Efficient electrocatalytic approach to spiro[furo[3,2-*b*]pyran-2,5'-pyrimidine scaffold as inhibitor of aldose reductase

Michail N. Elinson[1,] *, Anatoly N. Vereshchagin[1], Yuliya E. Ryzhkova[1], Fedor V. Ryzhkov[1], Artem N. Fakhrutdinov[1] and Mikhail P. Egorov[1]

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 690041 Moscow, Russia; anatoly103@yandex.ru (A.N.V.); julia4912@mail.ru (Y.E.R.); ryzhkov.fe@ya.ru (F.V.R.); fart@ioc.ac.ru (A.N.F.); mpe@ioc.ac.ru (M.P.E.)

* Correspondence: elinson@ioc.ac.ru; Tel.: +7-499-137-28-42

Supporting Information

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1. ^{1}H and ^{13}C Spectra of Compounds

5-(Hydroxymethyl)-1',3'-dimethyl-3-phenyl-2'H-spiro[furo[3,2-b]pyran-2,5'-pyrimidine]-2',4',6',7(1'H,3H,3'H)-tetraone 2a

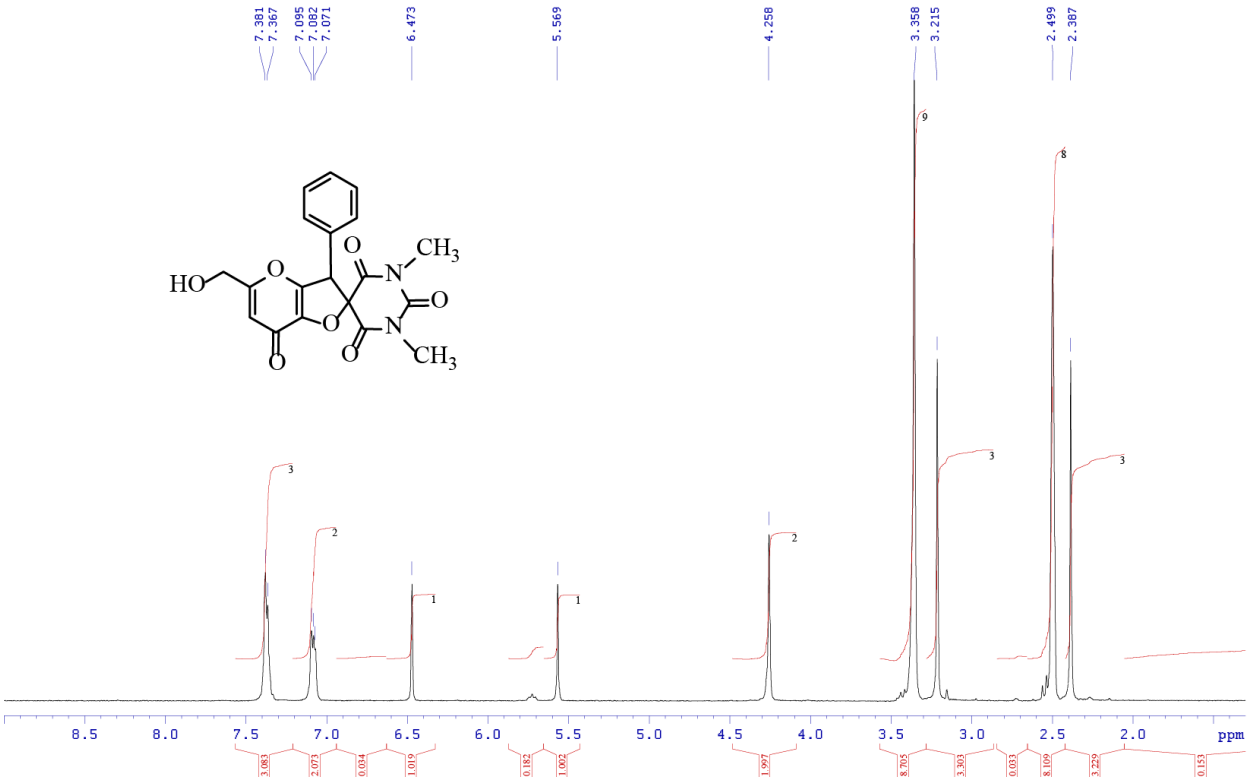

Figure S1. Compound **2a.**

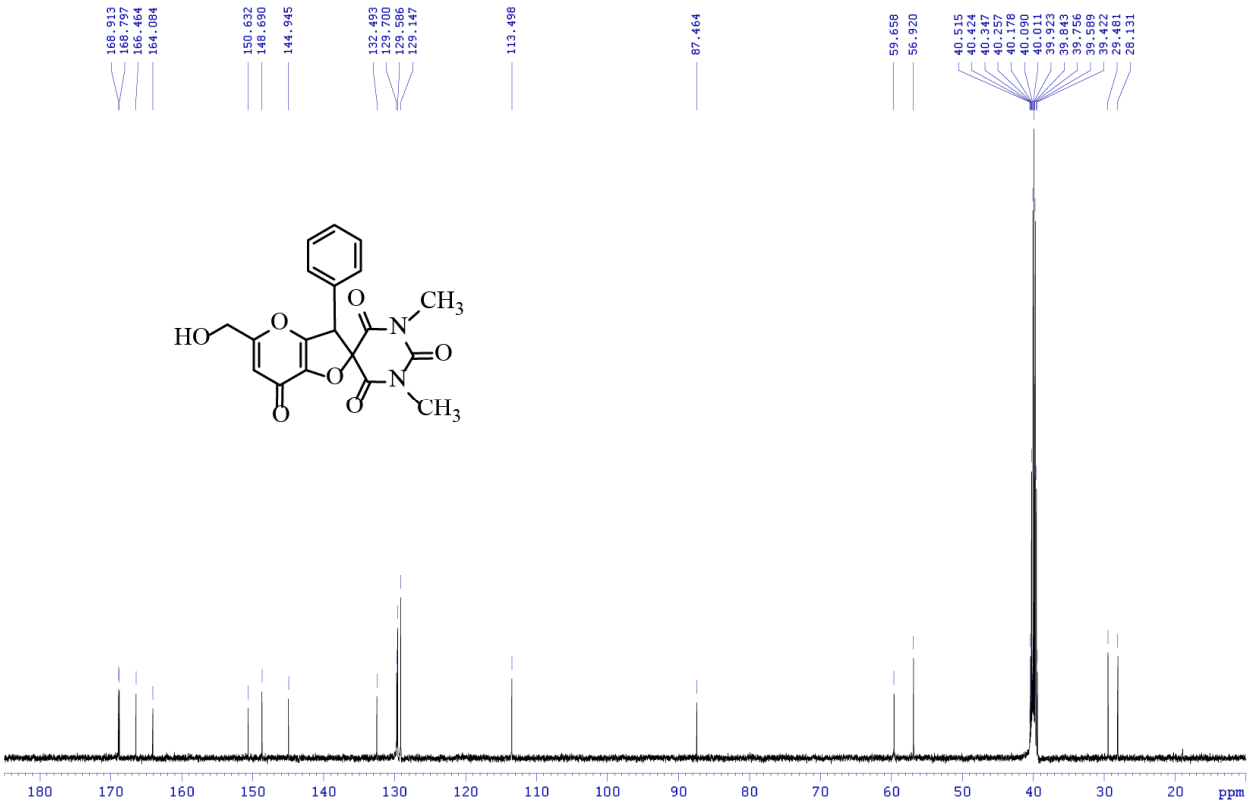

Figure S2. Compound **2a.**

5-(Hydroxymethyl)-3-(2-hydroxyphenyl)-1',3'-dimethyl-2'H-spiro[furo[3,2-b]pyran-2,5'-pyrimidine]-2',4',6',7(1'H,3H,3'H)-tetraone 2b

