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Supporting information for article:

Macozinone: revised synthesis and crystal structure of a promising new drug for treating drug-sensitive and drug-resistant tuberculosis

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Table S1 Crystal data and structure refinement for Macozinone.

Identification code	**Macozinone**
Empirical formula	C20 H23 F3 N4 O3 S
Formula weight	456.48
Temperature	205.0 K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P $2_1/c$
Unit cell dimensions	a = 15.051(7) Å
	b = 5.295(2) Å
	c = 26.548(11) Å
Volume	2098.3(15) $Å^3$
Z	4
Density (calculated)	1.445 Mg/m^3
Absorption coefficient	0.211 mm^{-1}
F(000)	952
Crystal size	0.16 × 0.15 × 0.12 mm^3
Theta range for data collection	1.927 to 27.712°.
Index ranges	-19<=h<=18, -6<=k<=6, -26<=l<=34
Reflections collected	11854
Independent reflections	4794 [R(int) = 0.0248]
Completeness to theta = 25.242°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7456 and 0.6410
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4794 / 36 / 326
Goodness-of-fit on F^2	1.052
Final R indices [I>2sigma(I)]	R1 = 0.0473, wR2 = 0.1064

Computer programs: SMART (Bruker, 2000), SAINT (Bruker, 2000), SHELXT97/2016 (Sheldrick, 2015a), SHELXL97/2016 (Sheldrick, 2015b), SHELXTL (Bruker, 2000), PLATON (Spek, 2009), Mercury 3.8 (Macrae et al., 2008), ORTEP-3 (Farrugia, 2012) , and OLEX 2-1.2 (Dolomanov et al., 2009; Bourhis et al., 2015).

Table S2 Bond Lengths [Å] and for Macozinone. Partial crystal disorder exists at the nitro and trifluoromethyl positions of the target compound. Atoms are numbered according to atomic site occupancy.

S(1)-C(1)	1.776(2)
S(1)-C(4)	1.739(2)
F(1)-C(8)	1.262(10)
F(1A)-C(8)	1.305(11)
F(2)-C(8)	1.342(9)
F(2A)-C(8)	1.229(11)
F(3)-C(8)	1.293(9)
F(3A)-C(8)	1.347(10)
O(1)-C(2)	1.216(3)
O(2)-N(2)	1.200(16)
O(3)-N(2)	1.253(14)
N(1)-C(1)	1.296(3)
N(1)-C(2)	1.353(3)
N(2)-C(5)	1.455(3)
N(2)-O(3A)	1.203(14)
N(2)-O(2A)	1.211(18)
N(3)-C(1)	1.330(2)
N(3)-C(10)	1.470(3)
N(3)-C(13)	1.455(3)
N(4)-C(11)	1.444(3)
N(4)-C(12)	1.449(2)
N(4)-C(14)	1.459(2)
C(2)-C(3)	1.496(3)
C(3)-C(4)	1.390(3)
C(3)-C(9)	1.390(3)
C(4)-C(5)	1.407(3)
C(5)-C(6)	1.373(3)
C(6)-H(6)	0.9400
C(6)-C(7)	1.368(3)
C(7)-C(8)	1.492(3)
C(7)-C(9)	1.372(3)

C(9)-H(9)	0.9400
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-C(11)	1.496(3)
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-C(13)	1.506(3)
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-C(15)	1.516(3)
C(15)-H(15)	0.9900
C(15)-C(16)	1.504(3)
C(15)-C(20)	1.512(3)
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-C(17)	1.508(3)
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-C(18)	1.501(4)
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-C(19)	1.494(4)
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-C(20)	1.505(3)
C(20)-H(20A)	0.9800
C(20)-H(20B)	0.9800

Angles [°]

C(4)-S(1)-C(1)	100.61(10)
C(1)-N(1)-C(2)	124.30(17)
O(2)-N(2)-O(3)	121.8(11)
O(2)-N(2)-C(5)	119.3(6)

