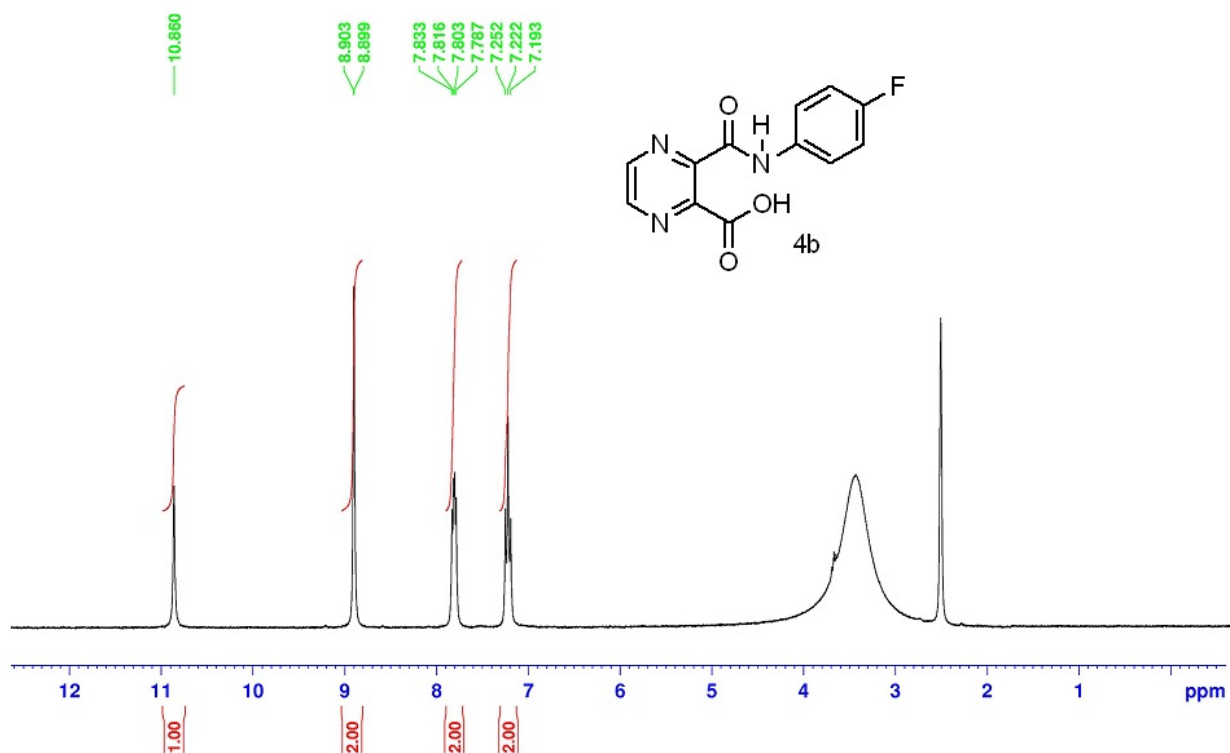
3-((4-fluorophenyl)carbamoyl)pyrazine-2-carboxylic acid (4b)

HRMS



^1H NMR (300 MHz, DMSO)

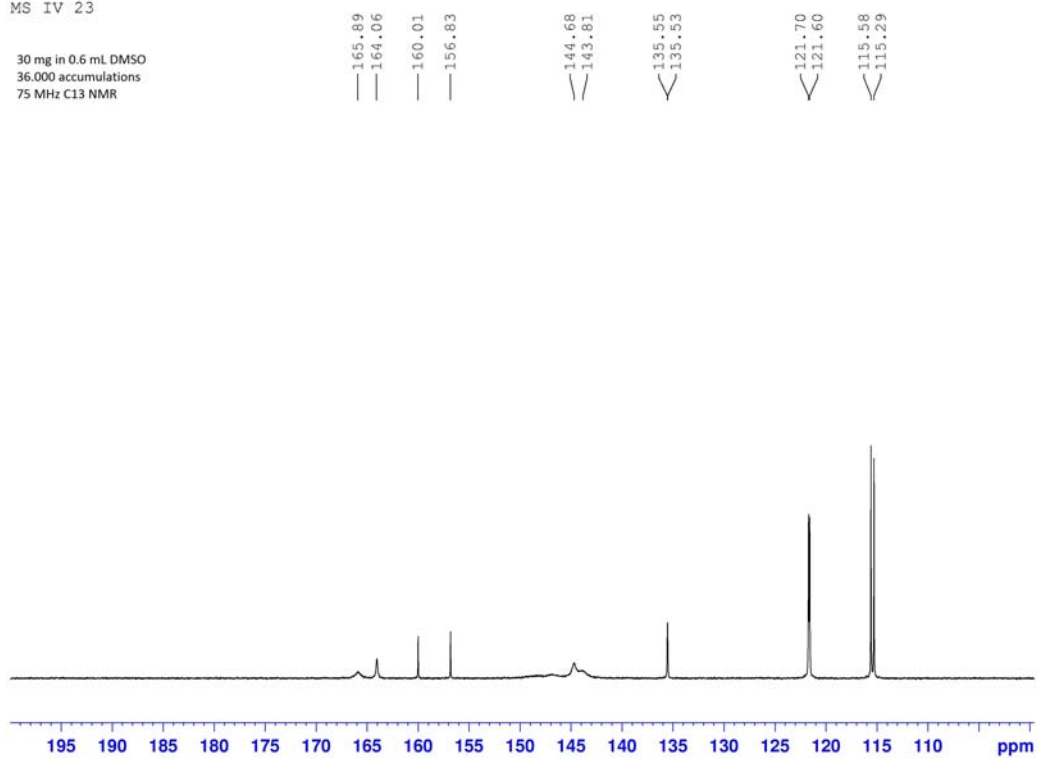
MS-IV-23 in DMSO
02/11/2011



^{13}C NMR (75 MHz, DMSO)

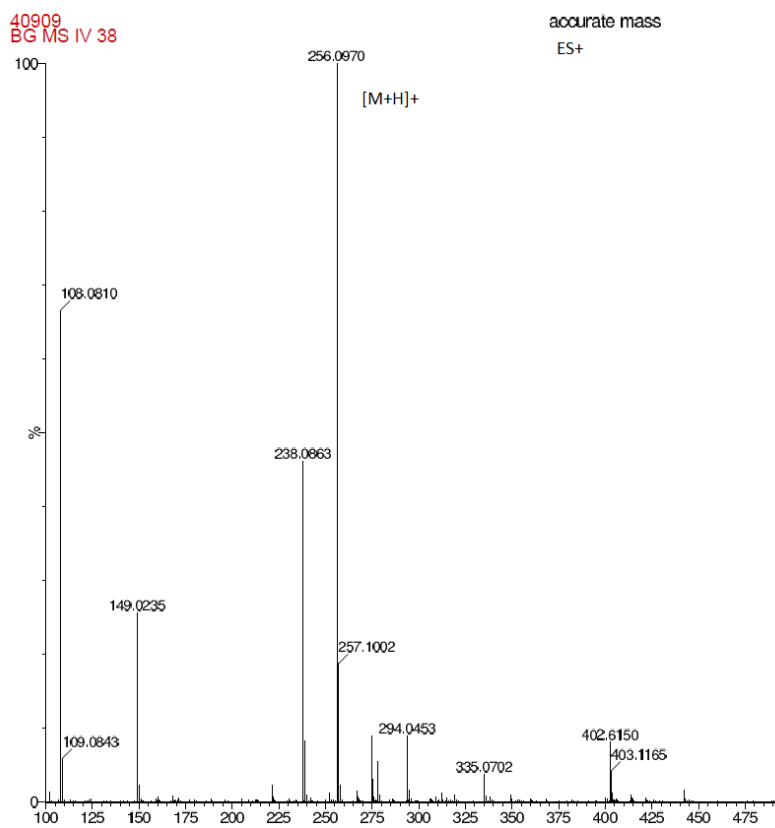
MS IV 23

30 mg in 0.6 mL DMSO
36,000 accumulations
75 MHz ^{13}C NMR

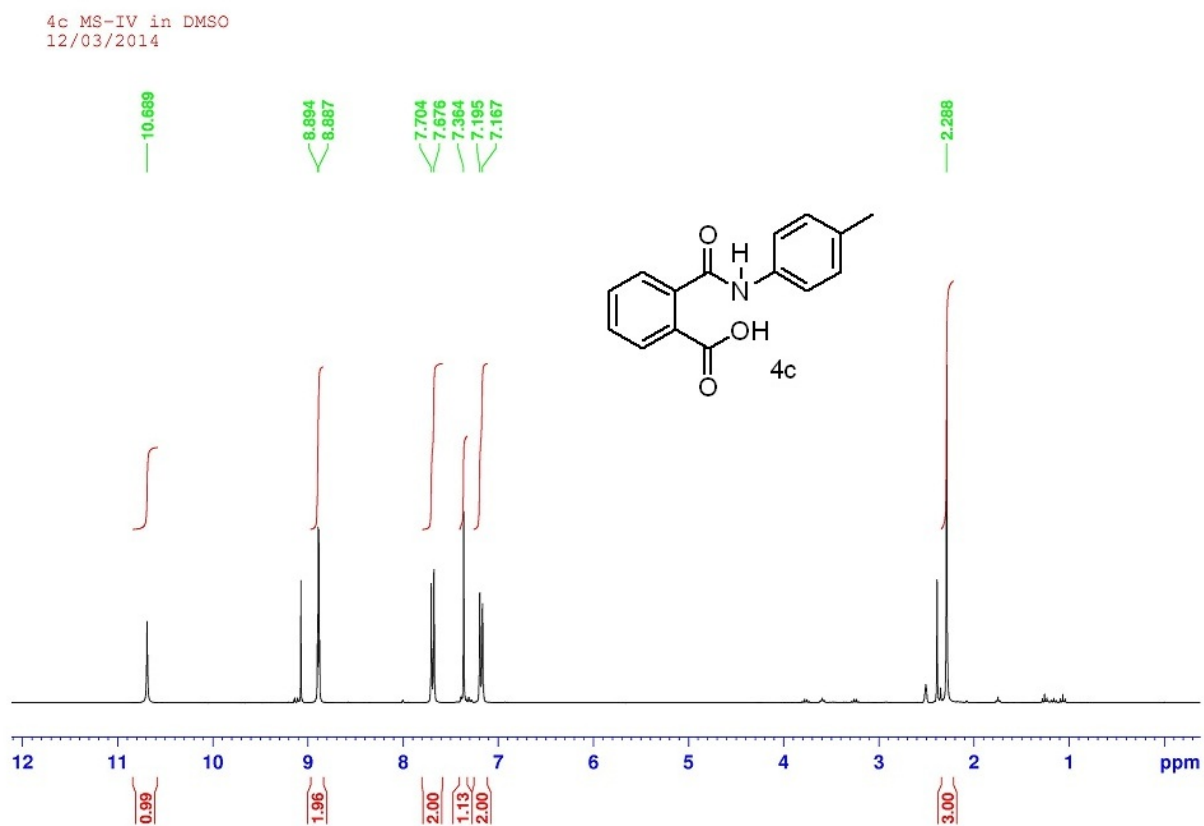


2-(p-tolylcarbamoyl)benzoic acid (4c)

HRMS

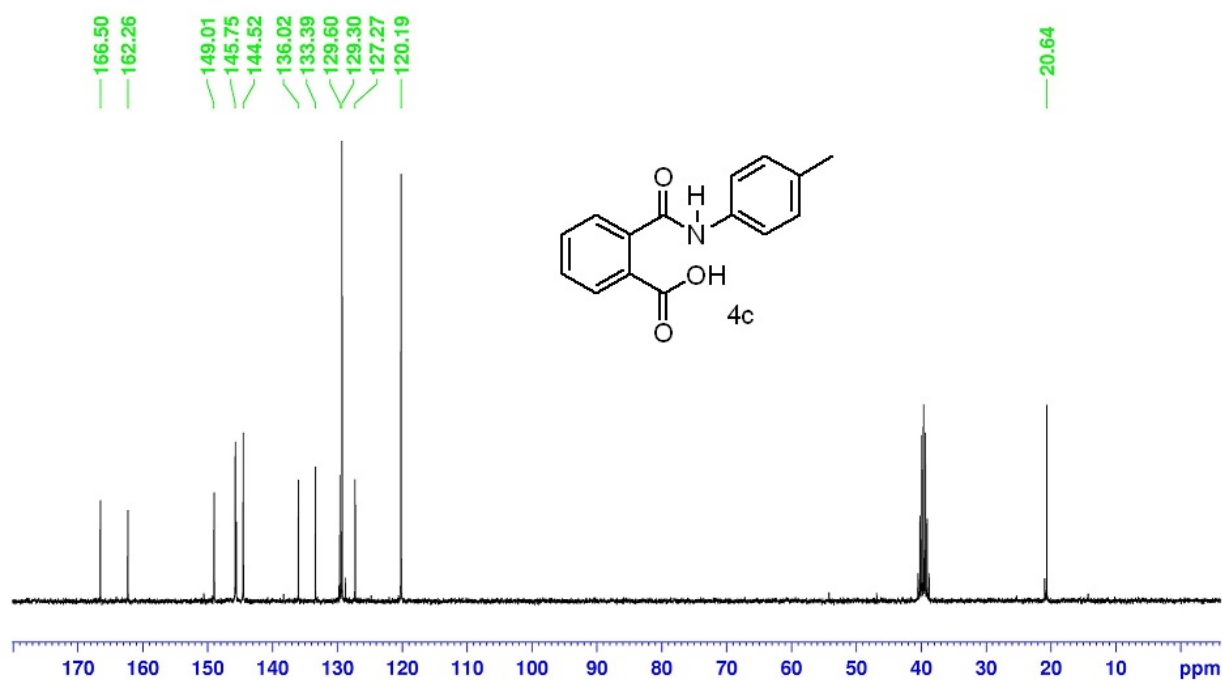


¹H NMR (300 MHz, DMSO)



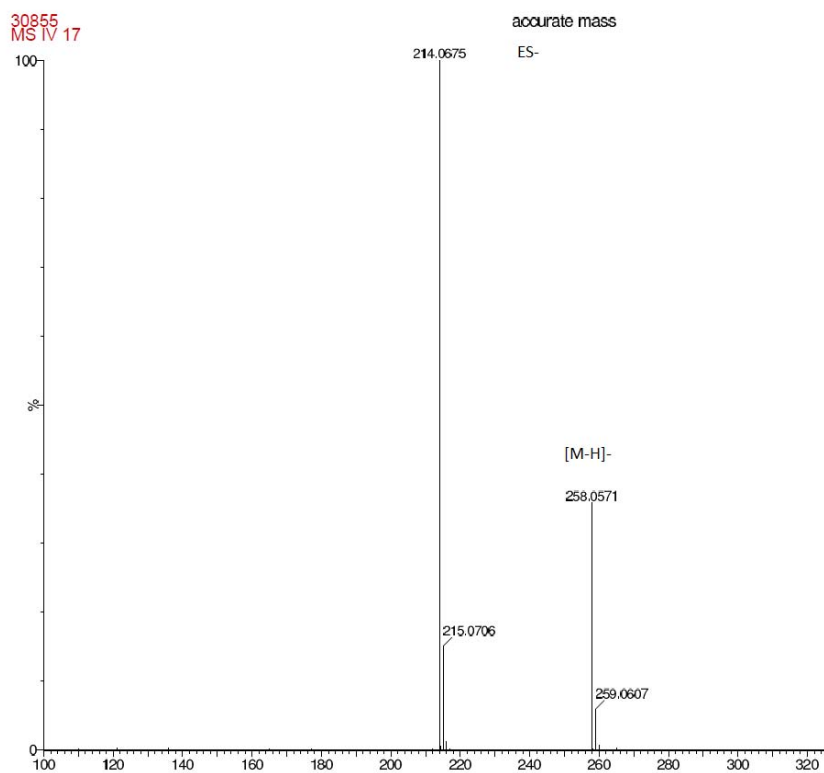
¹³C NMR (75 MHz, DMSO)

4c MS-IV C13 in DMSO
12/03/2014



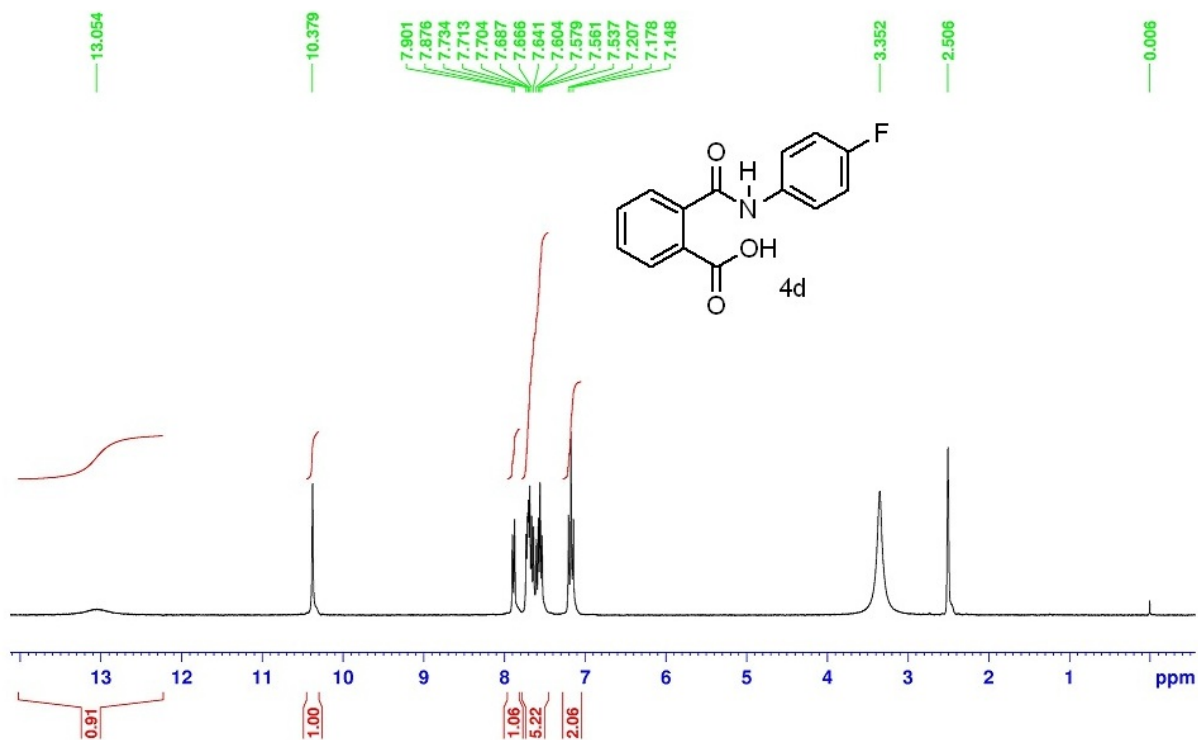
2-((4-fluorophenyl)carbamoyl)benzoic acid (4d)

HRMS



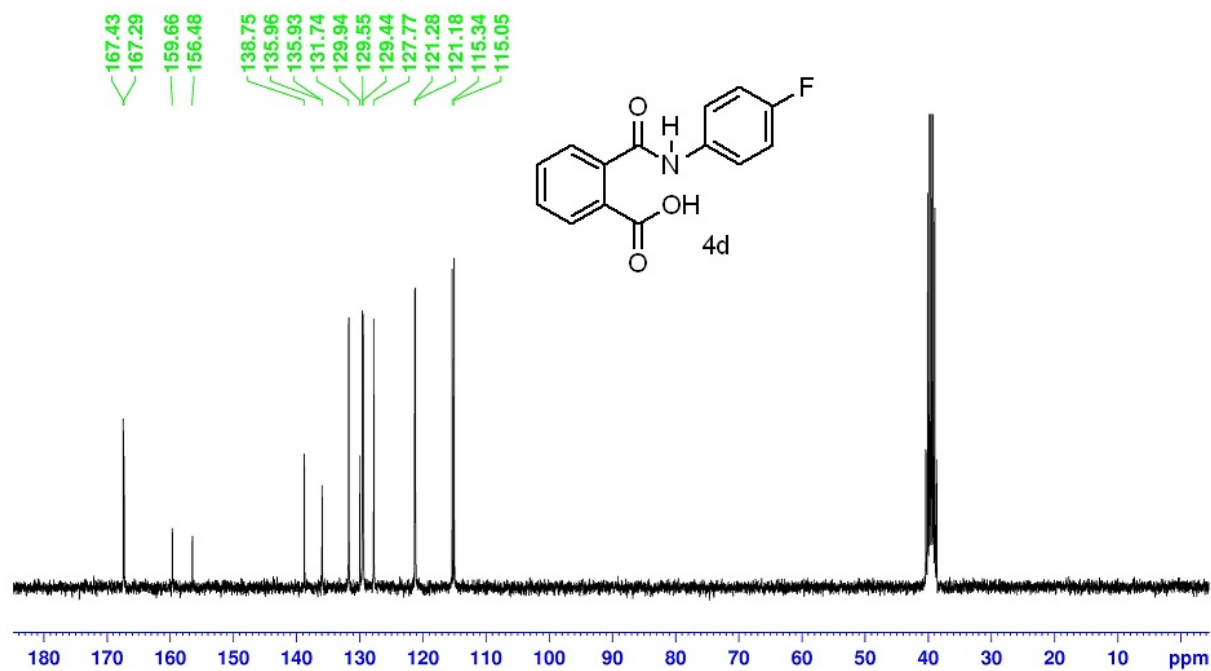
¹H NMR (300 MHz, DMSO)

MS-IV-17 in DMSO
19/10/2011

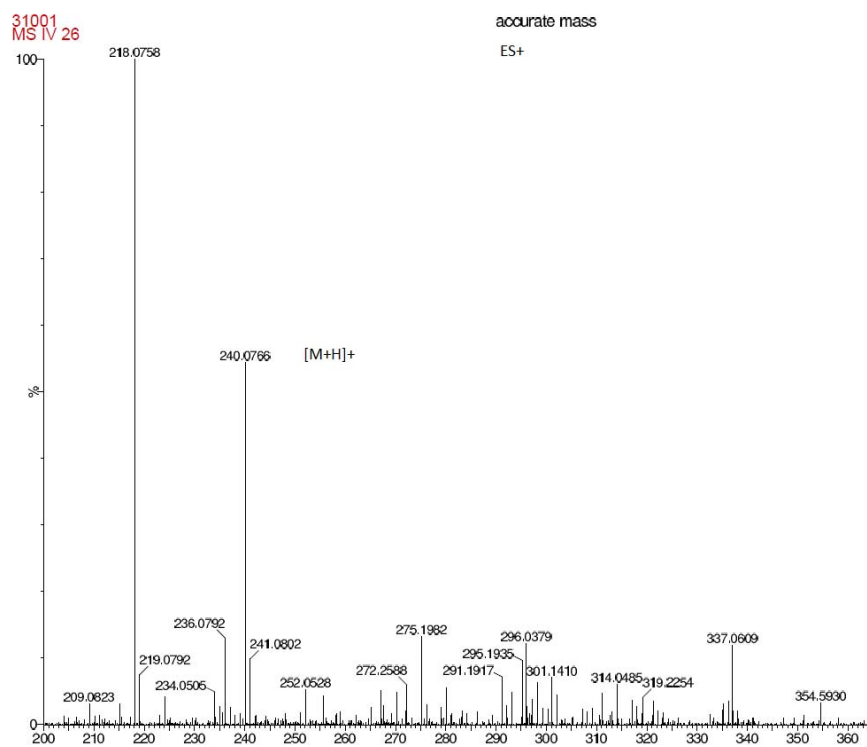


¹³C NMR (75 MHz, DMSO)

MS-IV-17 C13 in DMSO
19/10/2011

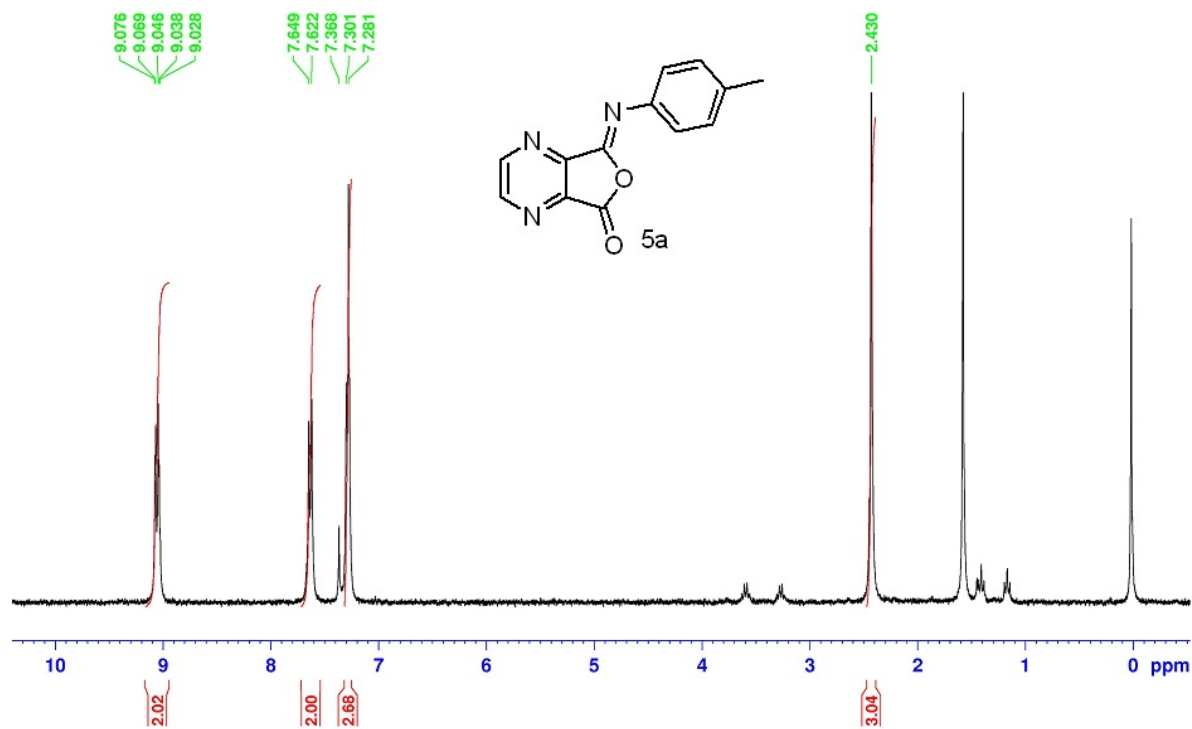


(Z)-7-(p-tolylimino)furo[3,4-b]pyrazin-5(7H)-one(5a)
HRMS



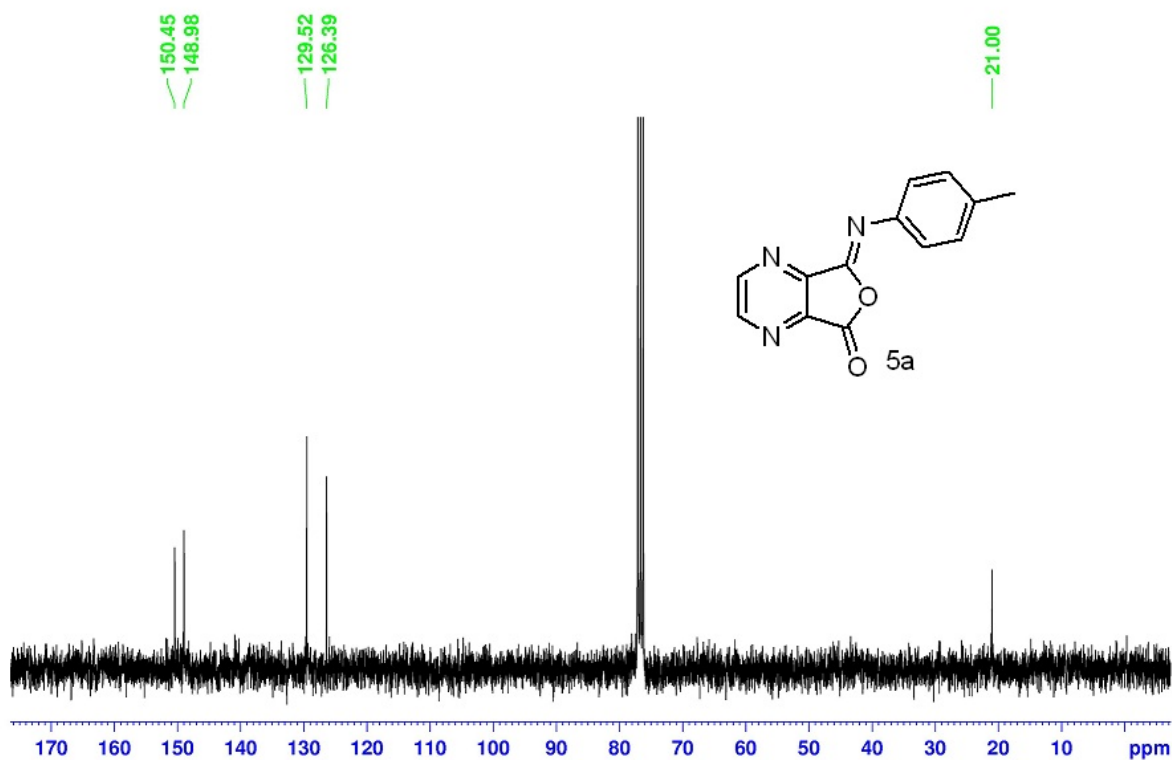
¹H NMR (300 MHz, CDCl₃)

MS-IV-26 in CDCl₃
03/11/2011



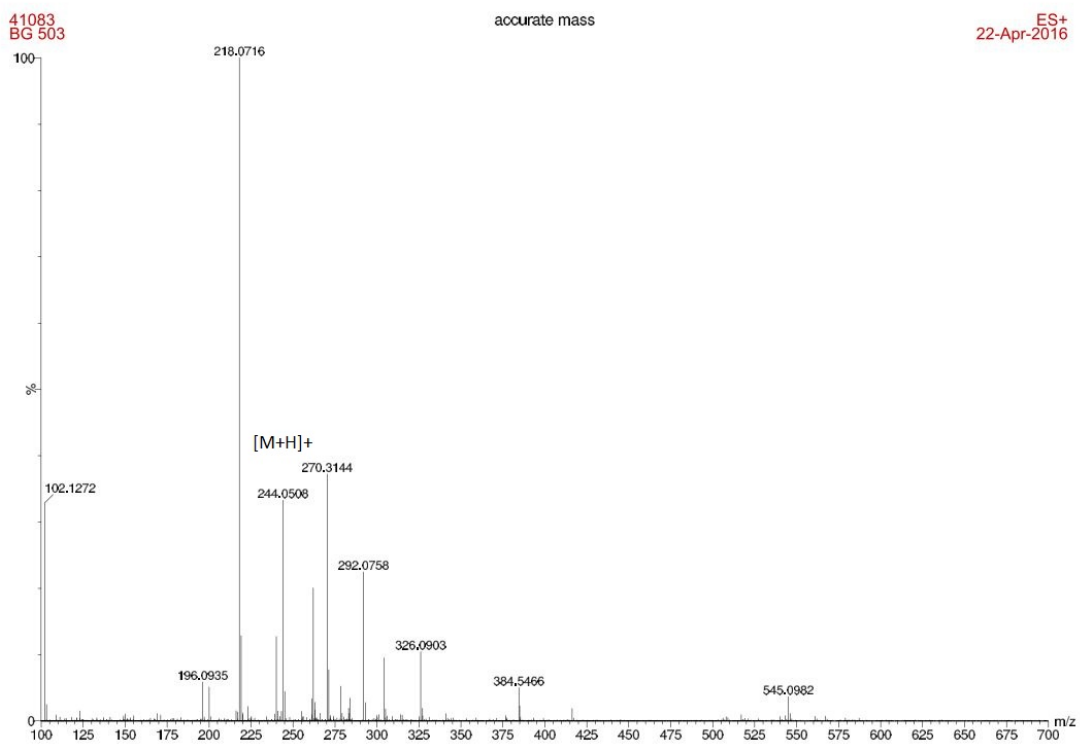
^{13}C NMR (75 MHz, CDCl_3)

MS-IV-26 C13 in CDCl_3
03/11/2011



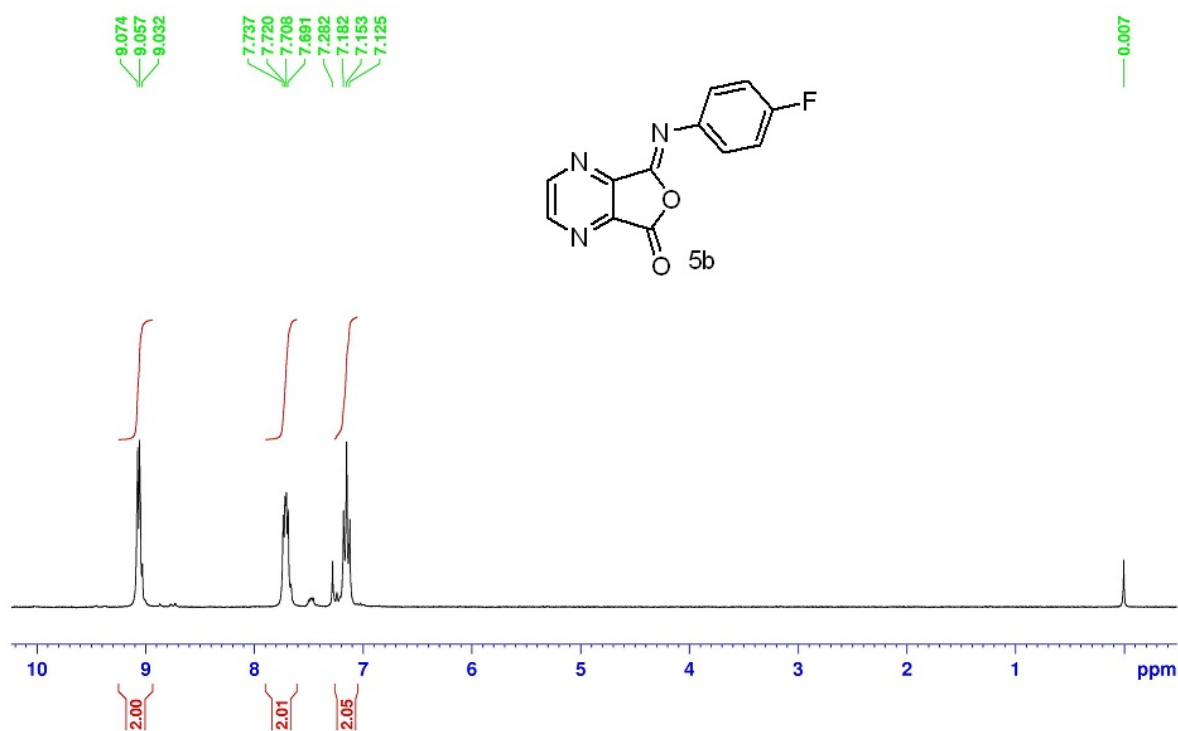
(Z)-7-((4-fluorophenyl)imino)furo[3,4-b]pyrazin-5(7H)-one (5b)

HRMS



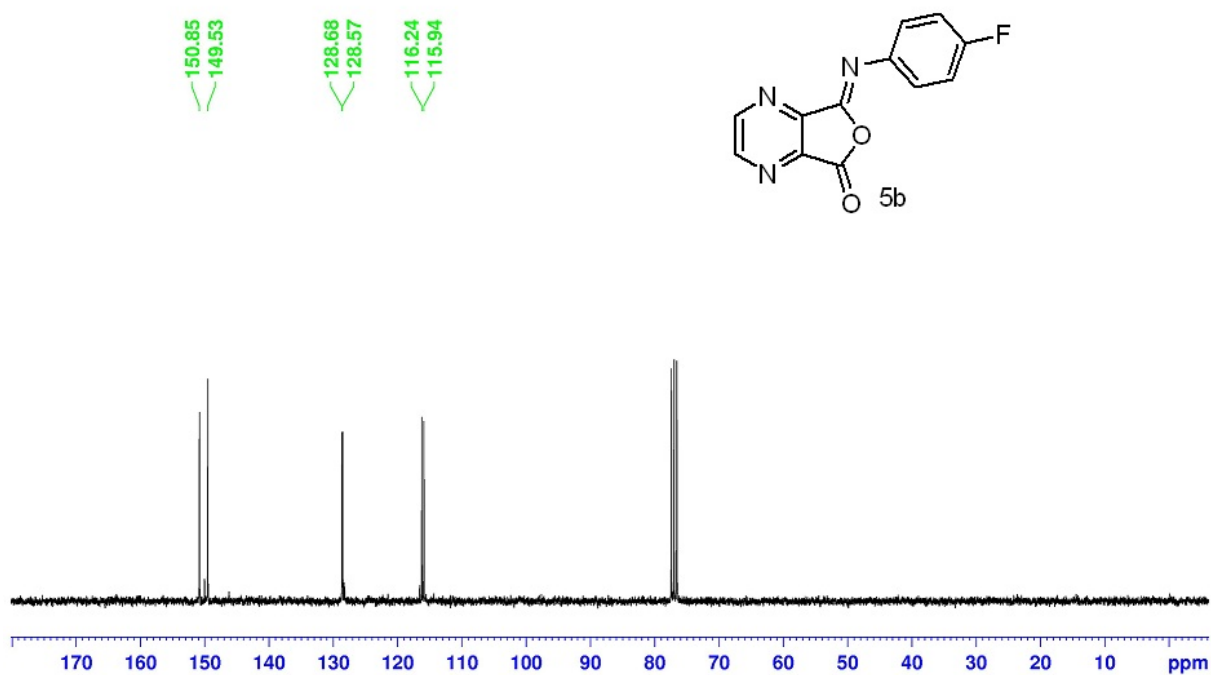
^1H NMR (300 MHz, CDCl_3)

MS-IV-25 in CDCl_3
25/01/2014

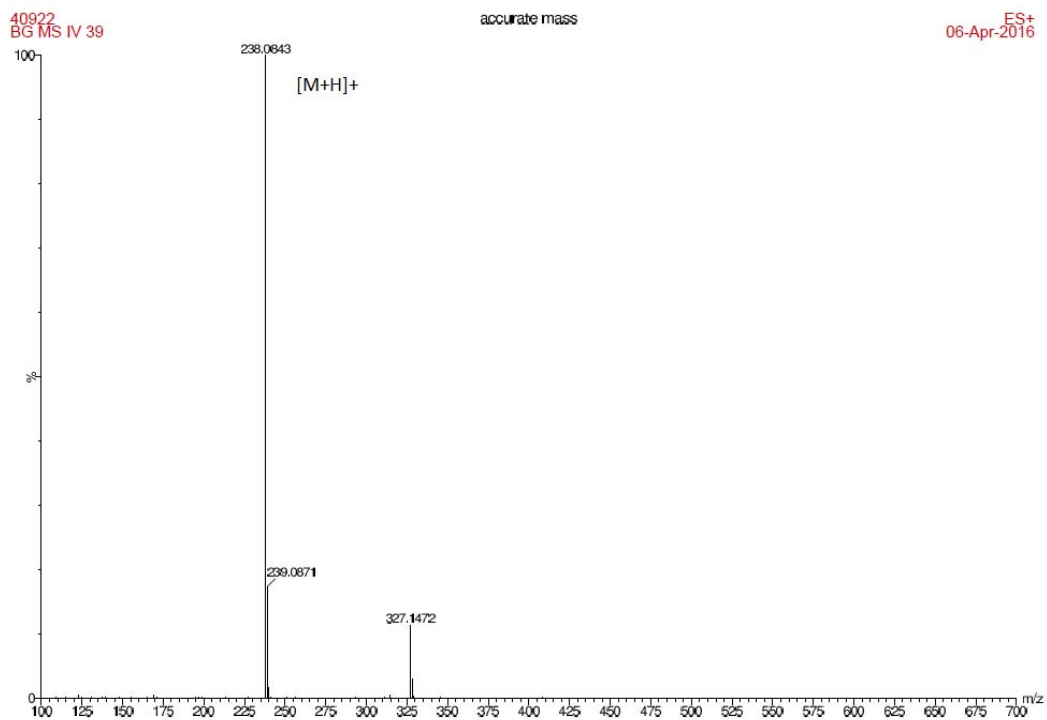


^{13}C NMR (75 MHz, CDCl_3)

MS-IV-25 C13 in CDCl_3 300 mhz
25/01/2014

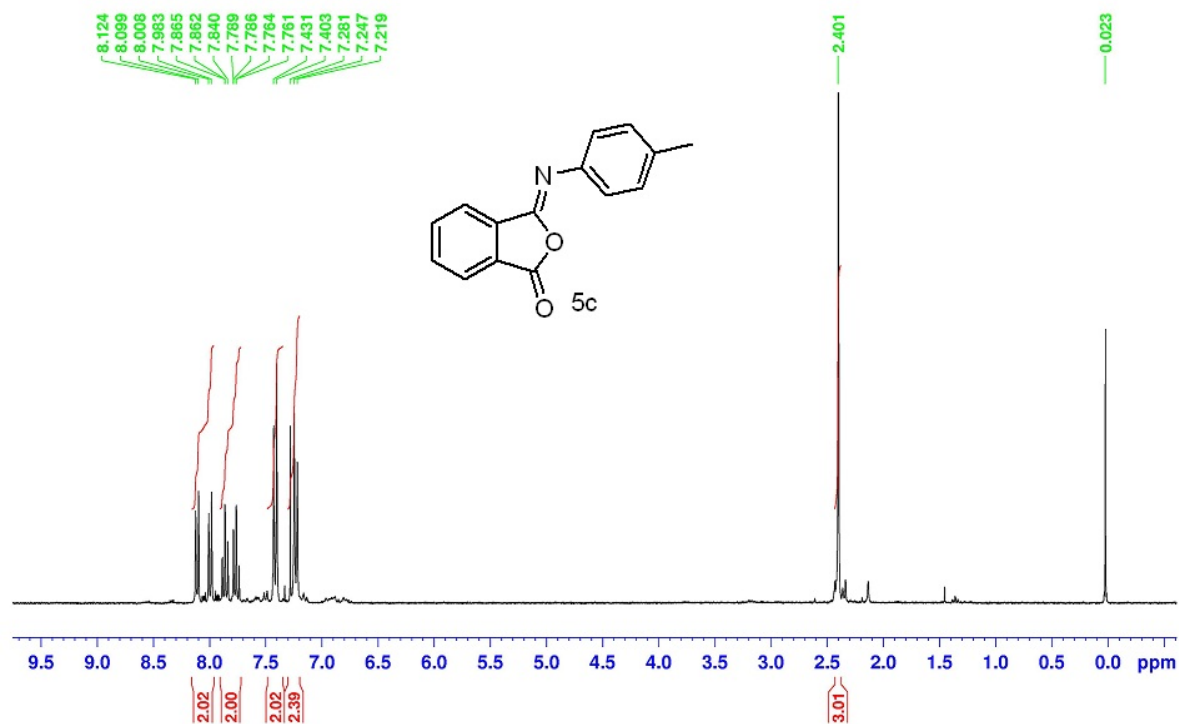


(Z)-3-(p-tolylimino)isobenzofuran-1(3H)-one (5c)
HRMS

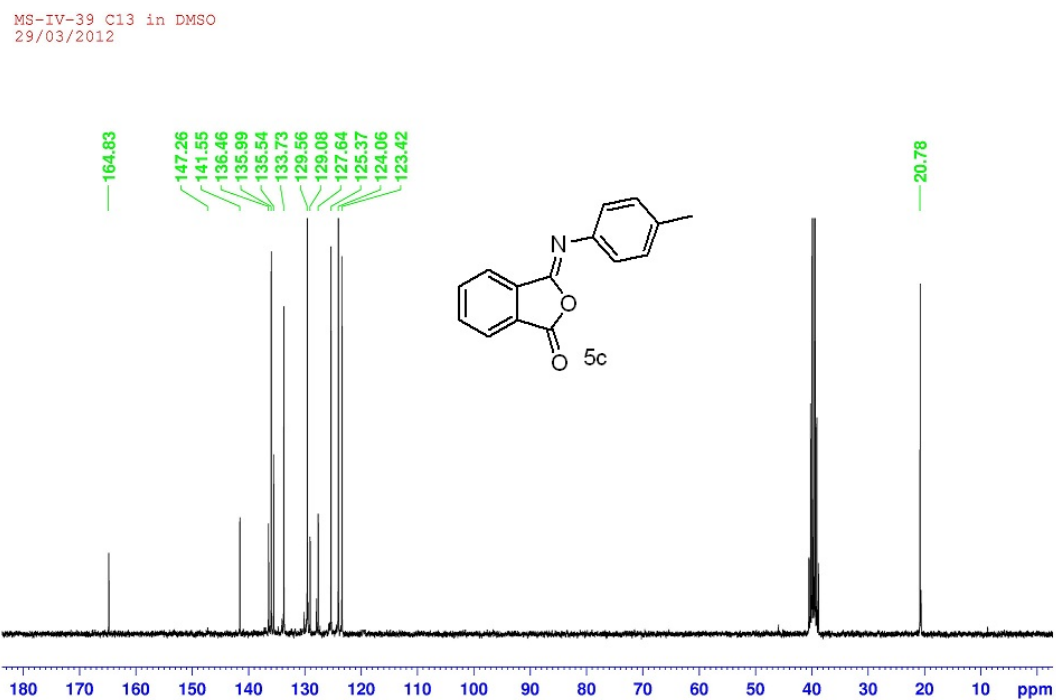


¹H NMR (300 MHz, CDCl₃)