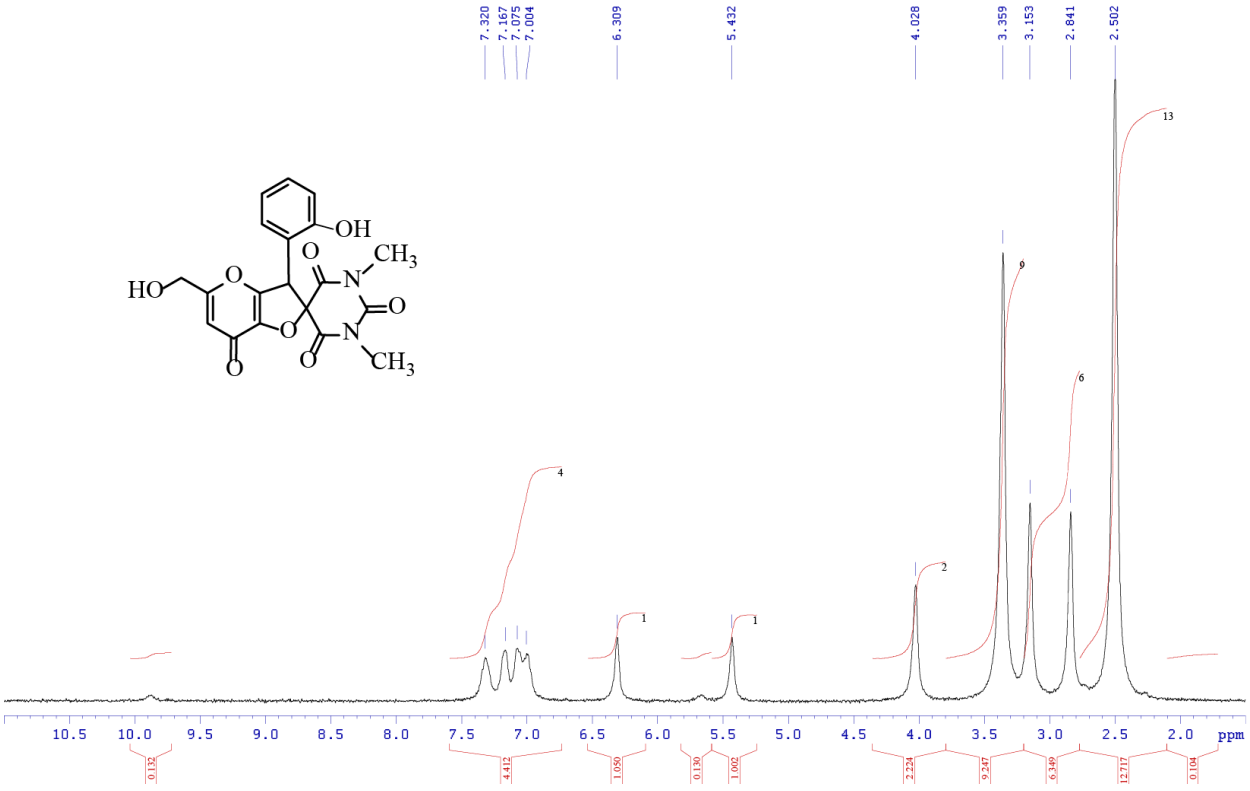

Figure S3. Compound **2b.**

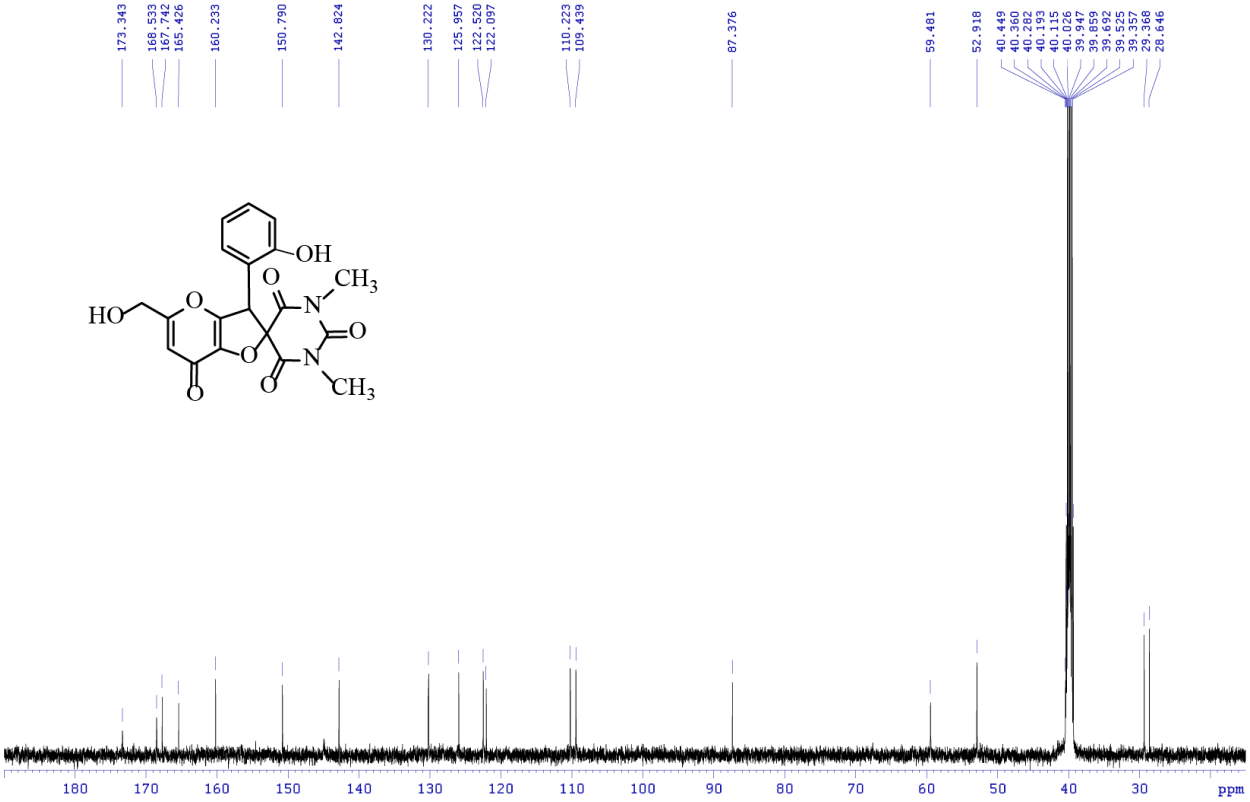

Figure S4. Compound **2b.**

5-(Hydroxymethyl)-3-(4-methoxyphenyl)-1',3'-dimethyl-2'H-spiro[furo[3,2-b]pyran-2,5'-pyrimidine]-2',4',6',7(1'H,3H,3'H)-tetraone 2c