O(3)-N(2)-C(5)	118.3(9)
O(3A)-N(2)-C(5)	116.8(9)
O(3A)-N(2)-O(2A)	123.7(11)
O(2A)-N(2)-C(5)	118.8(7)
C(1)-N(3)-C(10)	120.85(19)
C(1)-N(3)-C(13)	125.62(17)
C(13)-N(3)-C(10)	113.11(17)
C(11)-N(4)-C(12)	108.74(16)
C(11)-N(4)-C(14)	111.55(17)
C(12)-N(4)-C(14)	111.45(16)
N(1)-C(1)-S(1)	127.78(15)
N(1)-C(1)-N(3)	119.23(18)
N(3)-C(1)-S(1)	112.98(16)
O(1)-C(2)-N(1)	120.73(19)
O(1)-C(2)-C(3)	118.38(19)
N(1)-C(2)-C(3)	120.89(19)
C(4)-C(3)-C(2)	124.04(17)
C(9)-C(3)-C(2)	115.71(19)
C(9)-C(3)-C(4)	120.25(18)
C(3)-C(4)-S(1)	122.06(14)
C(3)-C(4)-C(5)	116.85(17)
C(5)-C(4)-S(1)	121.09(16)
C(4)-C(5)-N(2)	121.74(18)
C(6)-C(5)-N(2)	116.08(17)
C(6)-C(5)-C(4)	122.16(19)
C(5)-C(6)-H(6)	120.1
C(7)-C(6)-C(5)	119.89(18)
C(7)-C(6)-H(6)	120.1
C(6)-C(7)-C(8)	119.7(2)
C(6)-C(7)-C(9)	119.47(19)
C(9)-C(7)-C(8)	120.8(2)
F(1)-C(8)-F(2)	108.5(8)
F(1)-C(8)-F(3)	110.5(7)
F(1)-C(8)-C(7)	112.9(6)
F(1A)-C(8)-F(3A)	101.1(8)
F(1A)-C(8)-C(7)	114.4(5)

F(2)-C(8)-C(7)	108.4(5)
F(2A)-C(8)-F(1A)	105.8(9)
F(2A)-C(8)-F(3A)	108.2(7)
F(2A)-C(8)-C(7)	115.5(7)
F(3)-C(8)-F(2)	102.6(5)
F(3)-C(8)-C(7)	113.2(4)
F(3A)-C(8)-C(7)	110.6(5)
C(3)-C(9)-H(9)	119.3
C(7)-C(9)-C(3)	121.3(2)
C(7)-C(9)-H(9)	119.3
N(3)-C(10)-H(10A)	109.6
N(3)-C(10)-H(10B)	109.6
N(3)-C(10)-C(11)	110.19(17)
H(10A)-C(10)-H(10B)	108.1
C(11)-C(10)-H(10A)	109.6
C(11)-C(10)-H(10B)	109.6
N(4)-C(11)-C(10)	111.31(19)
N(4)-C(11)-H(11A)	109.4
N(4)-C(11)-H(11B)	109.4
C(10)-C(11)-H(11A)	109.4
C(10)-C(11)-H(11B)	109.4
H(11A)-C(11)-H(11B)	108.0
N(4)-C(12)-H(12A)	109.5
N(4)-C(12)-H(12B)	109.5
N(4)-C(12)-C(13)	110.69(18)
H(12A)-C(12)-H(12B)	108.1
C(13)-C(12)-H(12A)	109.5
C(13)-C(12)-H(12B)	109.5
N(3)-C(13)-C(12)	110.48(19)
N(3)-C(13)-H(13A)	109.6
N(3)-C(13)-H(13B)	109.6
C(12)-C(13)-H(13A)	109.6
C(12)-C(13)-H(13B)	109.6
H(13A)-C(13)-H(13B)	108.1
N(4)-C(14)-H(14A)	108.8
N(4)-C(14)-H(14B)	108.8