MS-IV-39 in CDCl₃
28/03/2012

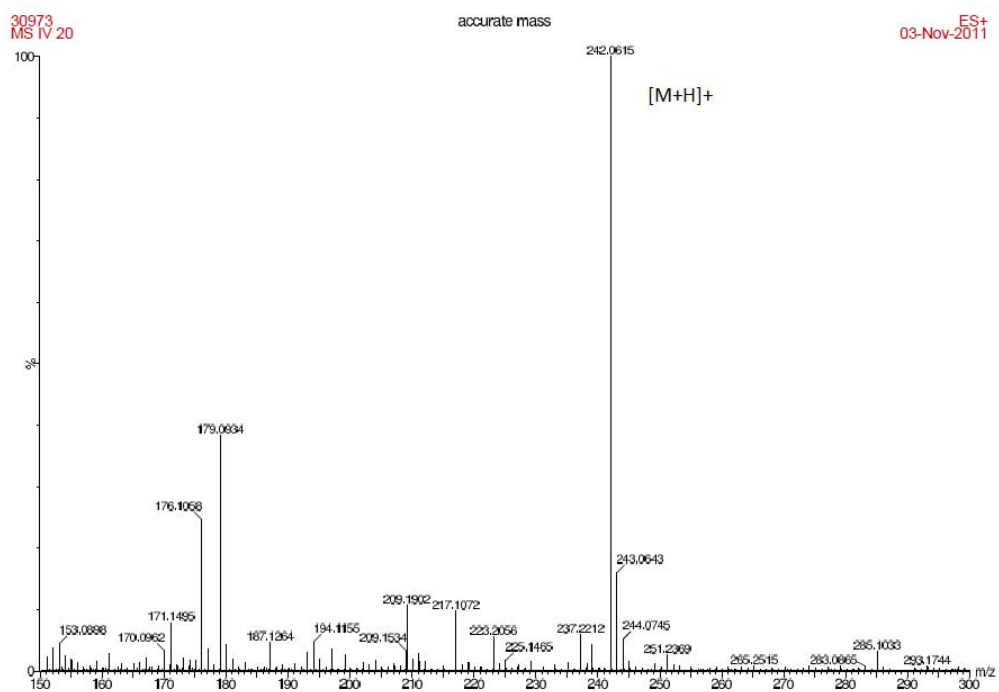


^{13}C NMR (75 MHz, DMSO)



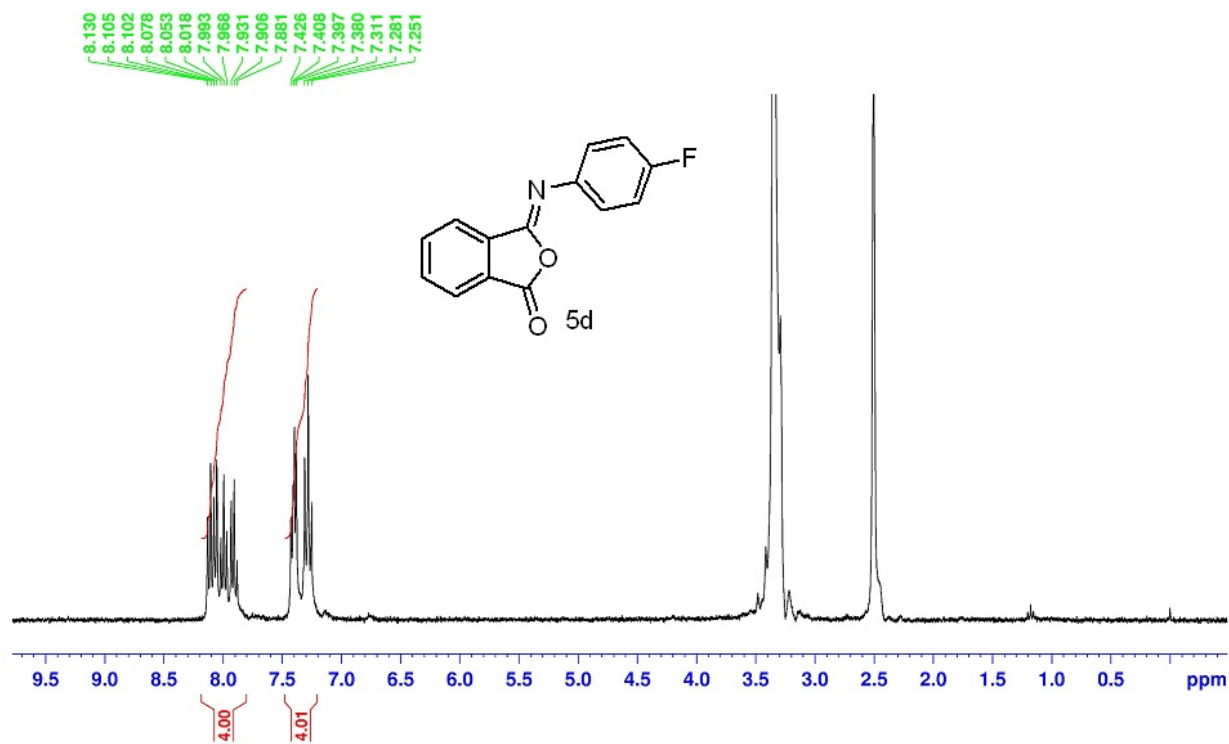
(Z)-3-((4-fluorophenyl)imino)isobenzofuran-1(3H)-one (5d)

HRMS



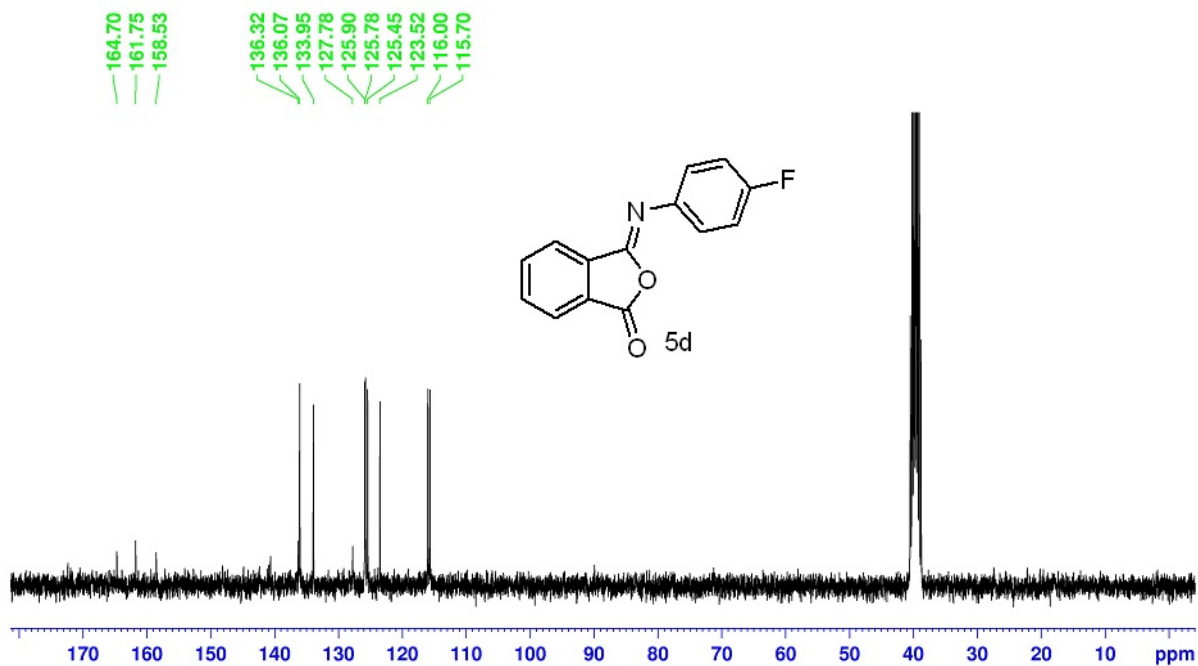
^1H NMR (300 MHz, DMSO)

MS-IV-20 in DMSO
31/10/2011



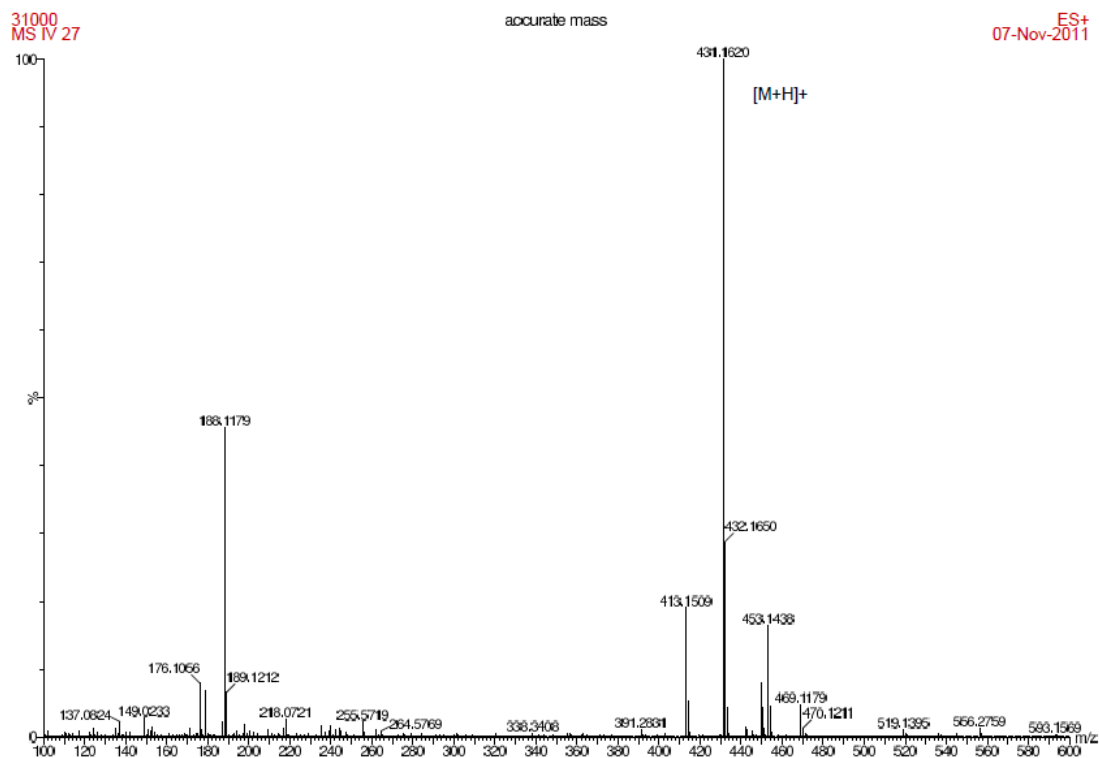
^{13}C NMR (75 MHz, DMSO)

MS-IV-20 C13 in DMSO
31/10/2011



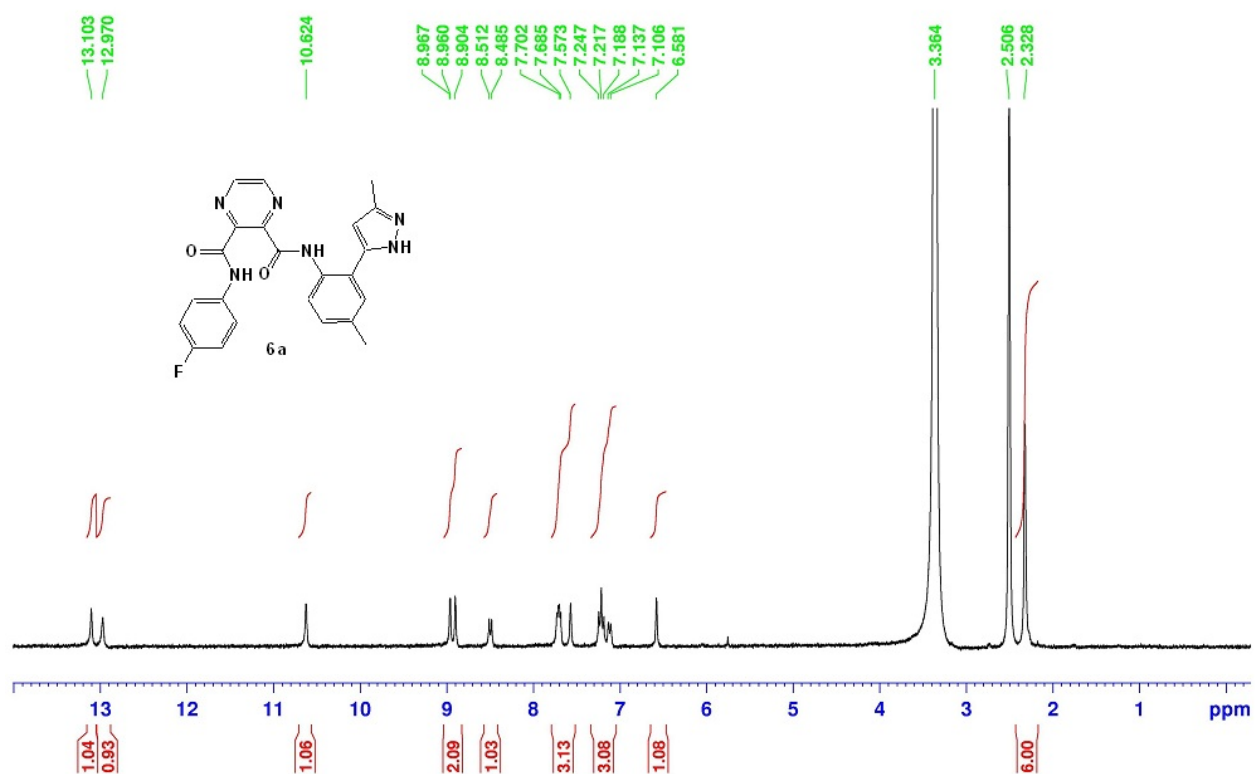
*N*²-(4-fluorophenyl)-*N*³-(4-methyl-2-(3-methyl-1H-pyrazol-5-yl)phenyl)pyrazine-2,3-dicarboxamide (6a):

HRMS



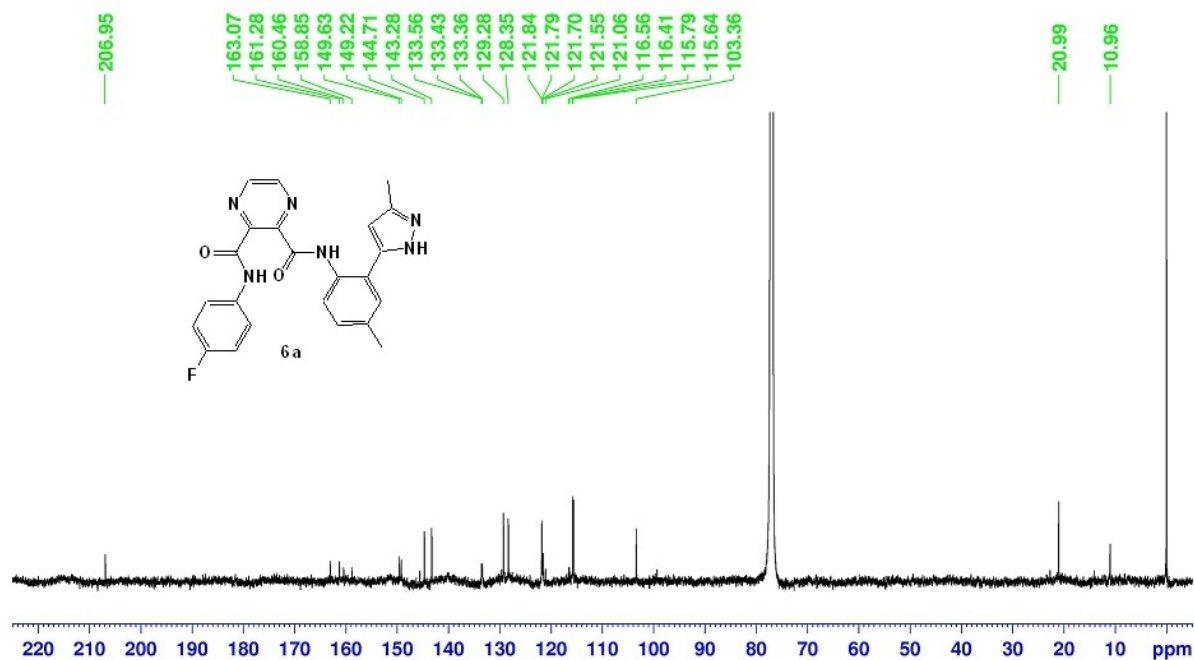
¹H NMR (300 MHz, DMSO)

MS-IV-27 in DMSO
04/11/2011



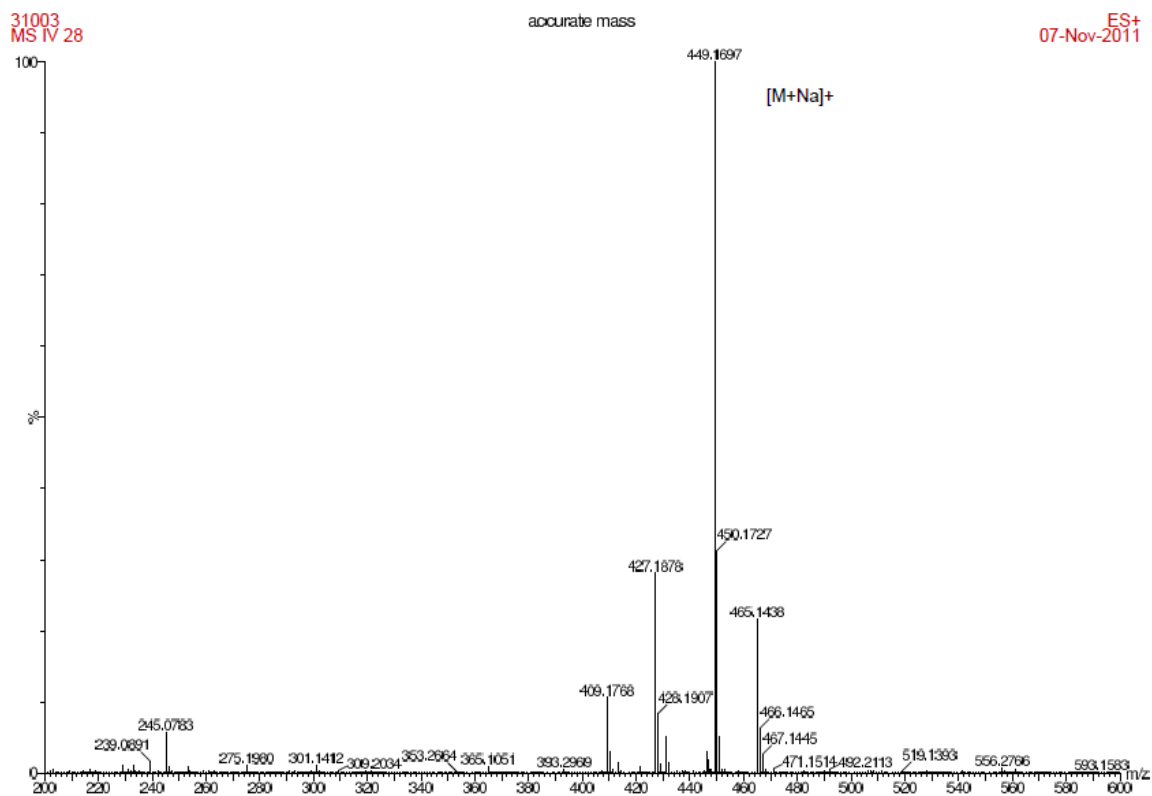
^{13}C NMR (150 MHz, CDCl_3)

MS-IV-27-600 in CDCl_3
13C
1H decoupled



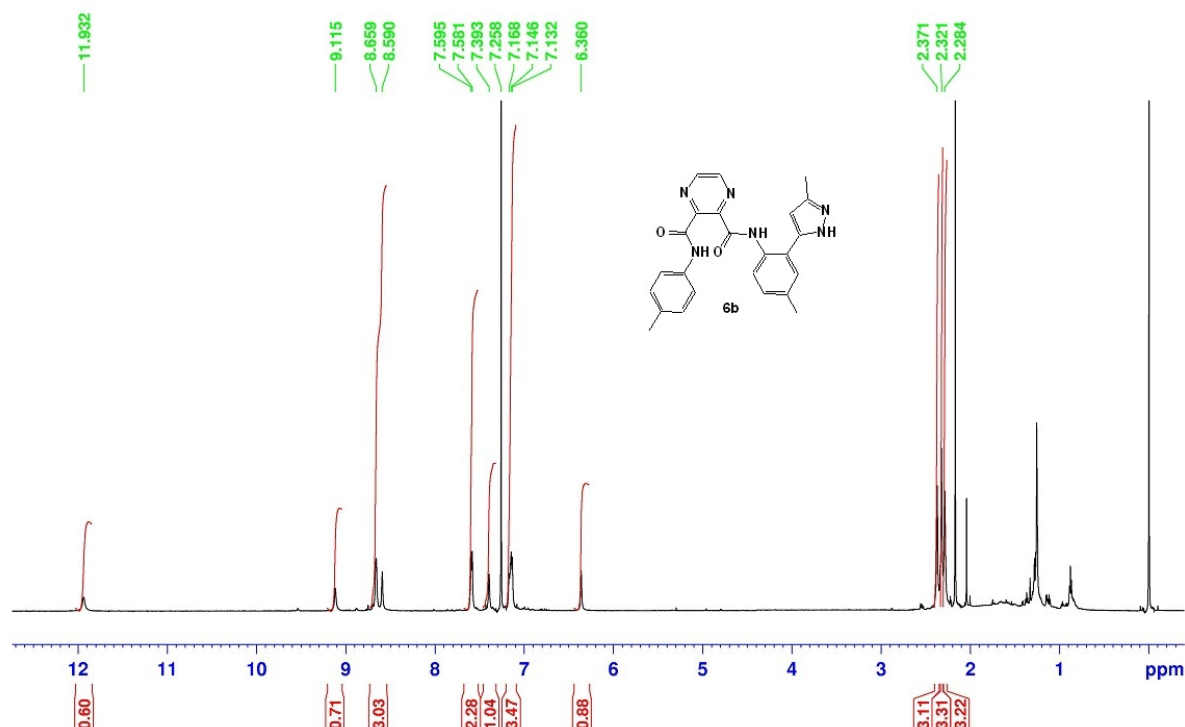
N^2 -(4-methyl-2-(3-methyl-1H-pyrazol-5-yl)phenyl)- N^3 -(p-tolyl)pyrazine-2,3-dicarboxamide (6b):

HRMS



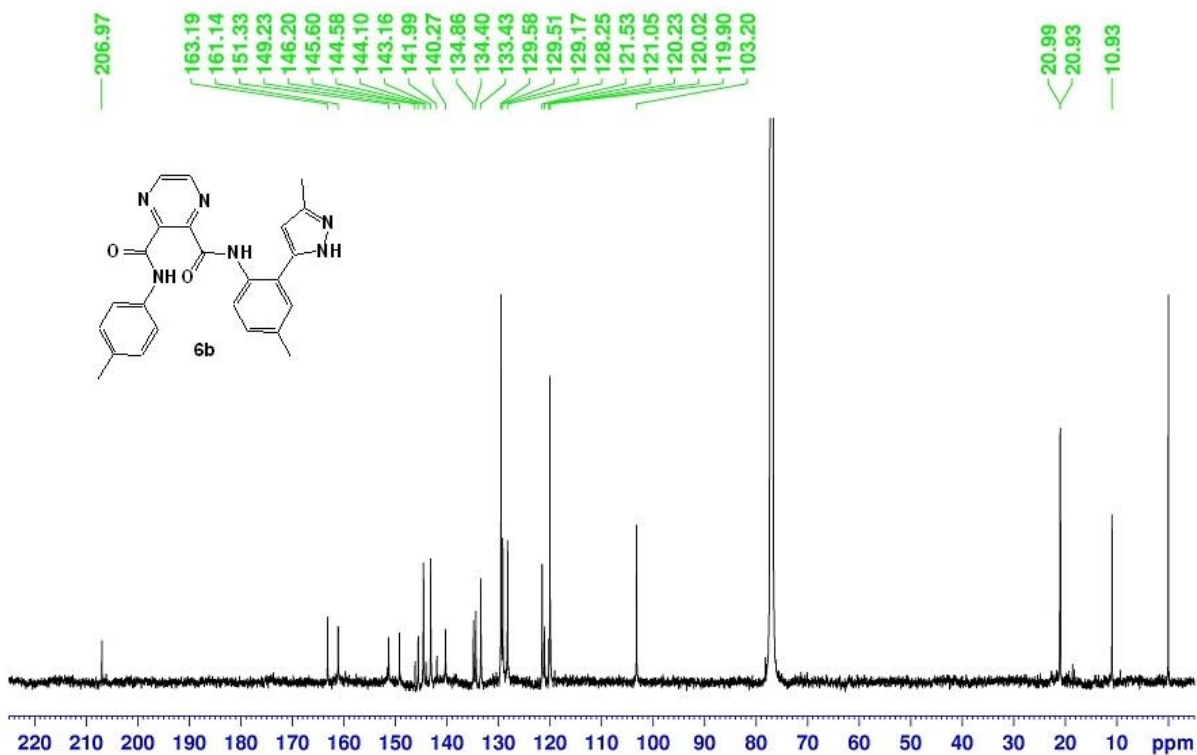
¹H NMR (600 MHz, CDCl₃)

MS-IV-28-600 in CDCl₃
proton spectrum
non-spinning
temp=25C

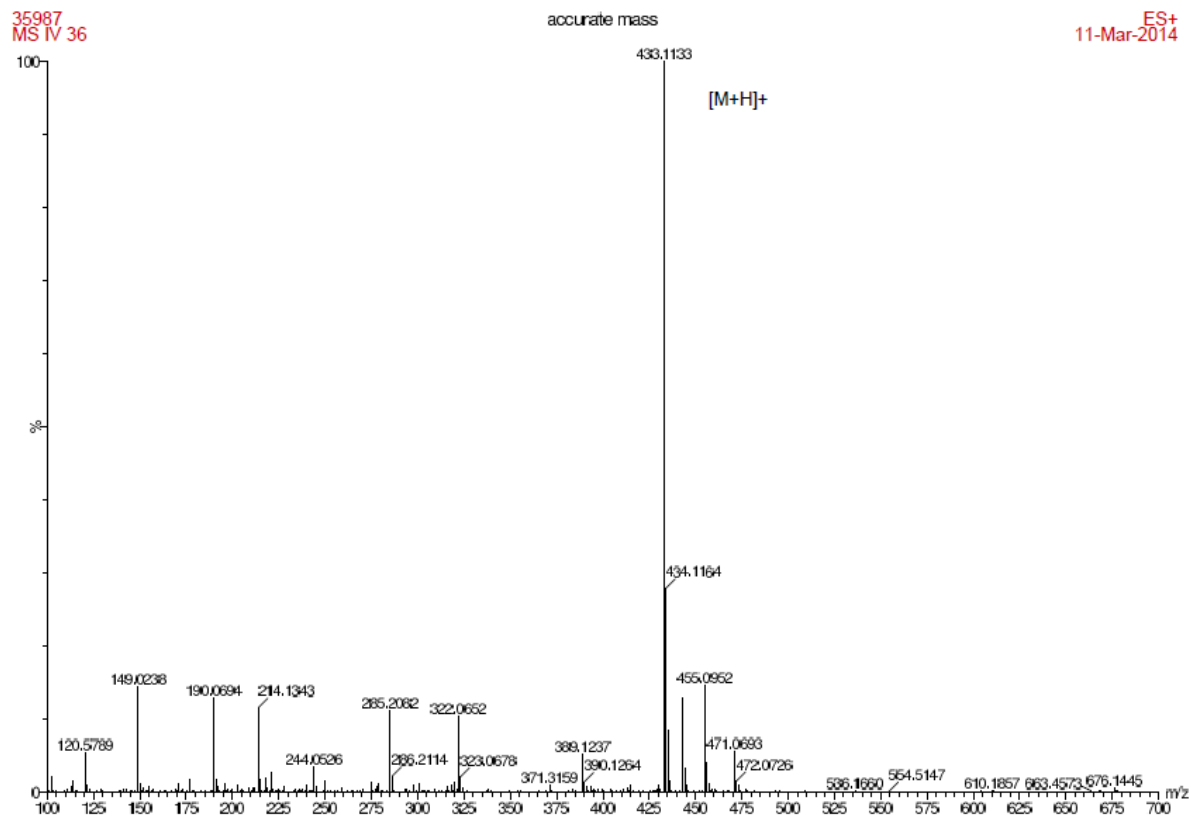


¹³C NMR (150 MHz, CDCl₃)

MS-IV-28-600 in CDCl₃
13C
1H decoupled



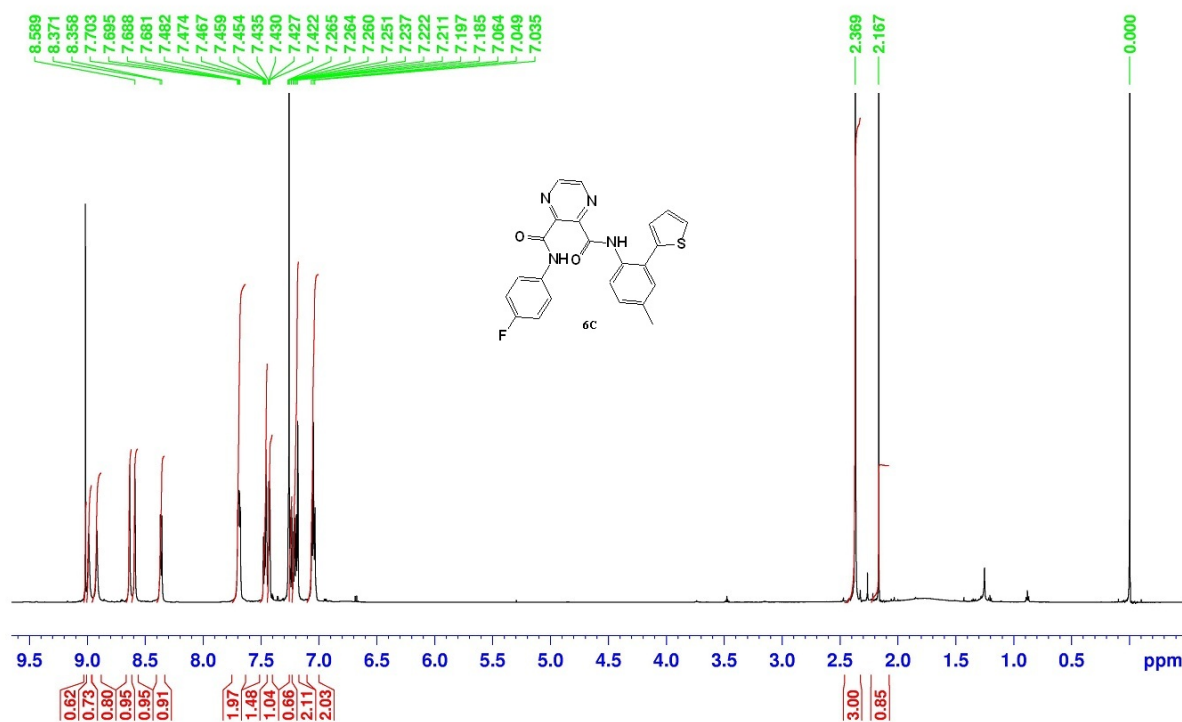
*N*²-(4-fluorophenyl)-*N*³-(4-methyl-2-(thiophen-2-yl)phenyl)pyrazine-2,3-dicarboxamide (6c)
HRMS



¹H NMR (600 MHz, CDCl₃)

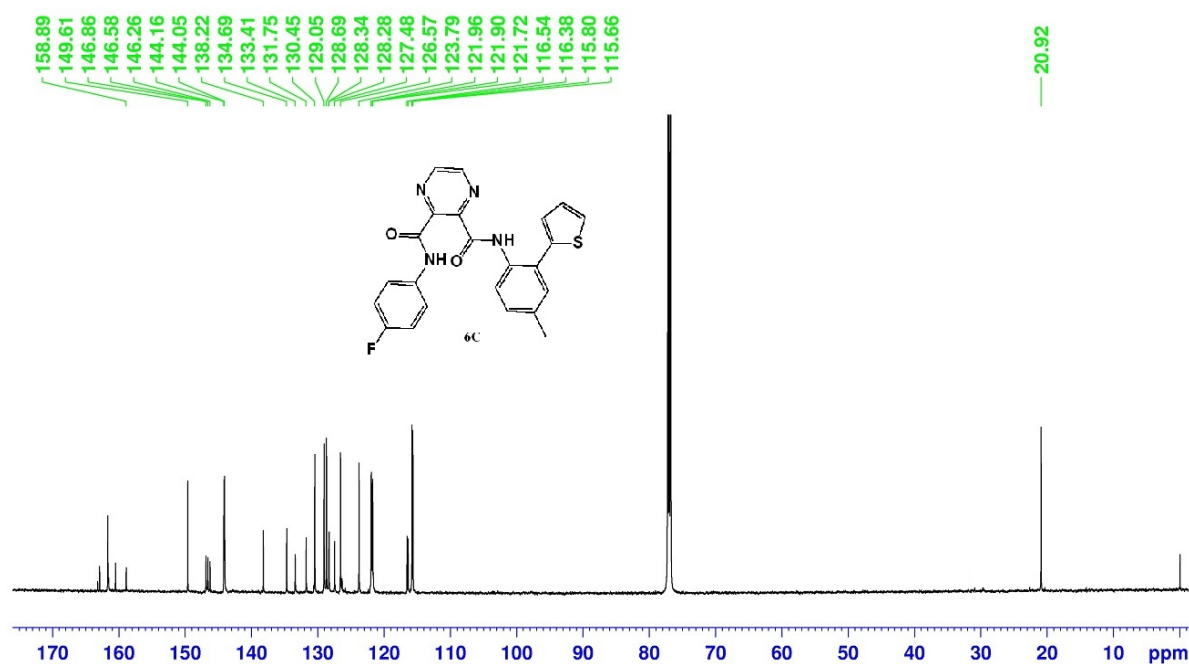
MS-IV-36-600 in CDCl₃
proton spectrum

temp=25C



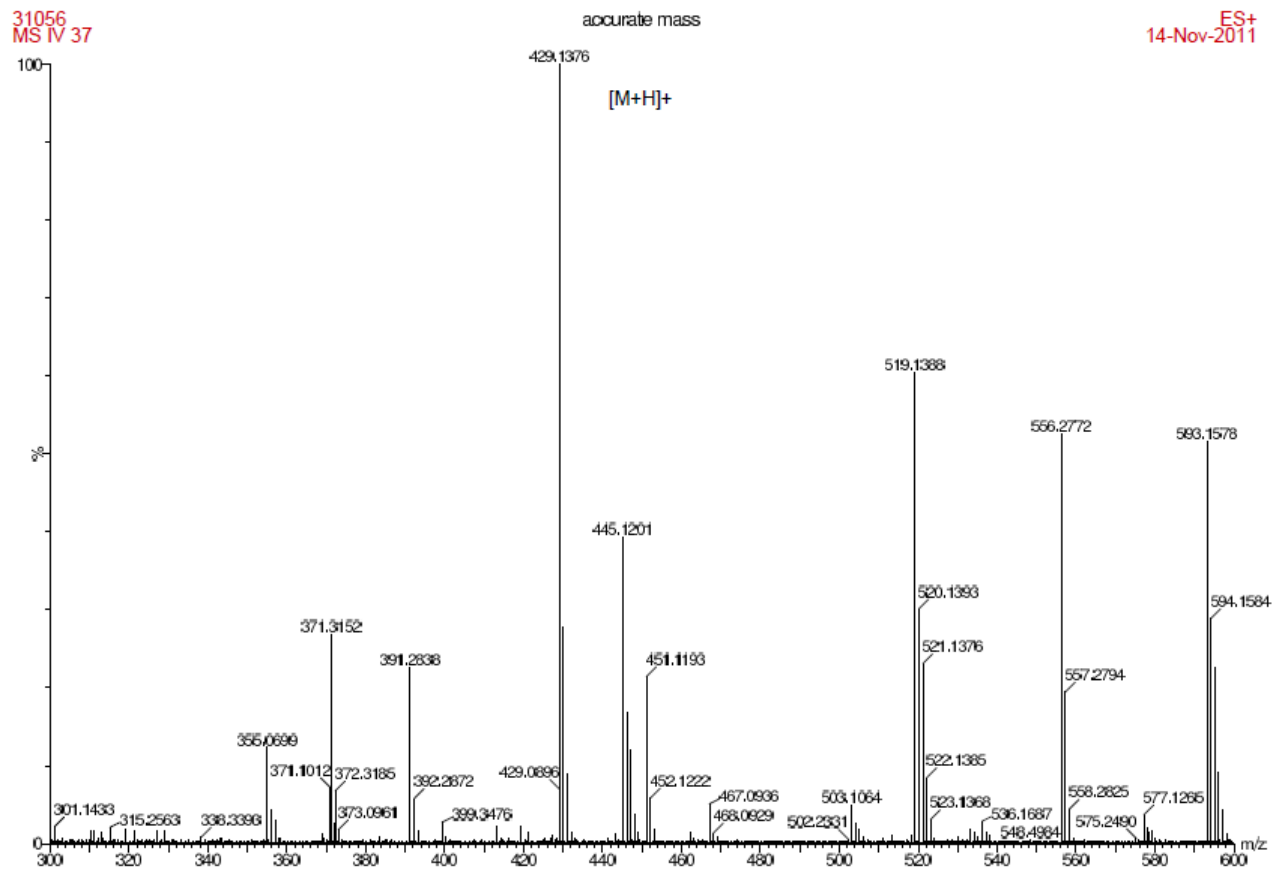
^{13}C NMR (150 MHz, CDCl_3)

MS-IV-36-600 in CDCl_3
13C



N^2 -(4-methyl-2-(thiophen-2-yl)phenyl)- N^3 -(p-tolyl)pyrazine-2,3-dicarboxamide (6d)

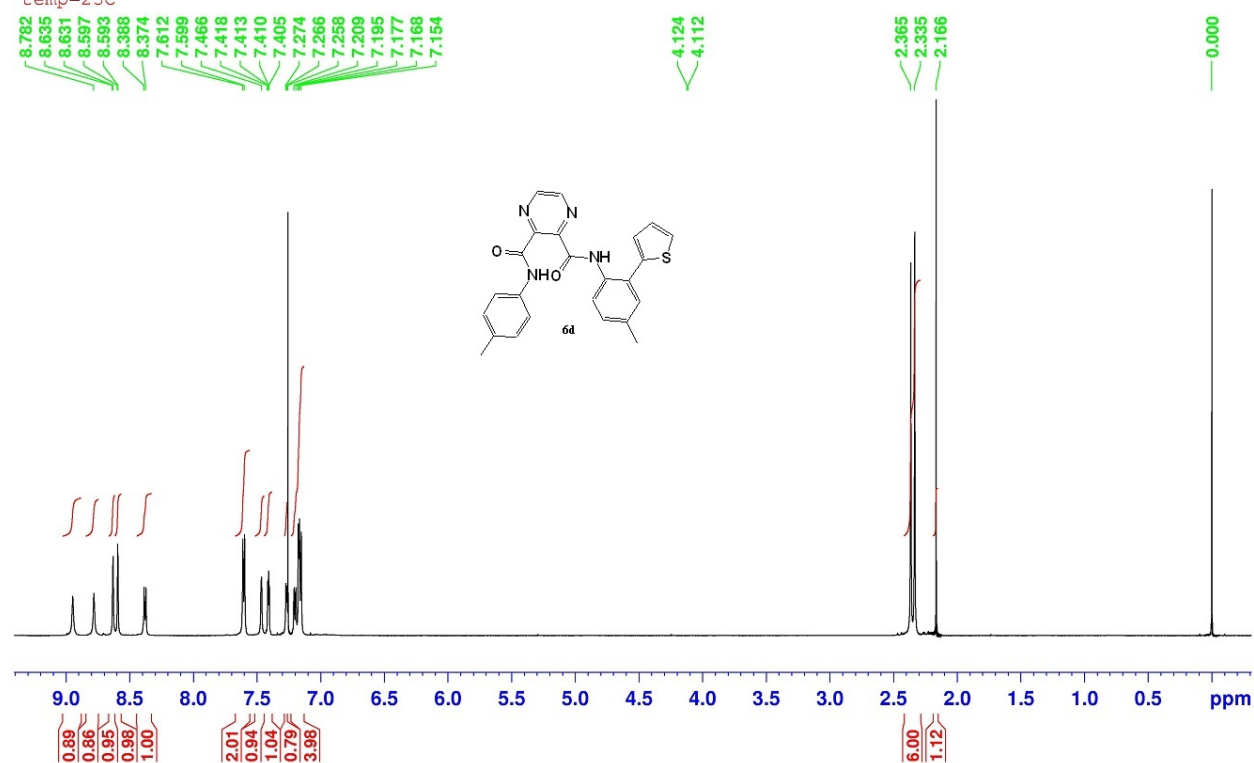
HRMS



¹H NMR (600 MHz, CDCl₃)

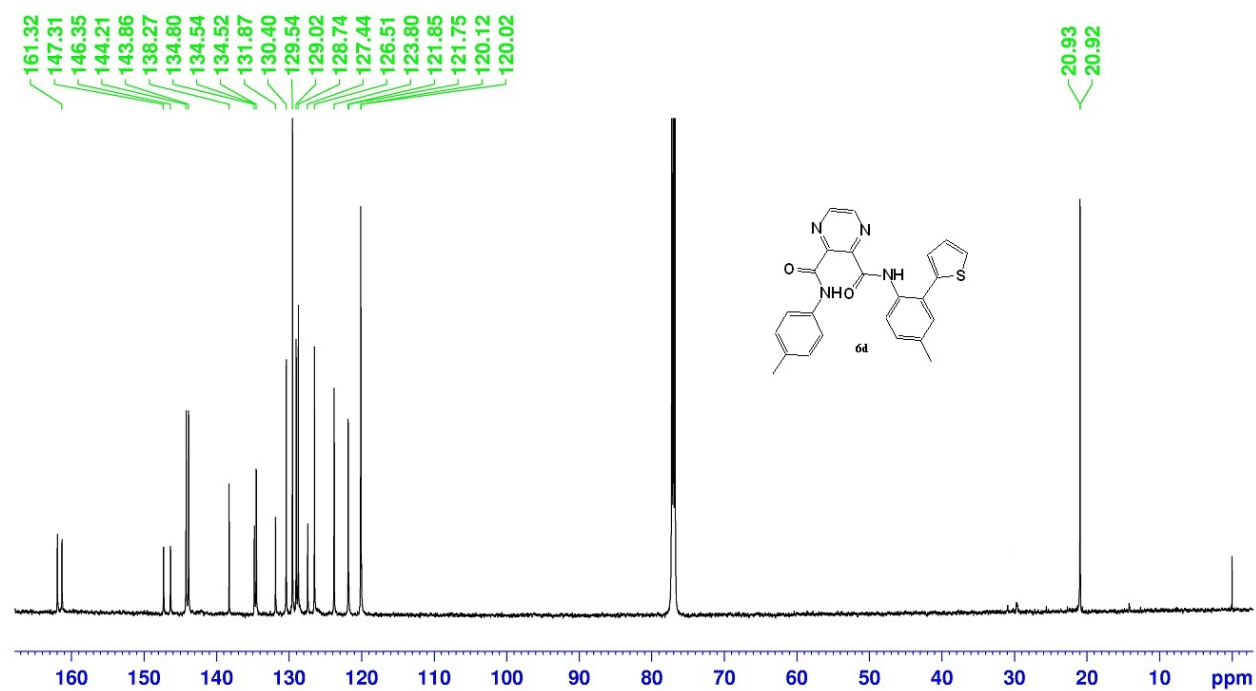
MS-IV-37-600 in CDCl₃
proton spectrum

temp=25C



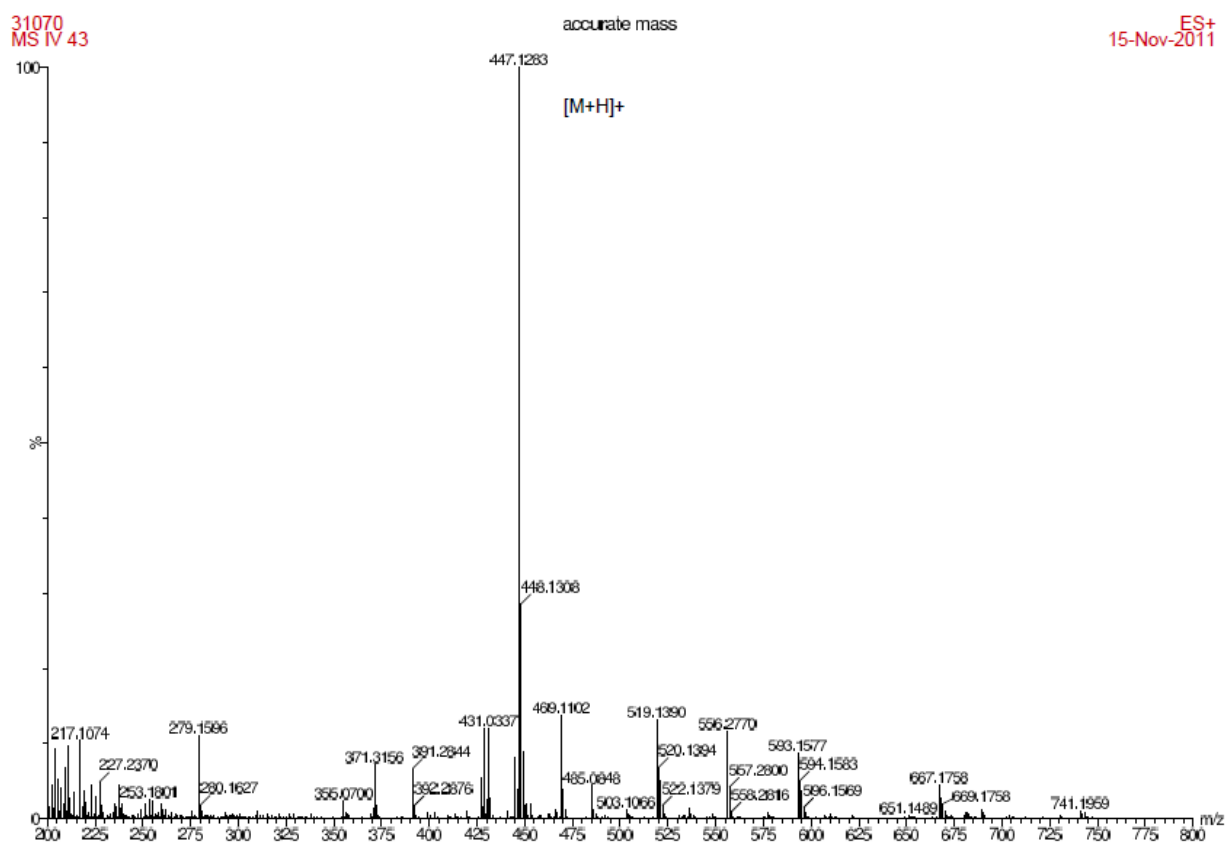
¹³C NMR (150 MHz, CDCl₃)