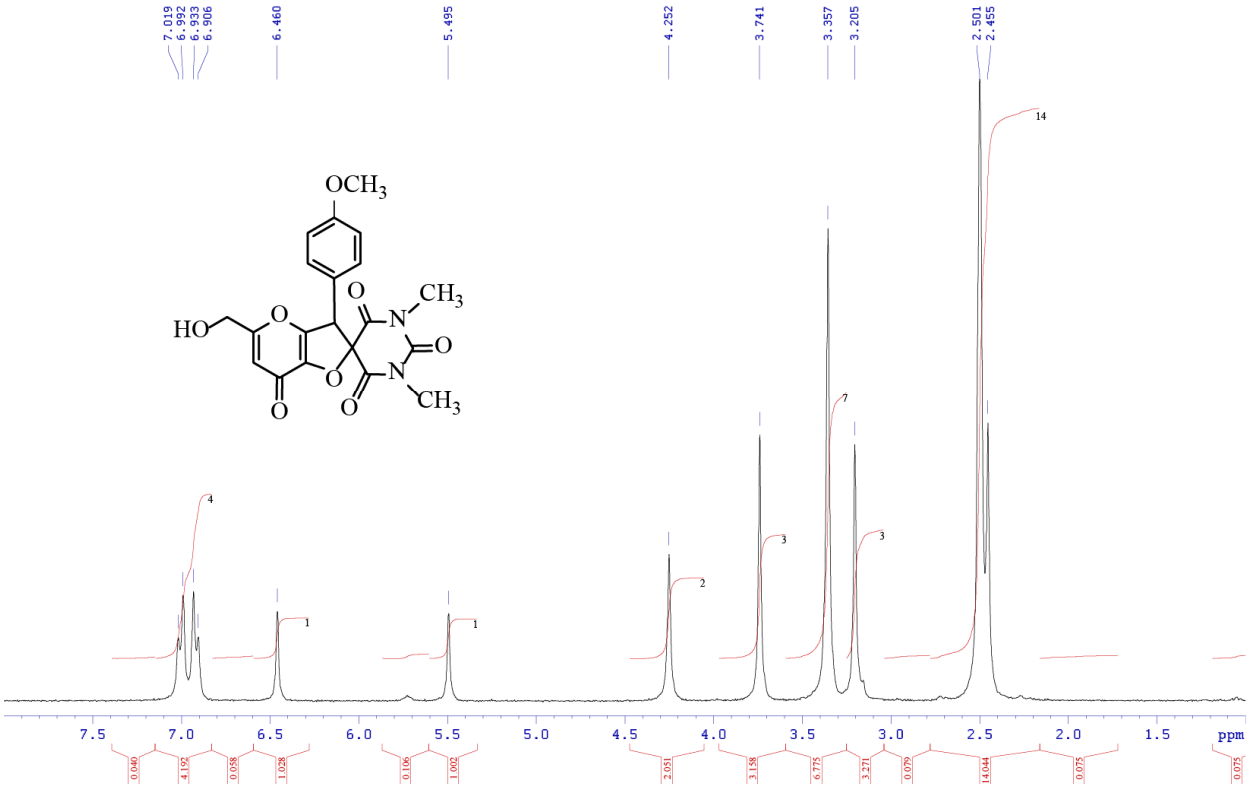

Figure S5. Compound **2c.**

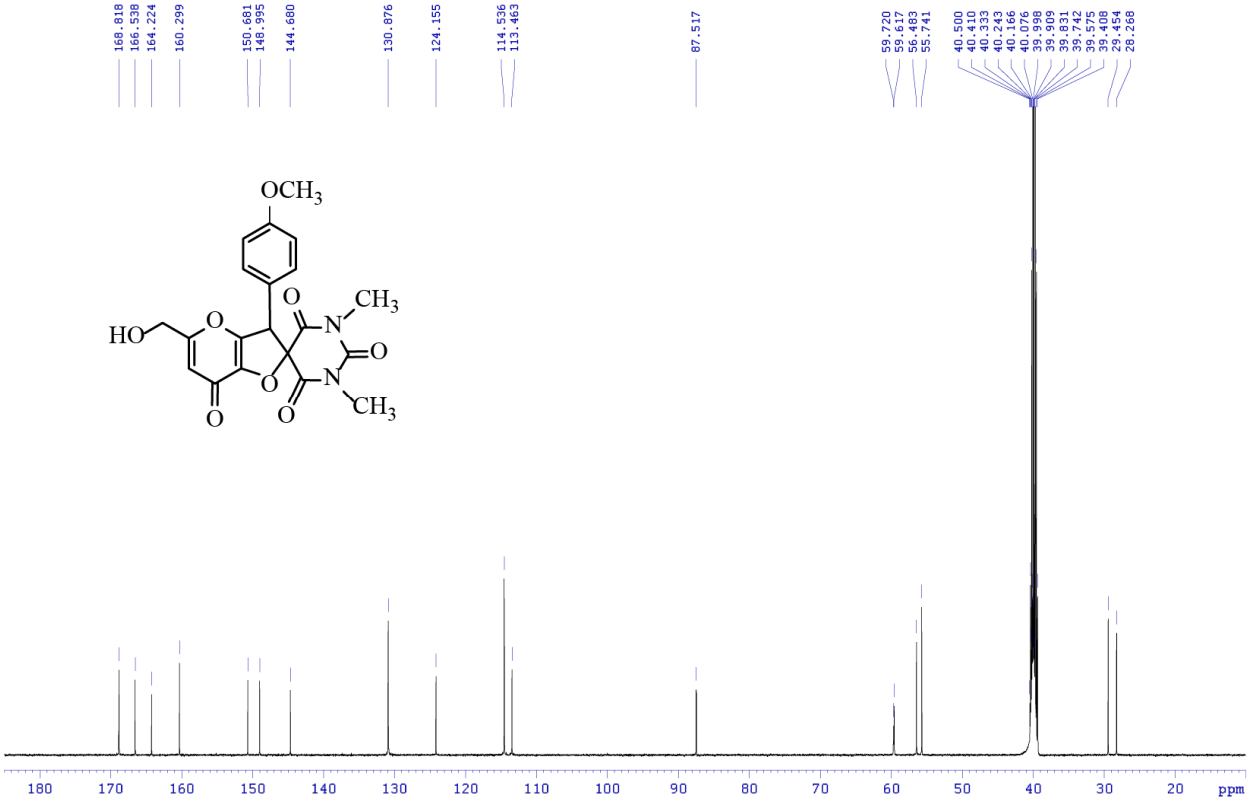

Figure S6. Compound **2c.**

5-(Hydroxymethyl)-1',3'-dimethyl-3-(p-tolyl)-2'H-spiro[furo[3,2-b]pyran-2,5'-pyrimidine]-2',4',6',7(1'H,3H,3'H)-tetraone 2d