N(4)-C(14)-C(15)	113.72(17)
H(14A)-C(14)-H(14B)	107.7
C(15)-C(14)-H(14A)	108.8
C(15)-C(14)-H(14B)	108.8
C(14)-C(15)-H(15)	107.9
C(16)-C(15)-C(14)	111.66(18)
C(16)-C(15)-H(15)	107.9
C(16)-C(15)-C(20)	110.74(19)
C(20)-C(15)-C(14)	110.58(18)
C(20)-C(15)-H(15)	107.9
C(15)-C(16)-H(16A)	109.1
C(15)-C(16)-H(16B)	109.1
C(15)-C(16)-C(17)	112.4(2)
H(16A)-C(16)-H(16B)	107.9
C(17)-C(16)-H(16A)	109.1
C(17)-C(16)-H(16B)	109.1
C(16)-C(17)-H(17A)	109.1
C(16)-C(17)-H(17B)	109.1
H(17A)-C(17)-H(17B)	107.8
C(18)-C(17)-C(16)	112.6(2)
C(18)-C(17)-H(17A)	109.1
C(18)-C(17)-H(17B)	109.1
C(17)-C(18)-H(18A)	109.3
C(17)-C(18)-H(18B)	109.3
H(18A)-C(18)-H(18B)	108.0
C(19)-C(18)-C(17)	111.5(2)
C(19)-C(18)-H(18A)	109.3
C(19)-C(18)-H(18B)	109.3
C(18)-C(19)-H(19A)	109.2
C(18)-C(19)-H(19B)	109.2
C(18)-C(19)-C(20)	111.9(2)
H(19A)-C(19)-H(19B)	107.9
C(20)-C(19)-H(19A)	109.2
C(20)-C(19)-H(19B)	109.2
C(15)-C(20)-H(20A)	109.0
C(15)-C(20)-H(20B)	109.0

C(19)-C(20)-C(15)	113.1(2)
C(19)-C(20)-H(20A)	109.0
C(19)-C(20)-H(20B)	109.0
H(20A)-C(20)-H(20B)	107.8

Table S3. Torsion angles [°] for Macozinone.

Atoms are numbered according to atomic site occupancy.

S(1)-C(4)-C(5)-N(2)	0.2(3)
S(1)-C(4)-C(5)-C(6)	-177.98(16)
O(1)-C(2)-C(3)-C(4)	-174.1(2)
O(1)-C(2)-C(3)-C(9)	6.2(3)
O(2)-N(2)-C(5)-C(4)	1.0(11)
O(2)-N(2)-C(5)-C(6)	179.3(11)
O(3)-N(2)-C(5)-C(4)	-170.4(7)
O(3)-N(2)-C(5)-C(6)	7.9(8)
N(1)-C(2)-C(3)-C(4)	5.9(3)
N(1)-C(2)-C(3)-C(9)	-173.8(2)
N(2)-C(5)-C(6)-C(7)	-179.0(2)
N(3)-C(10)-C(11)-N(4)	56.2(3)
N(4)-C(12)-C(13)-N(3)	-56.6(3)
N(4)-C(14)-C(15)-C(16)	-61.0(3)
N(4)-C(14)-C(15)-C(20)	175.2(2)
C(1)-S(1)-C(4)-C(3)	-2.88(19)
C(1)-S(1)-C(4)-C(5)	177.31(17)
C(1)-N(1)-C(2)-O(1)	174.7(2)
C(1)-N(1)-C(2)-C(3)	-5.3(3)
C(1)-N(3)-C(10)-C(11)	135.4(2)
C(1)-N(3)-C(13)-C(12)	-135.5(2)
C(2)-N(1)-C(1)-S(1)	0.1(3)
C(2)-N(1)-C(1)-N(3)	-178.6(2)
C(2)-C(3)-C(4)-S(1)	-1.2(3)
C(2)-C(3)-C(4)-C(5)	178.66(19)
C(2)-C(3)-C(9)-C(7)	179.5(2)
C(3)-C(4)-C(5)-N(2)	-179.62(18)