MS-IV-37-600 in CDCl₃
¹³C



*N*²-(4-fluorophenyl)-*N*³-(4-methyl-2-(5-methylthiophen-2-yl)phenyl)pyrazine-2,3-dicarboxamide (6e)

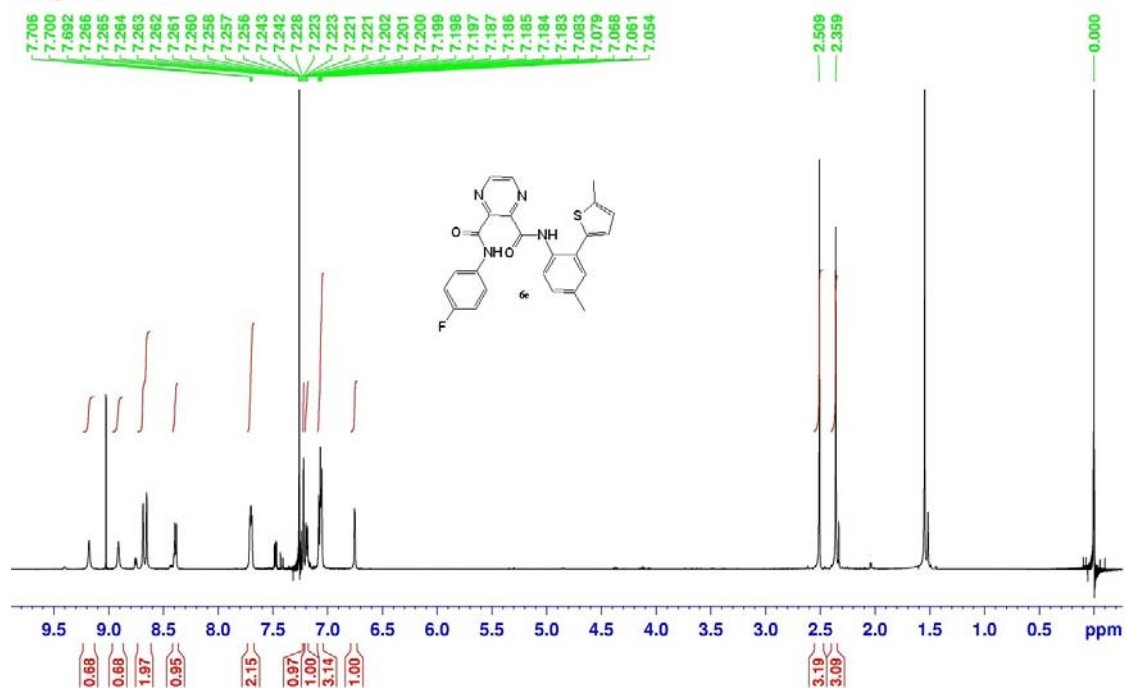
HRMS



¹H NMR (600 MHz, CDCl₃)

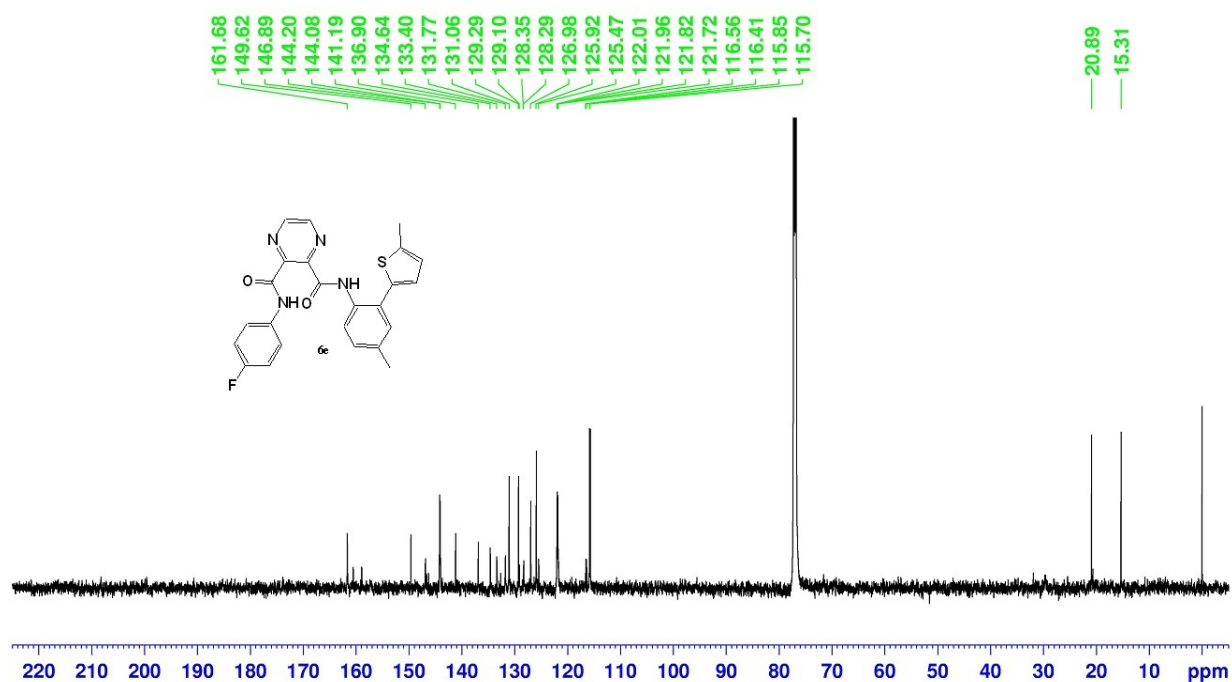
MS-IV-43-600 in CDCl₃
proton spectrum

temp=25C

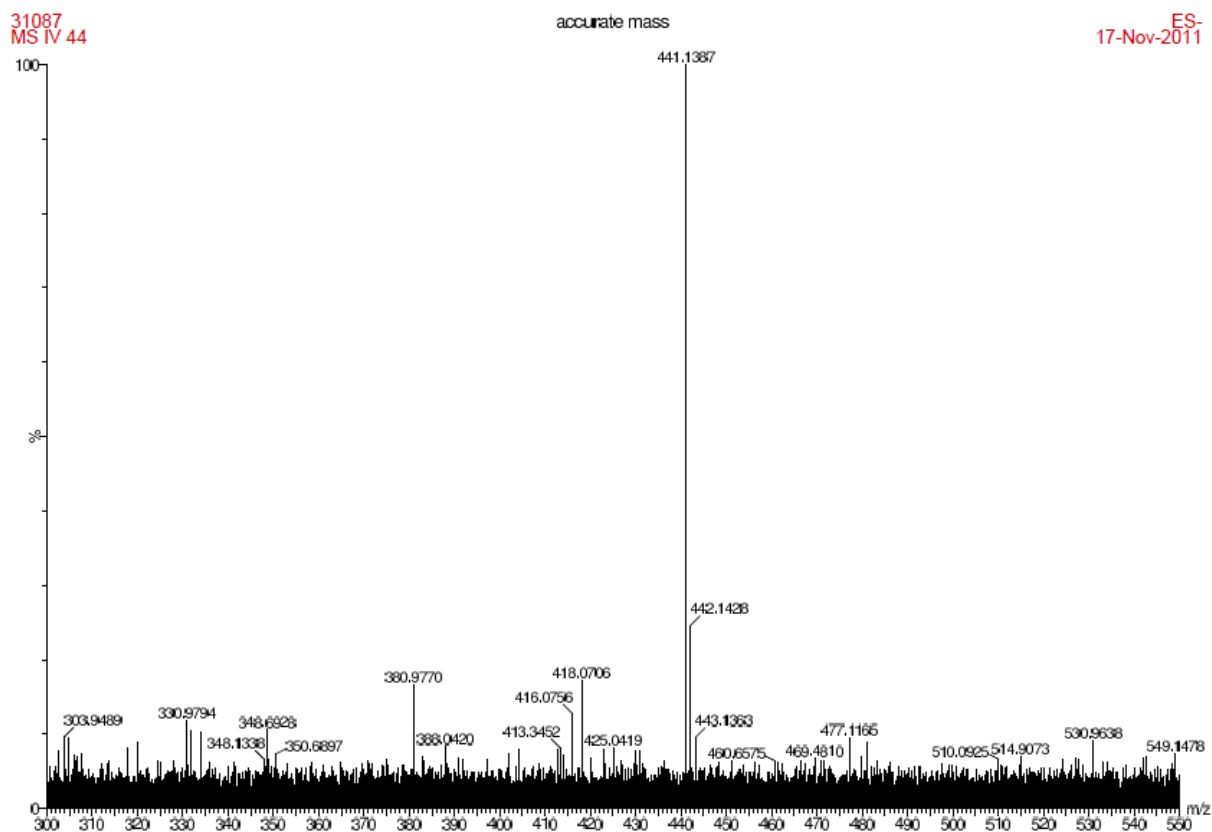


^{13}C NMR (150 MHz, CDCl_3)

MS-IV-43-600 in CDCl_3
 ^{13}C

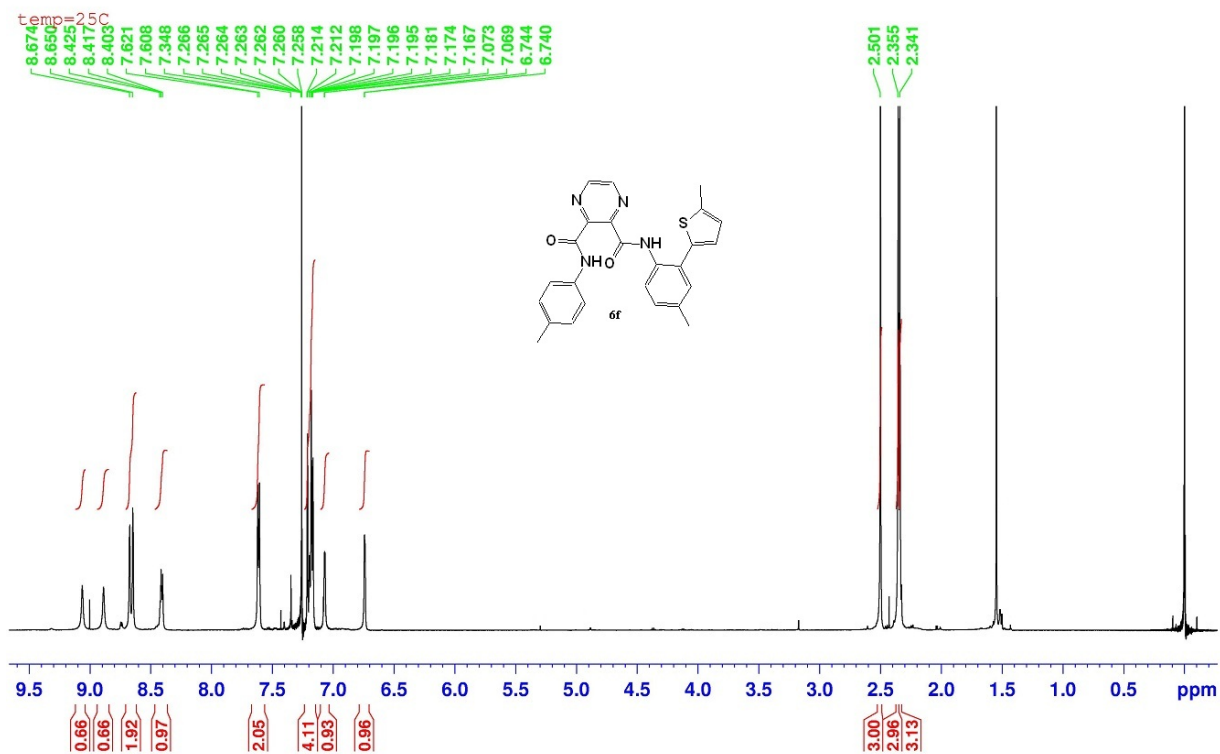


N^2 -(4-methyl-2-(5-methylthiophen-2-yl)phenyl)- N^3 -(p-tolyl)pyrazine-2,3-dicarboxamide (6f)
HRMS



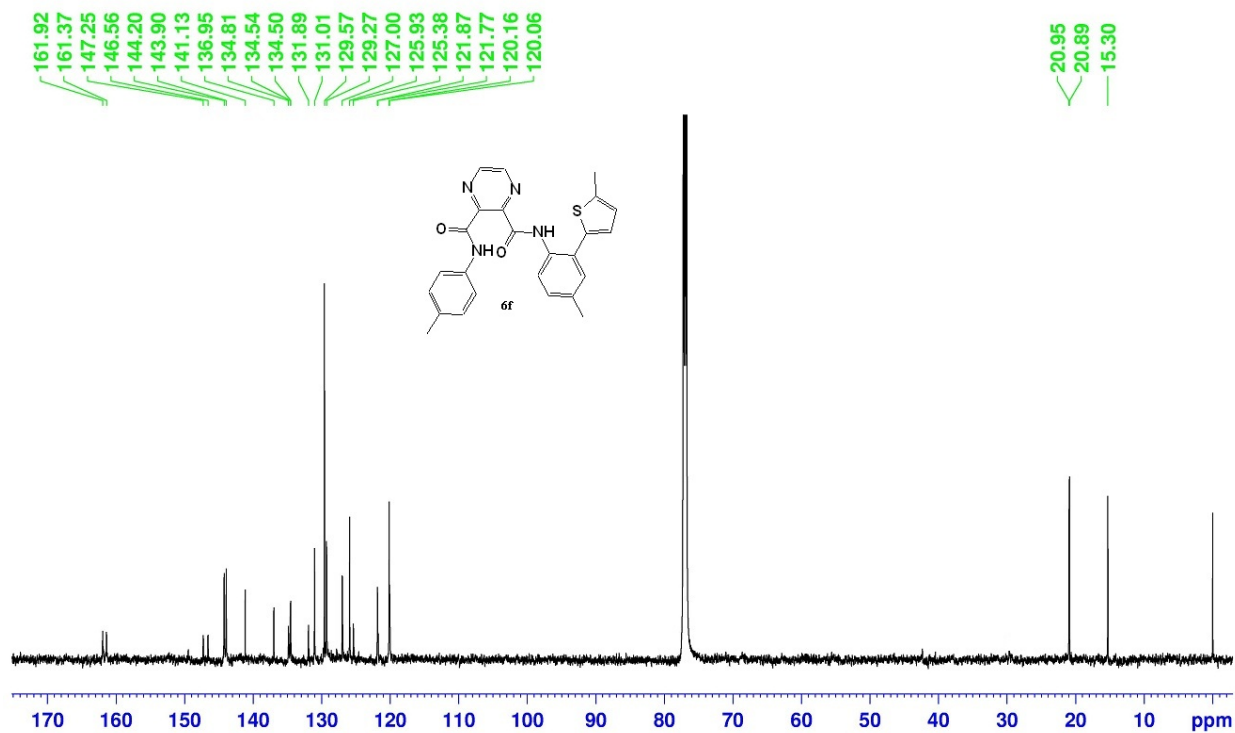
^1H NMR (600 MHz, CDCl_3)

MS-IV-44-600 in CDCl_3
proton spectrum



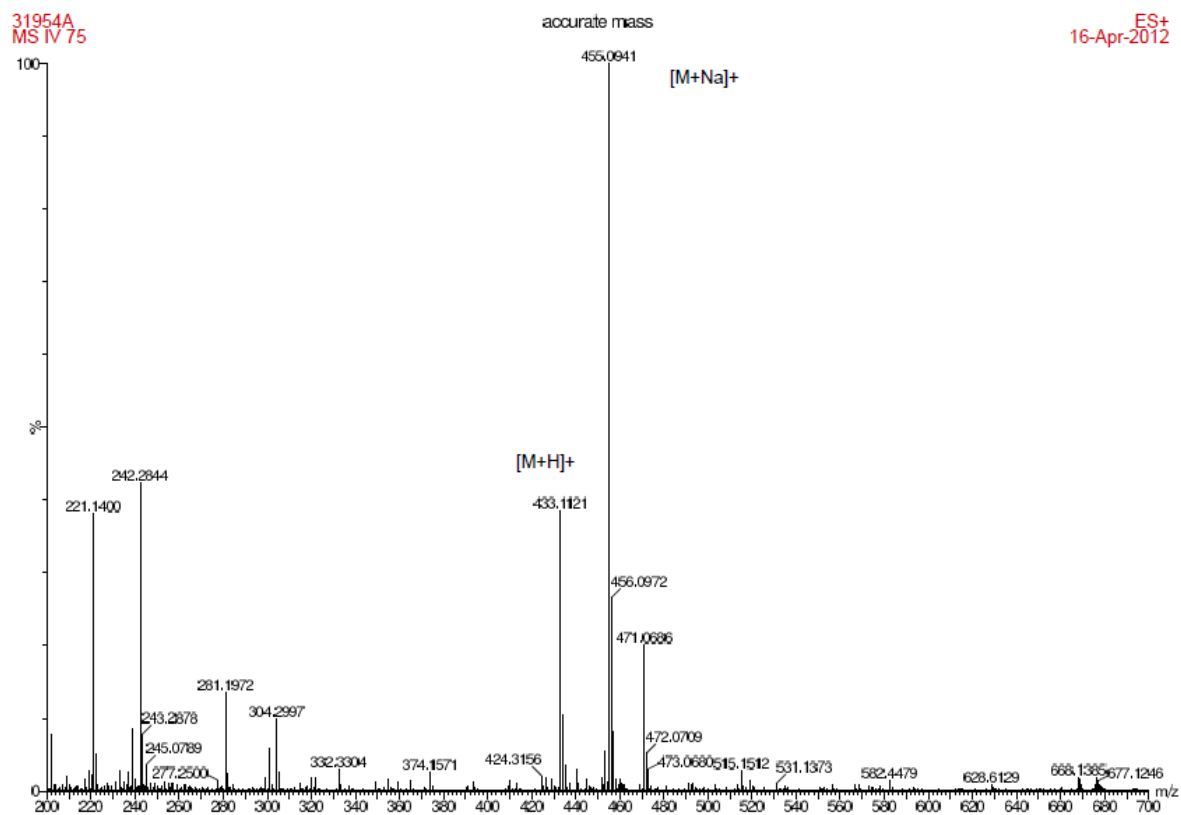
^{13}C NMR (150 MHz, CDCl_3)

MS-IV-44-600 in CDCl_3
 ^{13}C



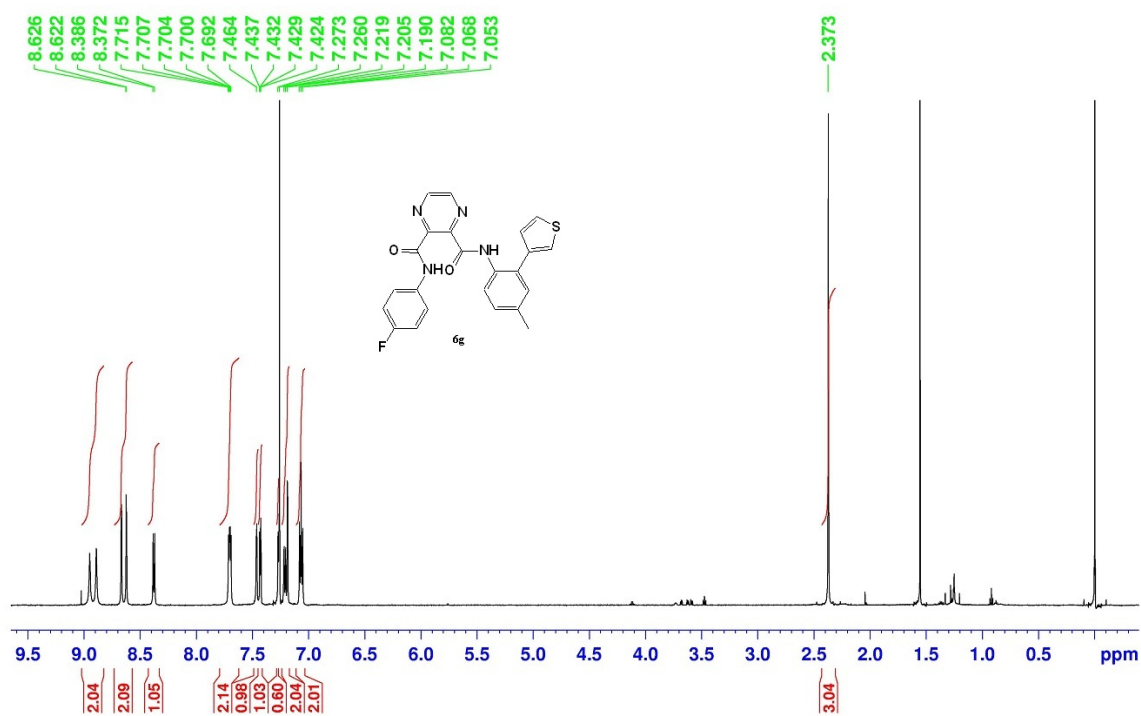
*N*²-(4-fluorophenyl)-*N*³-(4-methyl-2-(thiophen-3-yl)phenyl)pyrazine-2,3-dicarboxamide (6g)

HRMS



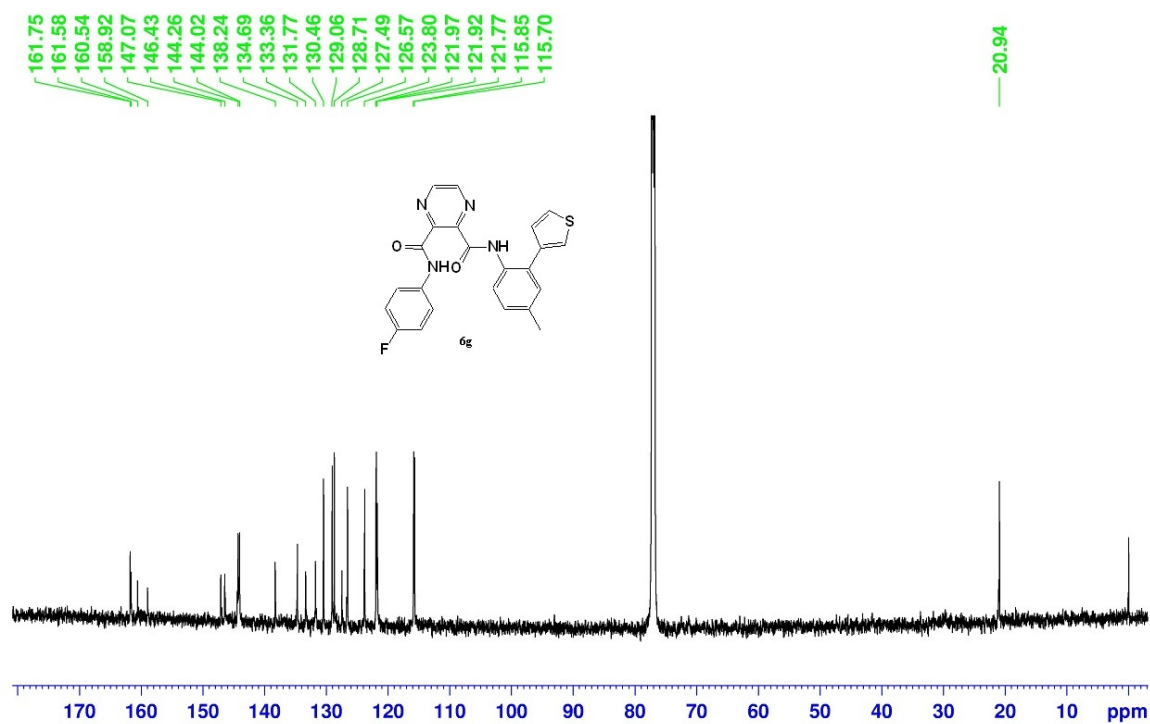
¹H NMR (500 MHz, CDCl₃)

MS-IV-75 in CDCl₃
proton spectrum
temp=25C

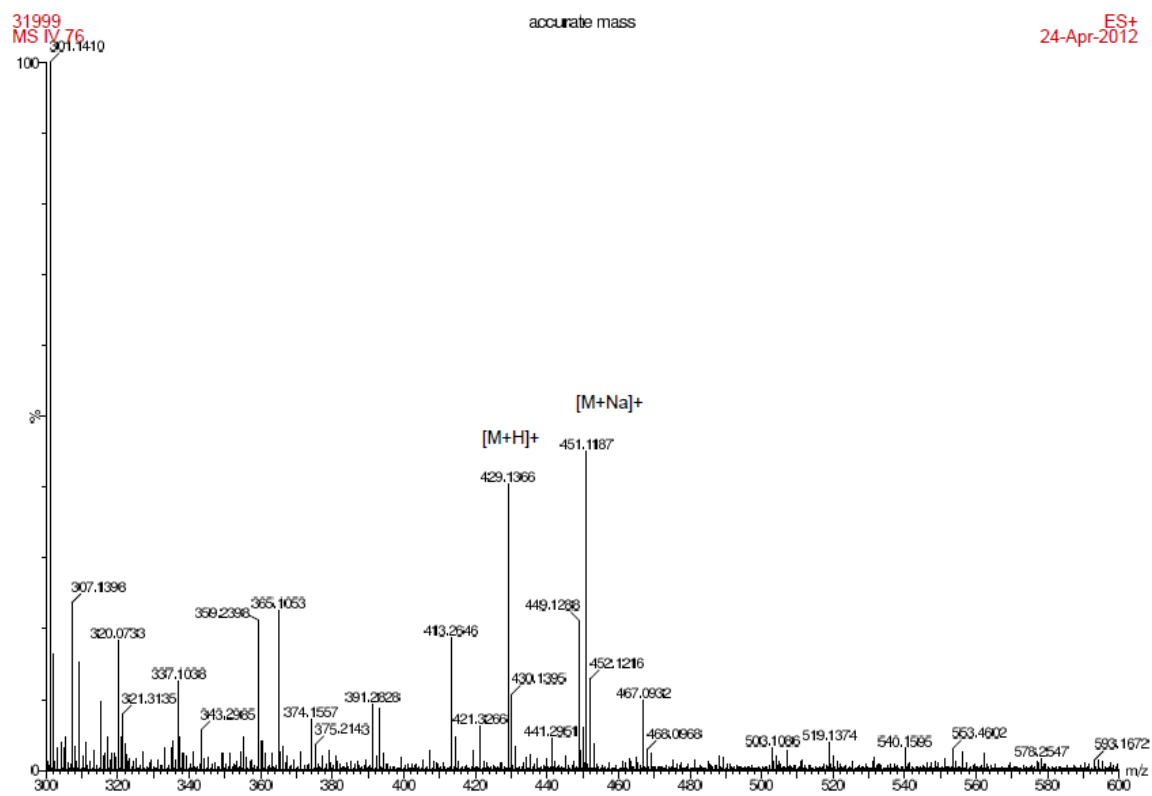


^{13}C NMR (125 MHz, CDCl_3)

MS-IV-75 in CDCl_3
temp = 25C
13C

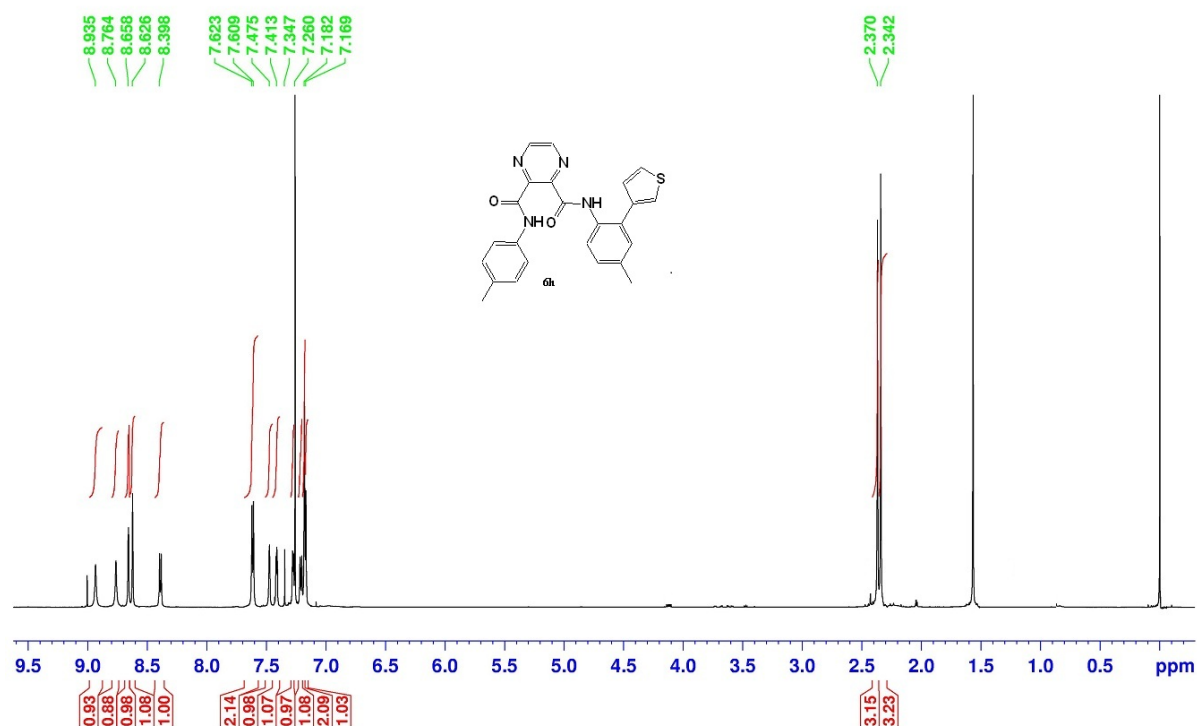


N^2 -(4-methyl-2-(thiophen-3-yl)phenyl)- N^3 -(p-tolyl)pyrazine-2,3-dicarboxamide (6h) HRMS



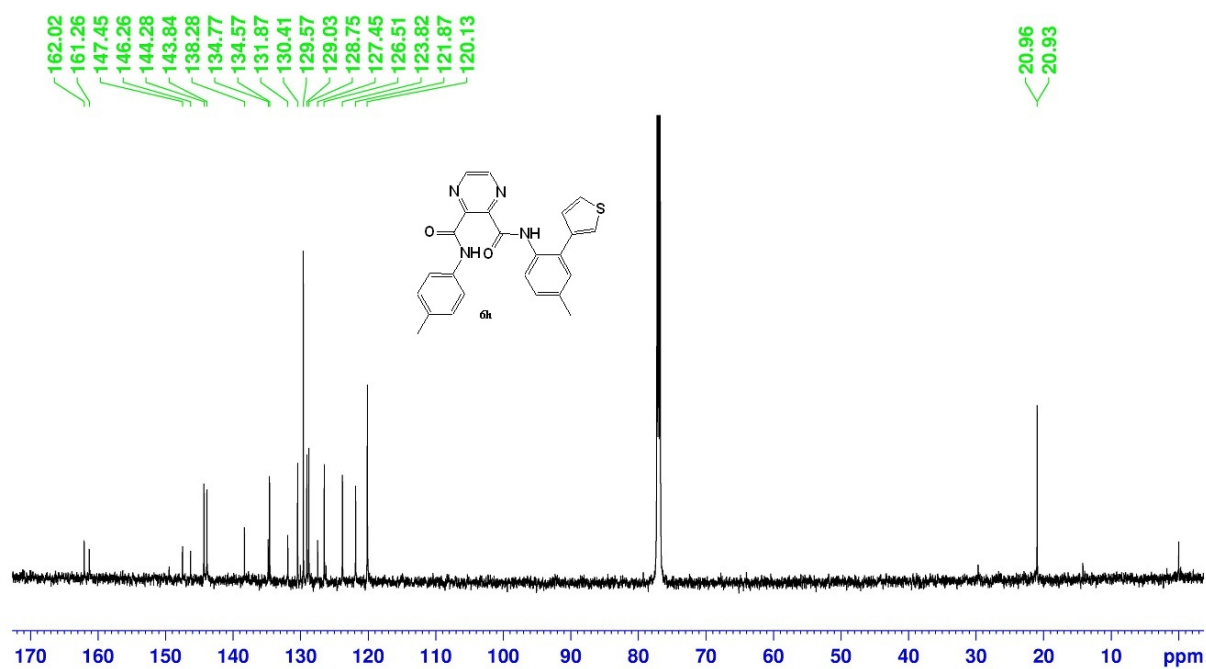
¹H NMR (500 MHz, CDCl₃)

MS-IV-76 in CDCl₃
proton spectrum
temp=25C



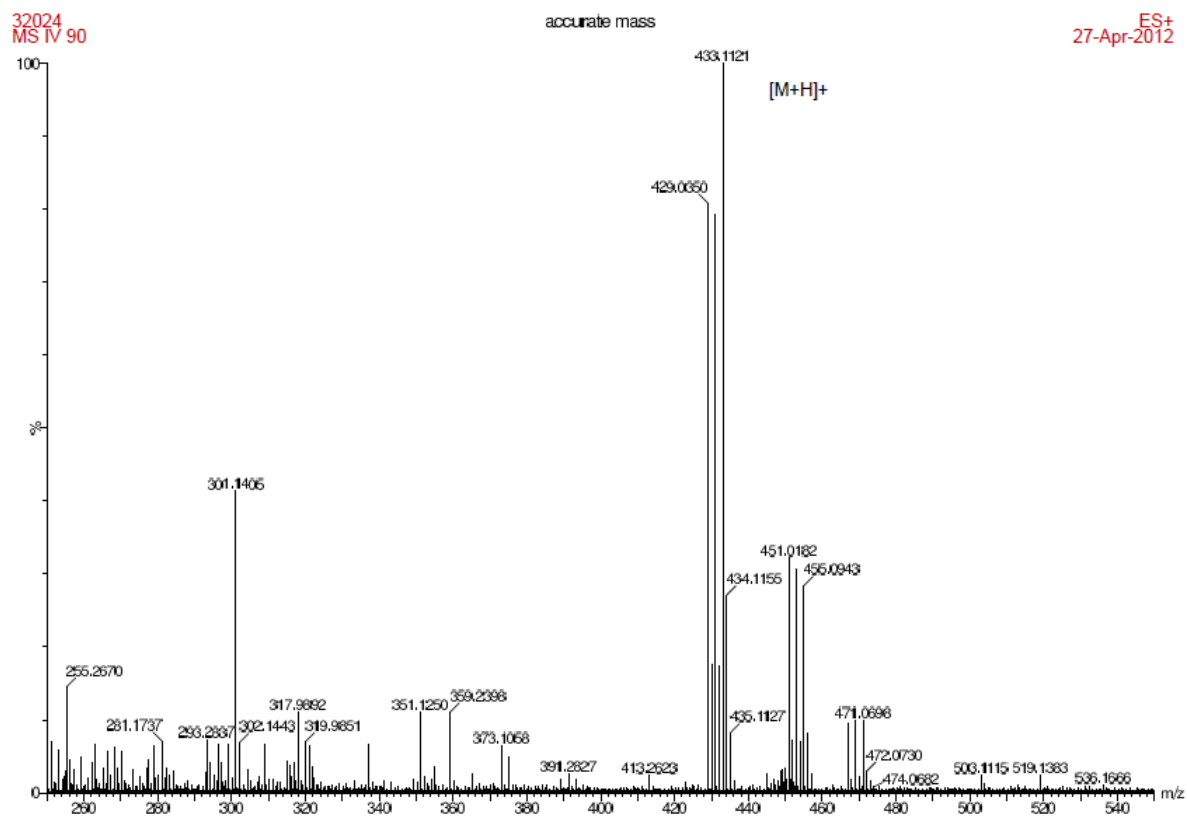
¹³C NMR (125 MHz, CDCl₃)

MS-IV-76 in CDCl₃
temp = 20C
13C

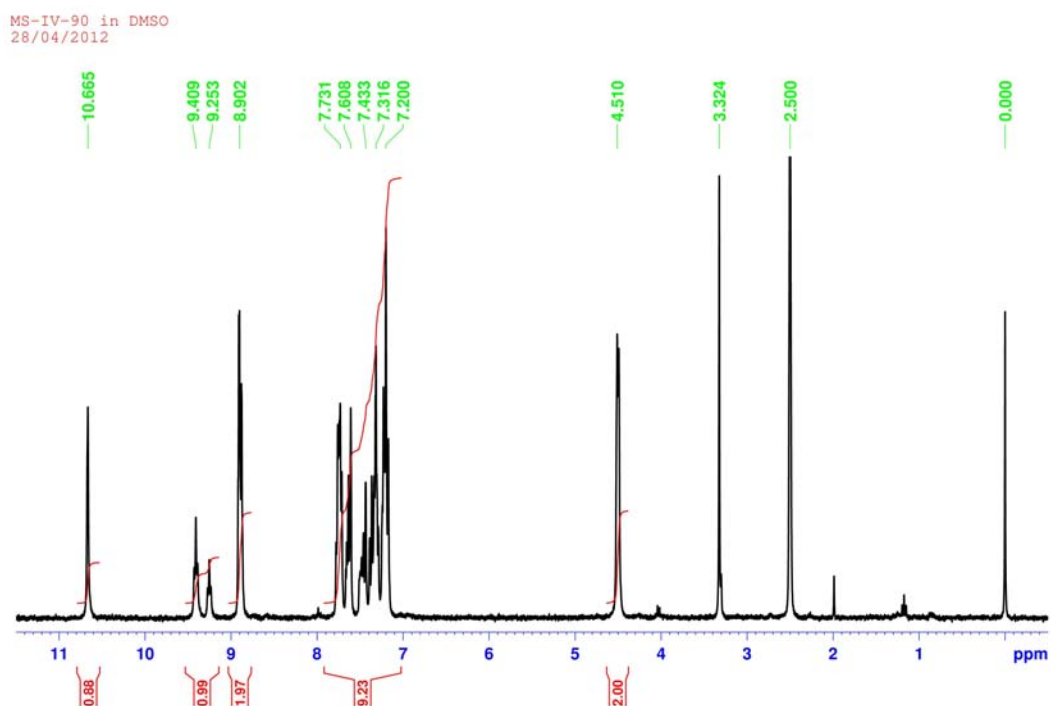


N^2 -(4-fluorophenyl)- N^3 -(2-(thiophen-3-yl)benzyl)pyrazine-2,3-dicarboxamide (6i)

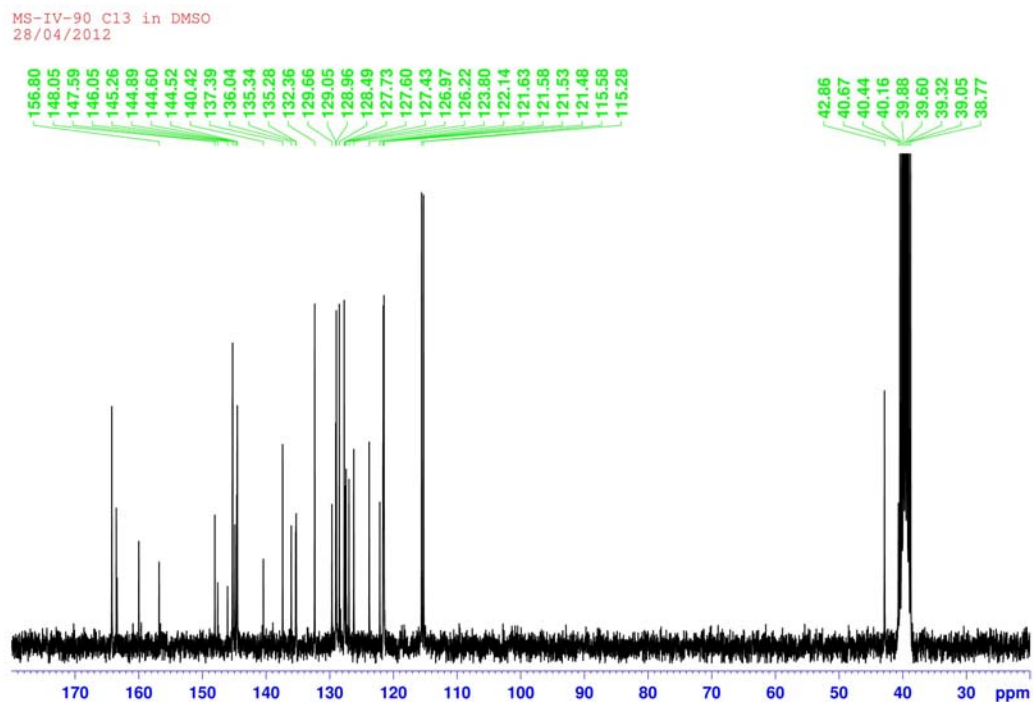
HRMS



^1H NMR (300 MHz, DMSO)

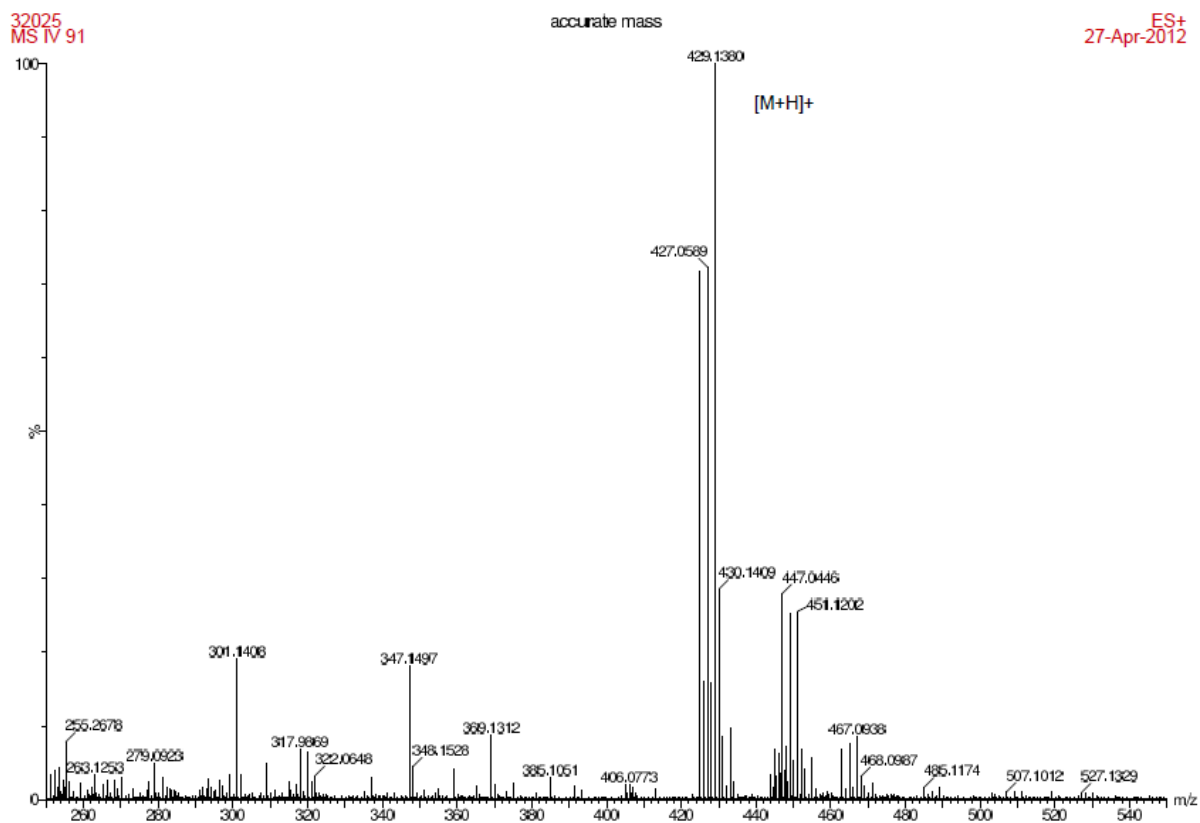


^{13}C NMR (75 MHz, DMSO)



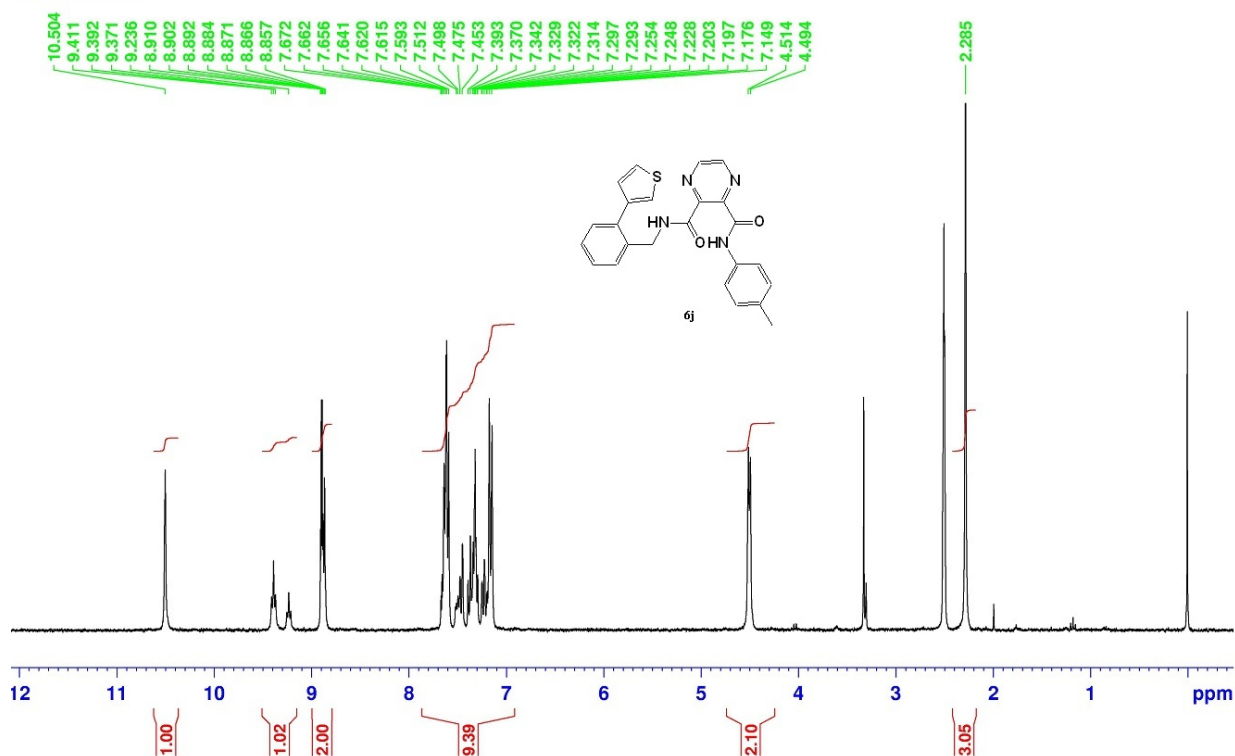
N^2 -(2-(thiophen-3-yl)benzyl)- N^3 -(p-tolyl)pyrazine-2,3-dicarboxamide (6j)