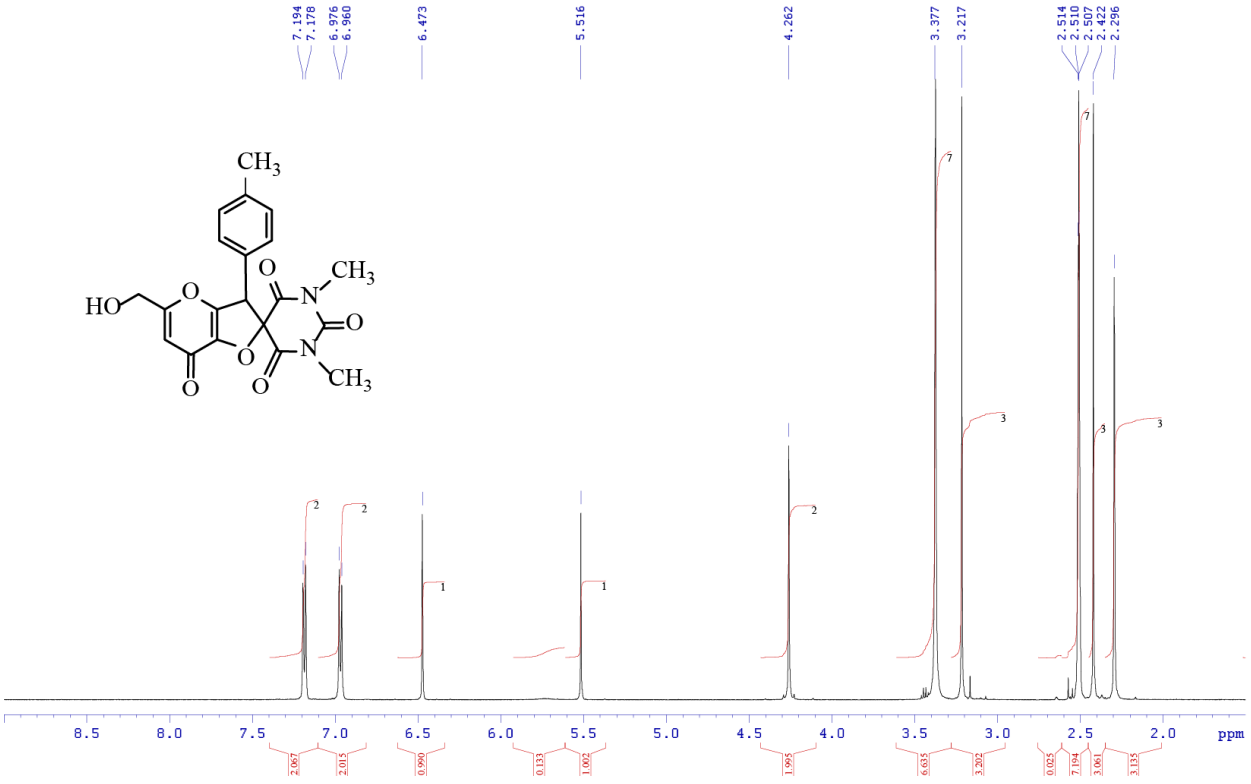

Figure S7. Compound **2d.**

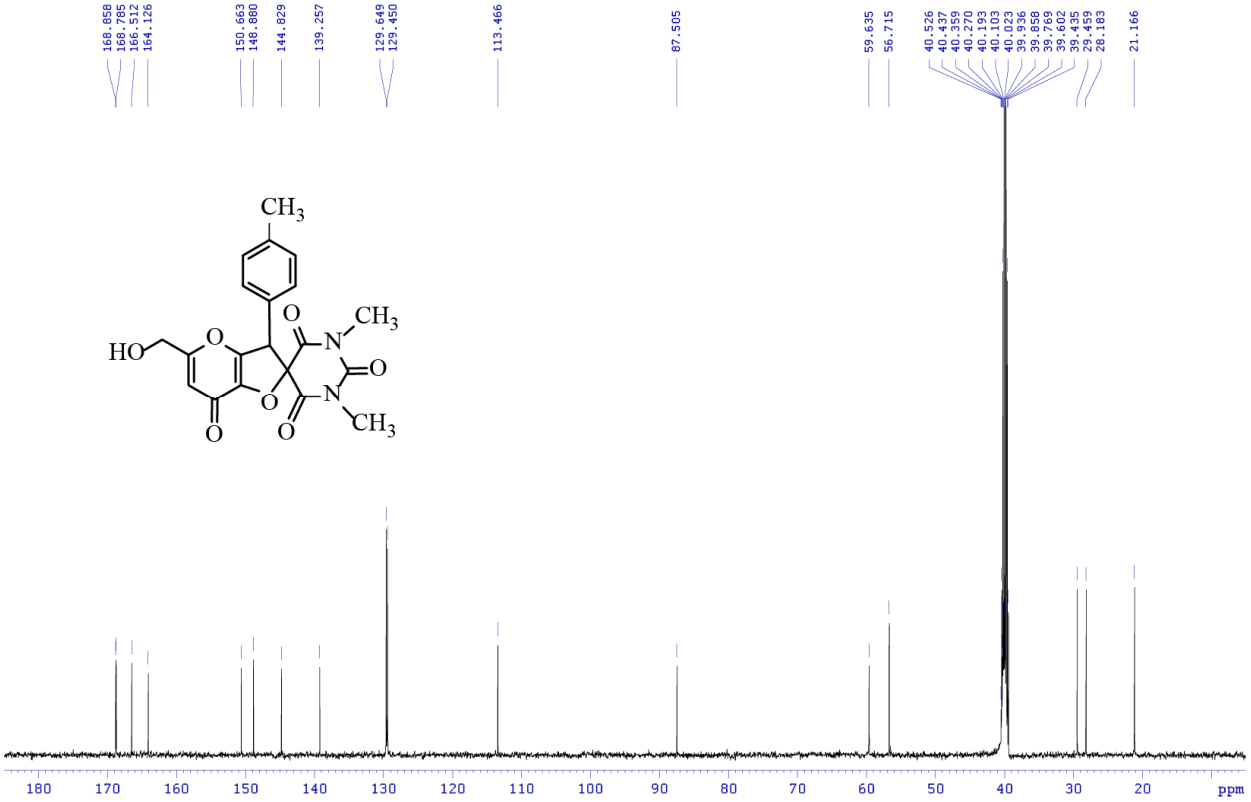

Figure S8. Compound **2d.**

3-(4-Ethylphenyl)-5-(hydroxymethyl)-1',3'-dimethyl-2'H-spiro[furo[3,2-b]pyran-2,5'-pyrimidine]-2',4',6',7(1'H,3H,3'H)-tetraone 2e