C(3)-C(4)-C(5)-C(6)	2.2(3)
C(4)-S(1)-C(1)-N(1)	3.8(2)
C(4)-S(1)-C(1)-N(3)	-177.46(16)
C(4)-C(3)-C(9)-C(7)	-0.2(3)
C(4)-C(5)-C(6)-C(7)	-0.8(3)
C(5)-C(6)-C(7)-C(8)	175.8(2)
C(5)-C(6)-C(7)-C(9)	-1.2(3)
C(6)-C(7)-C(8)-F(1)	145.3(9)
C(6)-C(7)-C(8)-F(1A)	169.7(10)
C(6)-C(7)-C(8)-F(2)	-94.5(8)
C(6)-C(7)-C(8)-F(2A)	-67.1(12)
C(6)-C(7)-C(8)-F(3)	18.7(9)
C(6)-C(7)-C(8)-F(3A)	56.3(13)
C(6)-C(7)-C(9)-C(3)	1.7(3)
C(8)-C(7)-C(9)-C(3)	-175.3(2)
C(9)-C(3)-C(4)-S(1)	178.49(16)
C(9)-C(3)-C(4)-C(5)	-1.7(3)
C(9)-C(7)-C(8)-F(1)	-37.8(9)
C(9)-C(7)-C(8)-F(1A)	-13.4(11)
C(9)-C(7)-C(8)-F(2)	82.5(9)
C(9)-C(7)-C(8)-F(2A)	109.9(12)
C(9)-C(7)-C(8)-F(3)	-164.3(8)
C(9)-C(7)-C(8)-F(3A)	-126.7(13)
C(10)-N(3)-C(1)-S(1)	173.83(17)
C(10)-N(3)-C(1)-N(1)	-7.3(3)
C(10)-N(3)-C(13)-C(12)	51.9(3)
C(11)-N(4)-C(12)-C(13)	61.2(2)
C(11)-N(4)-C(14)-C(15)	-73.9(2)
C(12)-N(4)-C(11)-C(10)	-61.4(2)
C(12)-N(4)-C(14)-C(15)	164.3(2)
C(13)-N(3)-C(1)-S(1)	1.8(3)
C(13)-N(3)-C(1)-N(1)	-179.3(2)
C(13)-N(3)-C(10)-C(11)	-51.6(3)
C(14)-N(4)-C(11)-C(10)	175.31(17)
C(14)-N(4)-C(12)-C(13)	-175.5(2)
C(14)-C(15)-C(16)-C(17)	-175.9(2)

C(14)-C(15)-C(20)-C(19)	177.0(2)
C(15)-C(16)-C(17)-C(18)	53.5(3)
C(16)-C(15)-C(20)-C(19)	52.7(3)
C(16)-C(17)-C(18)-C(19)	-53.5(4)
C(17)-C(18)-C(19)-C(20)	53.2(3)
C(18)-C(19)-C(20)-C(15)	-53.7(3)
C(20)-C(15)-C(16)-C(17)	-52.2(3)
O(3A)-N(2)-C(5)-C(4)	163.6(6)
O(3A)-N(2)-C(5)-C(6)	-18.1(7)
O(2A)-N(2)-C(5)-C(4)	-7.0(11)
O(2A)-N(2)-C(5)-C(6)	171.2(11)

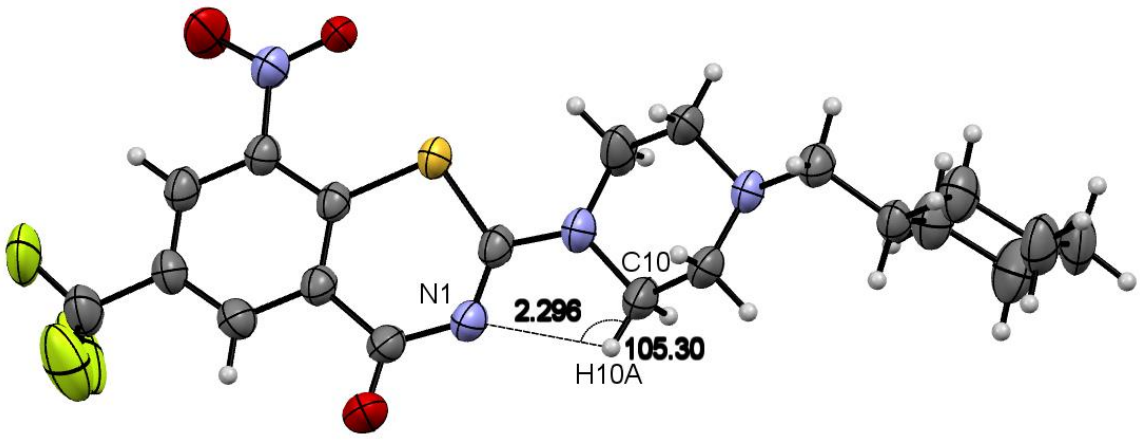


Fig.S1 Strong intramolecular hydrogen-bond for macozinone.