HRMS



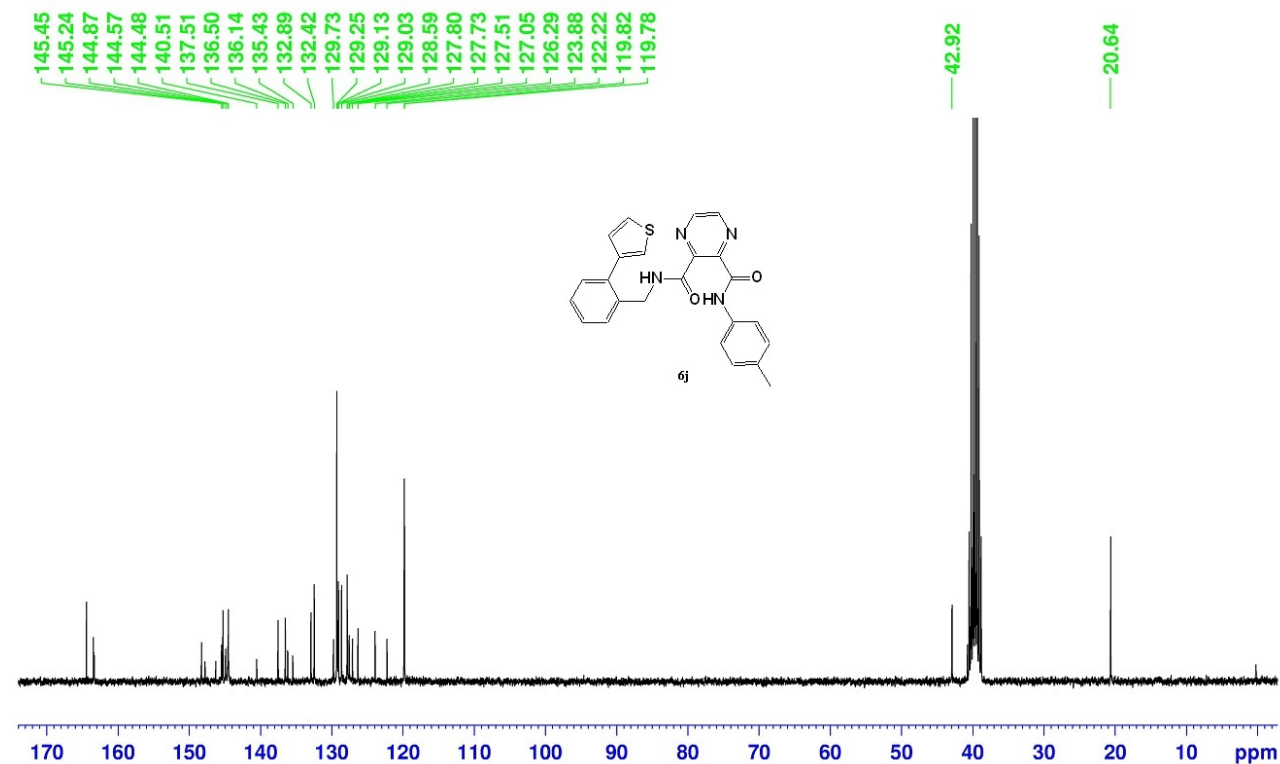
¹H NMR (300 MHz, DMSO)

MS-IV-91 in DMSO
28/04/2012



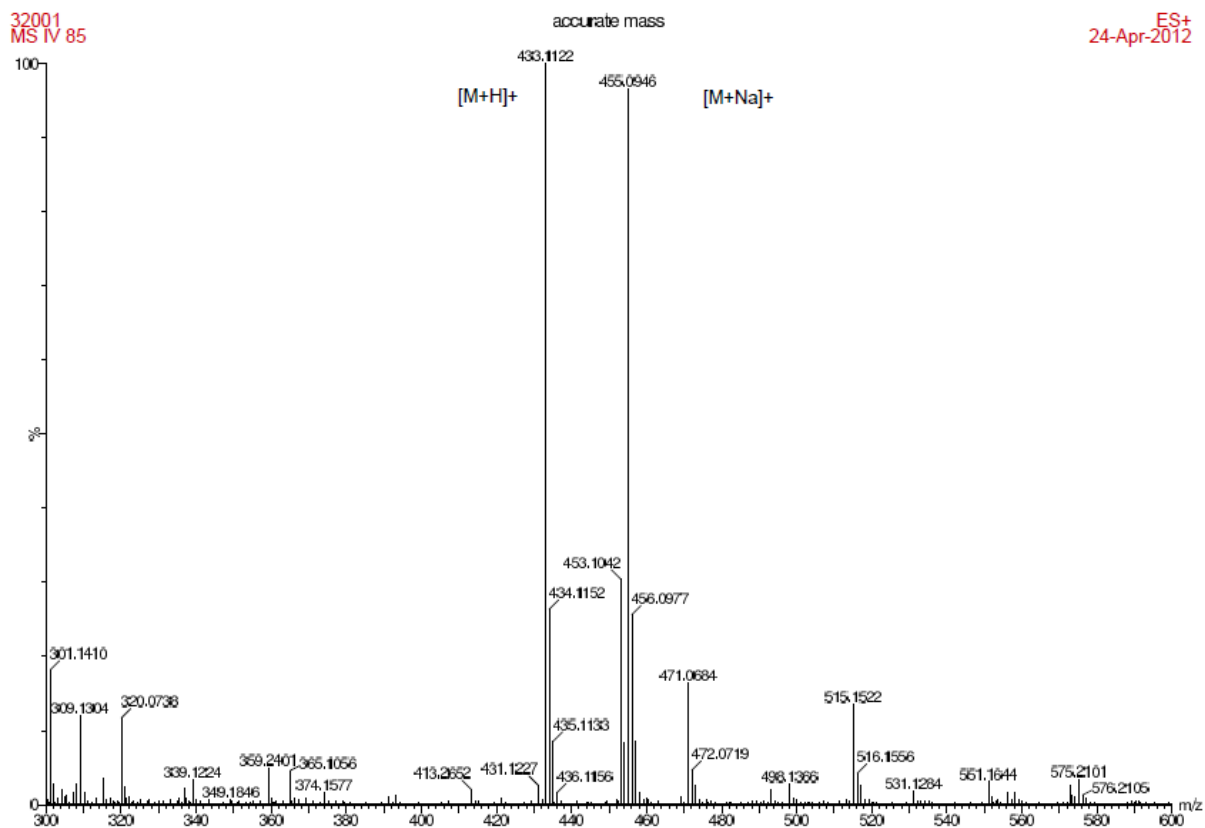
¹³C NMR (75 MHz, DMSO)

MS-IV-91 C13 in DMSO
28/04/2012



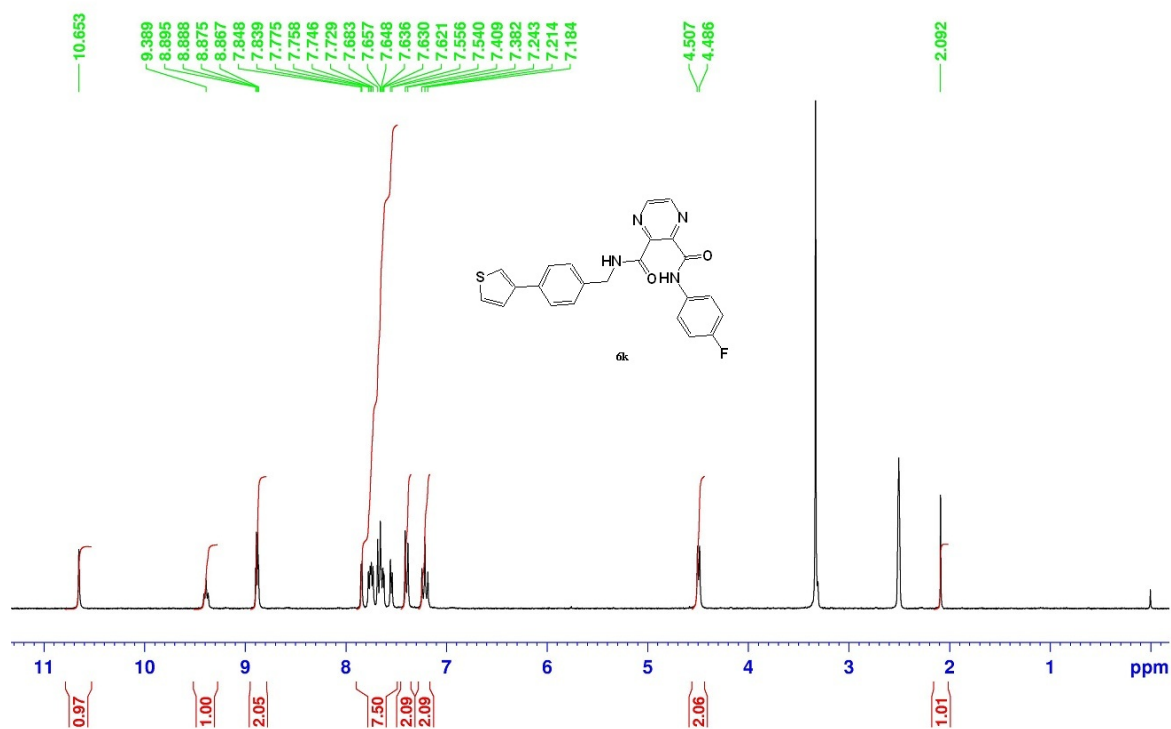
*N*²-(4-fluorophenyl)-*N*³-(4-(thiophen-3-yl)benzyl)pyrazine-2,3-dicarboxamide (6k)

HRMS



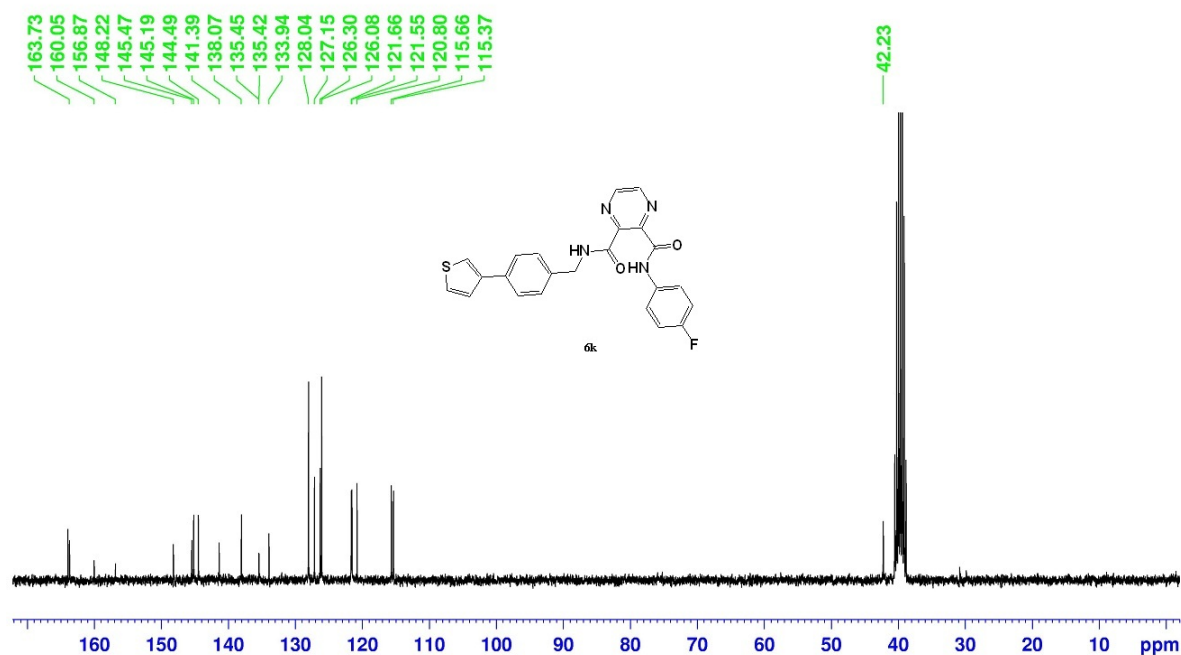
¹H NMR (300 MHz, DMSO)

MS-IV-85 in DMSO 25/04/2012



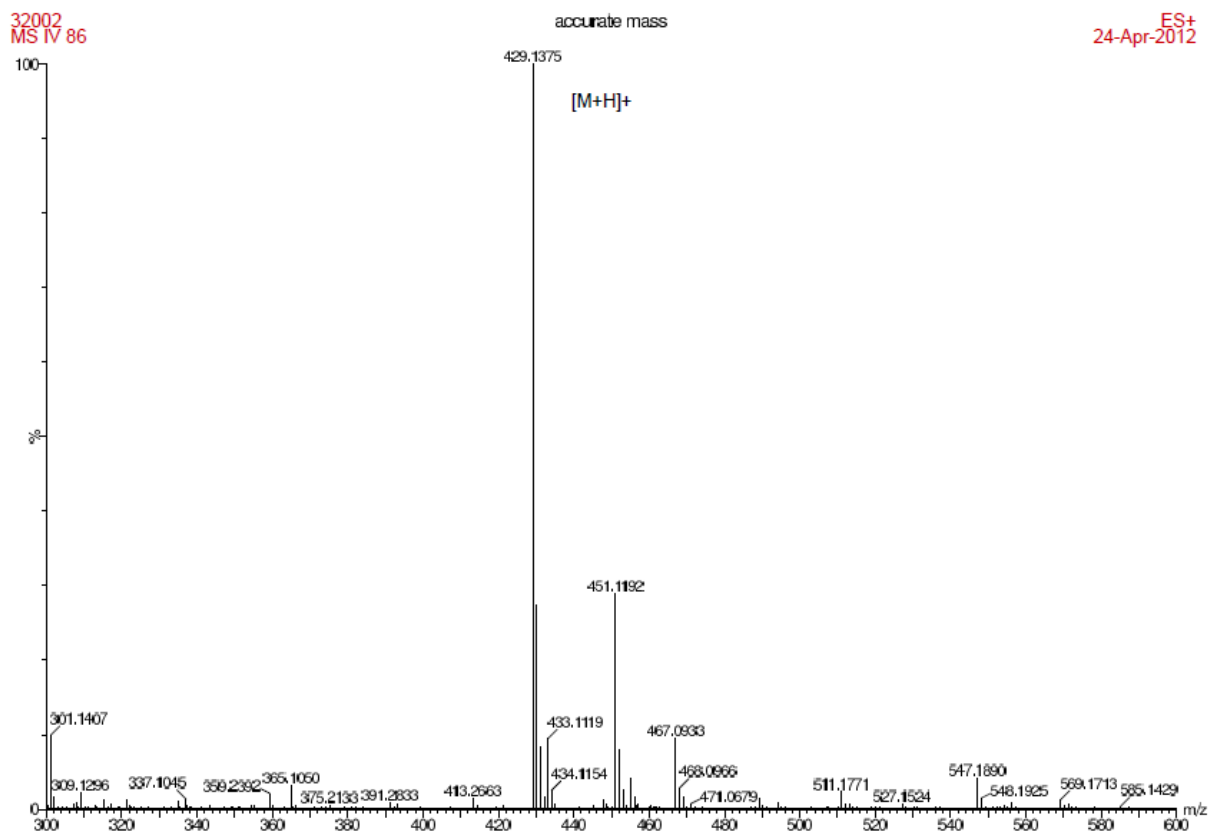
^{13}C NMR (75 MHz, DMSO)

MS-IV-85 C13 in DMSO
25/04/2012



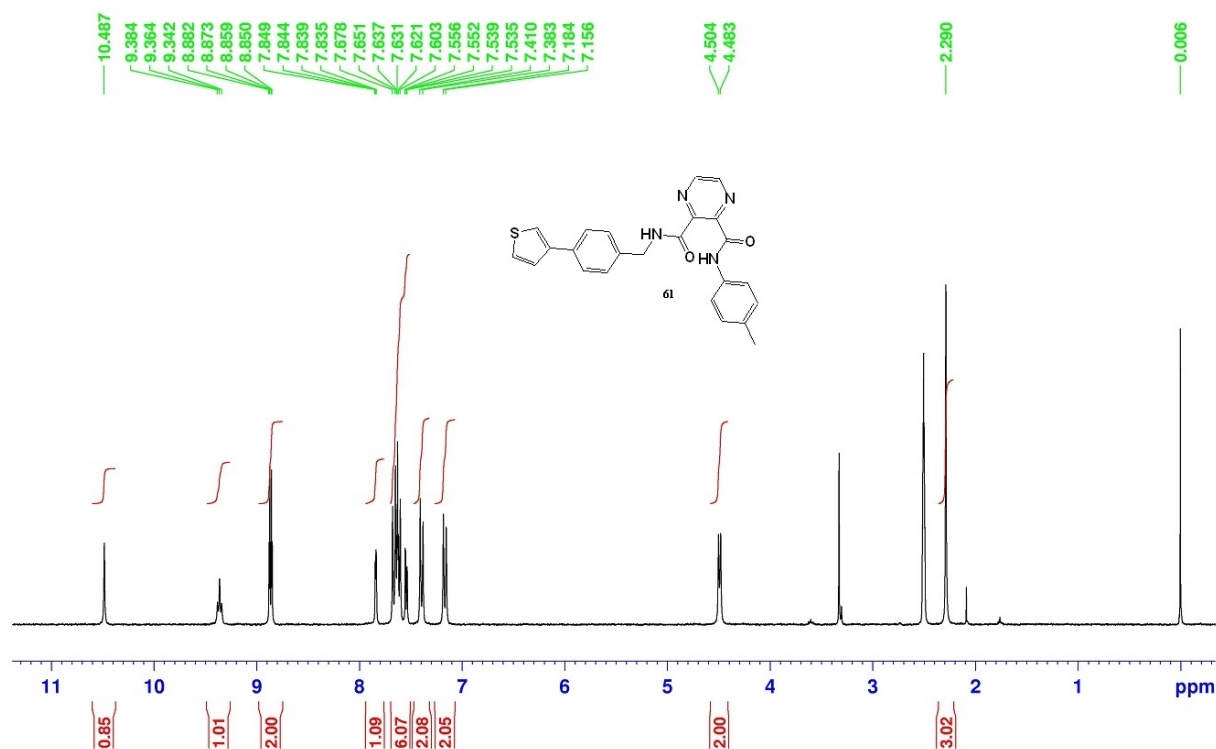
N^2 -(4-(thiophen-3-yl)benzyl)- N^3 -(p-tolyl)pyrazine-2,3-dicarboxamide (6l)

HRMS



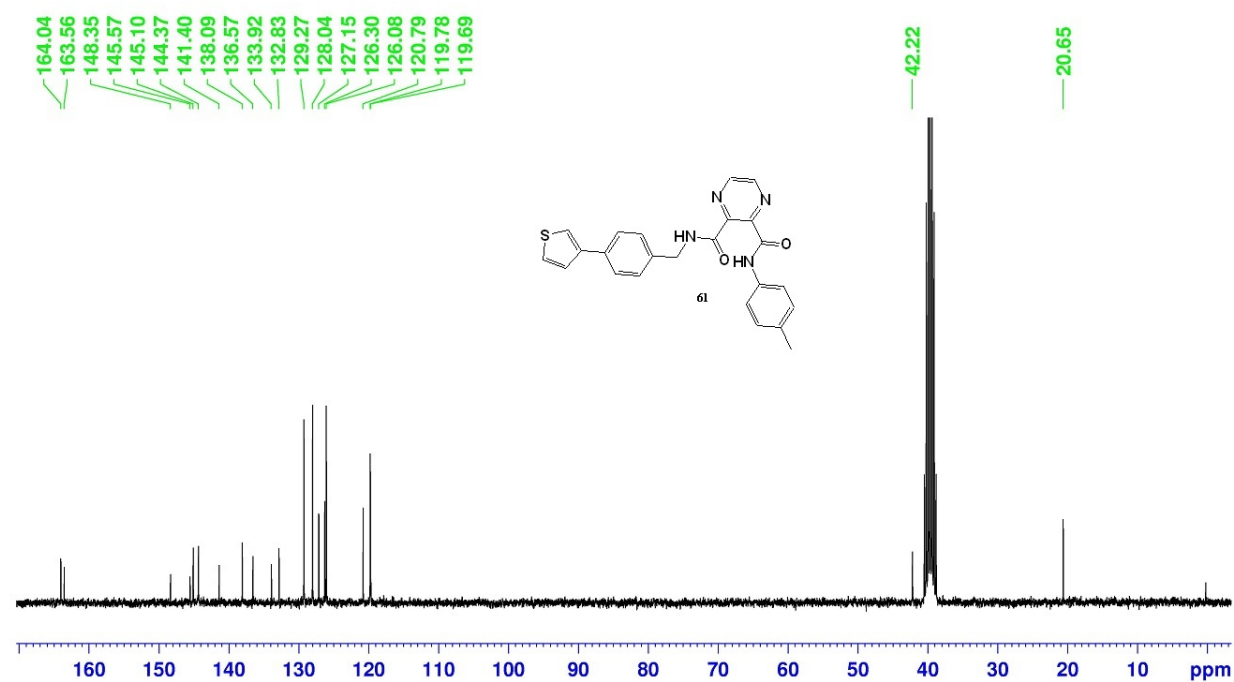
¹H NMR (300 MHz, DMSO)

MS-IV-86 in DMSO
26/04/2012



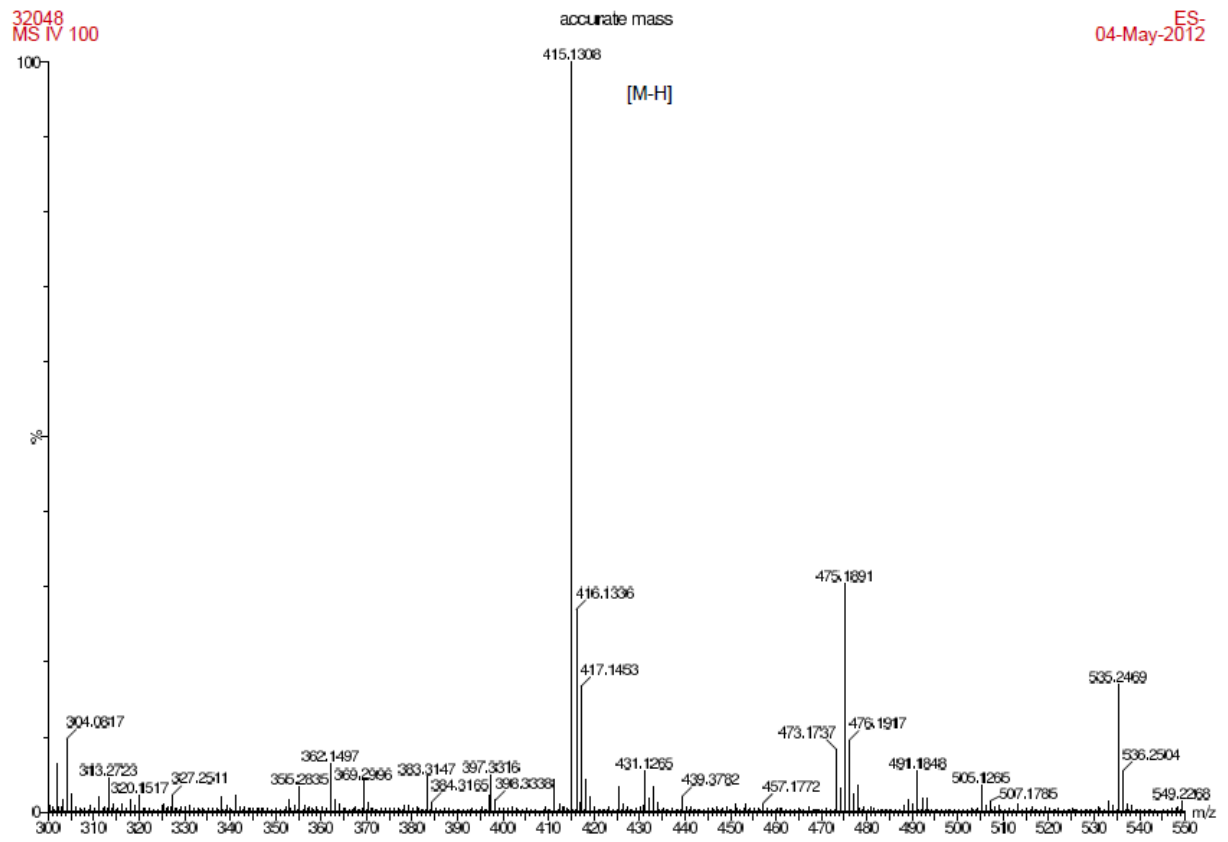
¹³C NMR (75 MHz, DMSO)

MS-IV-86 C13 in DMSO
26/04/2012



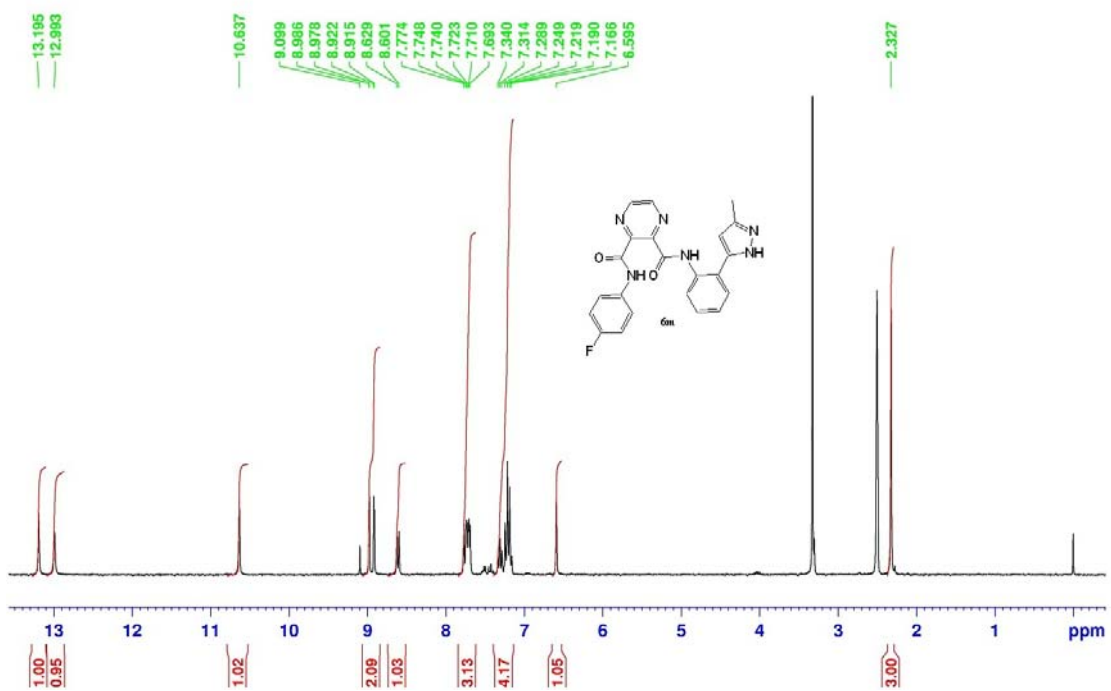
*N*²-(4-fluorophenyl)-*N*³-(2-(3-methyl-1H-pyrazol-5-yl)phenyl)pyrazine-2,3-dicarboxamide (6m)

HRMS



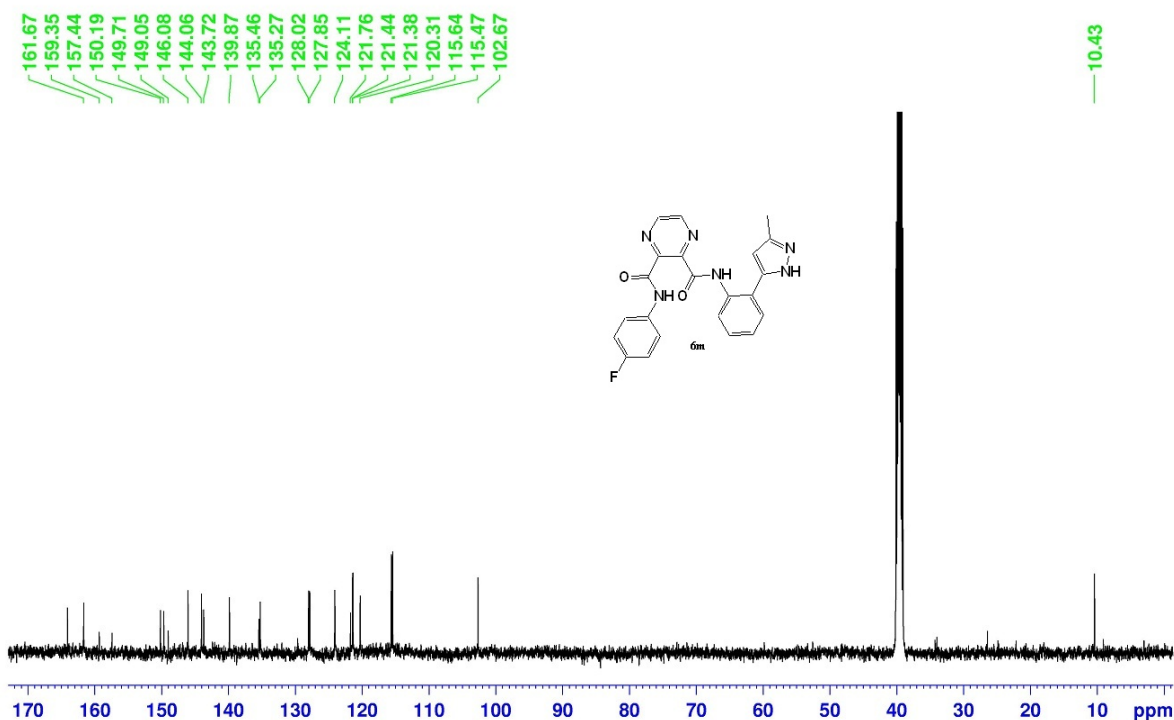
¹H NMR (300 MHz, DMSO)

MS-IV-100 in DMSO
03/05/2012

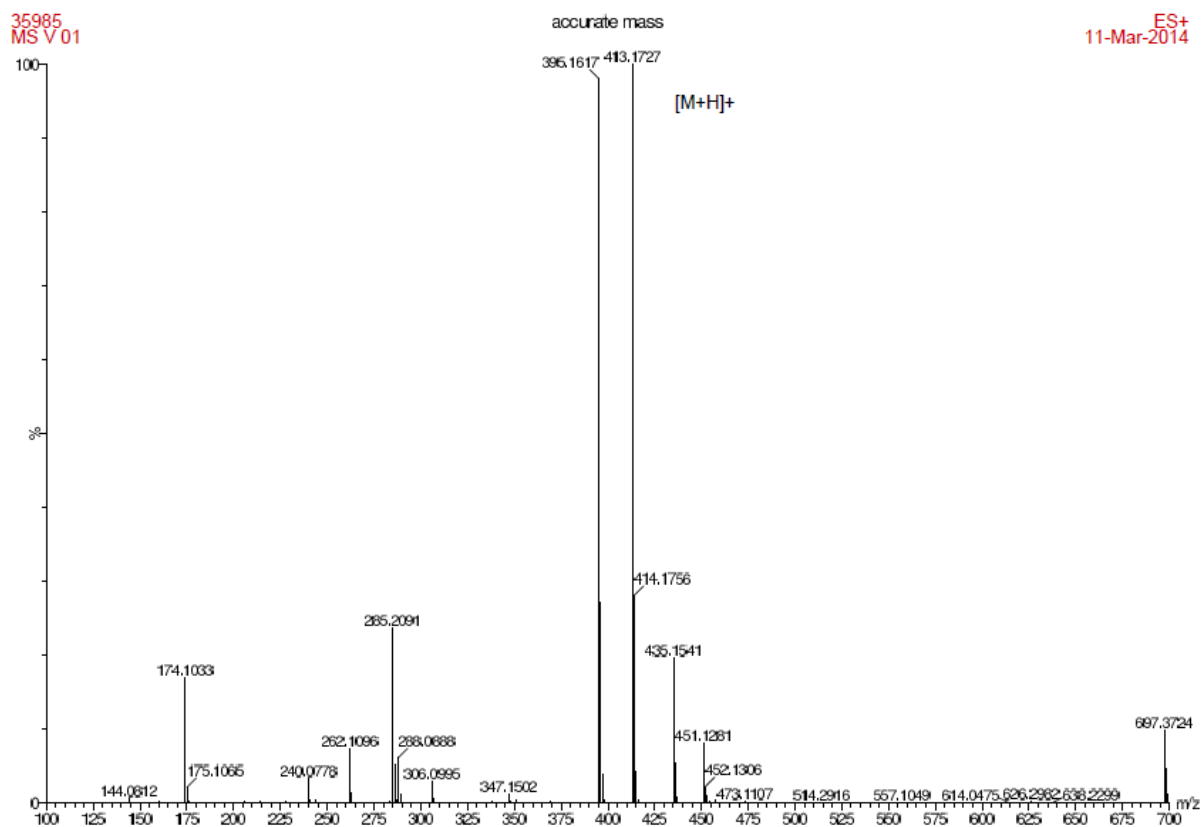


^{13}C NMR (75 MHz, DMSO)

MS-IV-100 in DMSO
carbon spectrum

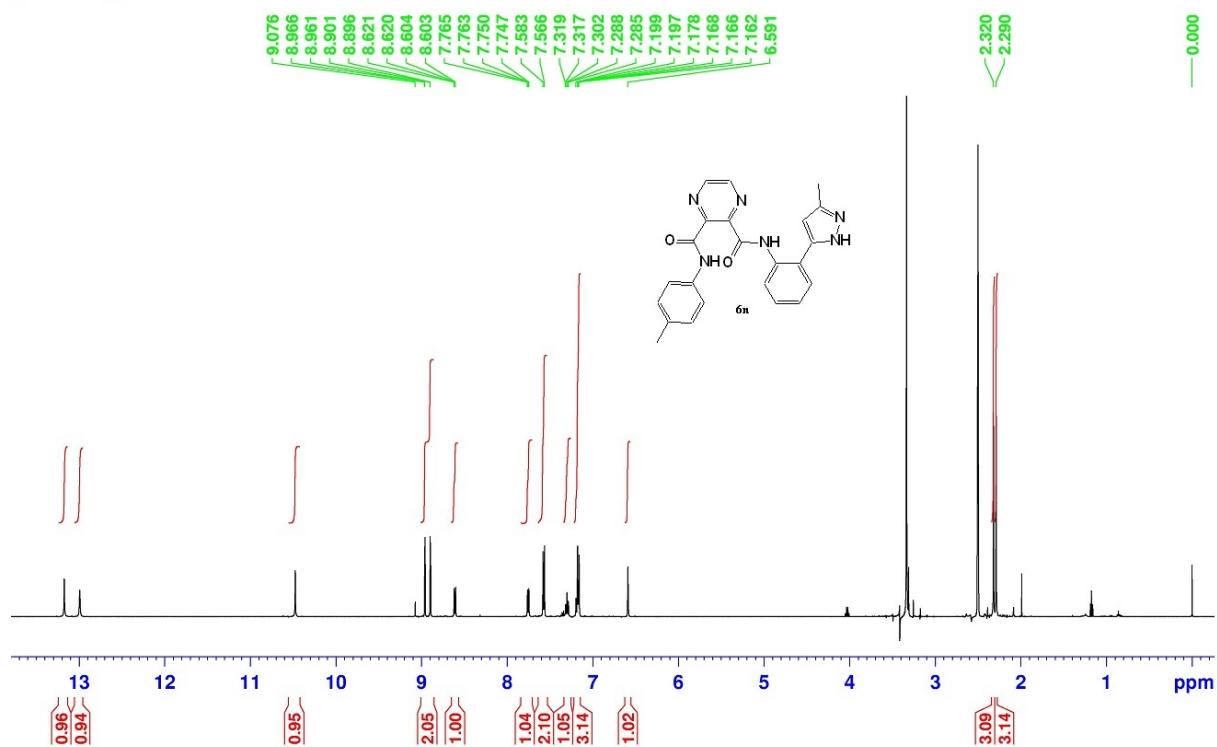


*N*²-(2-(3-methyl-1H-pyrazol-5-yl)phenyl)-*N*³-(p-tolyl)pyrazine-2,3-dicarboxamide
(6n)
HRMS



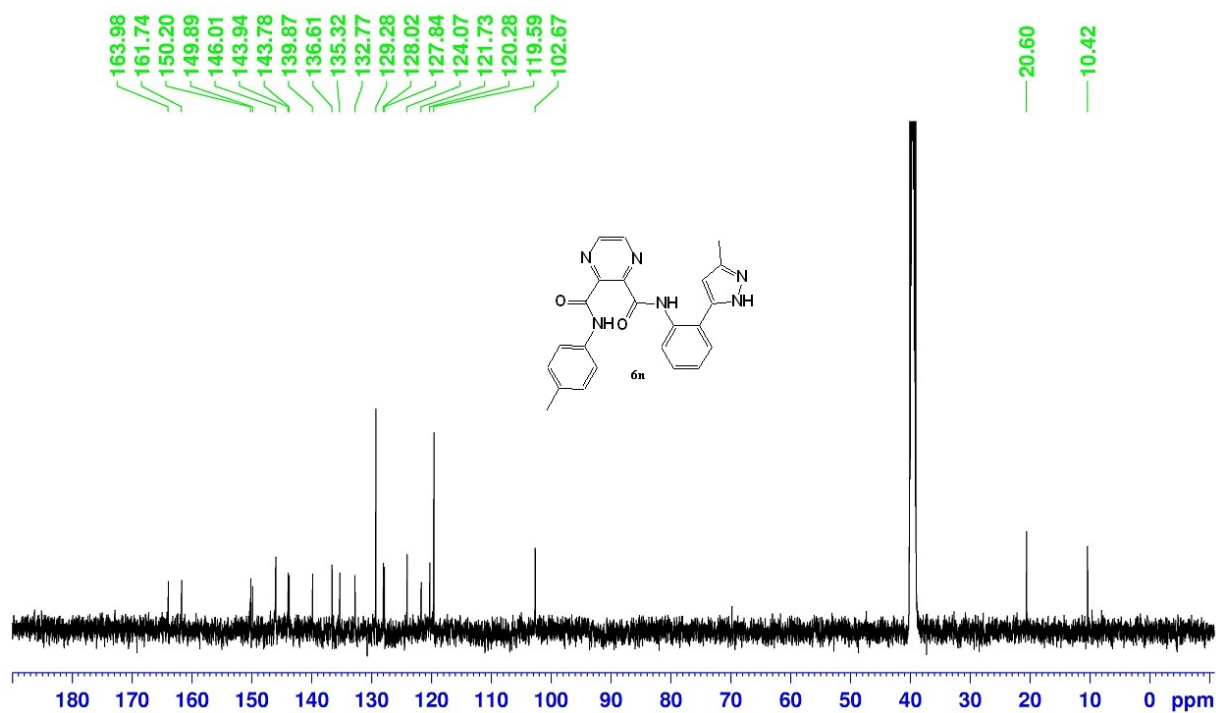
¹H NMR (300 MHz, DMSO)

MS-V-01 in DMSO
proton spectrum



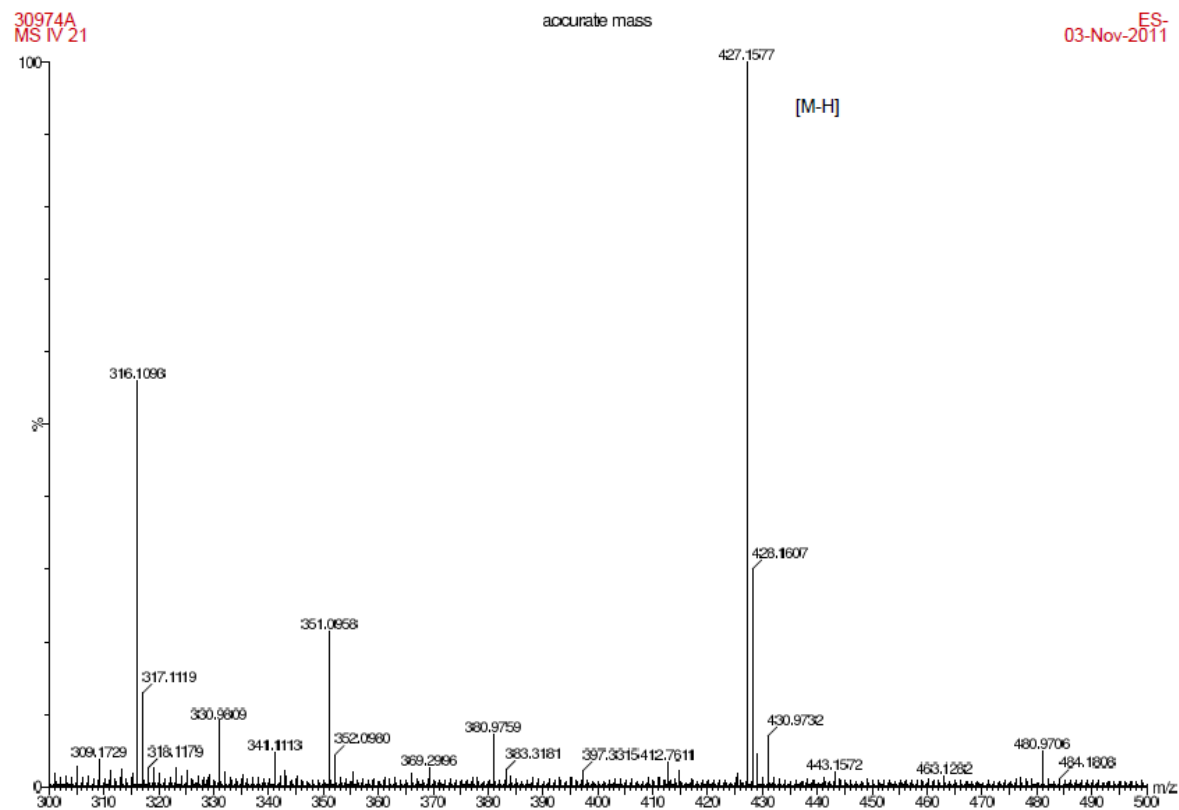
¹³C NMR (75 MHz, DMSO)

MS-V-01 in DMSO
carbon spectrum



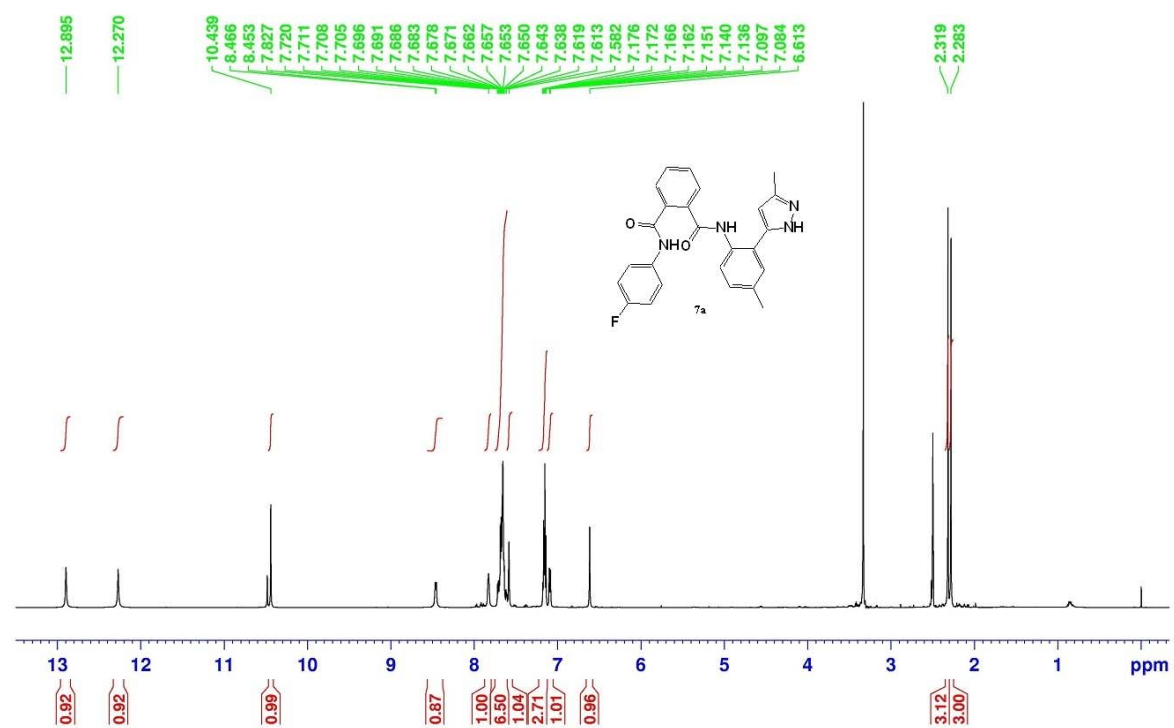
*N*¹-(4-fluorophenyl)-*N*²-(4-methyl-2-(3-methyl-1H-pyrazol-5-yl)phenyl)phthalamide
(7a)