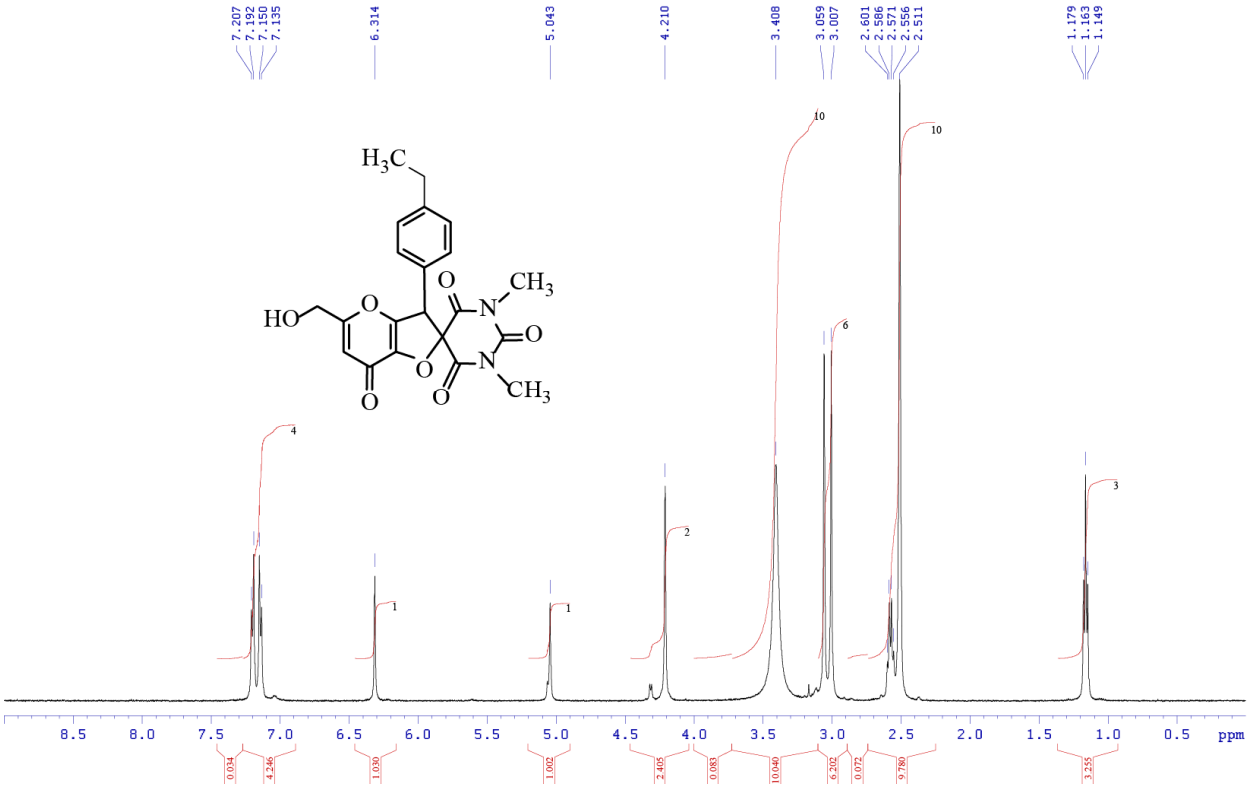

Figure S9. Compound **2e.**

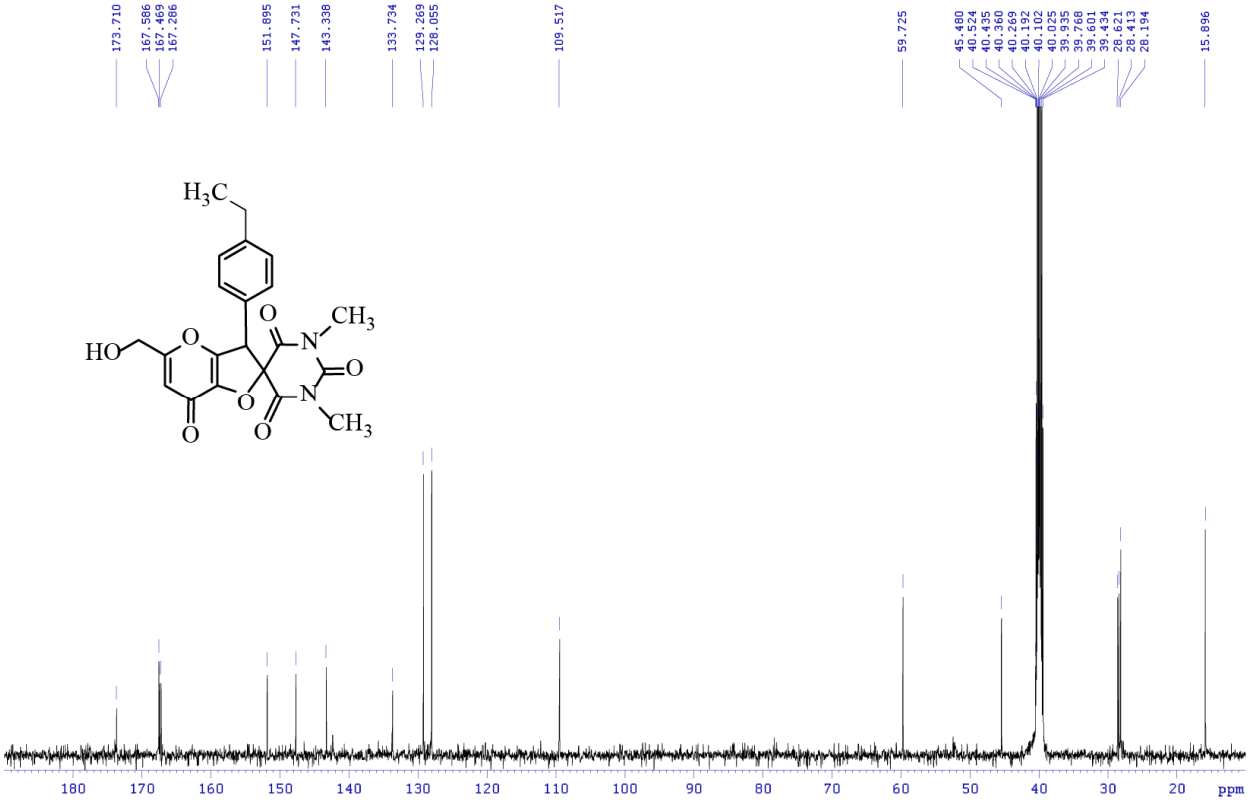

Figure S10. Compound **2e.**

3-(4-Chlorophenyl)-5-(hydroxymethyl)-1',3'-dimethyl-2'H-spiro[furo[3,2-b]pyran-2,5'-pyrimidine]-2',4',6',7(1'H,3H,3'H)-tetraone 2f