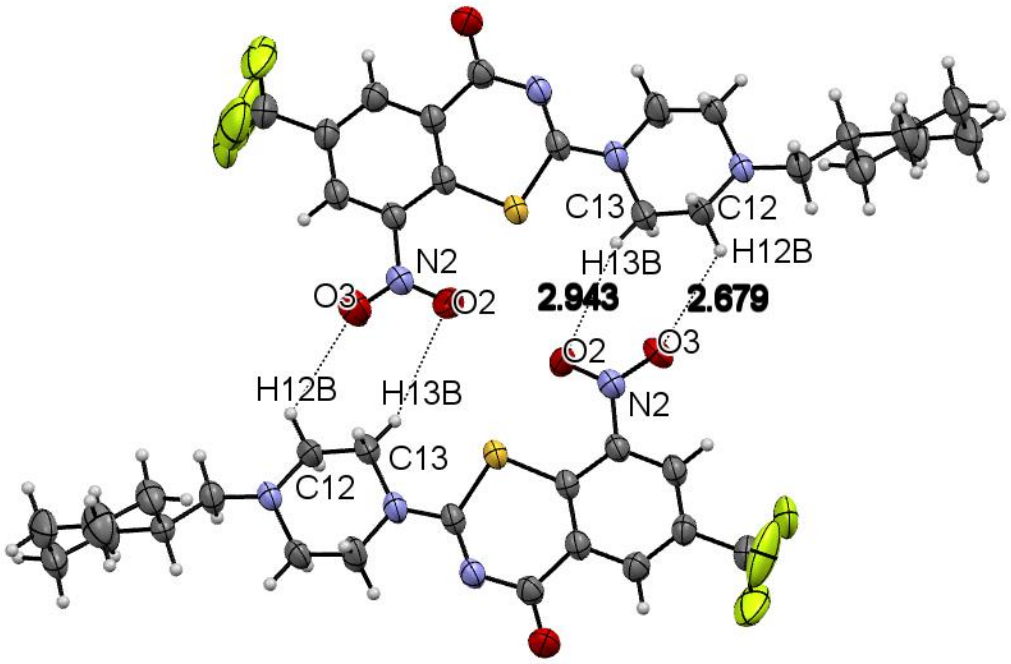
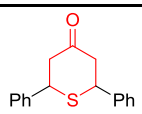
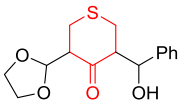
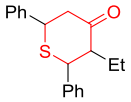
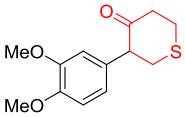


Fig.S2 The antiparallel intermolecular hydrogen-bond for macozinone.

Table S4 Ten available crystal compounds with the most similar structures

Compounds	Structures	References
1		Source: *Acta Crystallogr. C,* **2003**, *59*, (11), o620-o621. Deposition: IUCr DE1222
2		Source: *Tetrahedron,* **2003**, *59*, (9), 1421-1427. Deposition: CCDC 196852
3		Source: *J. Org. Chem.,* **1979**, *44*, (4), 477-486. Deposition: -
4		Source: *Eur. J. Org. Chem.,* **2006**, *2006*, (17), 4044-4054. Deposition: CCDC 605912

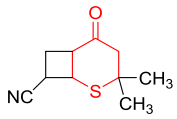
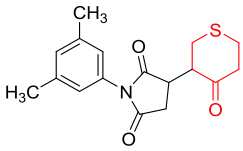
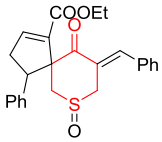
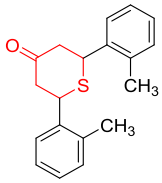
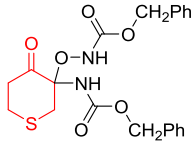
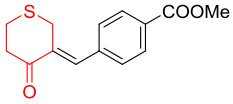
5		Source: *Helv. Chim. Acta,* **2005**, *88*, (7), 1922-1930. Deposition: CCDC 260927
6		Source: *Synlett,* **2011**, *2011*, (04), 473-476. Deposition: CCDC 664491
7		Source: *Adv. Synth. Catal.,* **2012**, *354*, (2-3), 408-414. Deposition: CCDC 834028
8		Source: *Eur. J. Org. Chem.,* **2015**, *2015*, (8), 1790-1796. Deposition: CCDC 1031022
9		Source: *Org. Lett.,* **2015**, *17*, (17), 4392-4395. Deposition: CCDC 1422387
10		Source: *Synthesis,* **2011**, *2011*, (23), 3821-3826. Deposition: CCDC 846075

Table S5 The selected crystal data of the bond lengths, bond angles and torsion angles of the title and control compounds.