HRMS



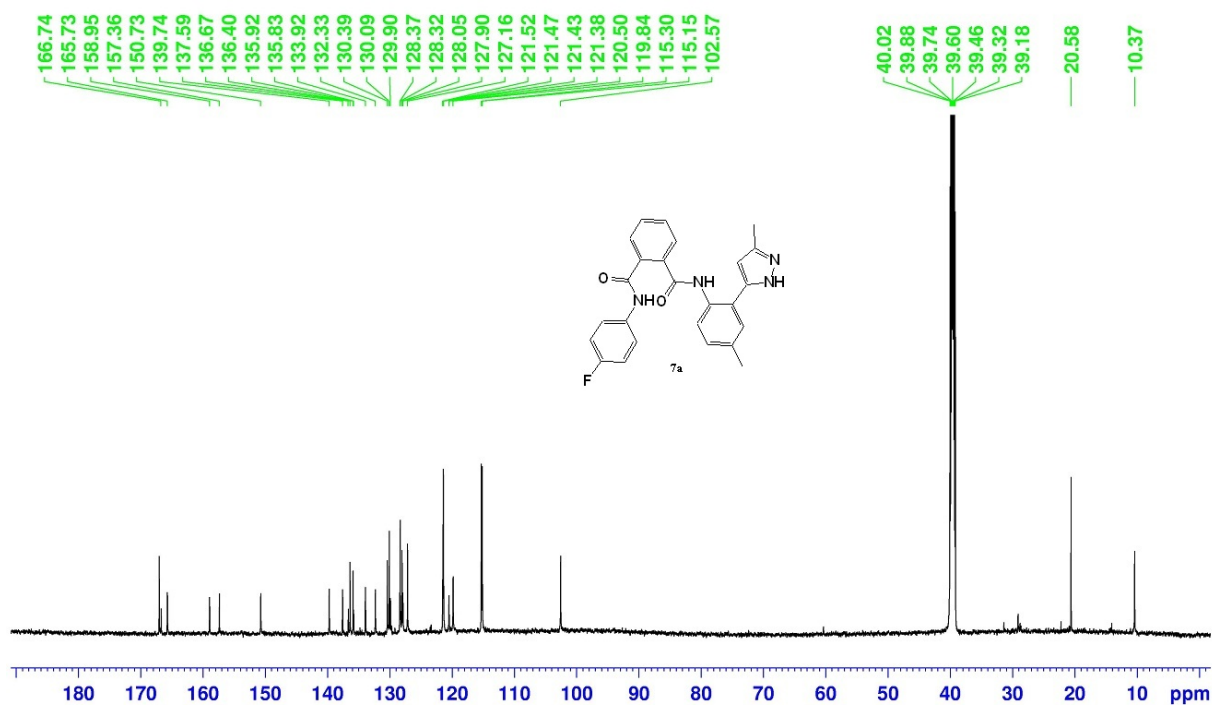
¹H NMR (600 MHz, DMSO)

MS-IV-21-600 in DMSO
proton spectrum
temp=25C



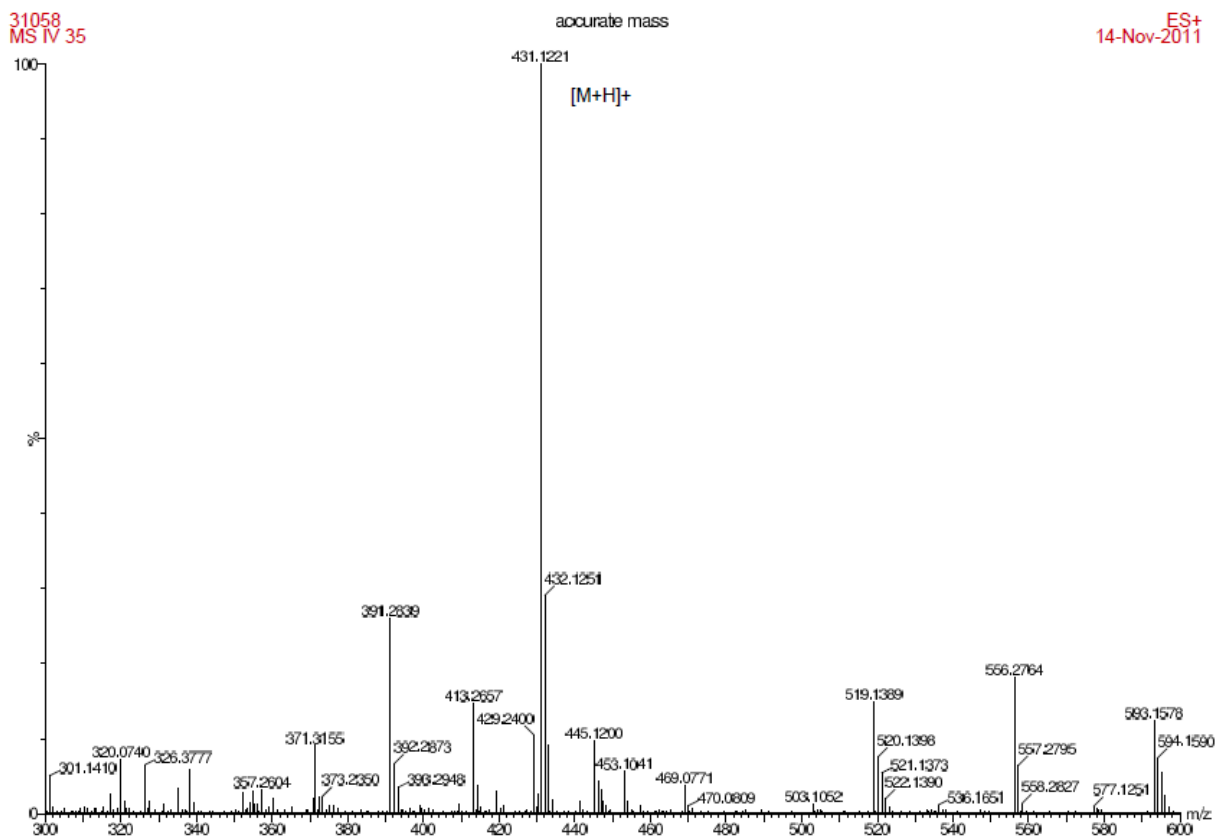
^{13}C NMR (150 MHz, DMSO)

MS-IV-21-600 in DMSO
 ^{13}C
 ^1H decoupled



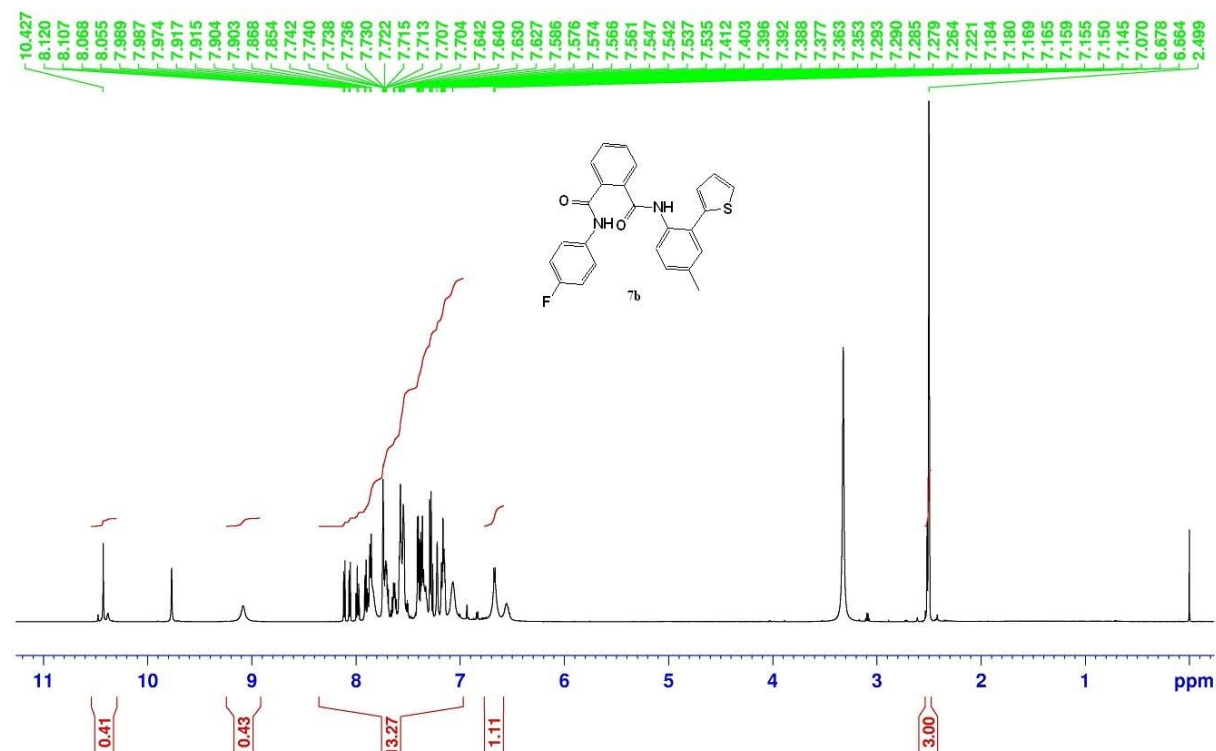
N^1 -(4-fluorophenyl)- N^2 -(4-methyl-2-(thiophen-2-yl)phenyl)phthalamide (7b)

HRMS



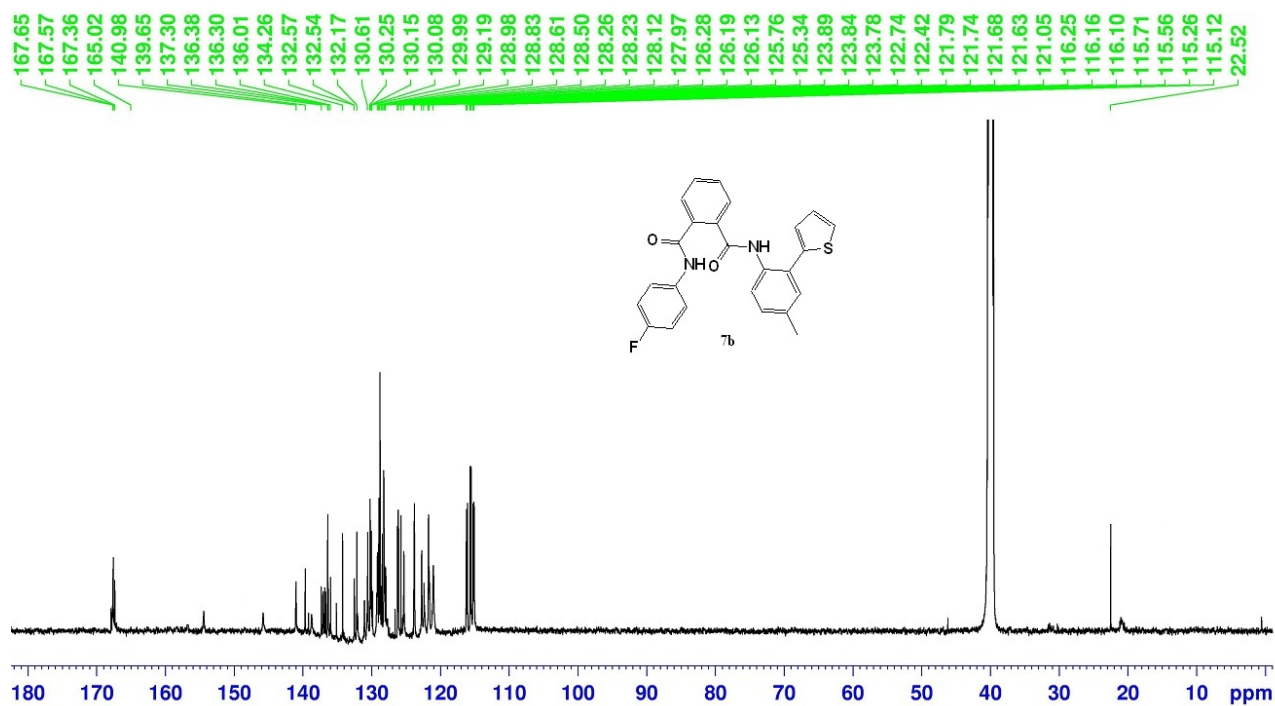
¹H NMR (600 MHz, DMSO)

MS-IV-35-600 in DMSO
proton spectrum
temp=25C



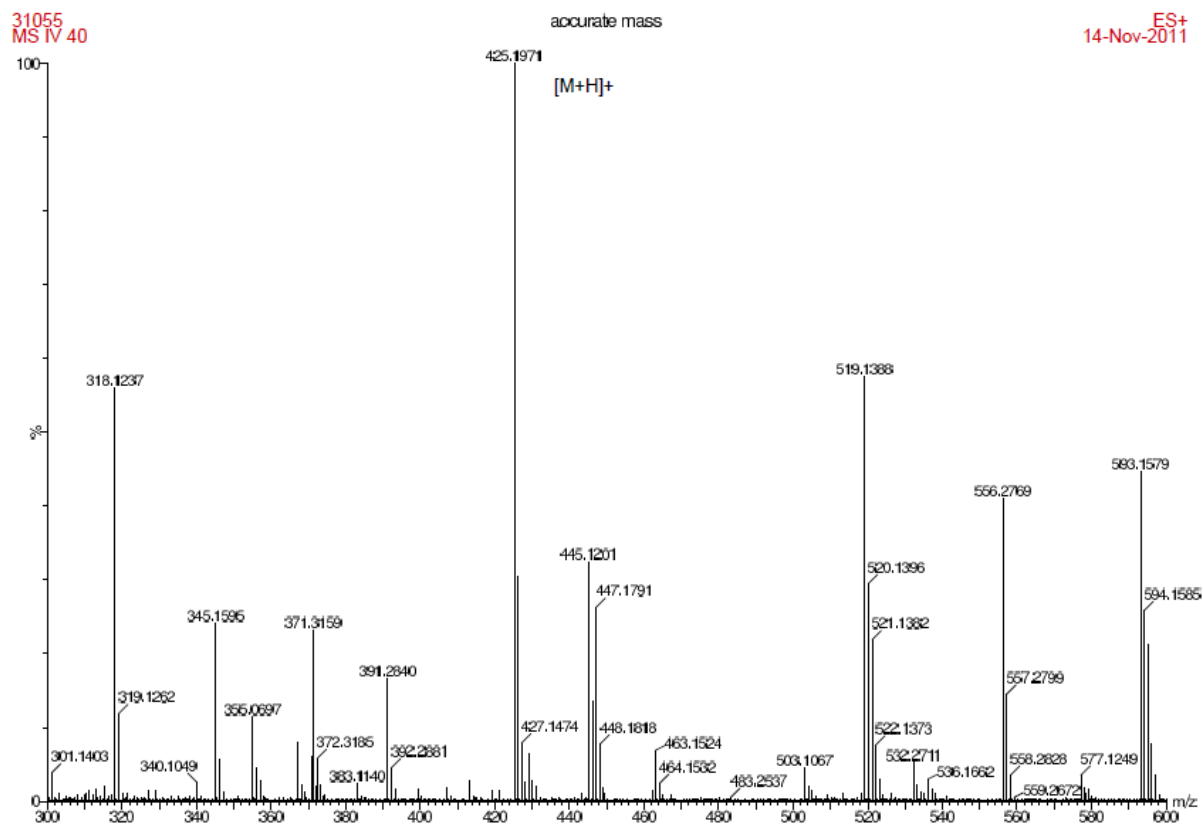
¹³C NMR (150 MHz, DMSO)

MS-IV-35-600 in DMSO
C13 spectrum
temp=25C



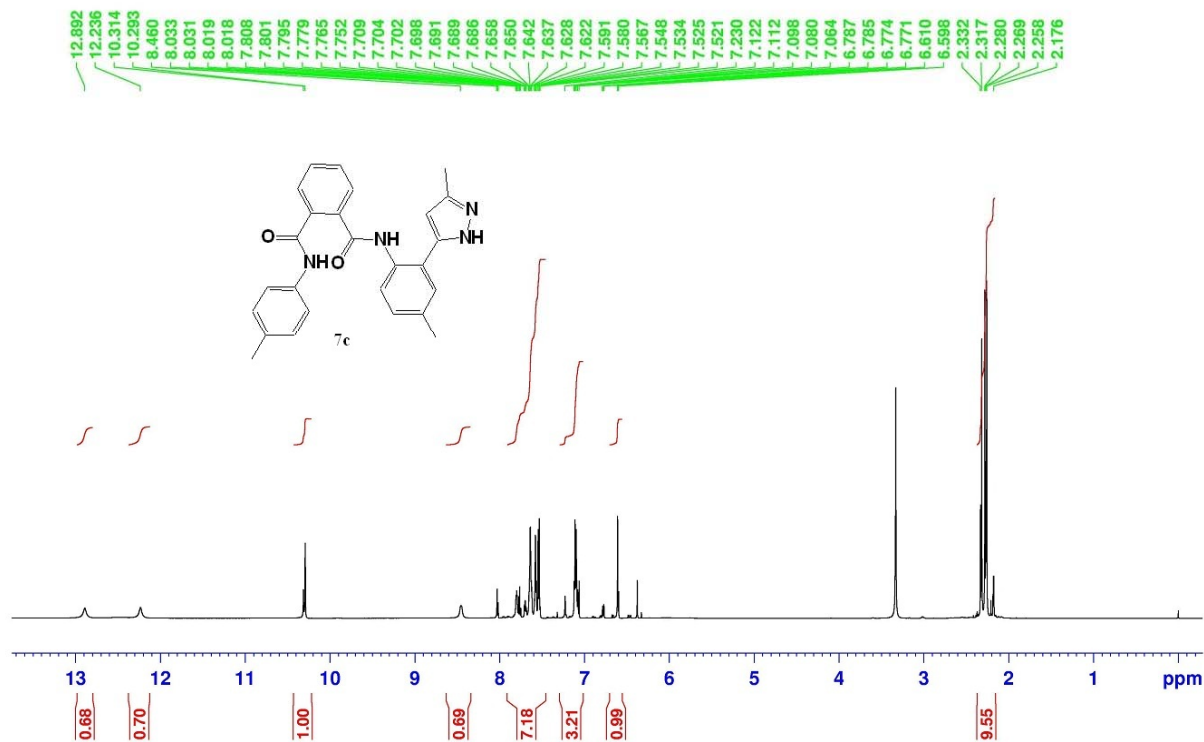
N^1 -(4-methyl-2-(3-methyl-1H-pyrazol-5-yl)phenyl)- N^2 -(p-tolyl)phthalamide (7c):

HRMS



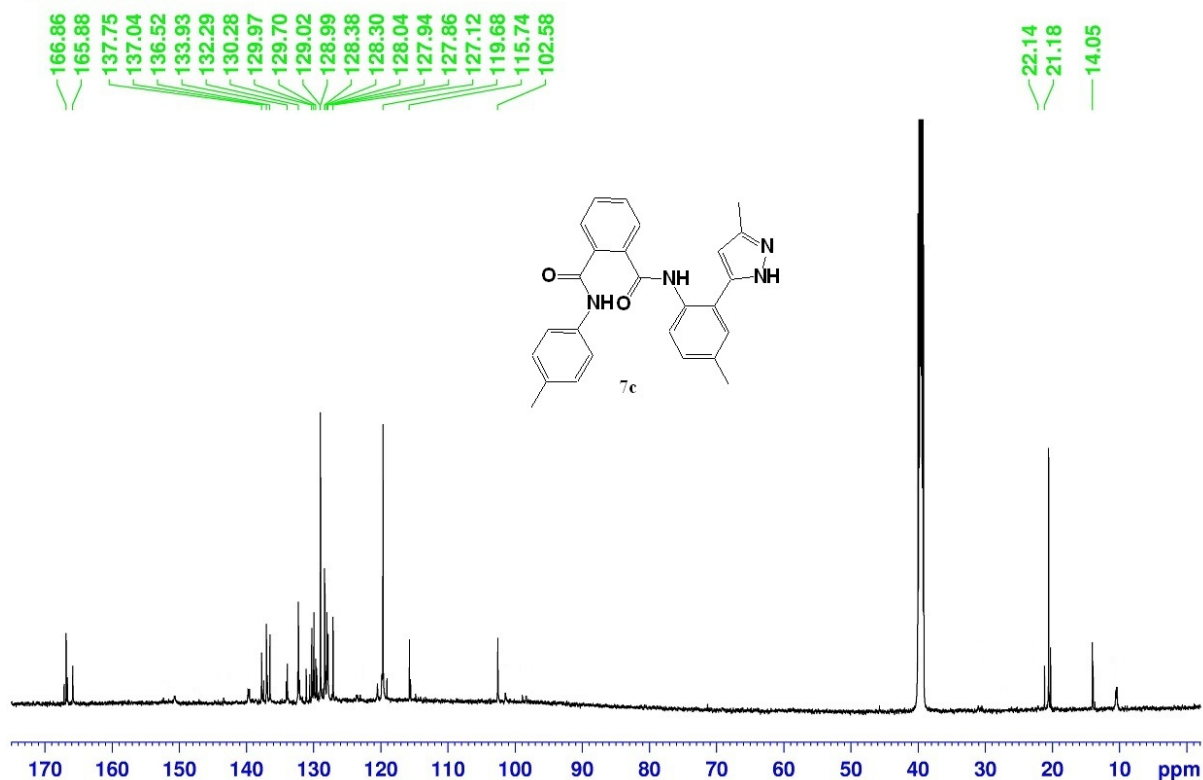
^1H NMR (600 MHz, DMSO)

MS-IV-40-600 in DMSO
proton spectrum
temp=25C



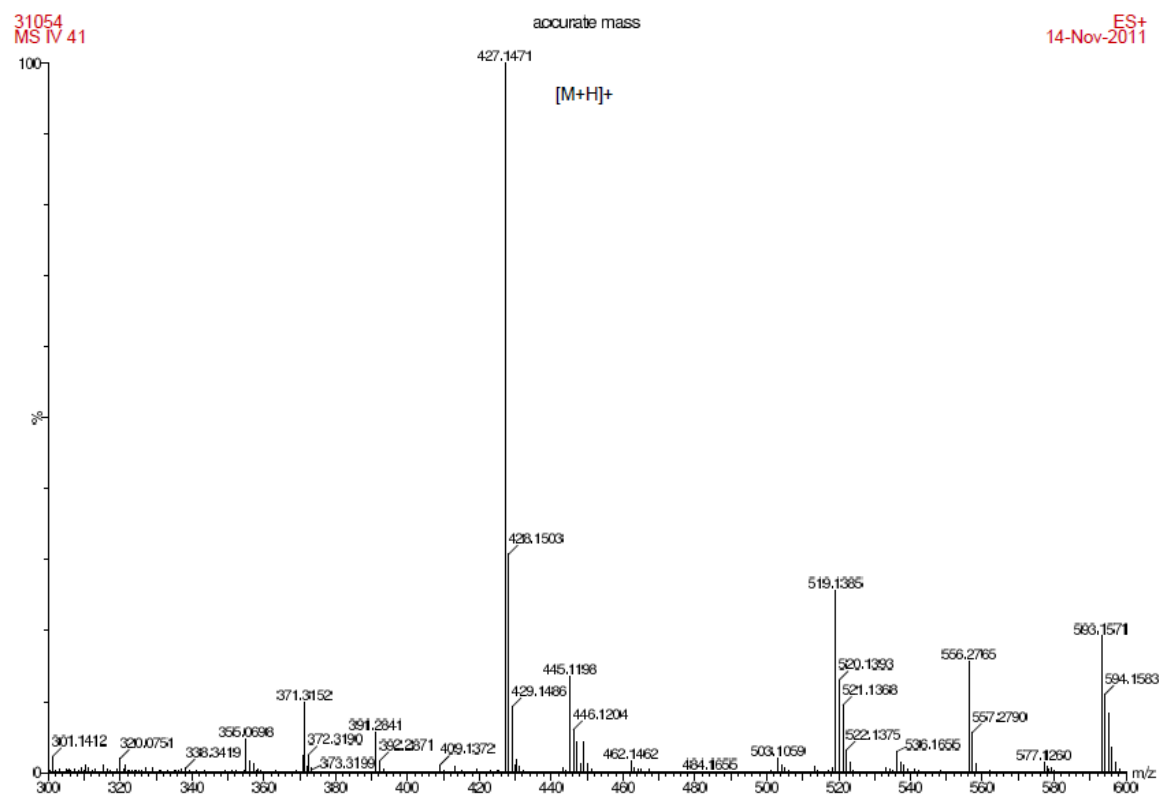
^{13}C NMR (150 MHz, DMSO)

MS-IV-40-600 in DMSO
 ^{13}C
 ^1H decoupled

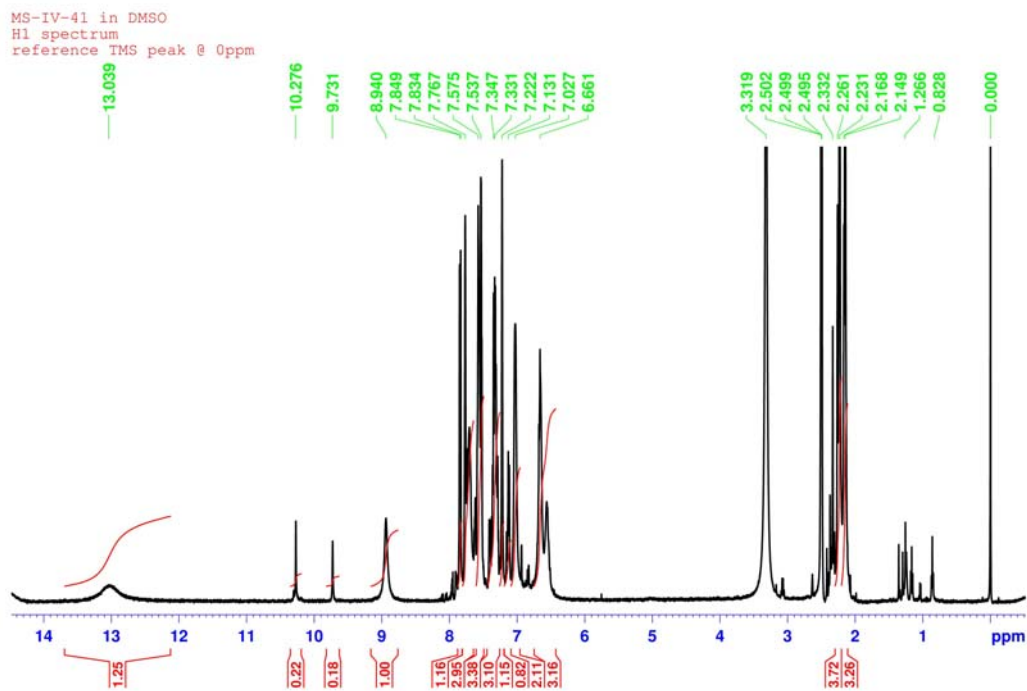


N^1 -(4-methyl-2-(thiophen-2-yl)phenyl)- N^2 -(p-tolyl)phthalamide (**7d**)

HRMS

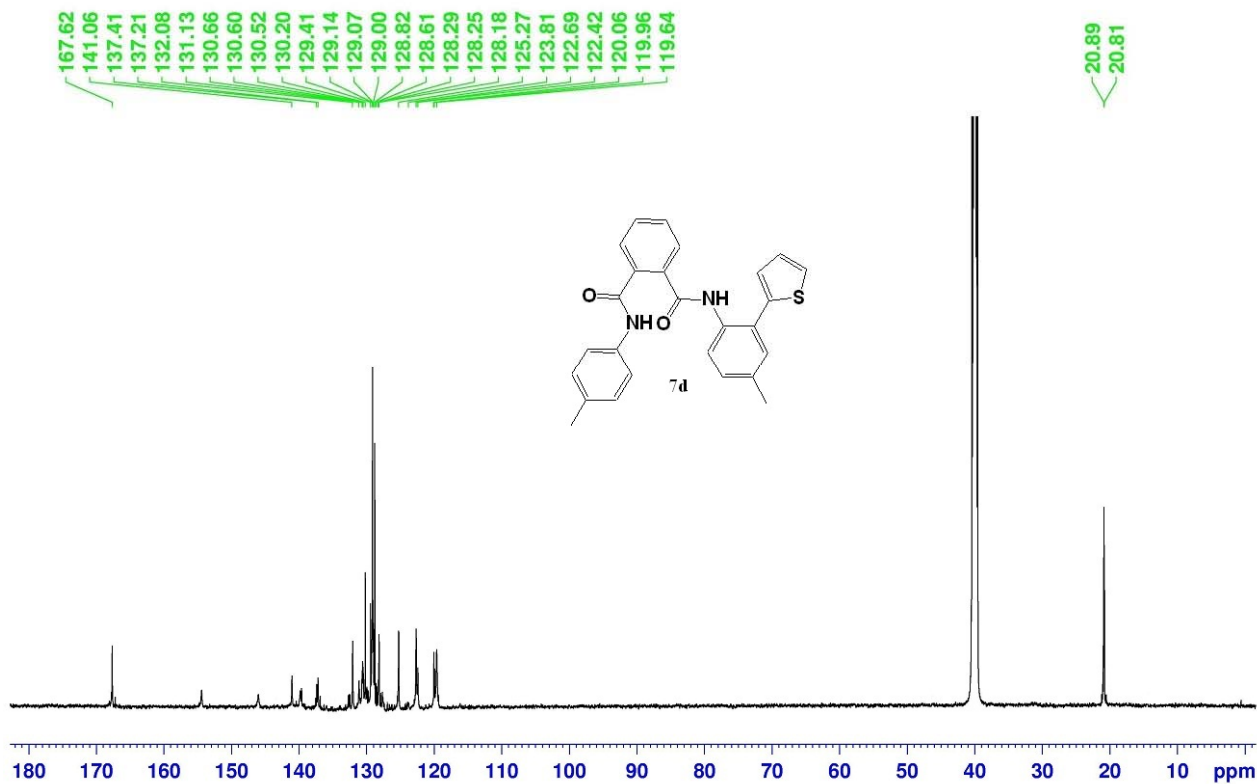


¹H NMR (500 MHz, DMSO)



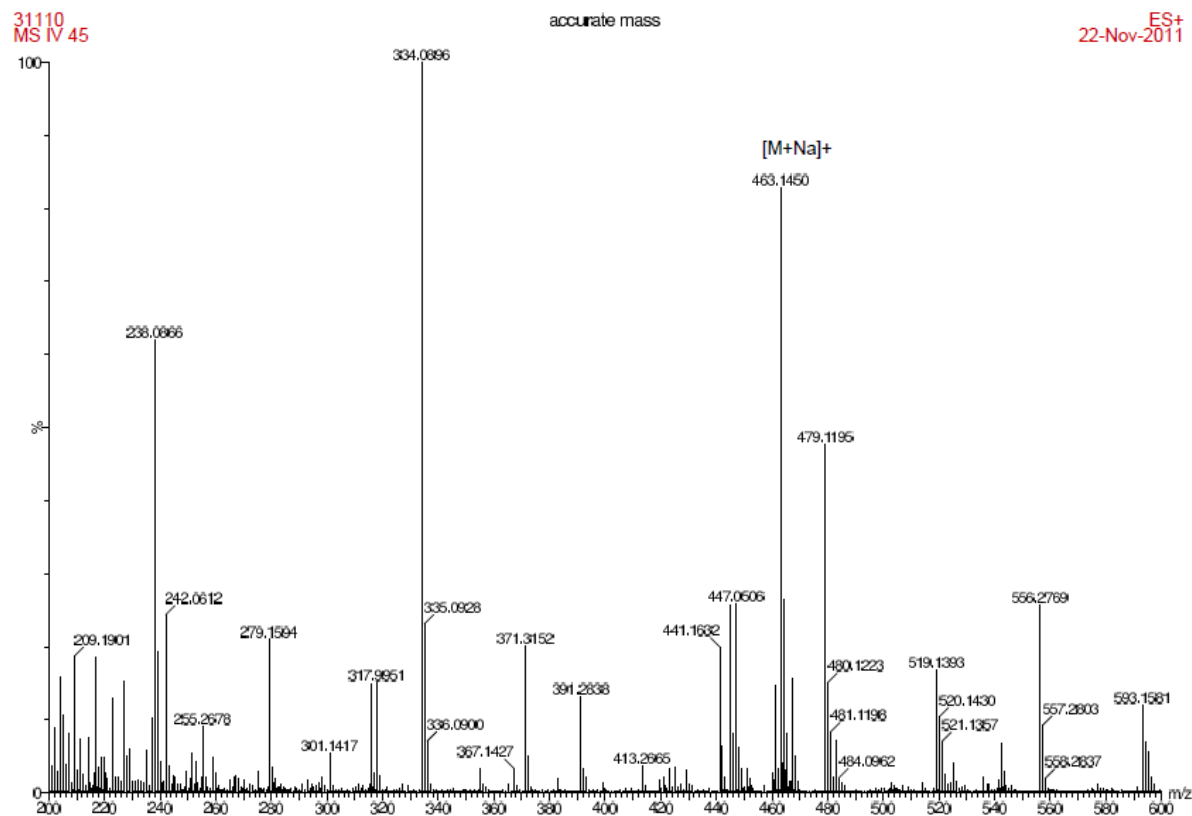
¹³C NMR (150 MHz, DMSO)

MS-IV-41-600 in DMSO
¹³C



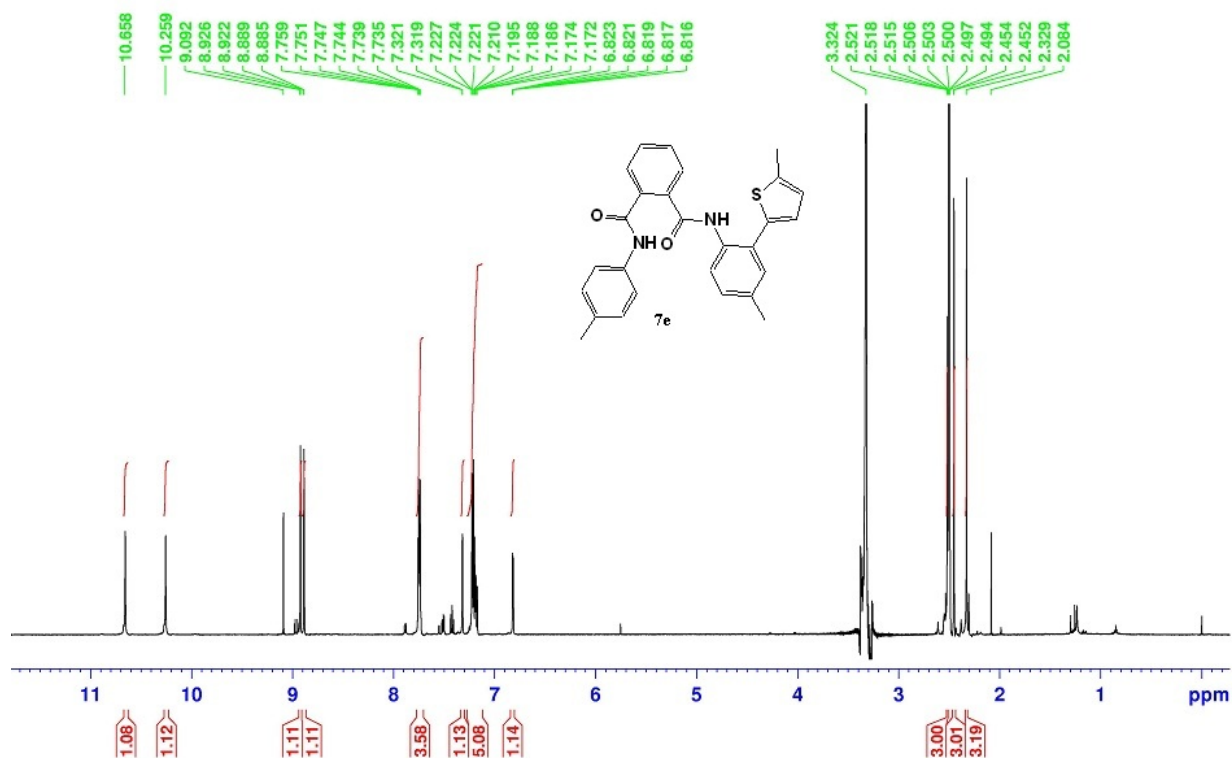
*N*¹-(4-methyl-2-(5-methylthiophen-2-yl)phenyl)-*N*²-(*p*-tolyl)phthalamide (7e)

HRMS



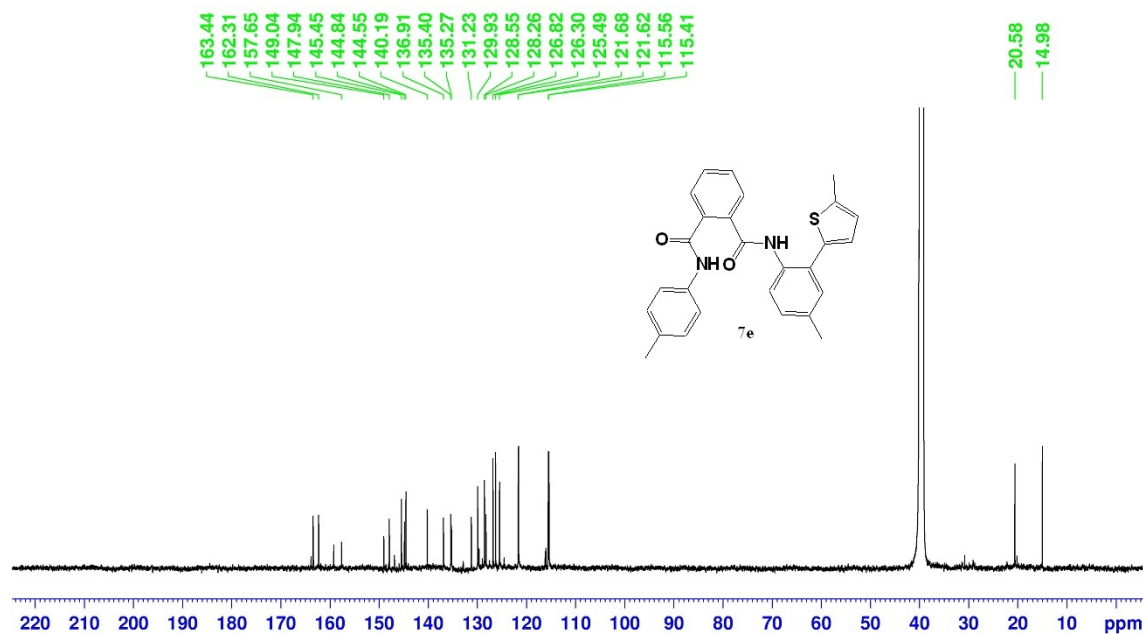
¹H NMR (500 MHz, DMSO)

MS-IV-45-600 in DMSO
proton spectrum
temp=25C



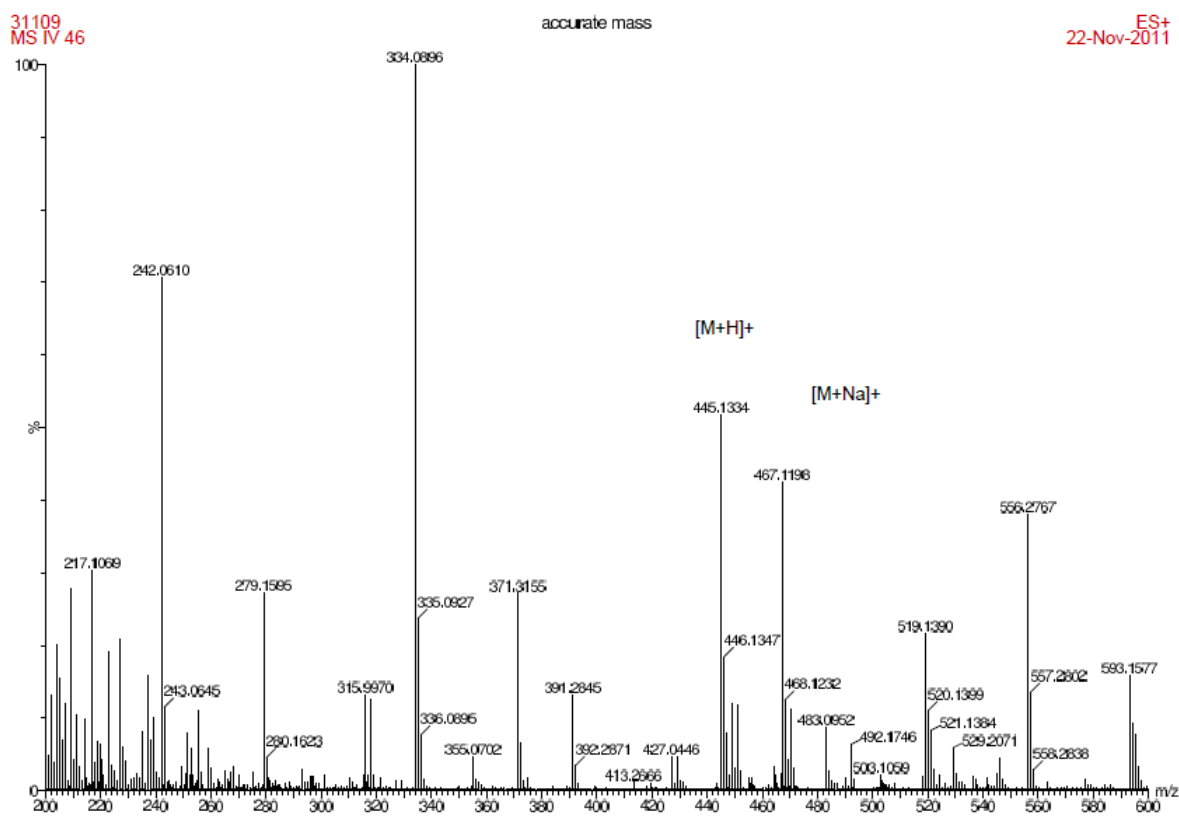
^{13}C NMR (125 MHz, DMSO)

MS-IV-45-600 in DMSO
 ^{13}C

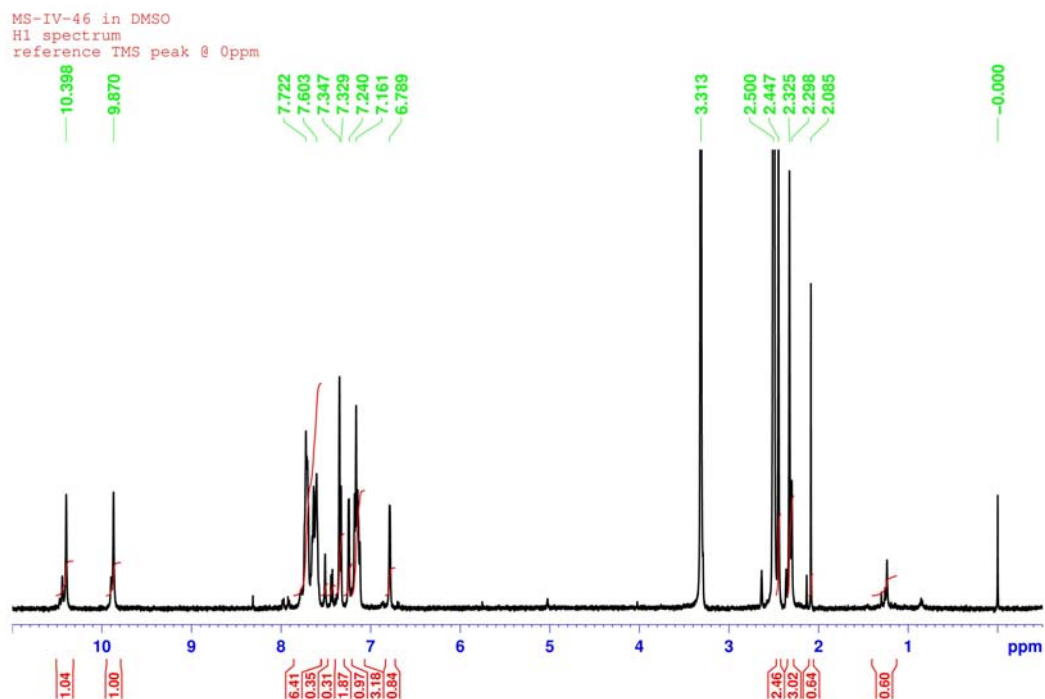


N^1 -(4-fluorophenyl)- N^2 -(4-methyl-2-(5-methylthiophen-2-yl)phenyl)phthalamide (**7f**)

HRMS

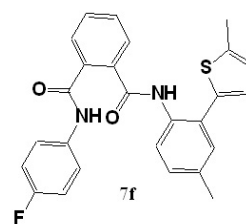
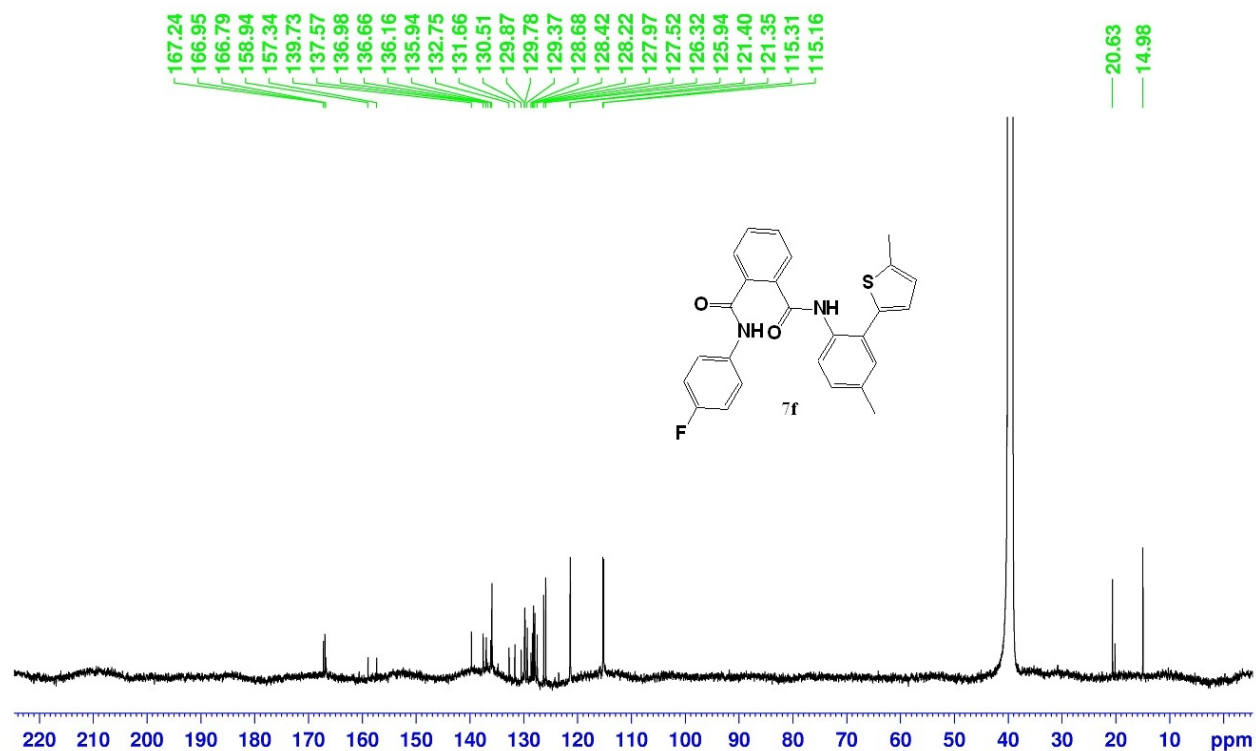