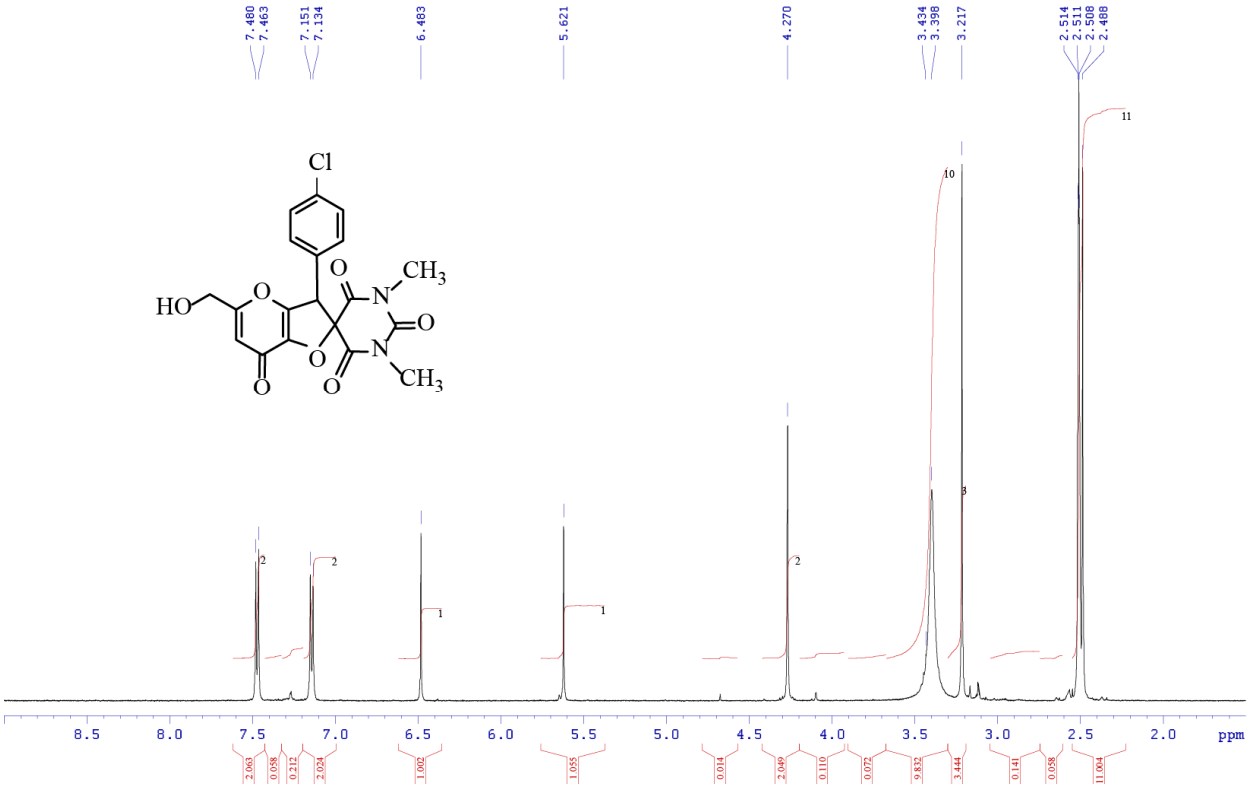

Figure S11. Compound **2f.**

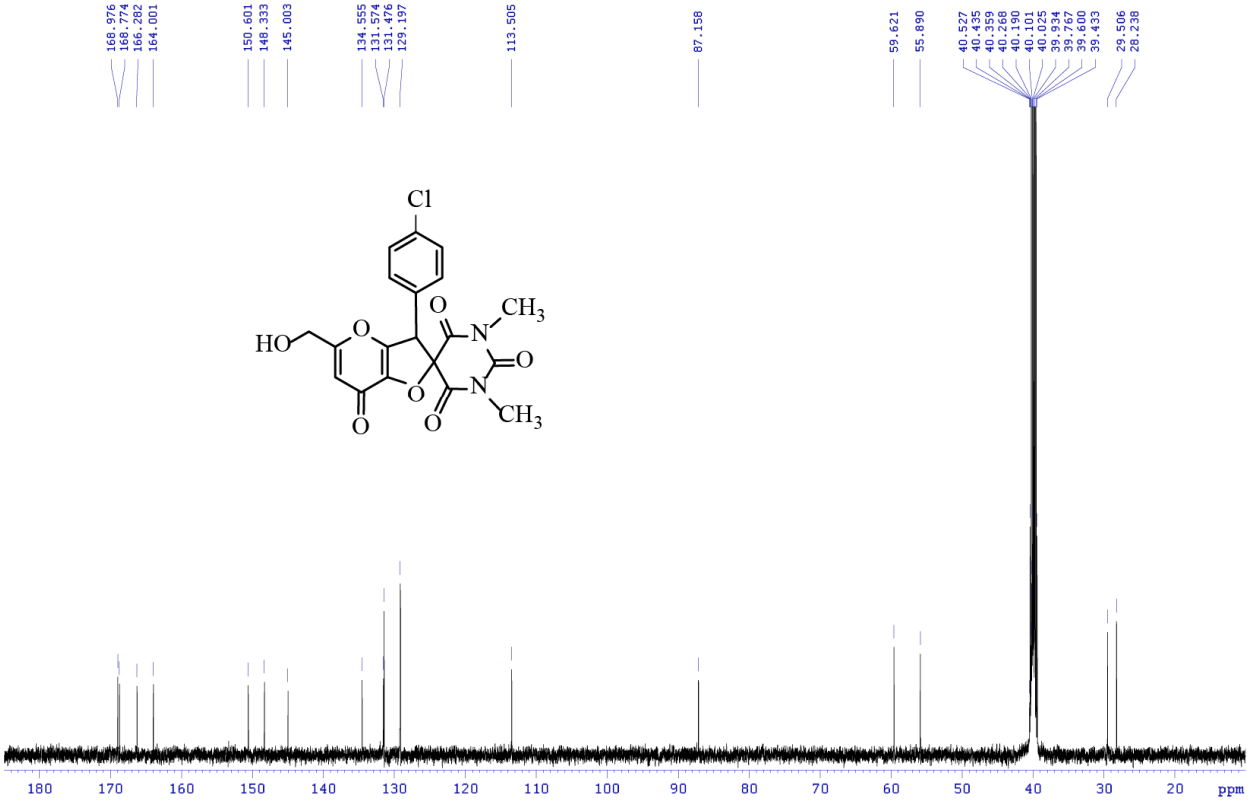

Figure S12. Compound **2f.**

3-(3-Bromophenyl)-5-(hydroxymethyl)-1',3'-dimethyl-2'H-spiro[furo[3,2-b]pyran-2,5'-pyrimidine]-2',4',6',7(1'H,3H,3'H)-tetraone 2g