Bond, Å/Angle, °	1	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
C1-S1	1.78(3)	1.79(5)	1.79(4)	1.81(10)	1.77(15)	1.78(6)	1.78(7)	1.78(9)	1.77(10)	1.79(3)	1.78(6)
C4-S1	1.74(2)	1.81(8)	1.80(2)	1.79(6)	1.80(5)	1.79(2)	1.81(8)	1.80(5)	1.78(4)	1.79(5)	1.80(4)
C1- S1-C4	100.66(6)	97.02(2)	98.13(4)	97.71(12)	99.40(2)	99.77(8)	98.44(4)	97.01(2)	98.65(7)	98.25(8)	99.30(10)

* The thiopyran-4-one fragments in control compounds have the same label numbers to the counterpart in Macozinone.

Table S6 Comparison of Angles between small-molecule crystal and NO-Macozinone from co-crystal

Angles	Small-molecule crystal	NO-Macozinone from co-crystal
The planes defined by BTZ core and C10/C11/C12/C13	38.56	66.51
The planes defined by N3/C10/C13 and C10/C11/C12/C13	47.25	65.50
The planes defined by N4/C11/C12 and C10/C11/C12/C13	55.00	27.02

Reference

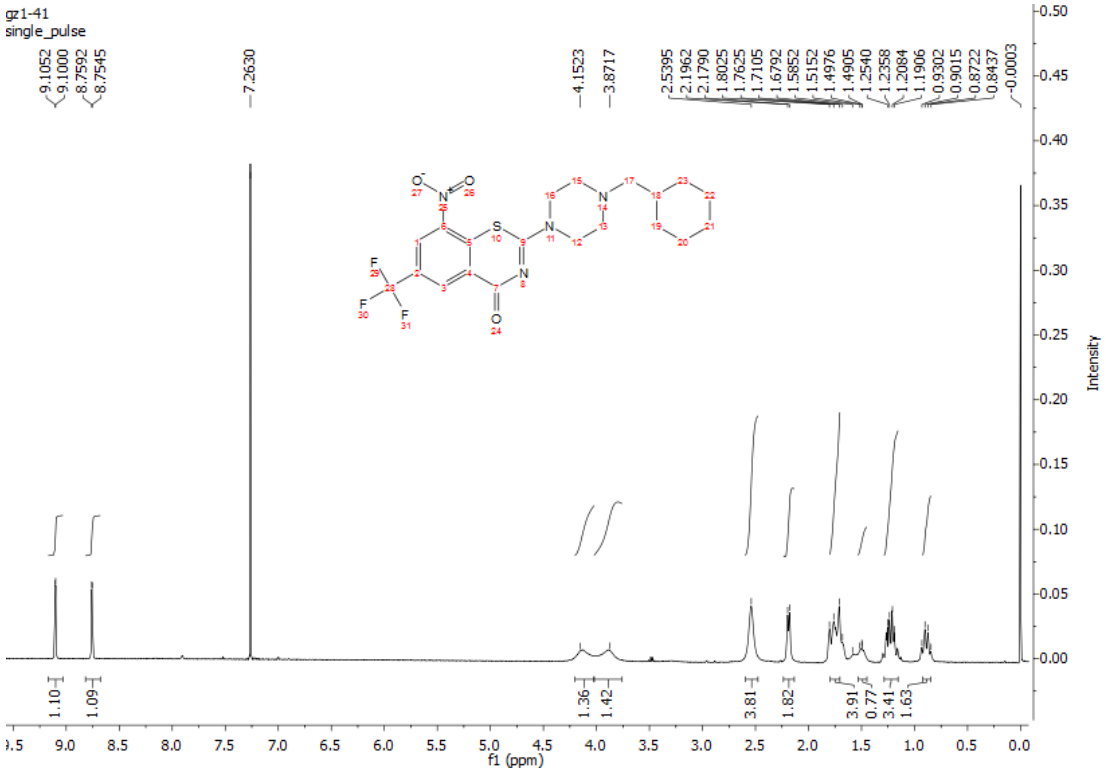
Sheldrick, G. M, *Acta Cryst.* **2015a**, A71, 3–8.