¹H NMR (500 MHz, DMSO)



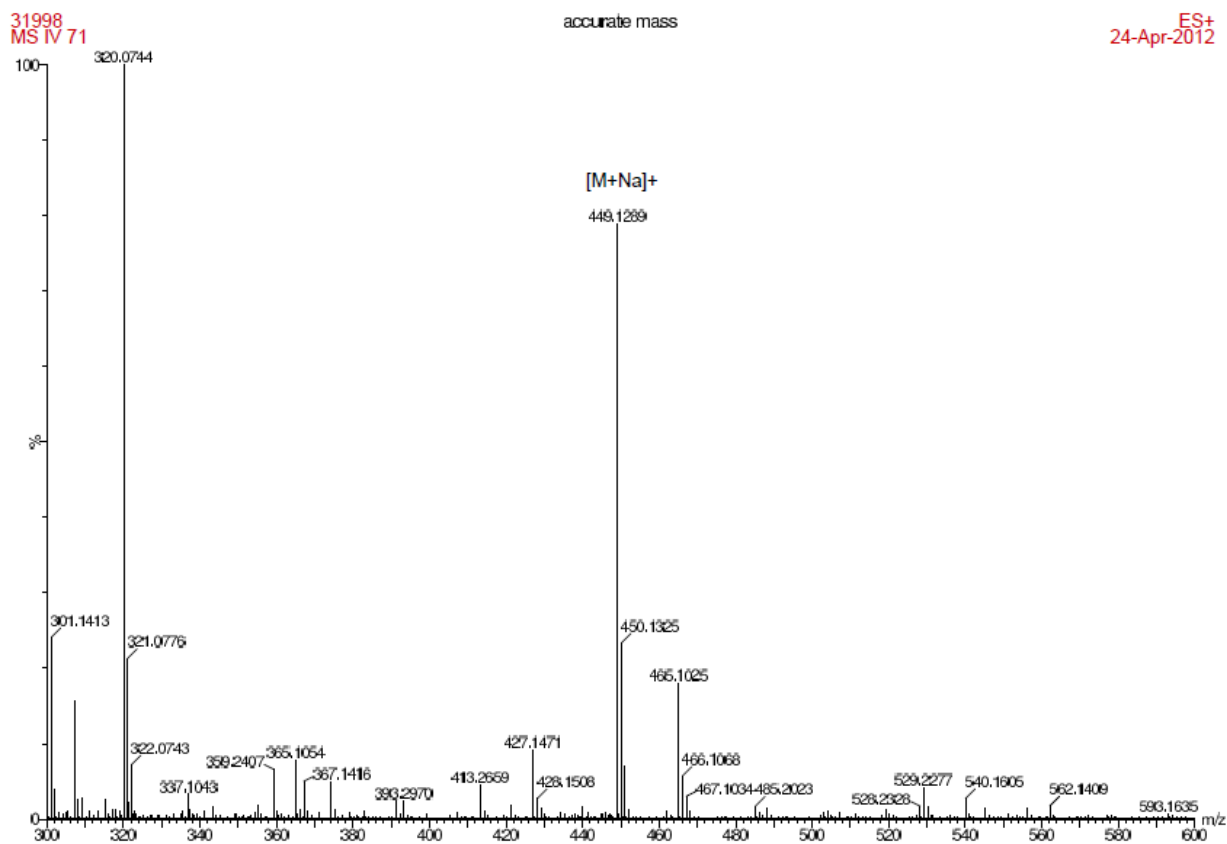
¹³C NMR (150 MHz, DMSO)

MS-IV-46-600 in DMSO
¹³C
¹H decoupled



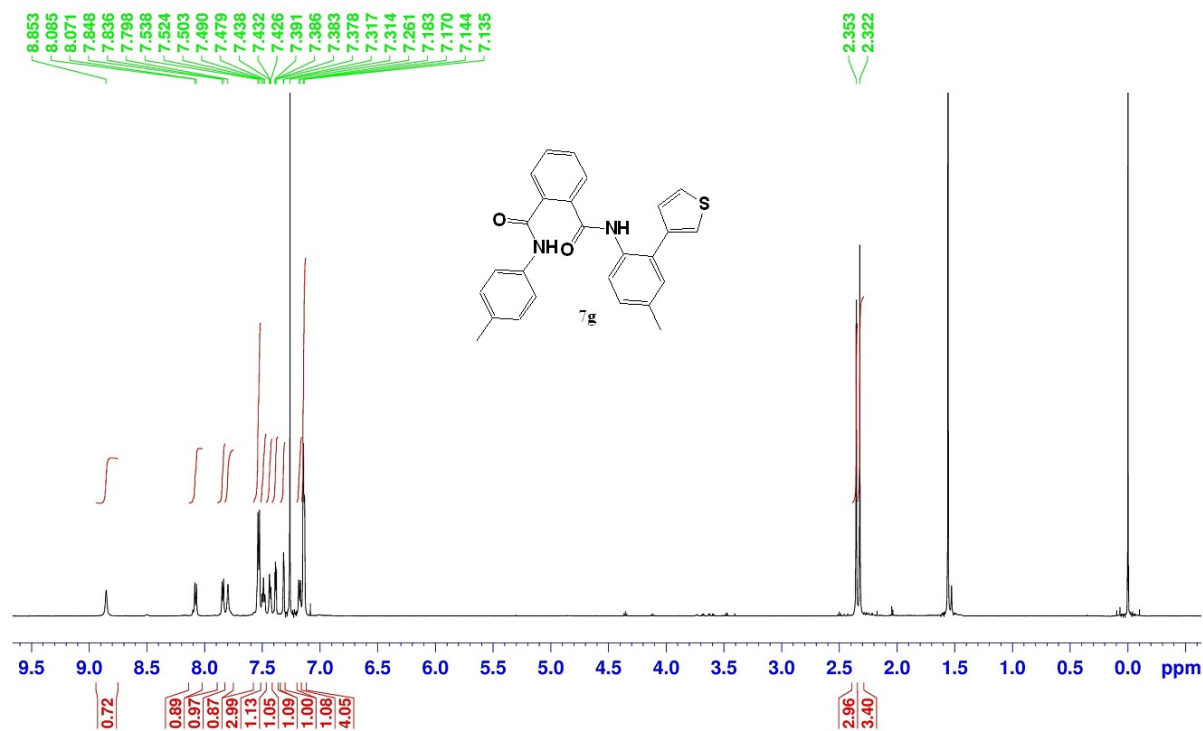
*N*¹-(4-methyl-2-(thiophen-3-yl)phenyl)-*N*²-(*p*-tolyl)phthalamide (7g)

HRMS



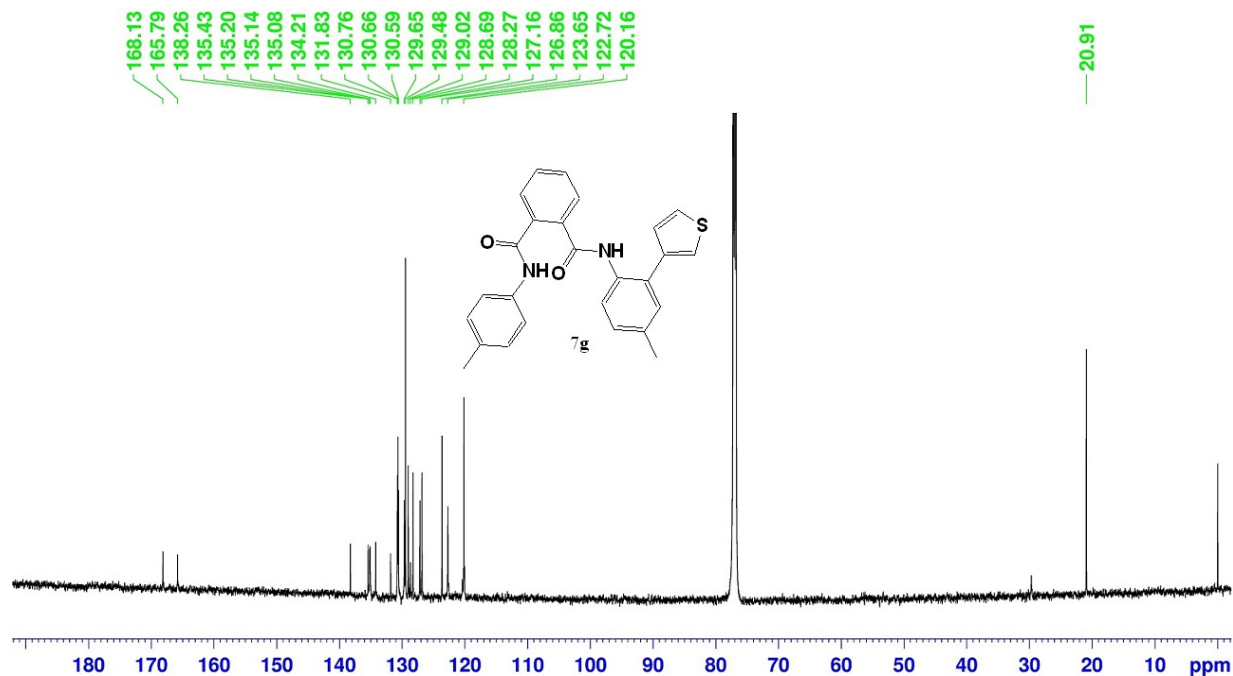
¹H NMR (500 MHz, CDCl₃)

MS-IV-71 in CDCl₃
proton spectrum
temp=25C



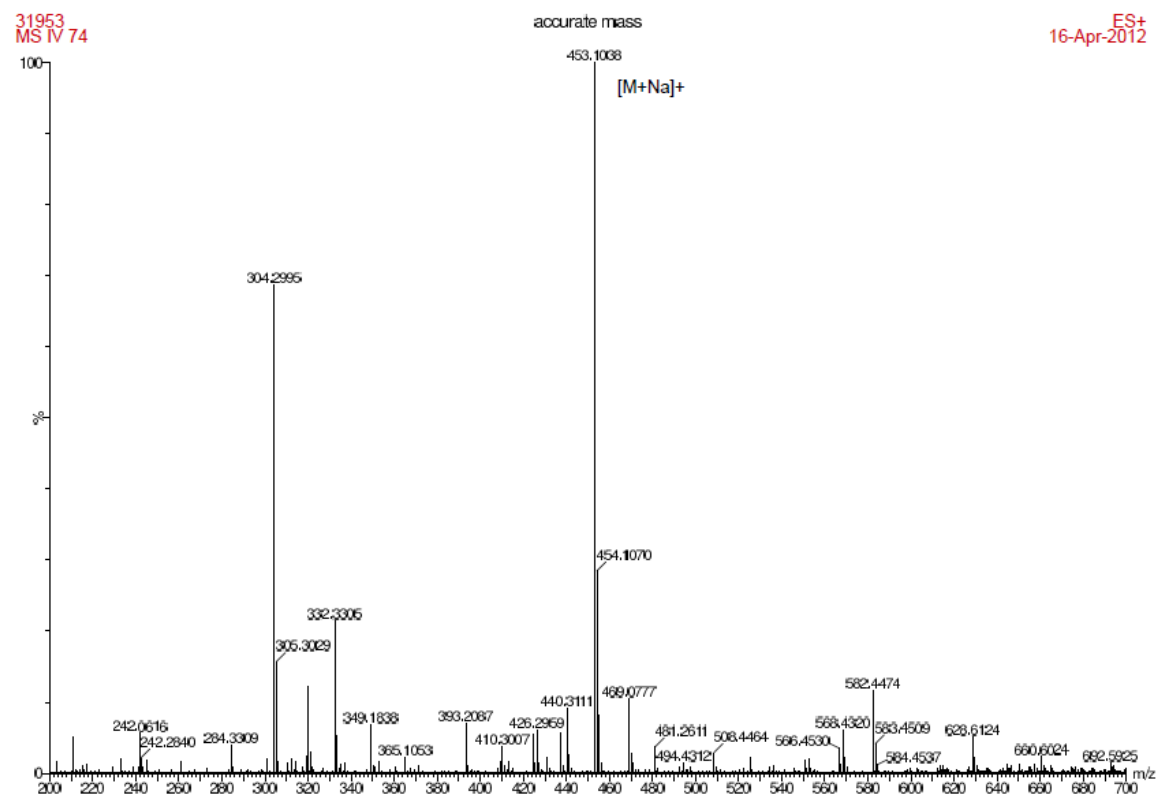
^{13}C NMR (125 MHz, CDCl_3)

MS-IV-71 in CDCl_3
temp = 20C
 ^{13}C



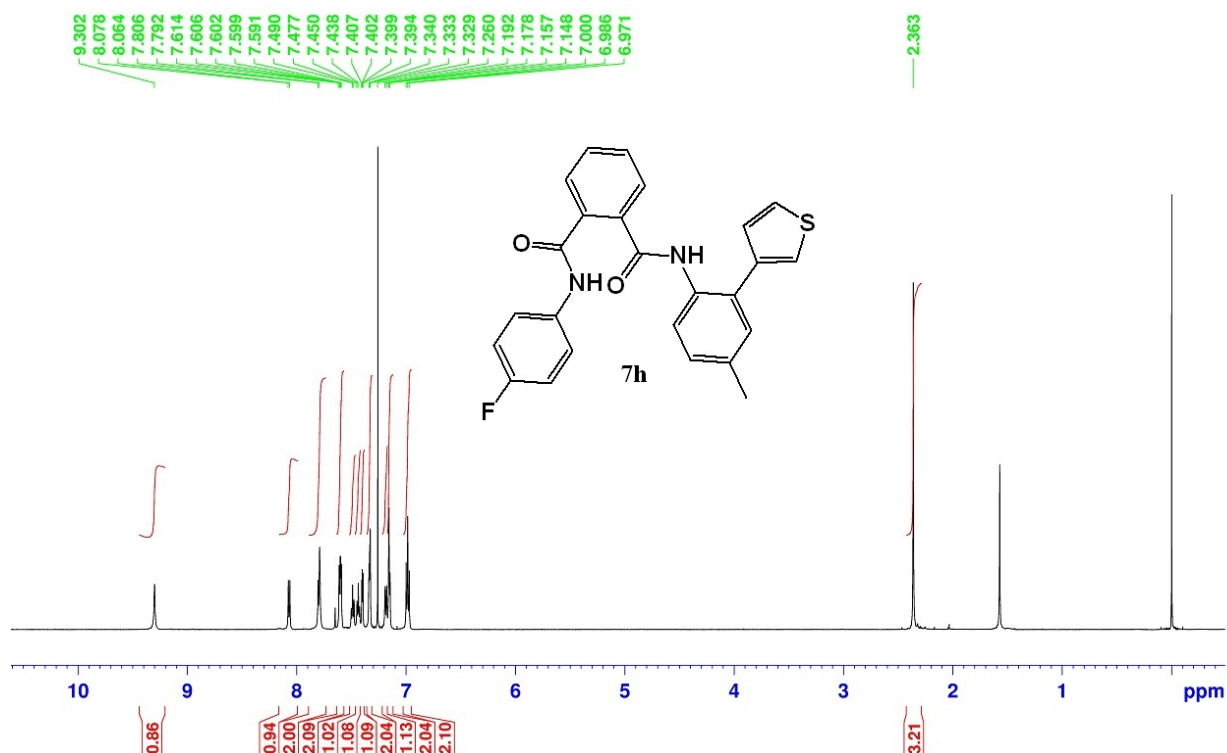
N^1 -(4-fluorophenyl)- N^2 -(4-methyl-2-(thiophen-3-yl)phenyl)phthalamide (7h)

HRMS



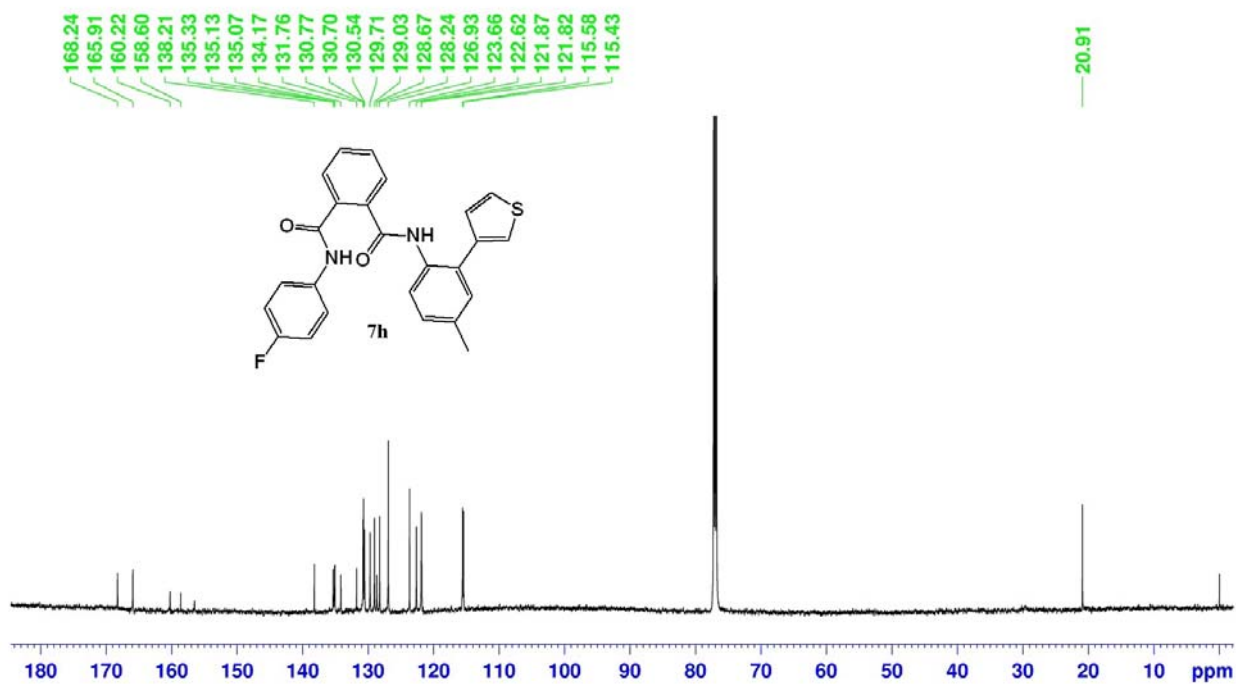
^1H NMR (500 MHz, CDCl_3)

MS-IV-74 in CDCl_3
proton spectrum
temp=25C



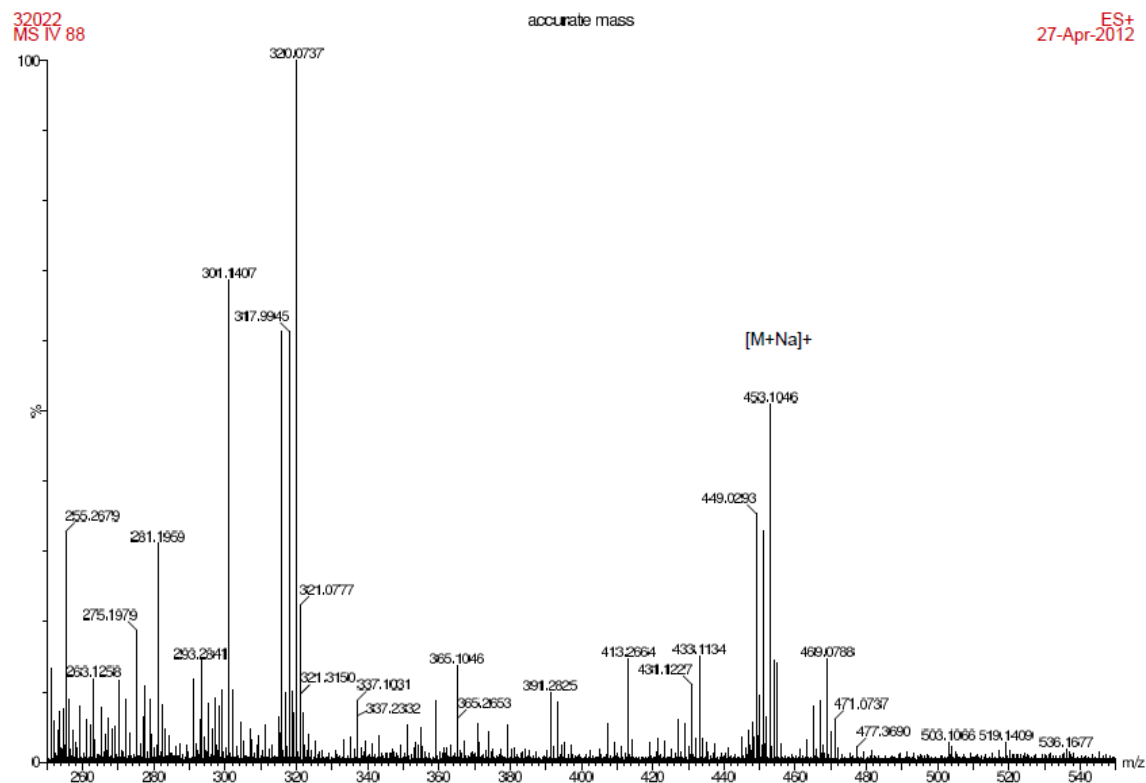
^{13}C NMR (125 MHz, CDCl_3)

MS-IV-74 in CDCl_3
temp = 25C
 ^{13}C
 ^1H decoupled

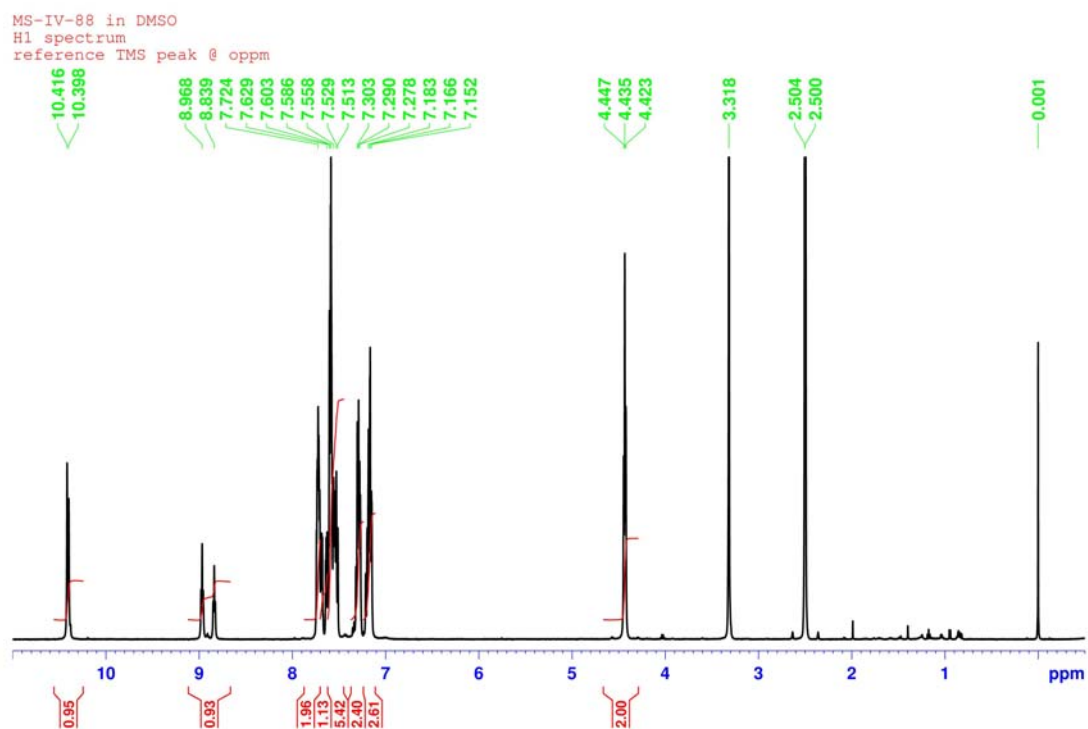


N^1 -(4-fluorophenyl)- N^2 -(2-(thiophen-3-yl)benzyl)phthalamide (7i)

HRMS

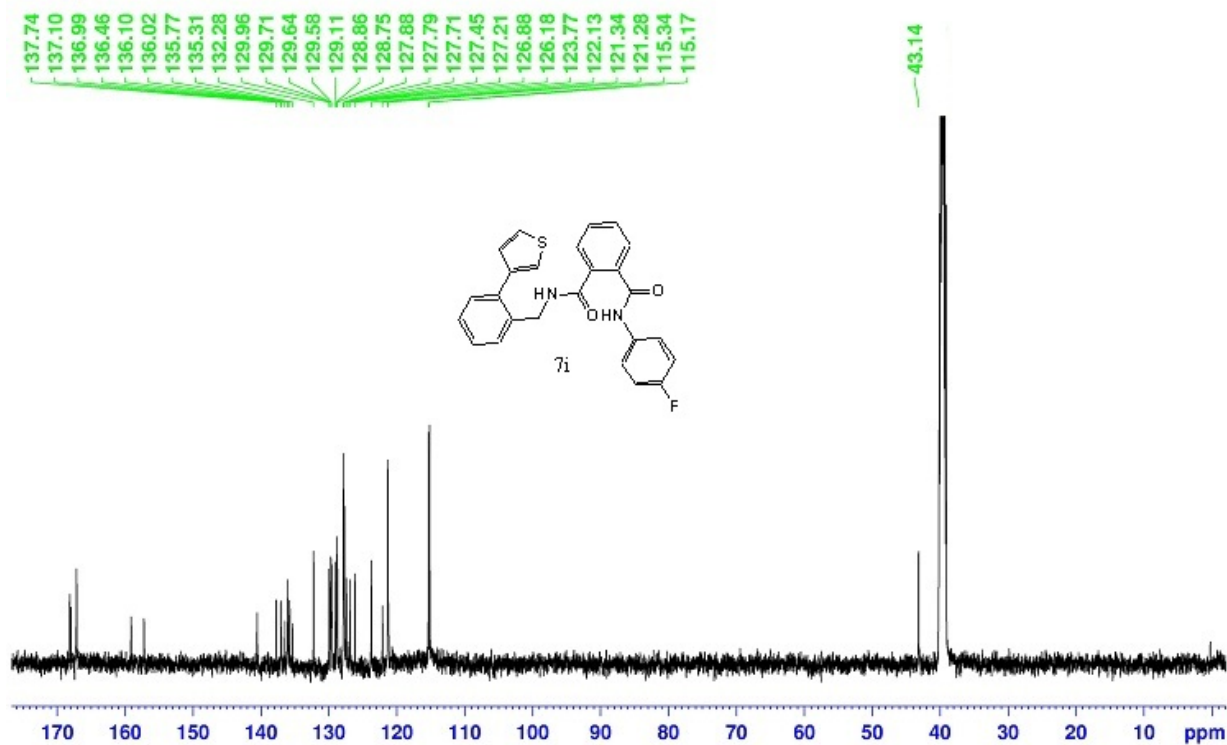


^1H NMR (500 MHz, DMSO)



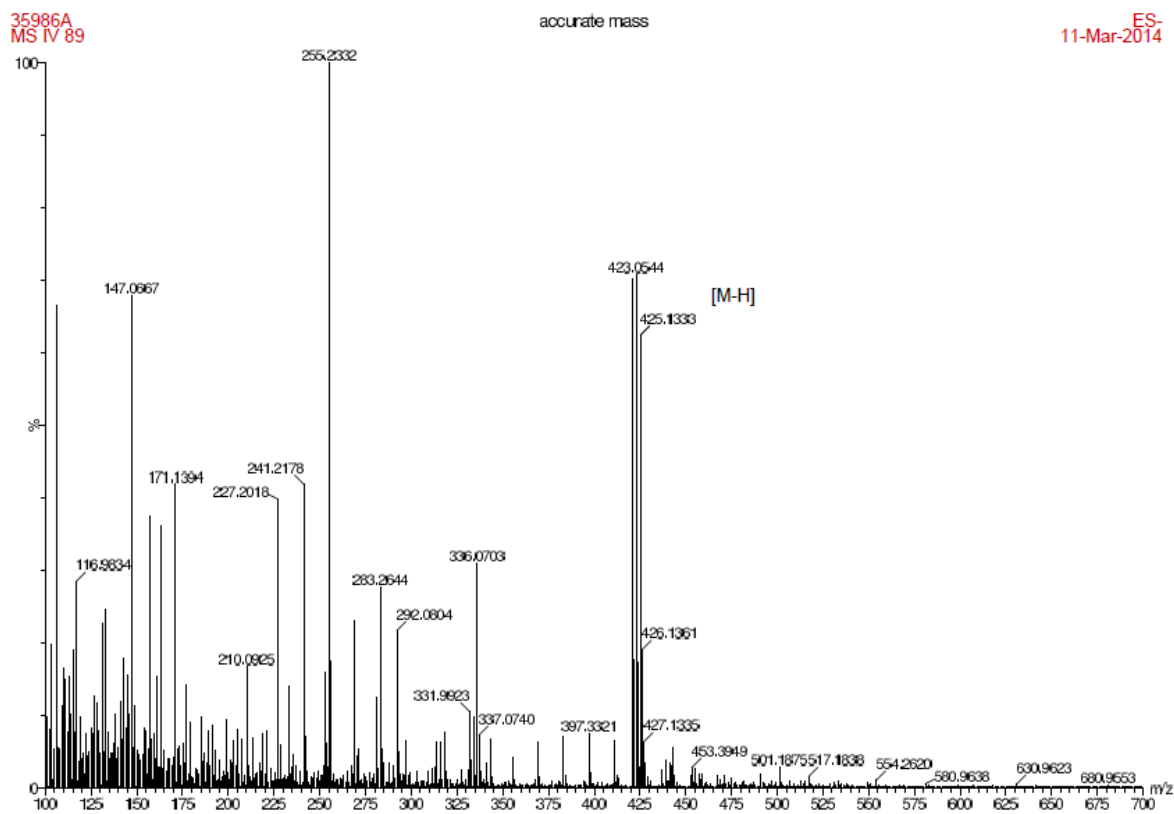
^{13}C NMR (75 MHz, DMSO)

MS-IV-88 in DMSO
C13 spectrum



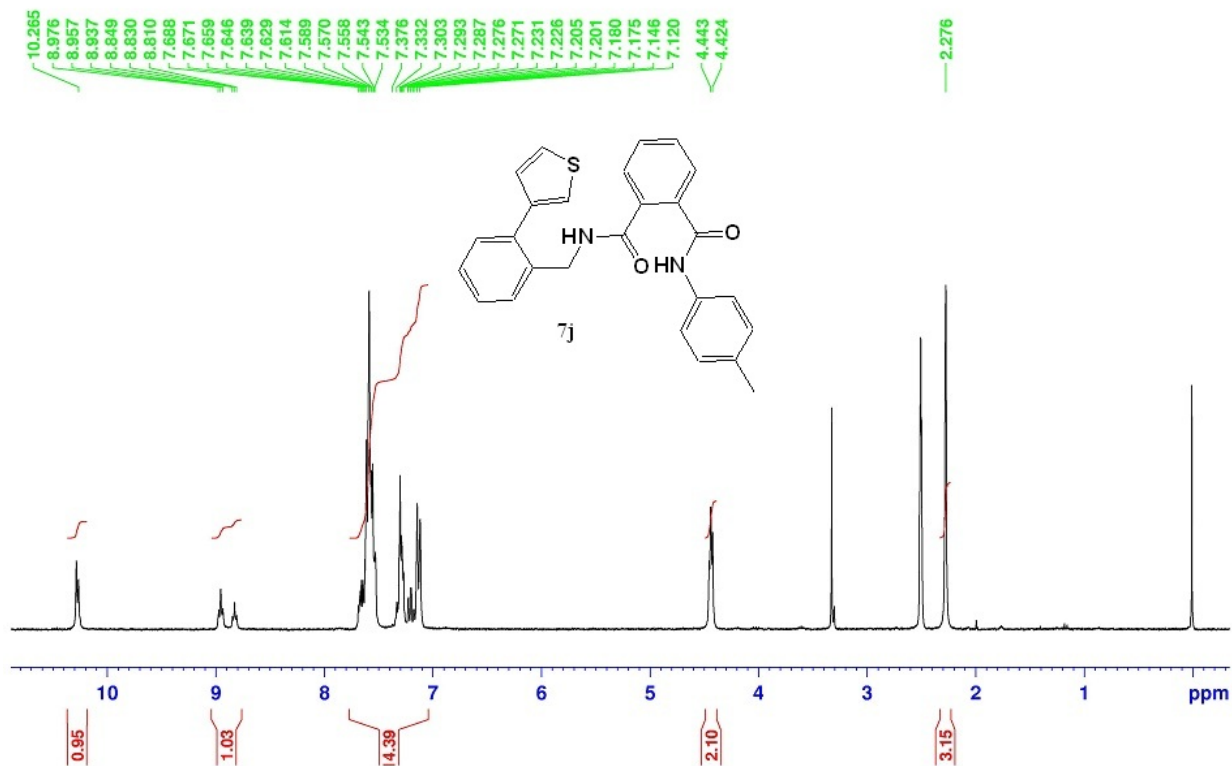
N^1 -(2-(thiophen-3-yl)benzyl)- N^2 -(p-tolyl)phthalamide (7j)

HRMS



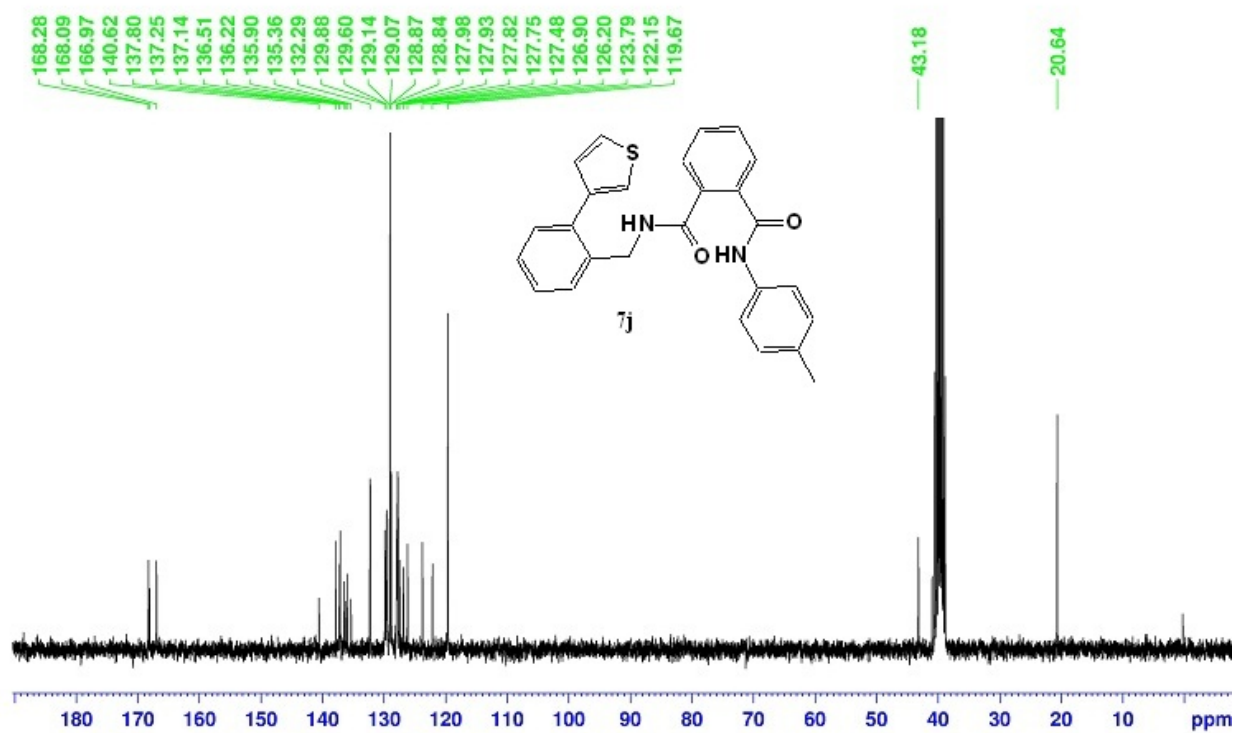
¹H NMR (300 MHz, DMSO)

MS-IV-89 in DMSO
27/04/2012



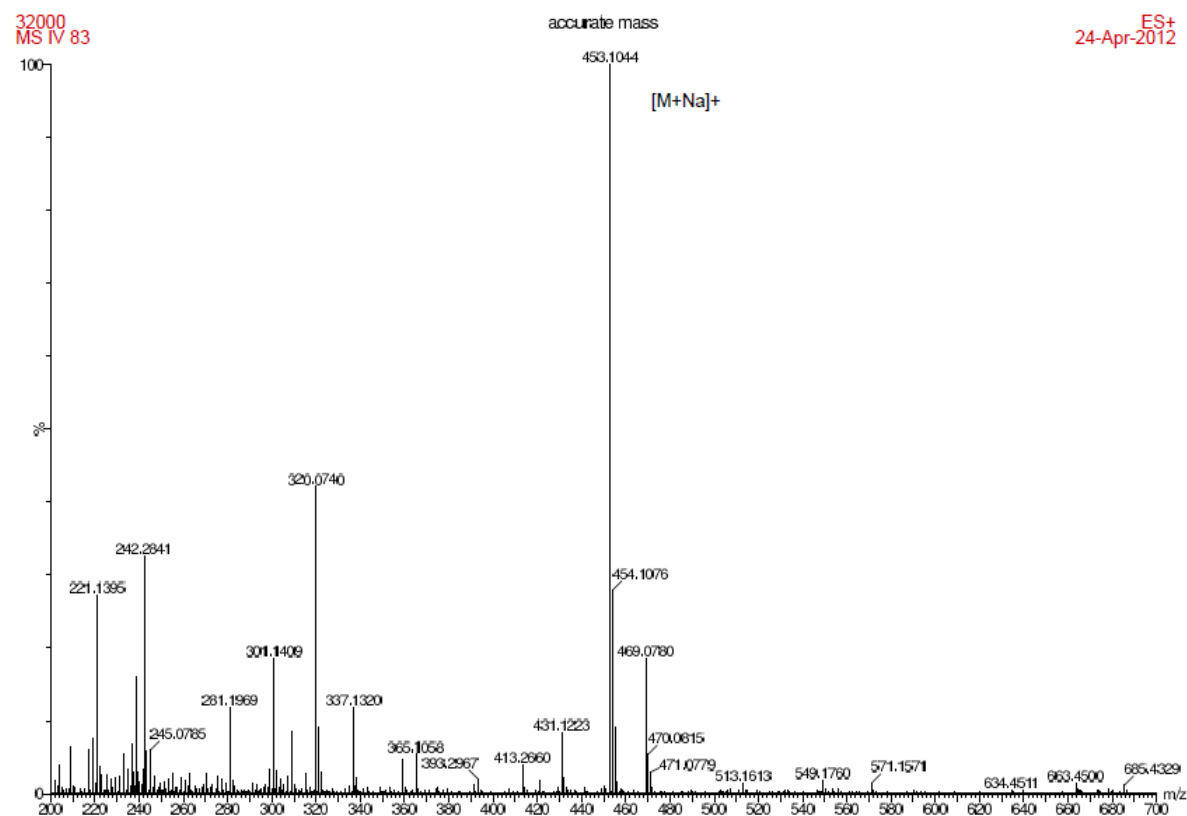
¹³C NMR (75 MHz, DMSO)

MS-IV-89 C13 in DMSO
27/04/2012

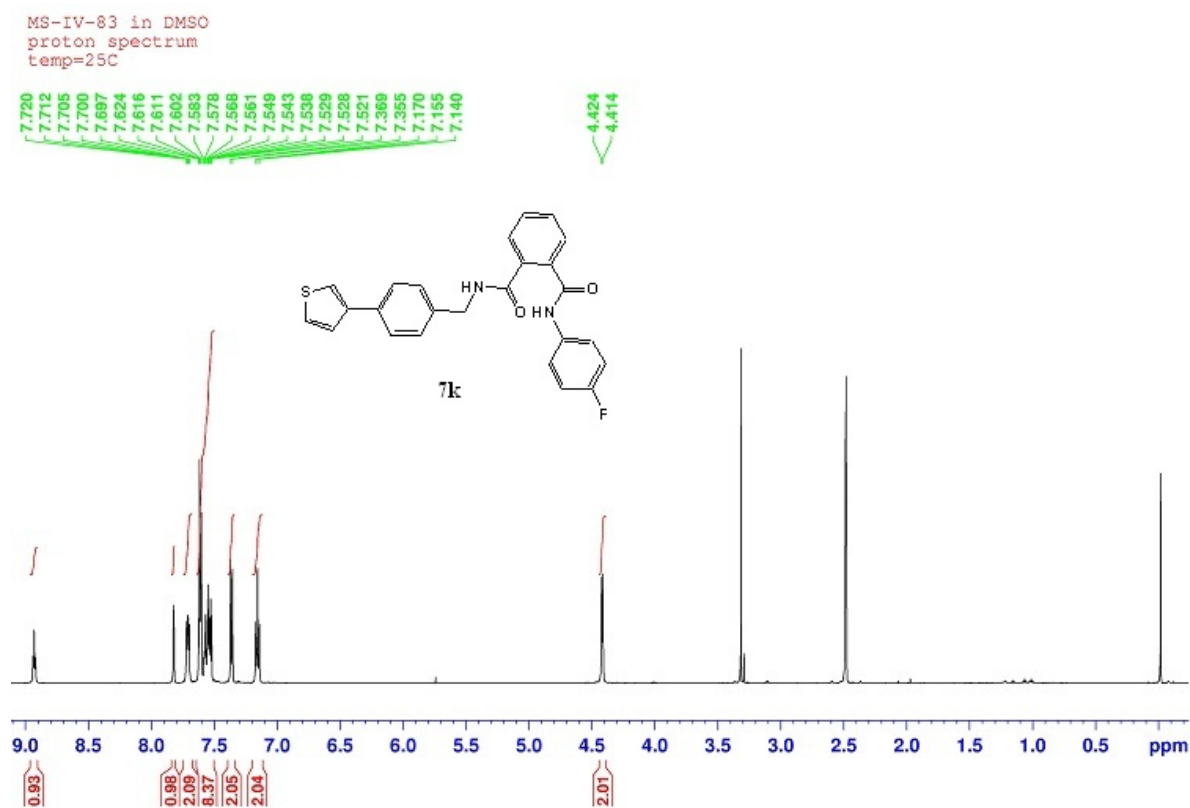


N^1 -(4-fluorophenyl)- N^2 -(4-(thiophen-3-yl)benzyl)phthalamide (7k)

HRMS

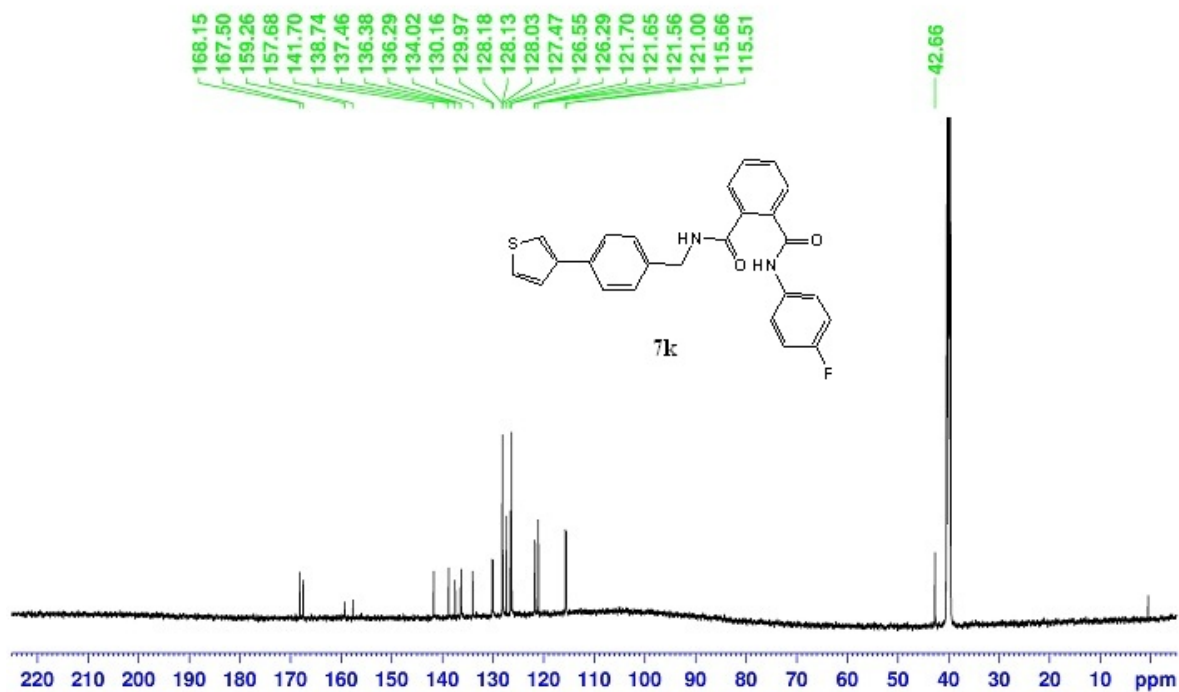


^1H NMR (500 MHz, DMSO)



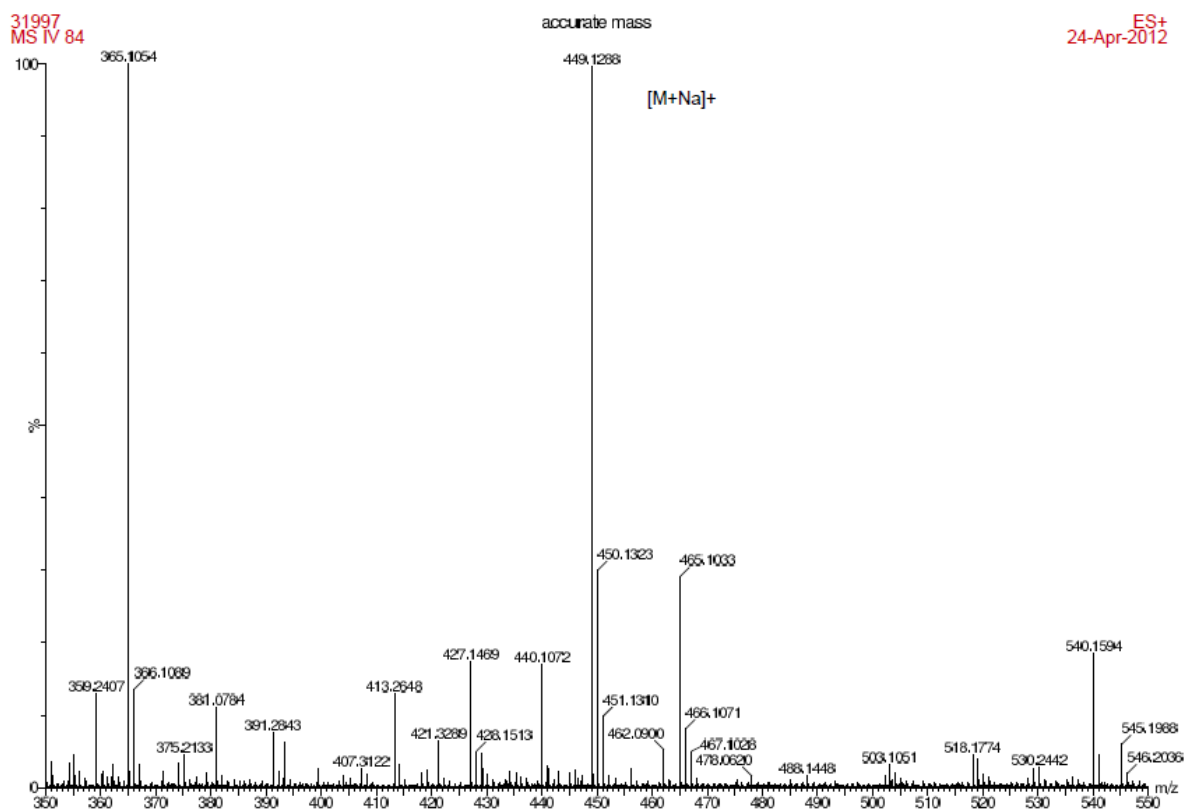
^{13}C NMR (125 MHz, DMSO)

MS-IV-83 in DMSO
temp = 25C
 ^{13}C
 ^1H decoupled



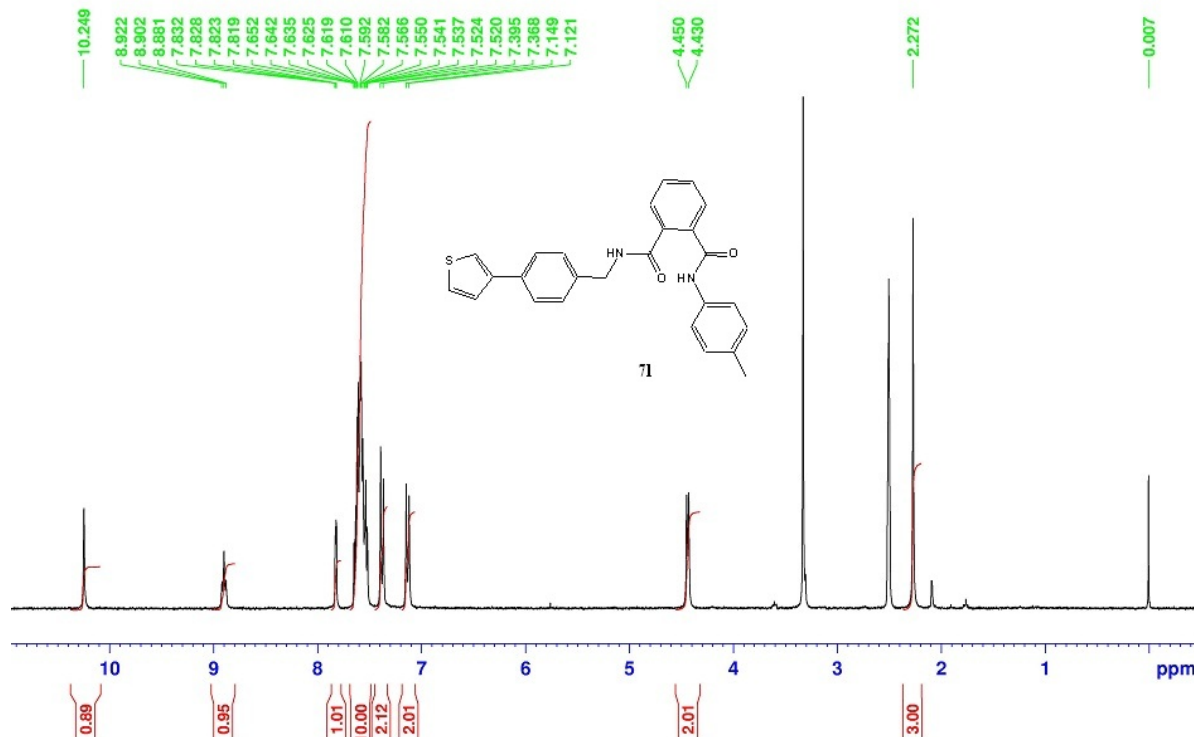
N^1 -(4-(thiophen-3-yl)benzyl)- N^2 -(p-tolyl)phthalamide (**7l**):

HRMS



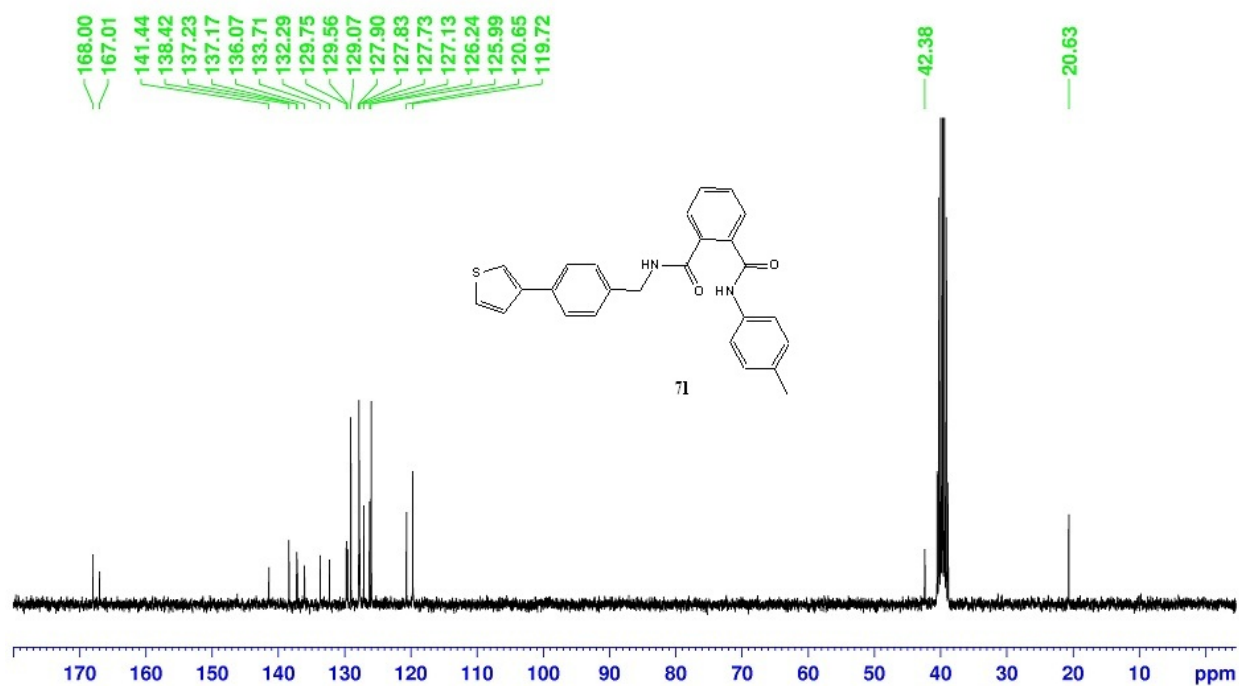
¹H NMR (300 MHz, DMSO)

MS-IV-84 in DMSO
24/04/2012



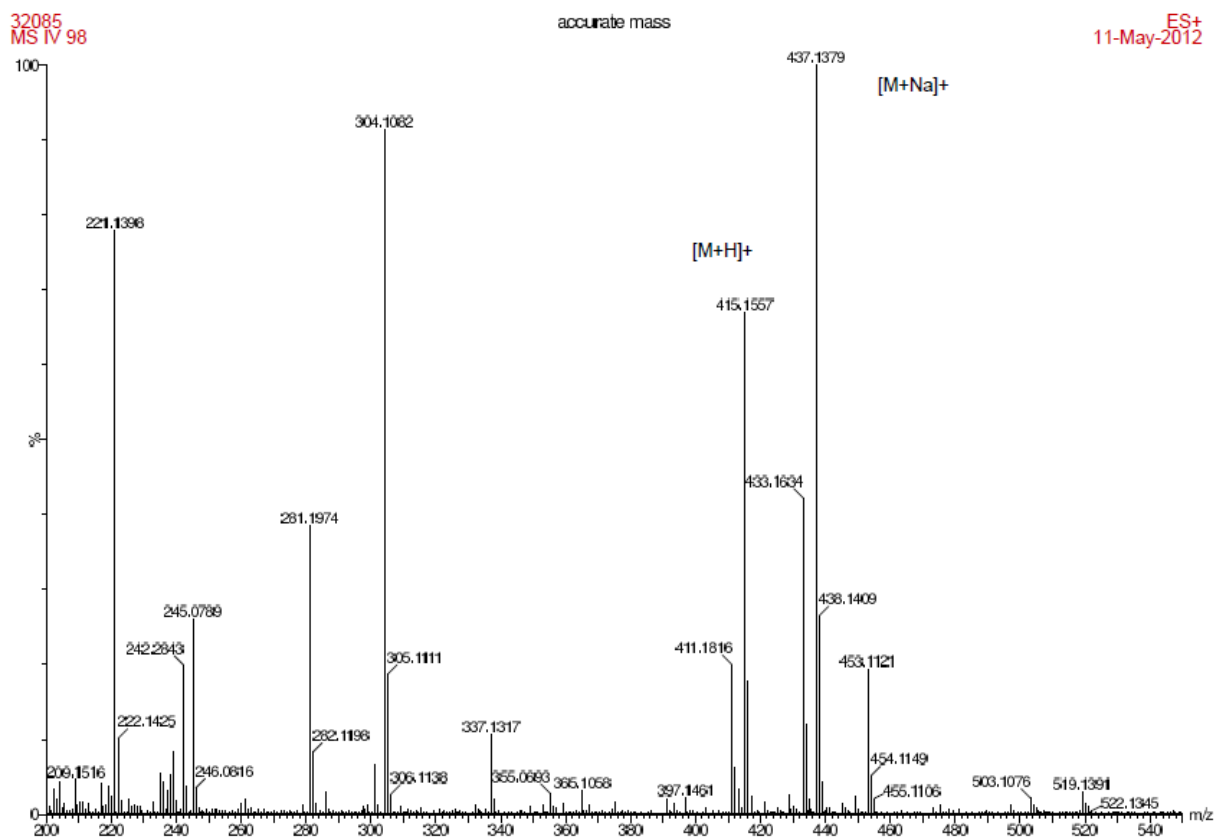
¹³C NMR (75 MHz, DMSO)

MS-IV-84 C13 in DMSO
24/04/2012



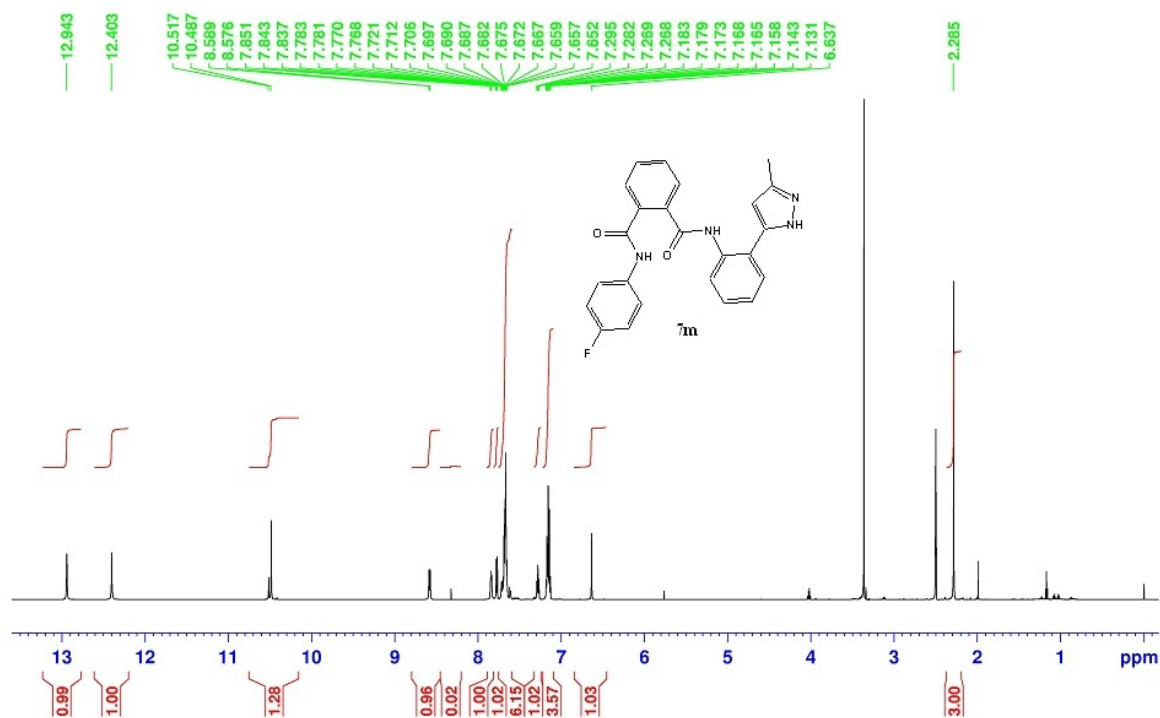
N^1 -(4-fluorophenyl)- N^2 -(2-(3-methyl-1H-pyrazol-5-yl)phenyl)phthalamide (7m):

HRMS



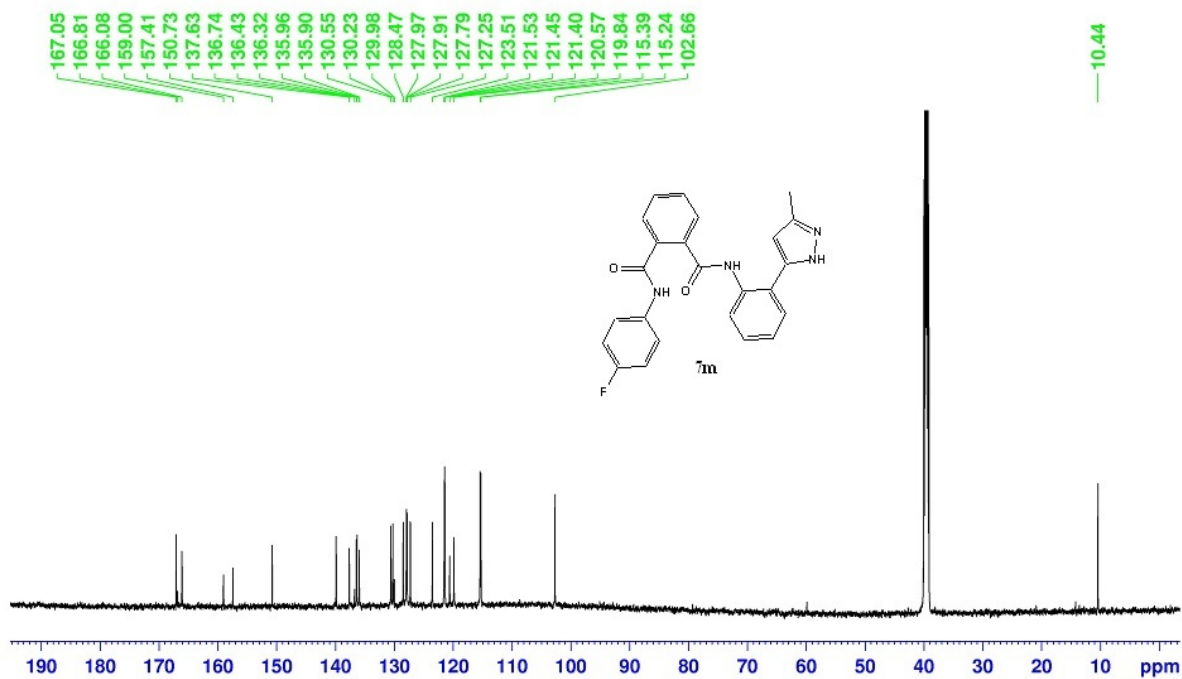
^1H NMR (500 MHz, DMSO)

MS-IV-98 in DMSO
proton spectrum
temp=25C



^{13}C NMR (125 MHz, DMSO)

MS-IV-98 in DMSO
temp = 25C
13C
1H decoupled



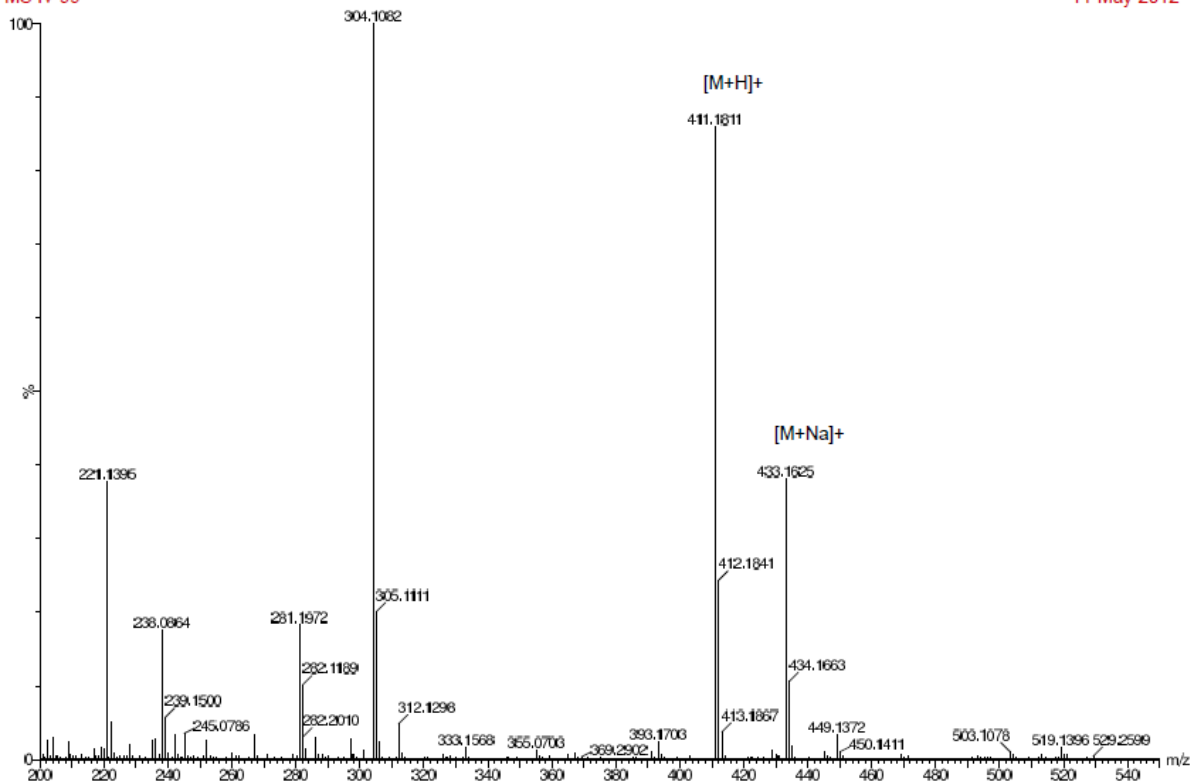
N^1 -(2-(3-methyl-1H-pyrazol-5-yl)phenyl)- N^2 -(p-tolyl)phthalamide (7n)

HRMS

32084
MS IV 99

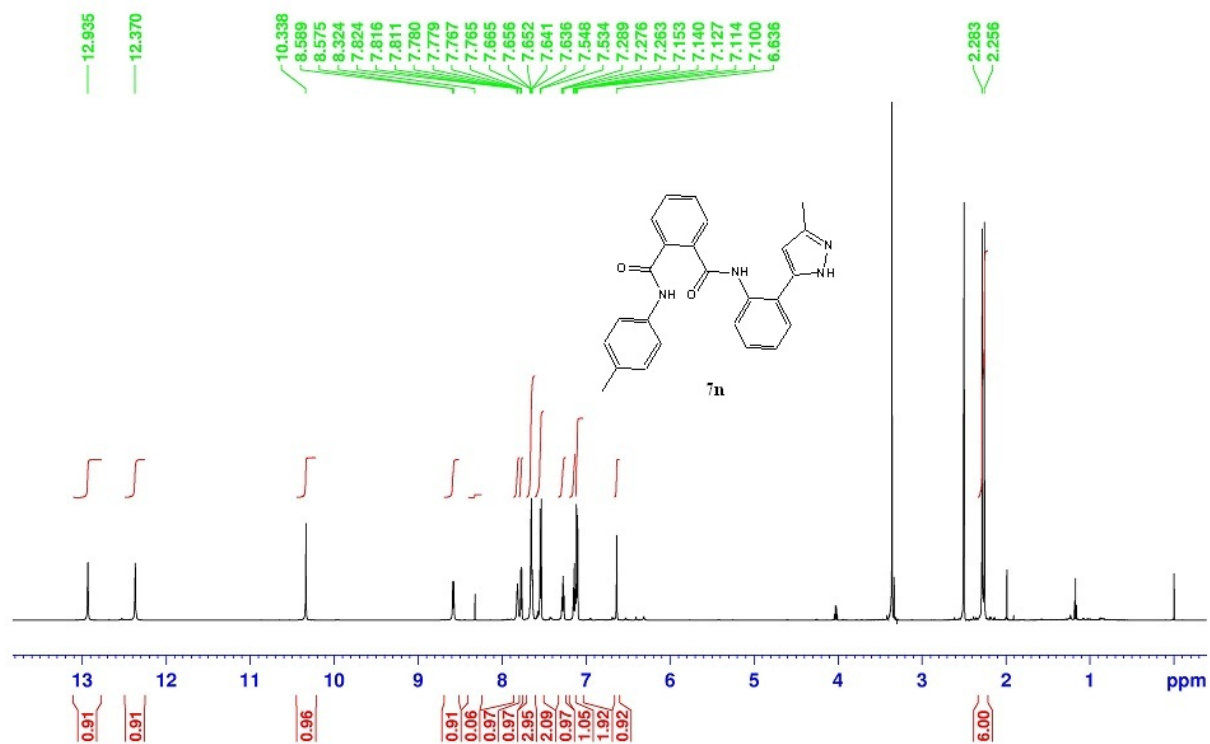
accurate mass

ES+
11-May-2012



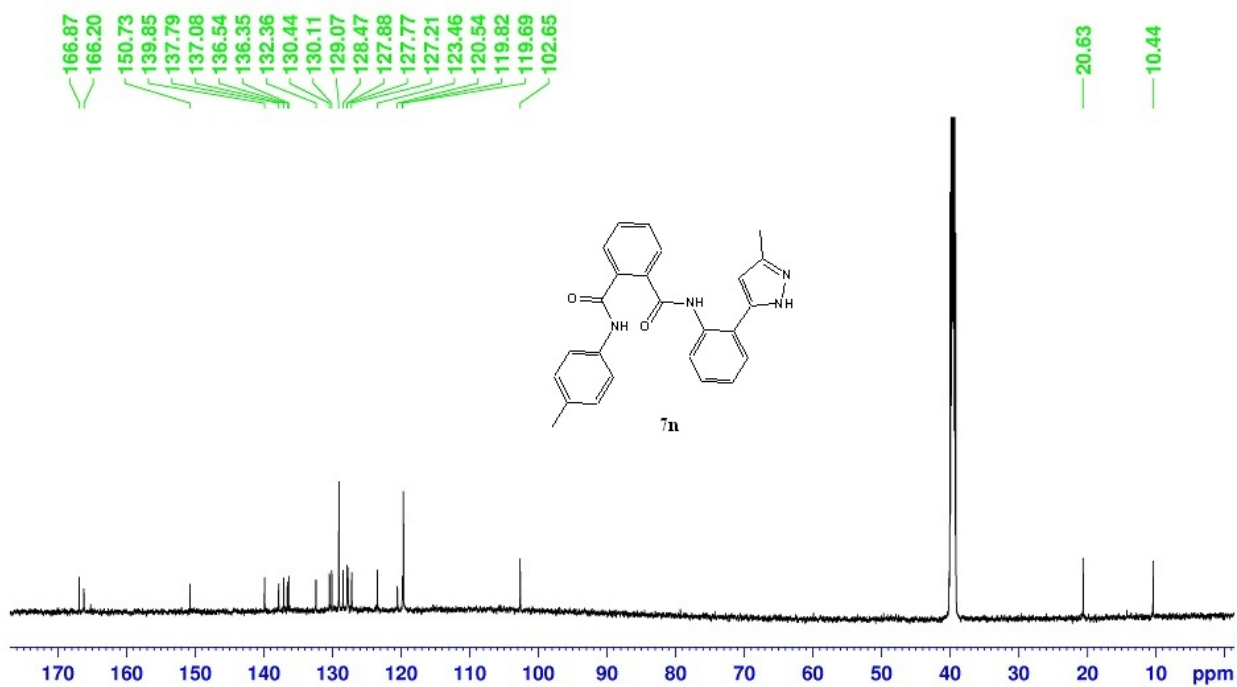
¹H NMR (500 MHz, DMSO)

MS-IV-99 in DMSO
proton spectrum
temp=25C



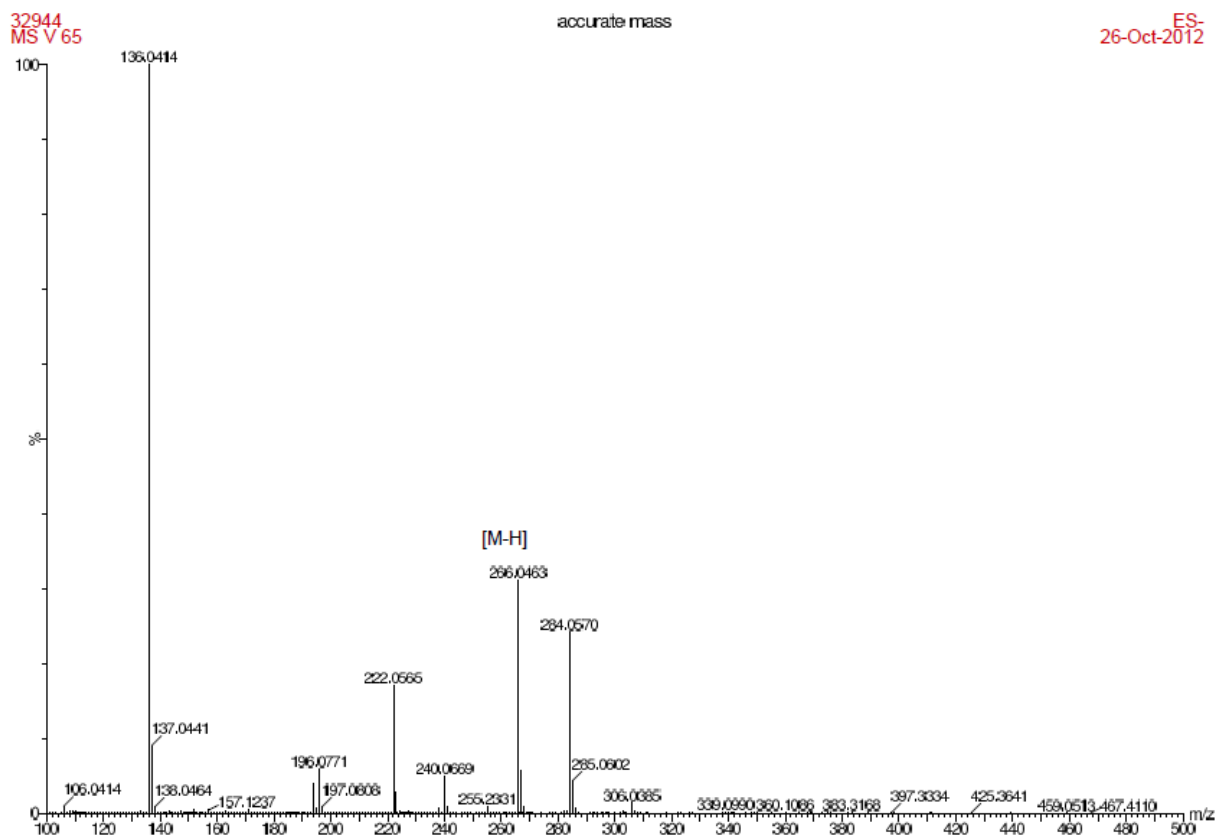
¹³C NMR (125 MHz, DMSO)

MS-IV-99 in DMSO
temp = 25C
¹³C
¹H decoupled



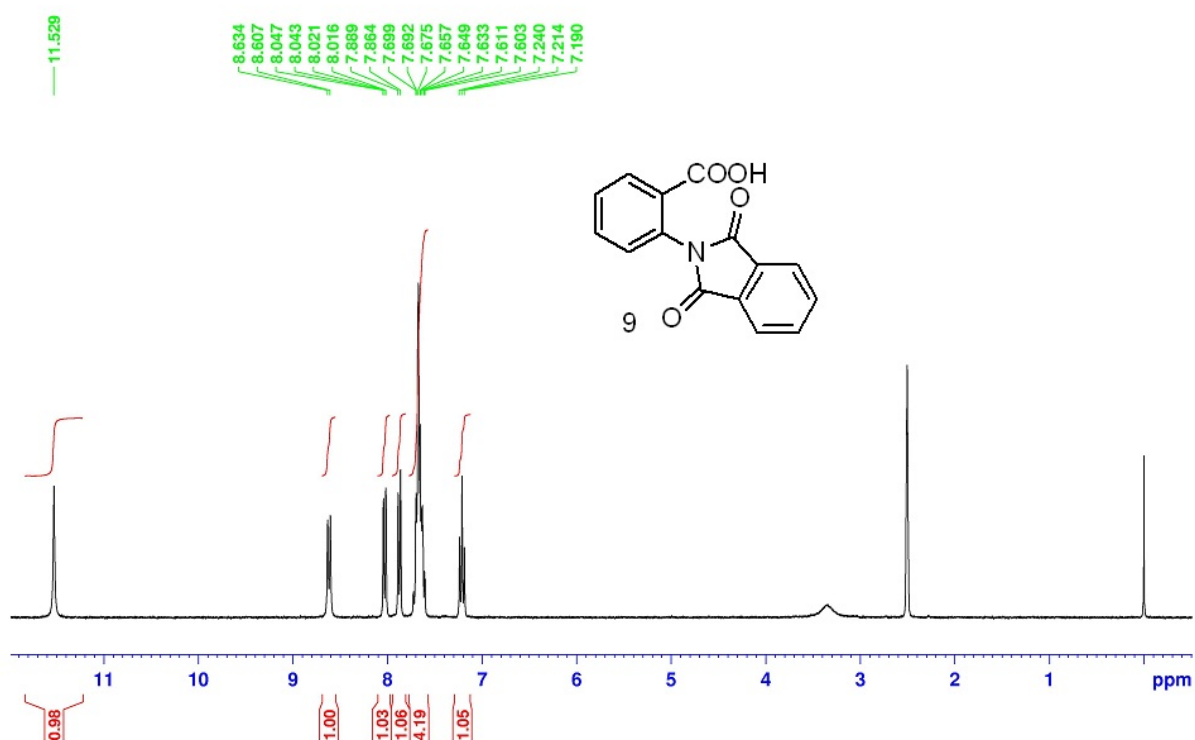
2-(1,3-dioxoisindolin-2-yl)benzoic acid (9)

HRMS

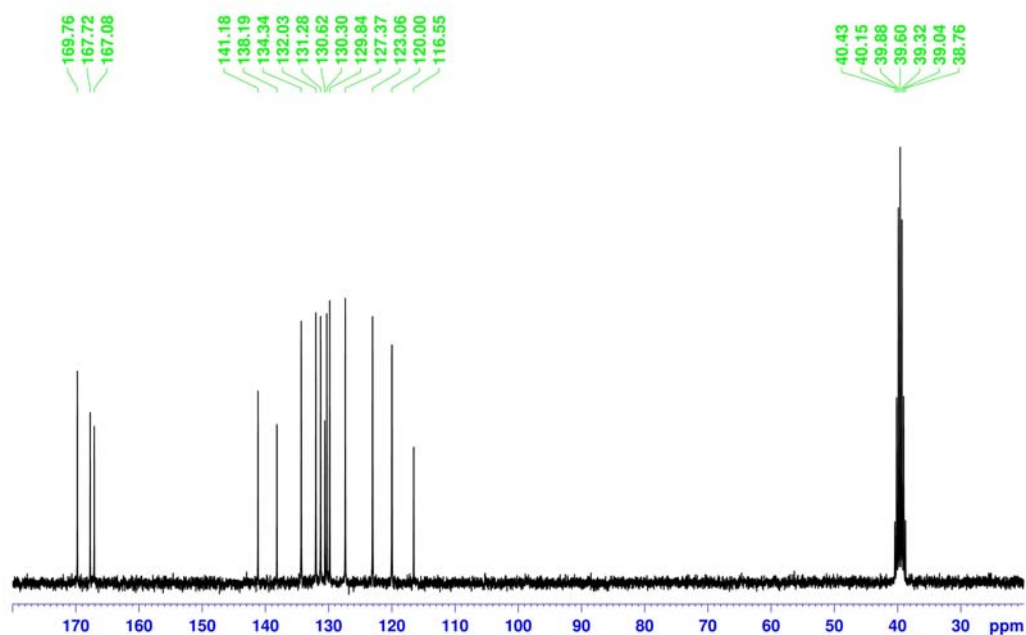


$^1\text{H NMR}$ (300 MHz, DMSO)

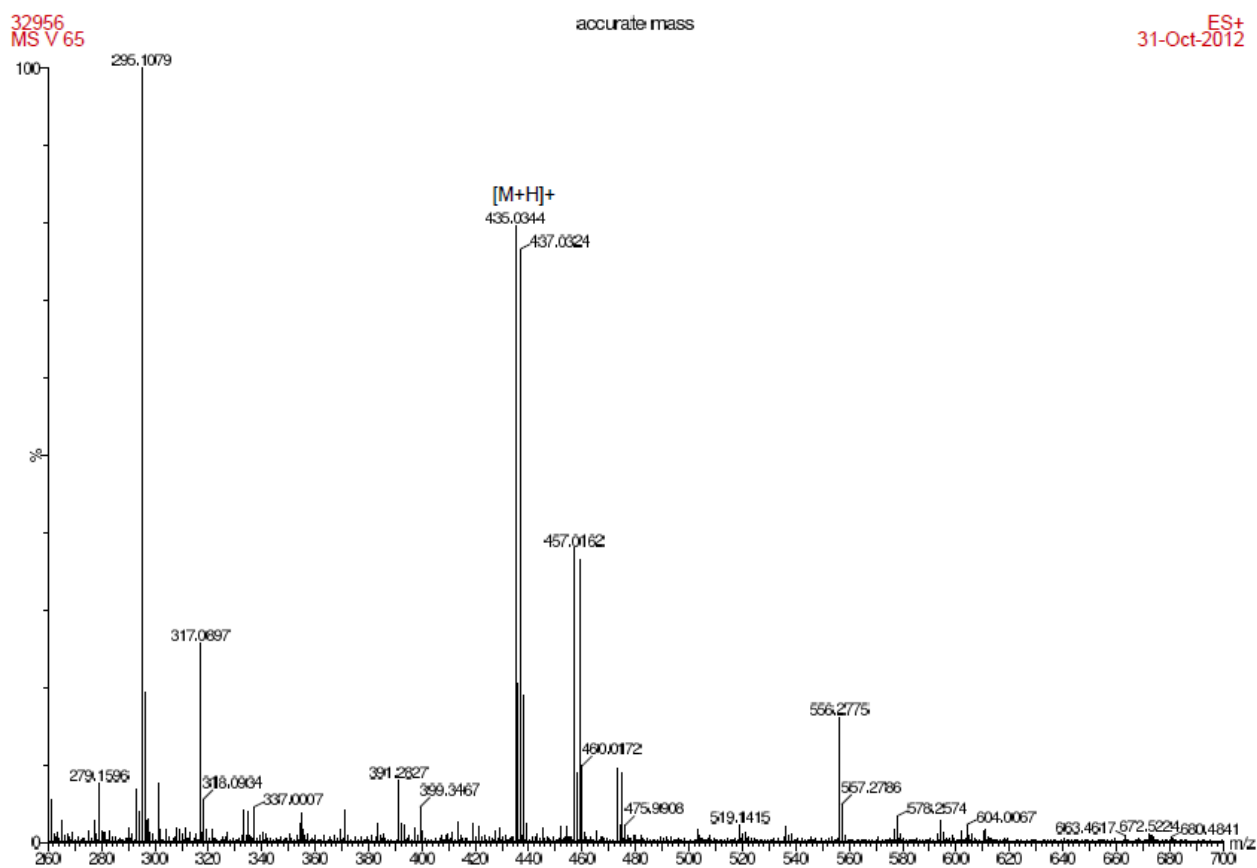
MS-V-64 in DMSO
26/10/2012



MS-V-64 in DMSO
11/03/2014

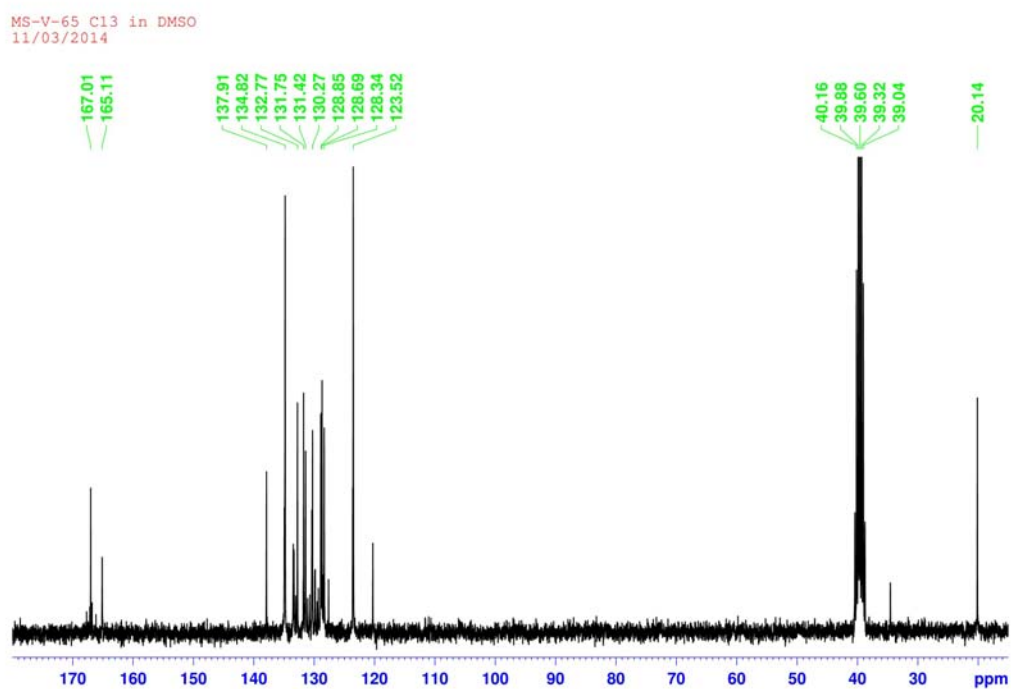
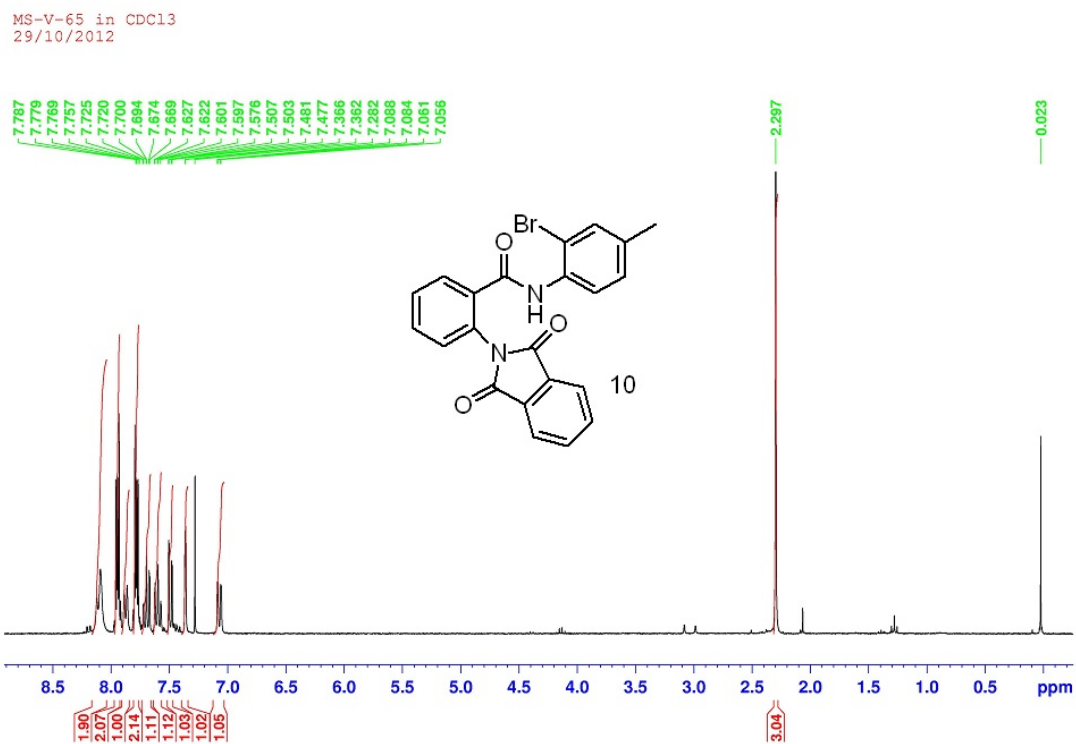


N-(2-bromo-4-methylphenyl)-2-(1,3-dioxisoindolin-2-yl)benzamide (10):
HRMS



ES+
31-Oct-2012

^1H NMR (300 MHz, CDCl_3)

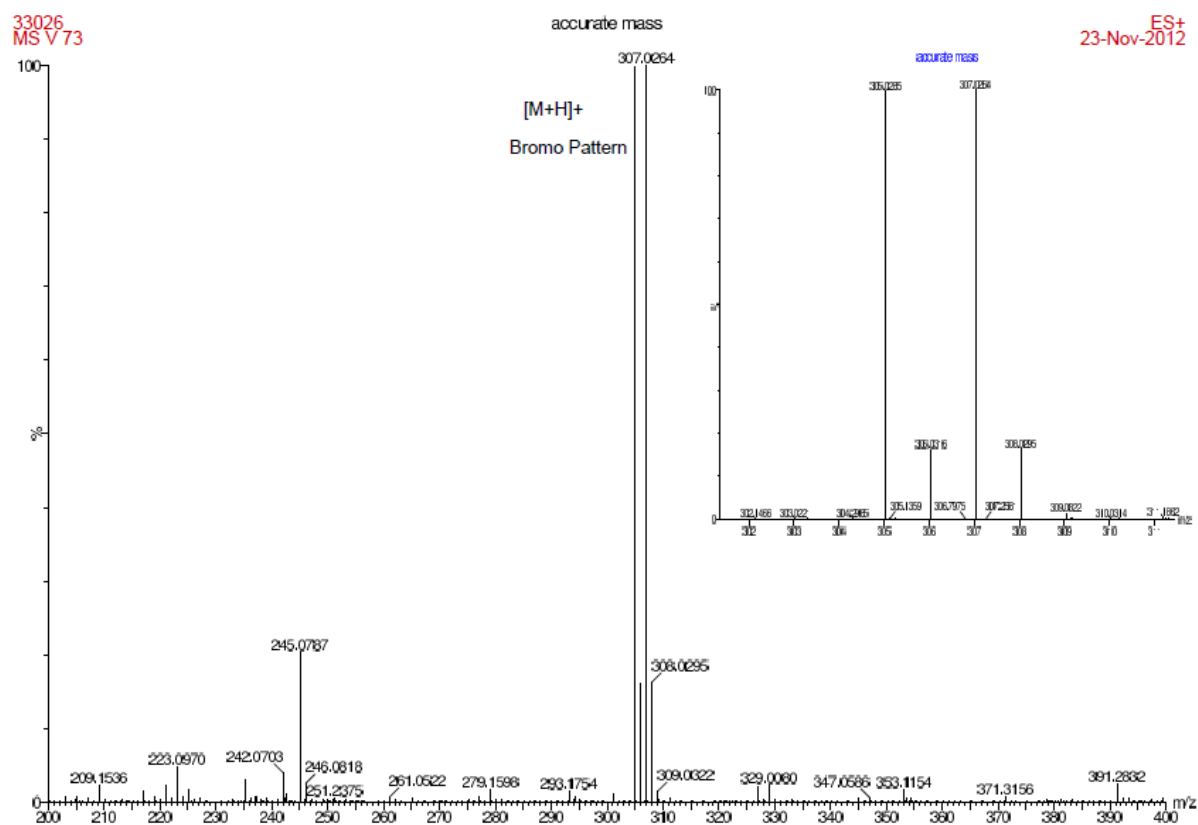


2-amino-*N*-(2-bromo-4-methylphenyl)benzamide (11)