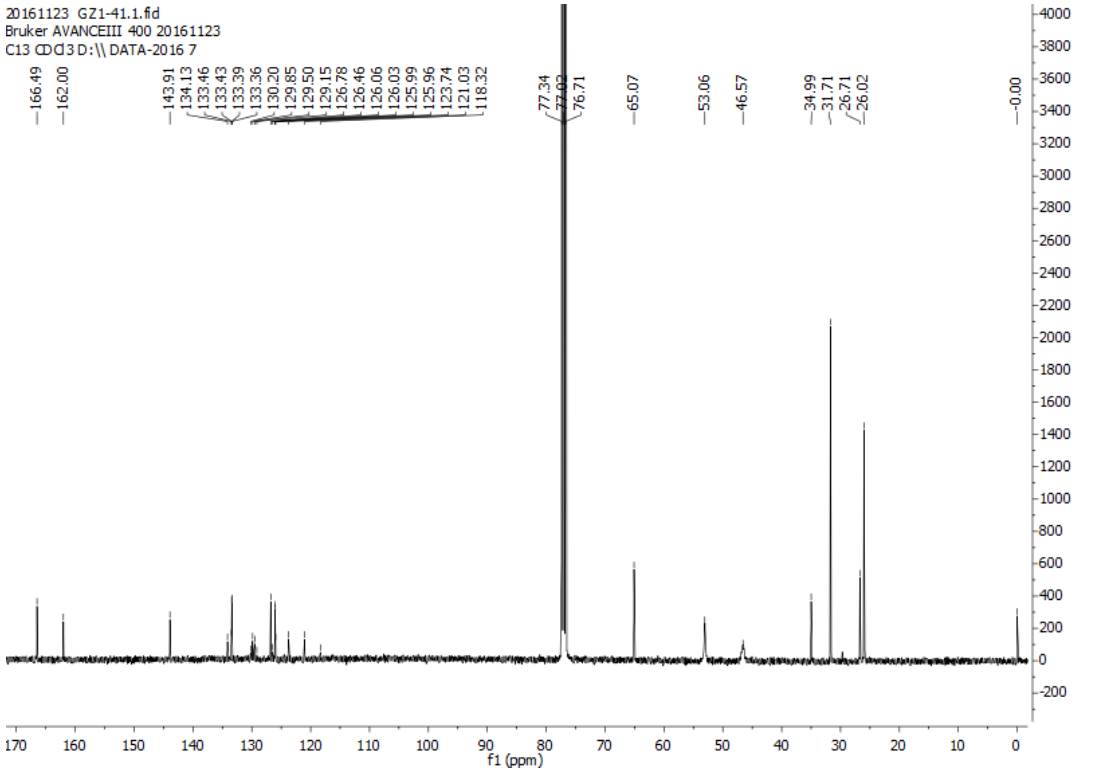
Sheldrick, G. M, *Acta Cryst.* **2015b**, C71, 3–8

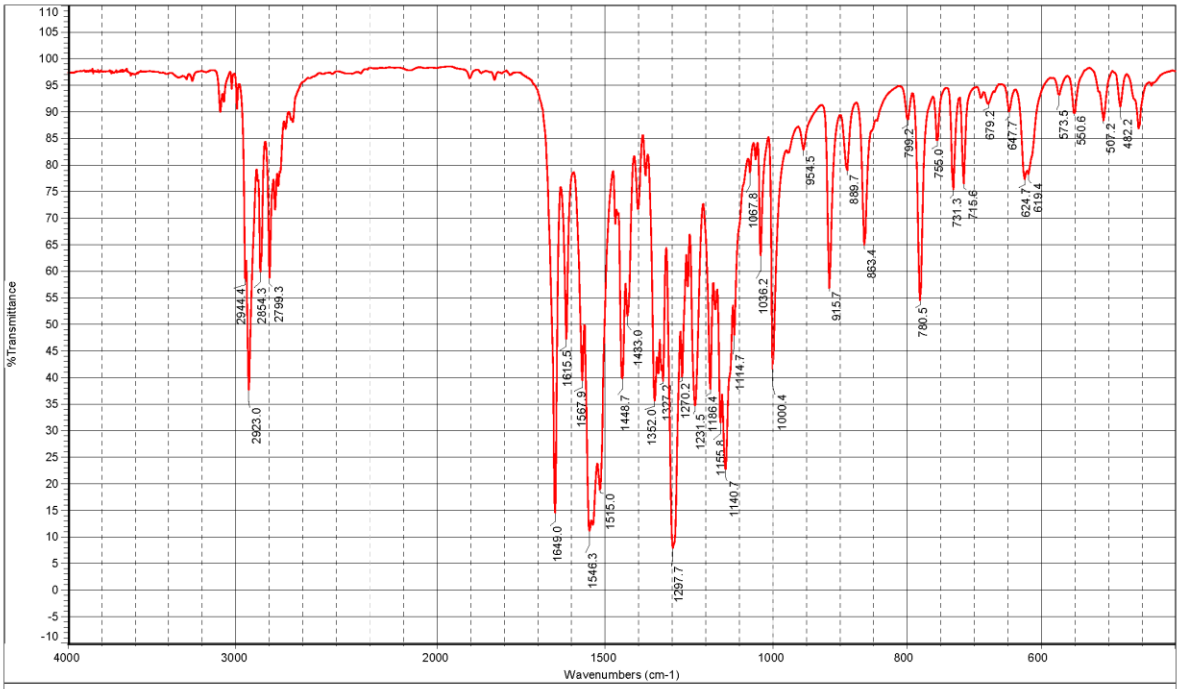
Groom, C. R., Bruno, I. J., Lightfoot, M. P. & Ward, S. C. (2016). *Acta Cryst*. B72, 171–179.

Bruker (**2000**). SMART, SAINT, SADABS and SHELXTL. Bruker ACS Inc., Madison, Wisconsin, USA.

NMR and IR Spectra






%Transmittance
Wavenumbers (cm-1)
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2799.3
2923.0
1615.5
1587.9
1649.0
1546.3
1515.0
1448.7
1433.0
1352.0
1337.2
1297.7
1270.2
1231.5
1188.4
1155.8
1140.7
1114.7
1067.8
1036.2
1000.4
954.5
915.7
889.7
863.4
799.2
780.5
755.0
731.3
715.6
679.2
647.7
624.7
619.4
573.5
560.6
507.2
482.2
日期: 星期三 5月 23 10:23:54 2018 (GMT+08:00) Sample Name： PBTZ 169
(KBr 压片法)
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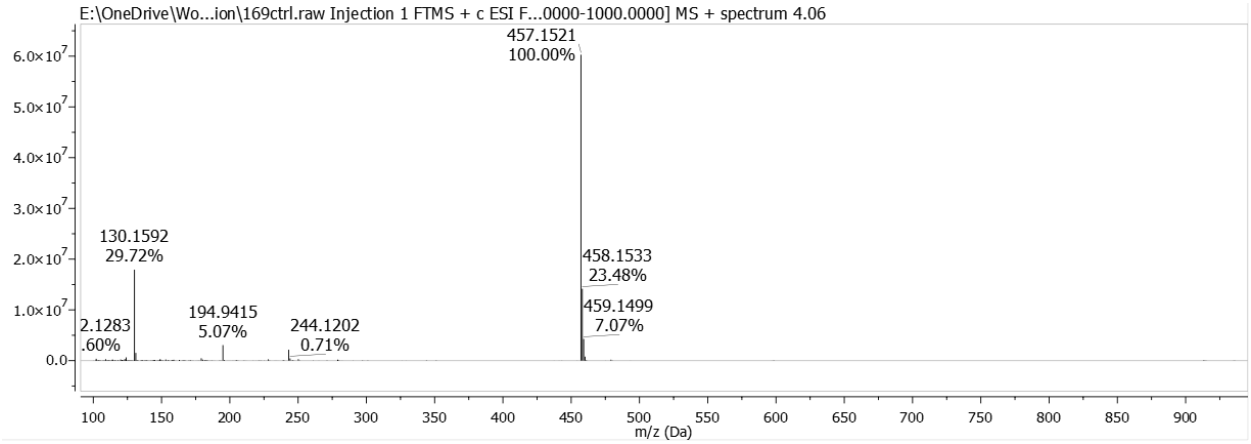
美国热电公司(Thermo)傅立叶变换红外光谱仪:Nicolet 5700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100.00%
130.1592
29.72%
458.1533
23.48%
459.1499
7.07%
194.9415
5.07%
244.1202
0.71%
2.1283
.60%
m/z (Da)