HRMS

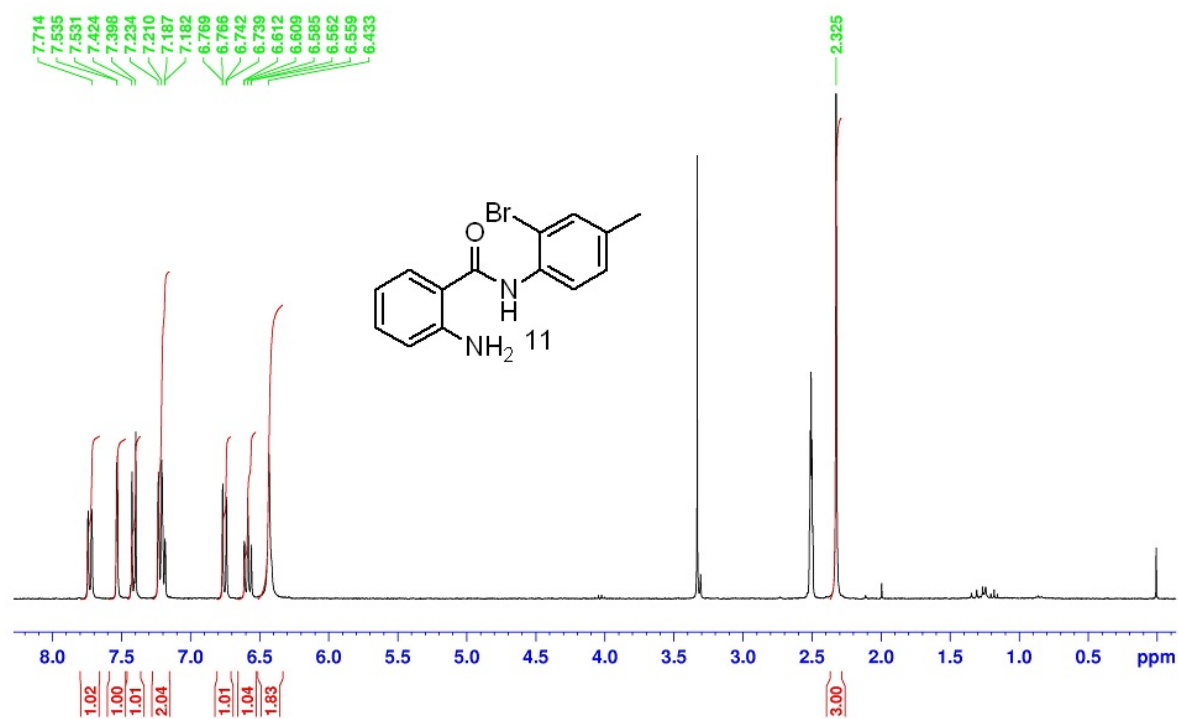
33026
MS V73

ES+
23-Nov-2012



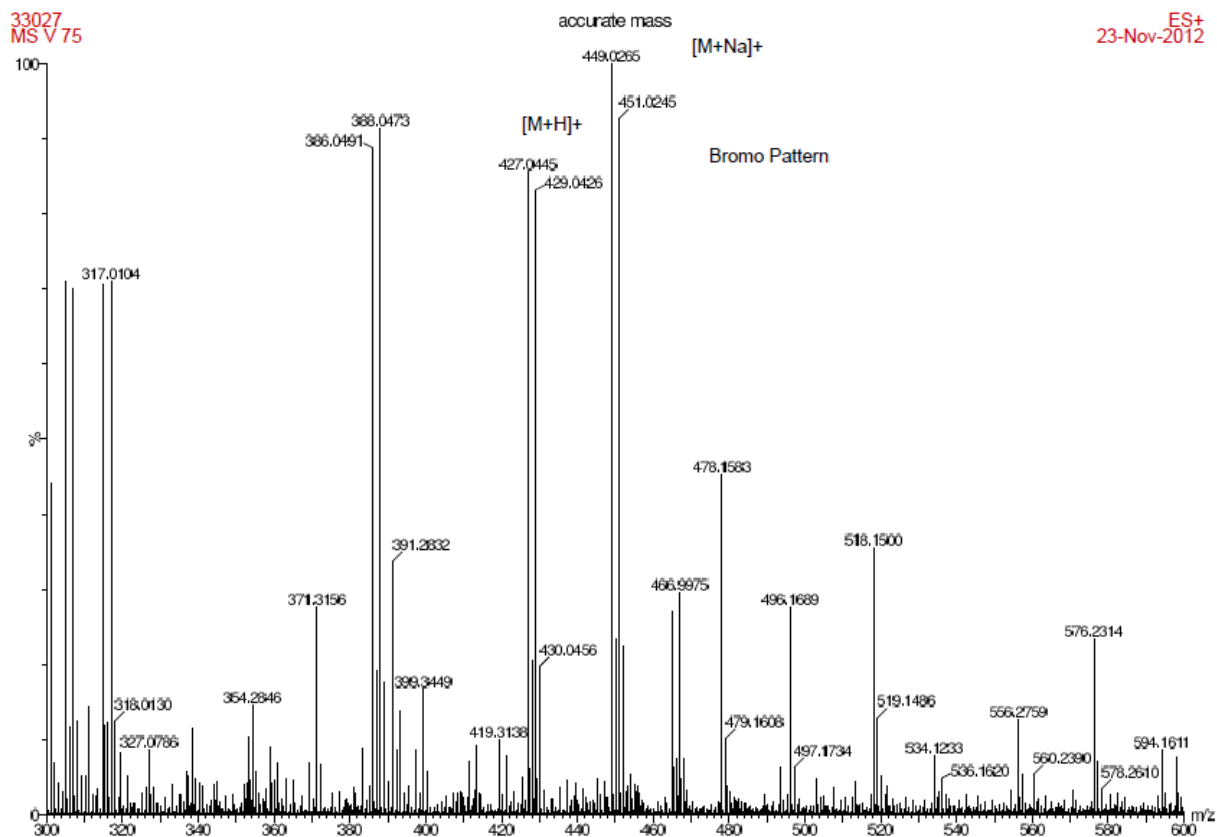
¹H NMR (300 MHz, DMSO)

MS-V-73 in DMSO
19/11/2012



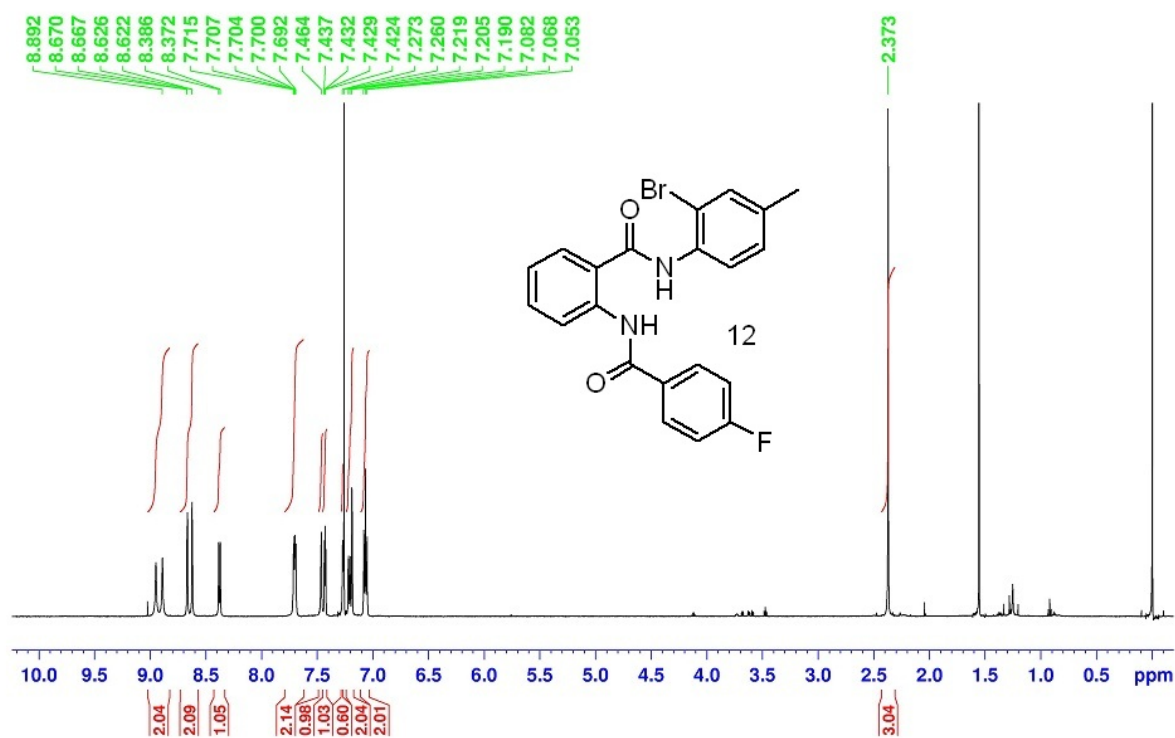
N-(2-bromo-4-methylphenyl)-2-(4-fluorobenzamido)benzamide (12)

HRMS



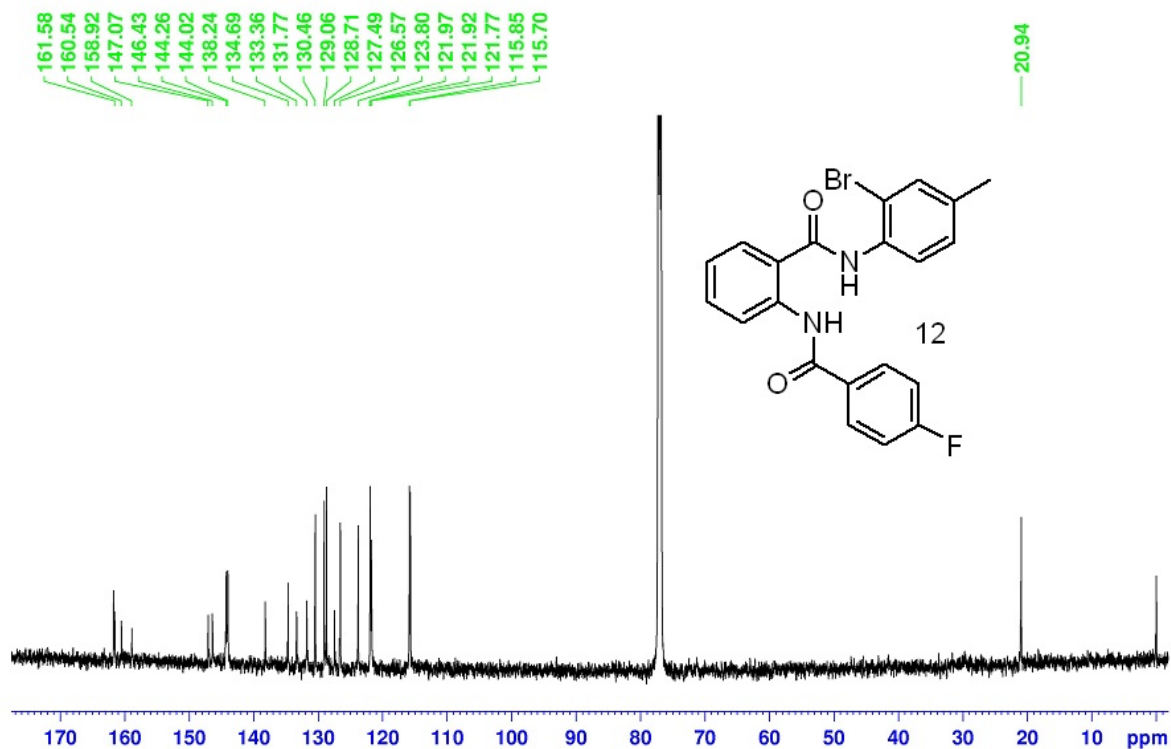
¹H NMR (500 MHz, CDCl₃)

MS-IV-75 in CDCl₃
proton spectrum
temp=25C



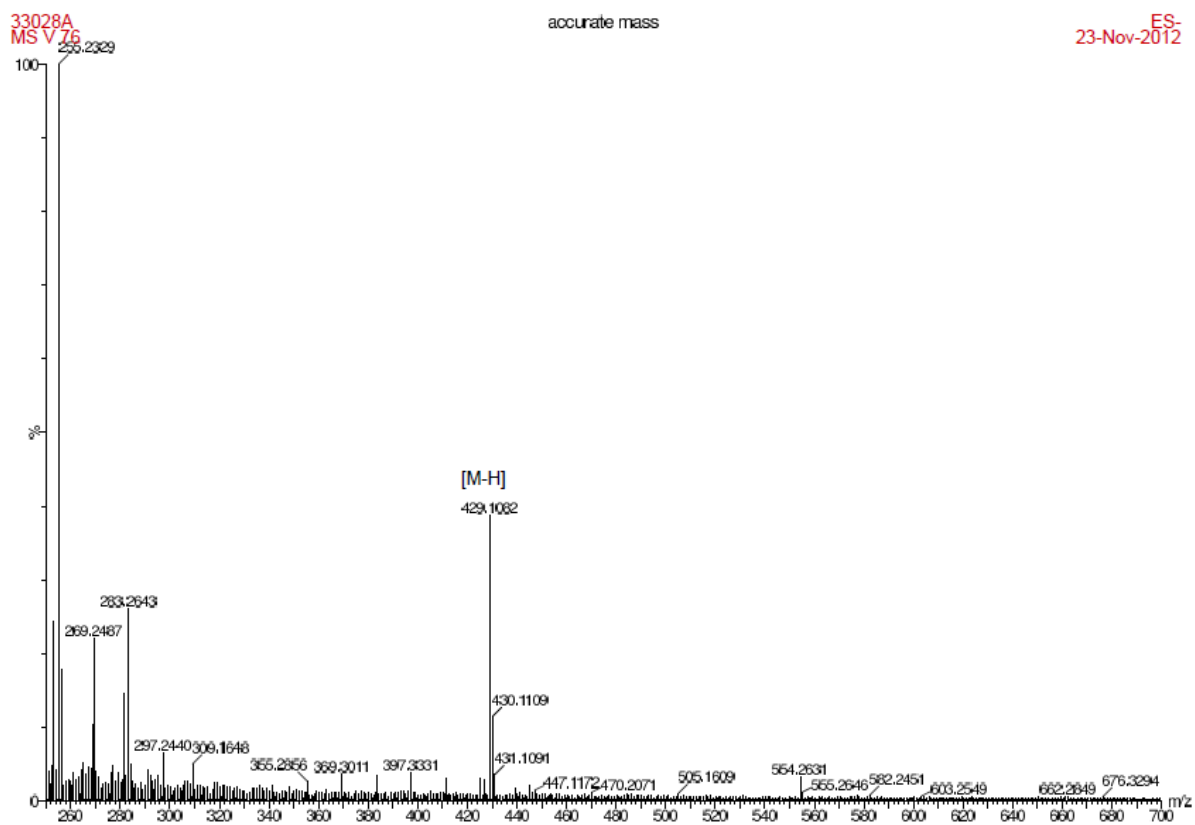
¹³C NMR (125 MHz, CDCl₃)

MS-IV-75 in CDCl₃
temp = 25C
13C



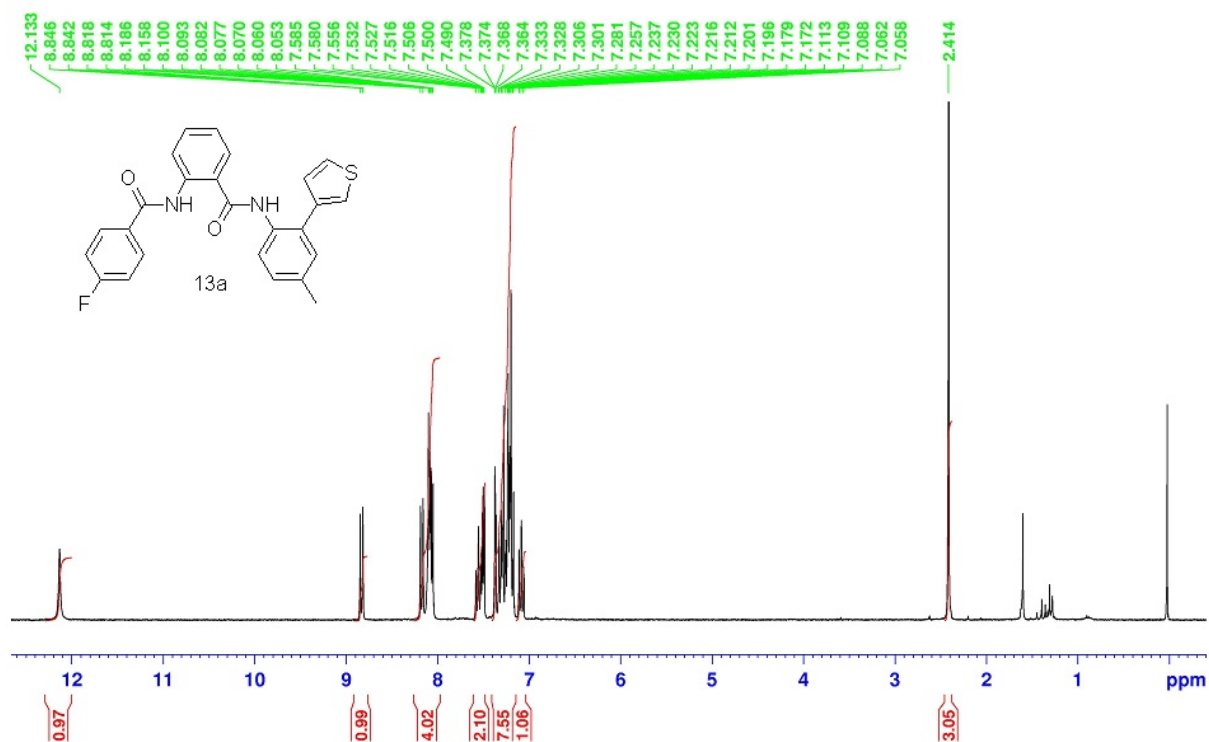
2-(4-fluorobenzamido)-N-(4-methyl-2-(thiophen-3-yl)phenyl)benzamide (13a)

HRMS



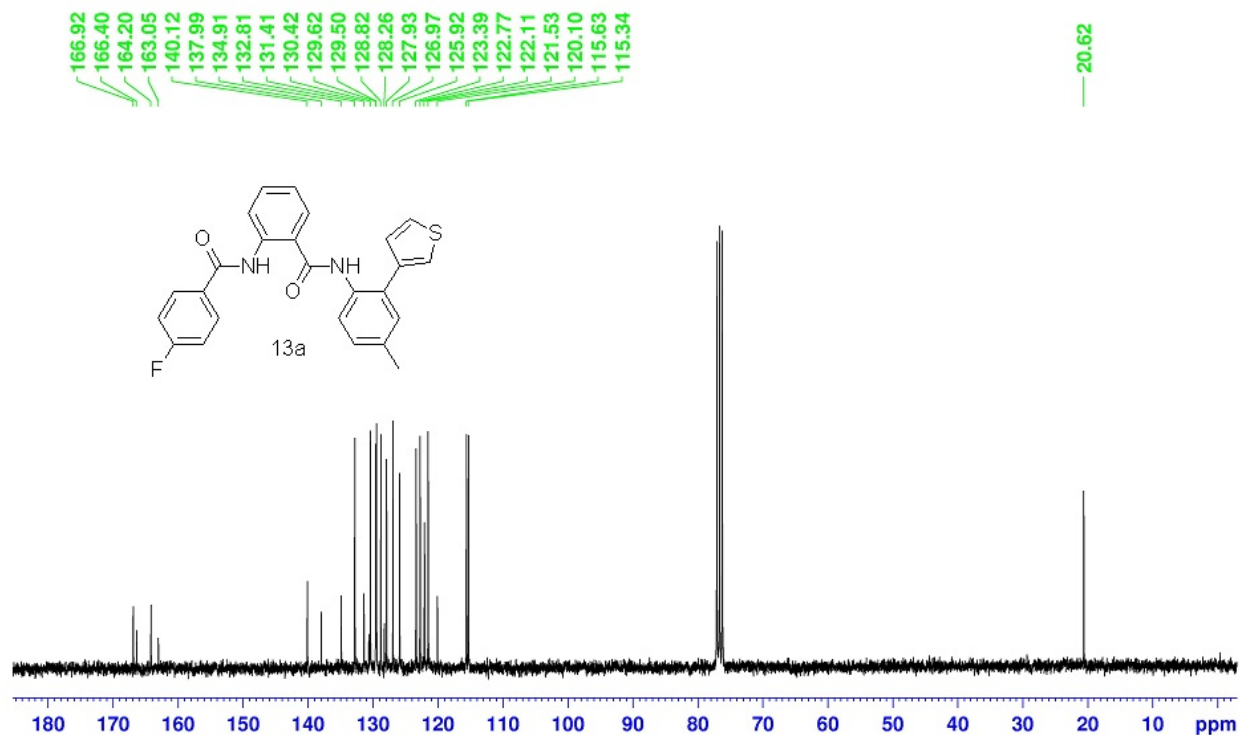
¹H NMR (300 MHz, CDCl₃)

MS-V-76 in CDCl₃
23/11/2012

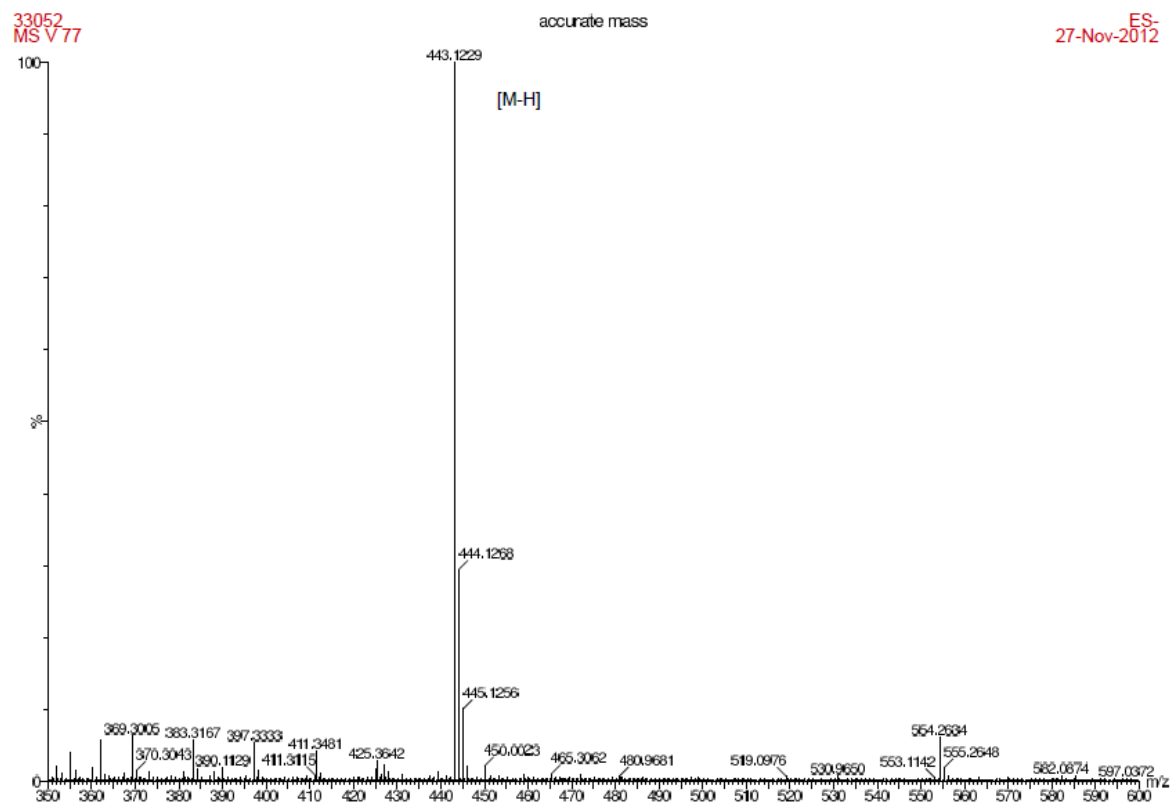


¹³C NMR (75 MHz, CDCl₃)

MS-V-76 C13 in CDCl₃
23/11/2012

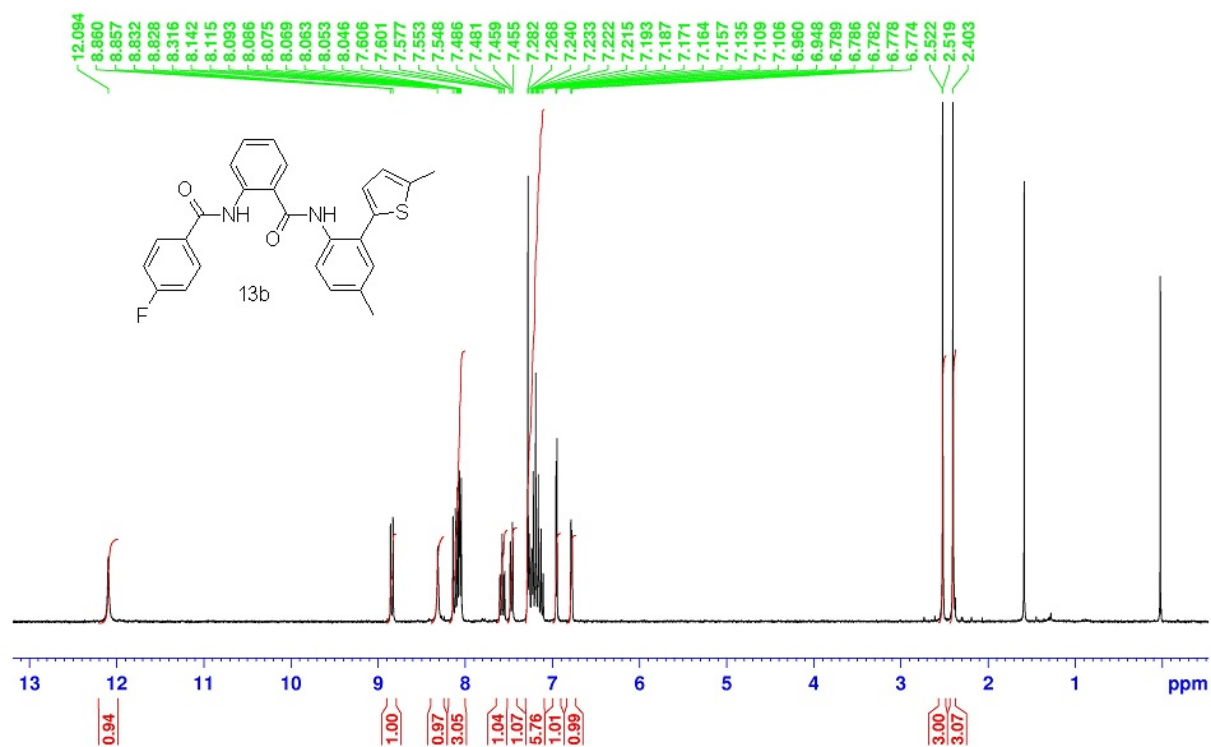


2-(4-fluorobenzamido)-*N*-(4-methyl-2-(5-methylthiophen-2-yl)phenyl)benzamide
 (13b)
 HRMS



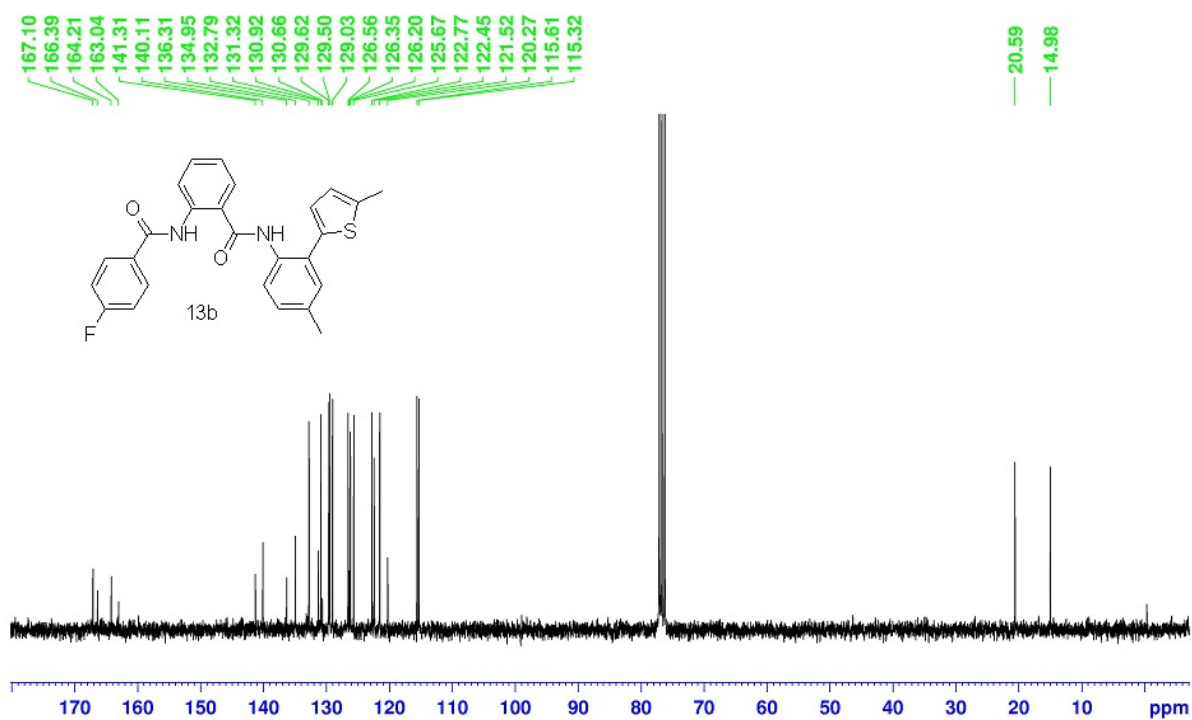
¹H NMR (300 MHz, CDCl₃)

MS-V-77 in CDCl₃
 26/11/2012



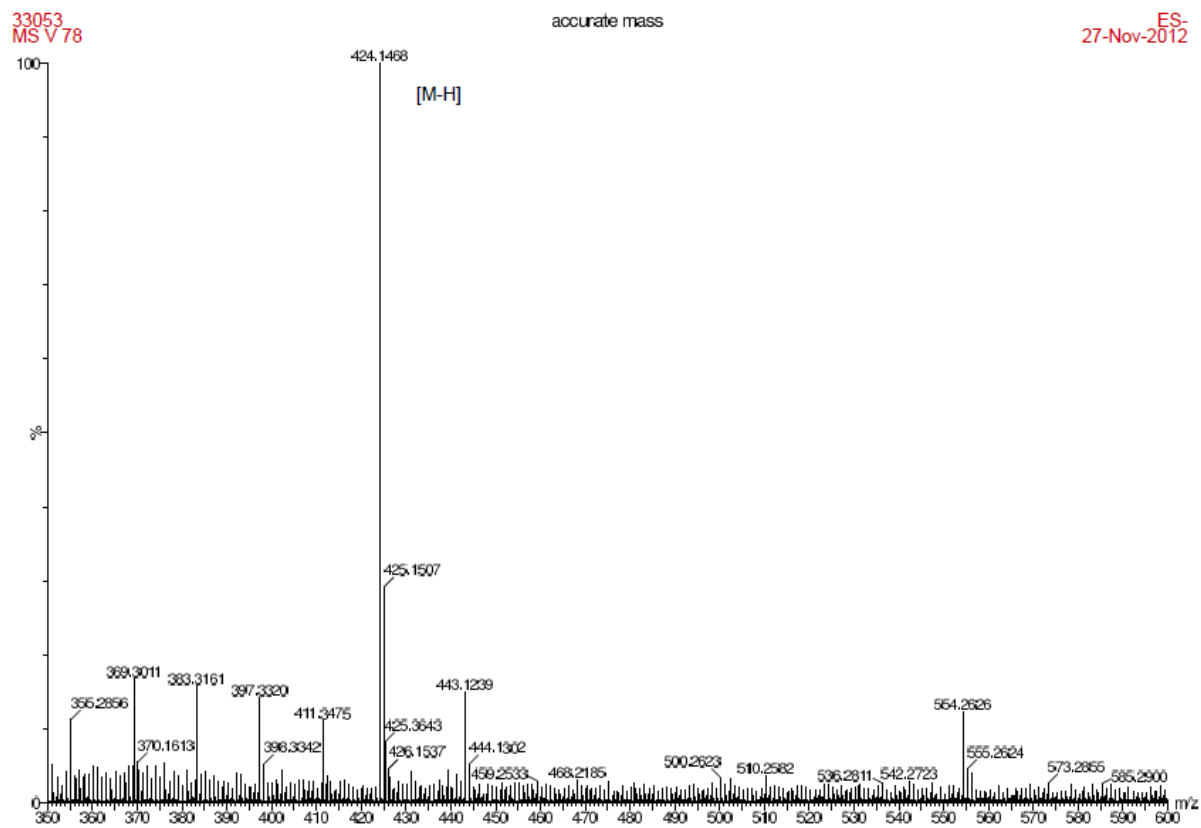
^{13}C NMR (75 MHz, CDCl_3)

MS-V-77 C13 in CDCl_3
26/11/2012



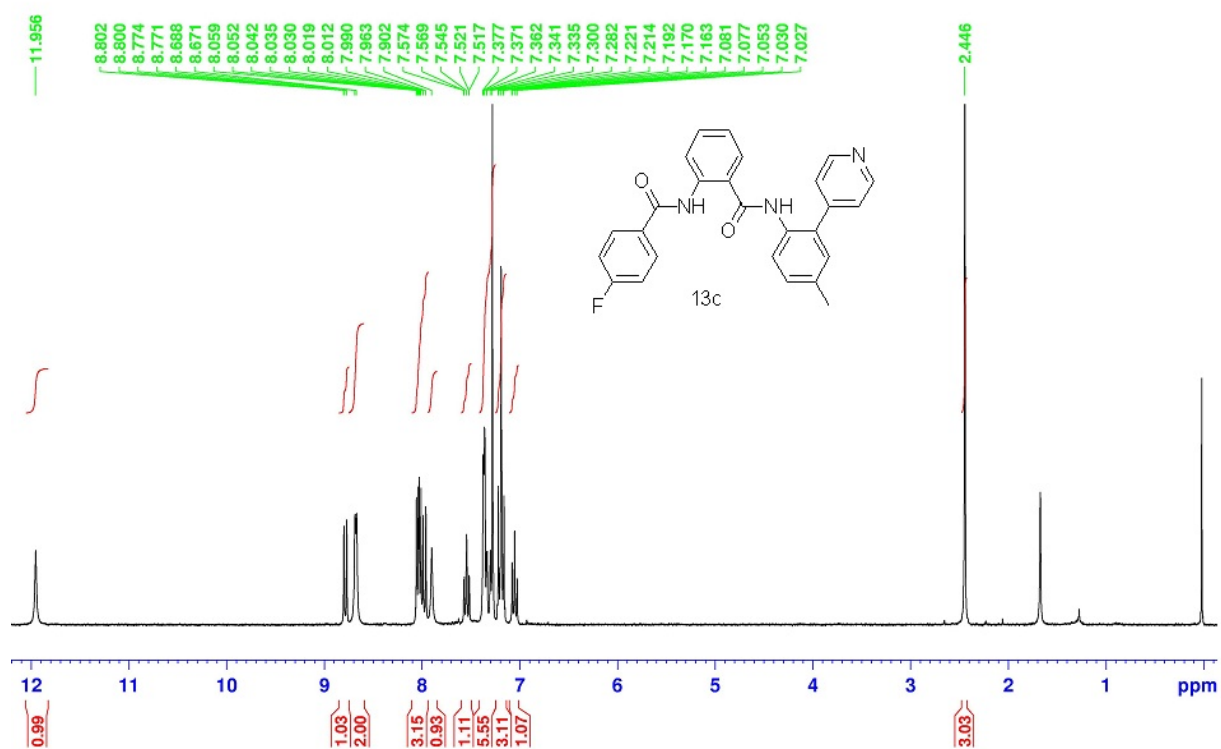
2-(4-fluorobenzamido)-*N*-(4-methyl-2-(pyridin-4-yl)phenyl)benzamide (13c)

HRMS



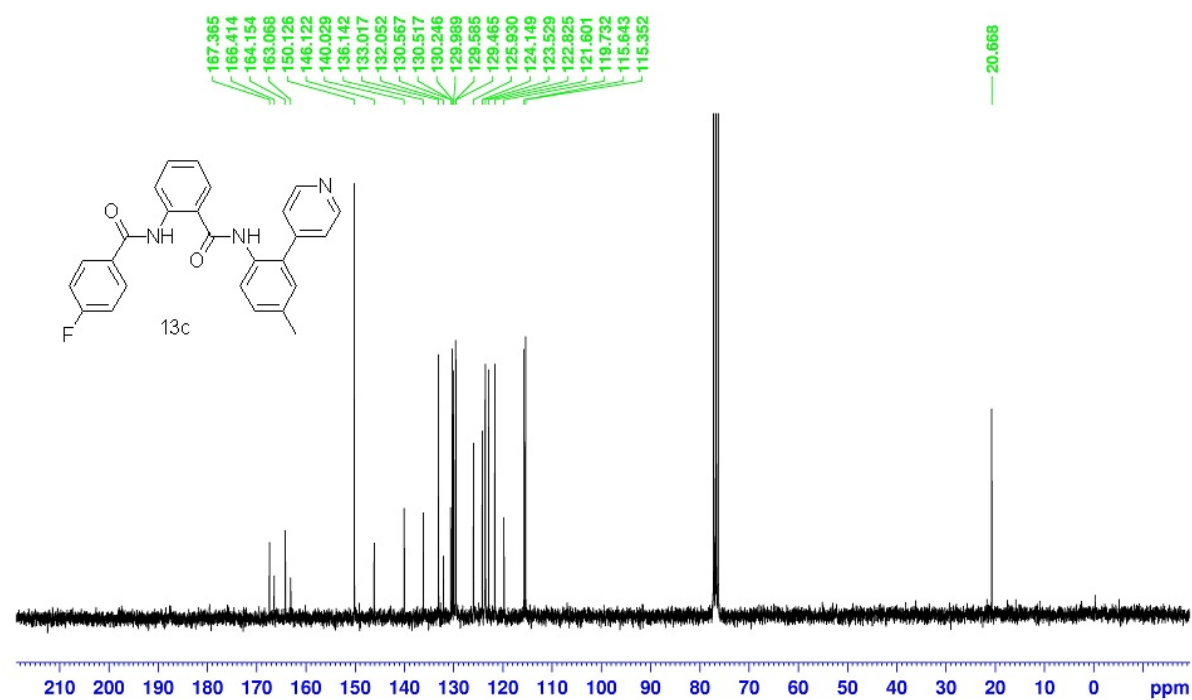
¹H NMR (300 MHz, CDCl₃)

MS-V-78 in CDCl₃
26/11/2012



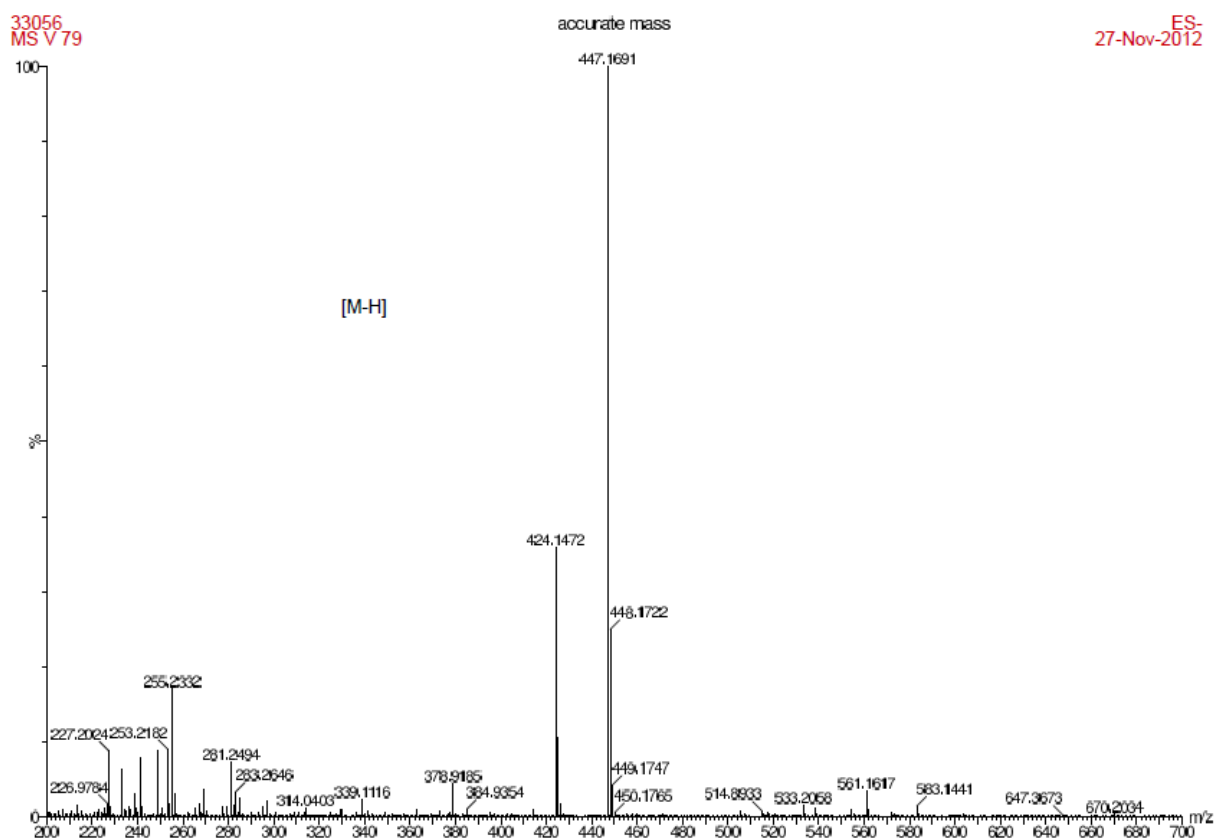
¹³C NMR (75 MHz, CDCl₃)

MS-V-78 C13 in CDCl₃
27/11/2012



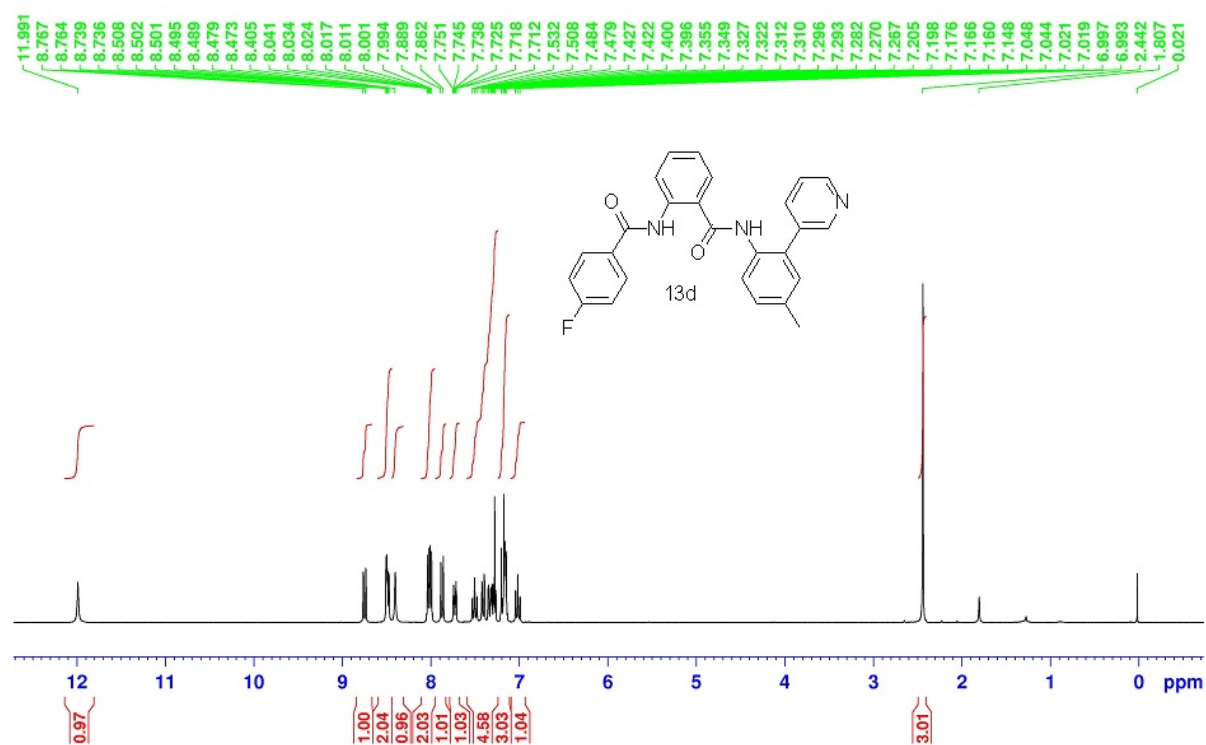
2-(4-fluorobenzamido)-*N*-(4-methyl-2-(pyridin-3-yl)phenyl)benzamide (13d)

HRMS



¹H NMR (300 MHz, CDCl₃)

MS-V-79 in CDCl₃
28/11/2012



¹³C NMR (75 MHz, DMSO)

MS-IV-79 in DMSO
temp = 20C
13C
1H decoupled