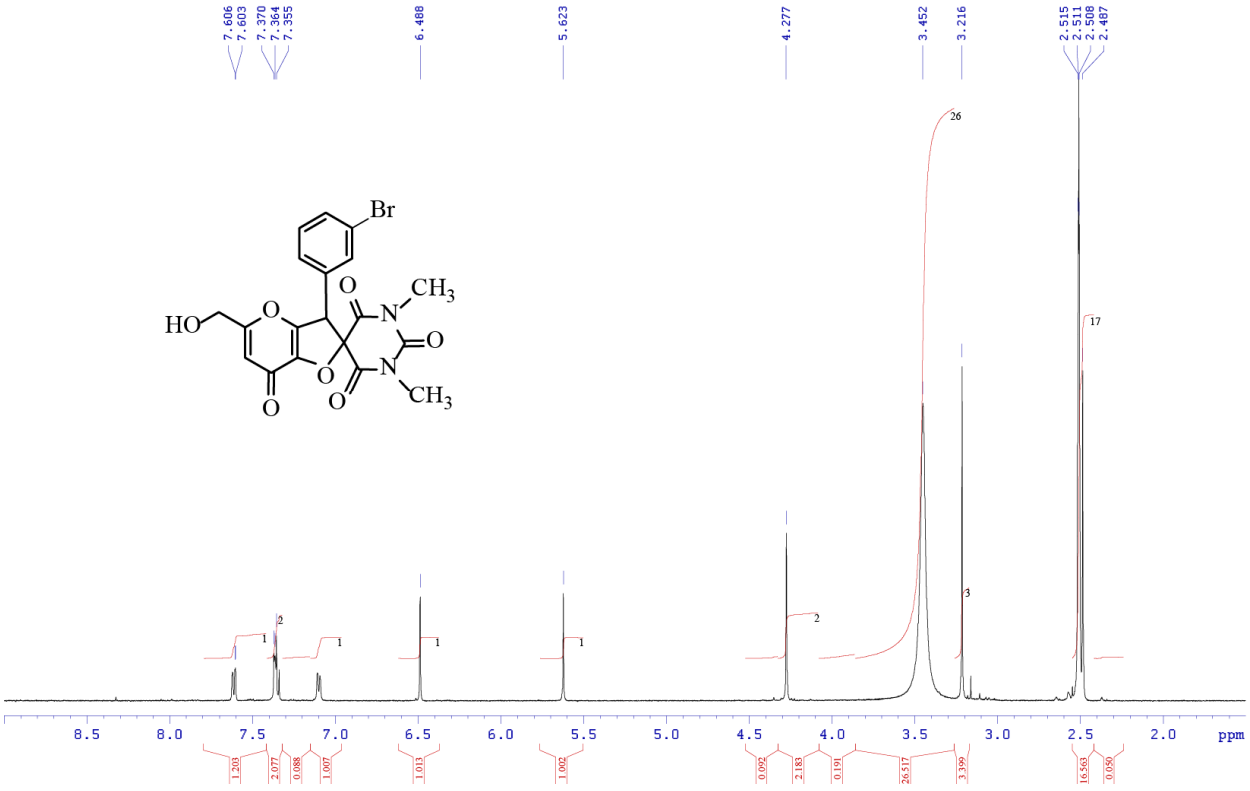

Figure S13. Compound **2g.**

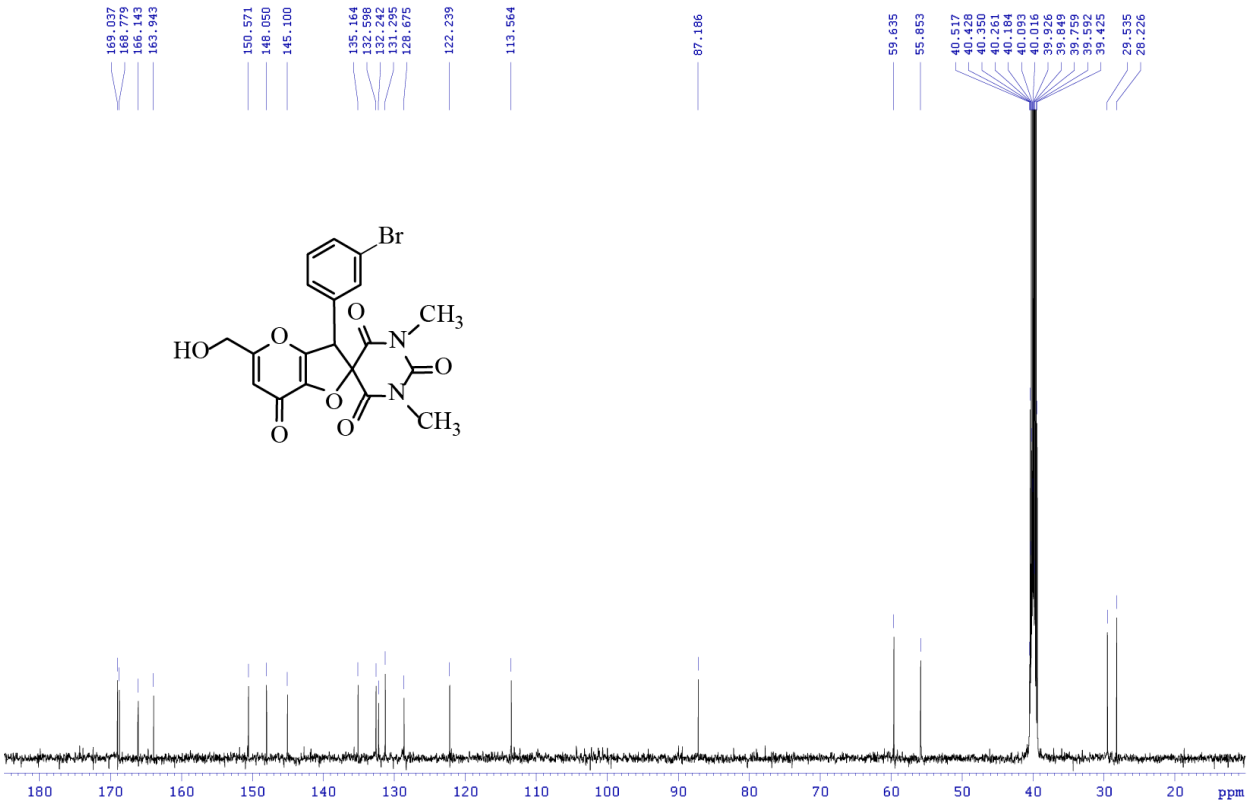

Figure S14. Compound **2g.**

5-(Hydroxymethyl)-1',3'-dimethyl-3-(4-nitrophenyl)-2'H-spiro[furo[3,2-b]pyran-2,5'-pyrimidine]-2',4',6',7(1'H,3H,3'H)-tetraone 2h

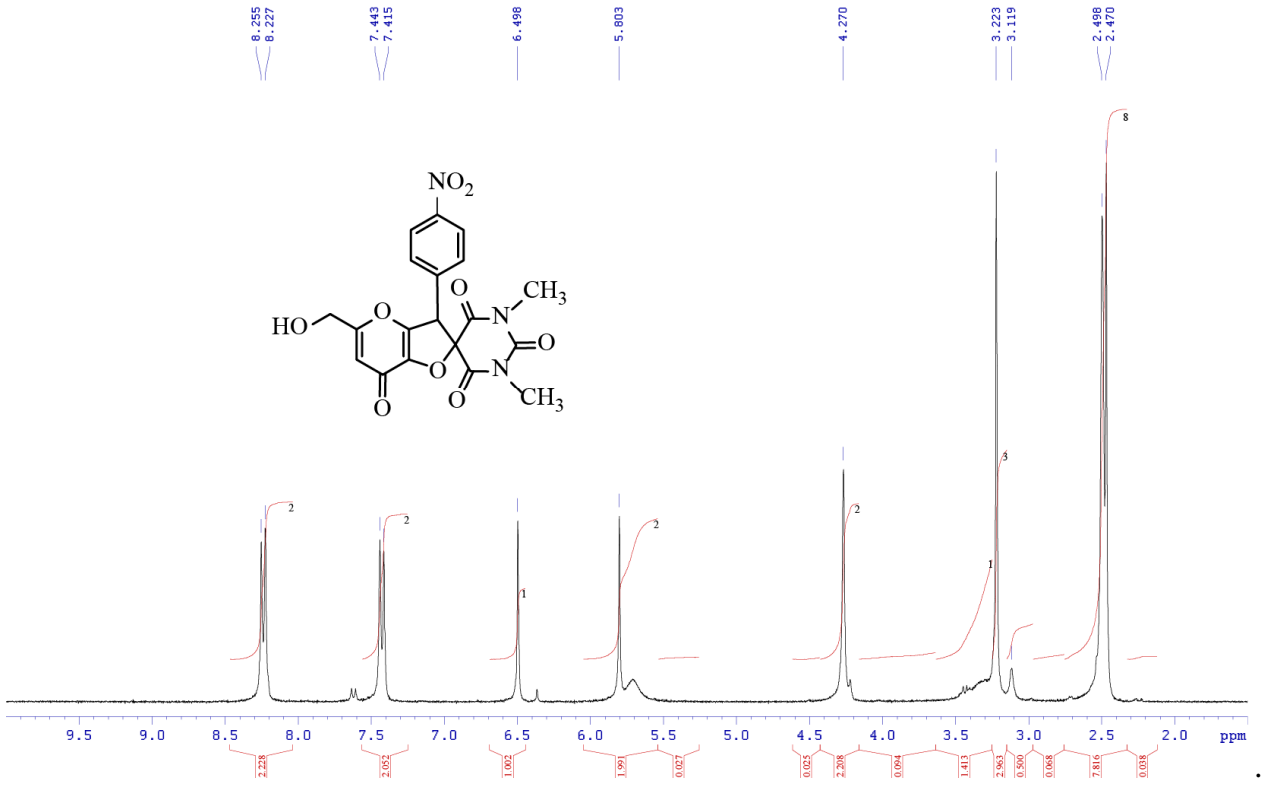

Figure S15. Compound **2h.**

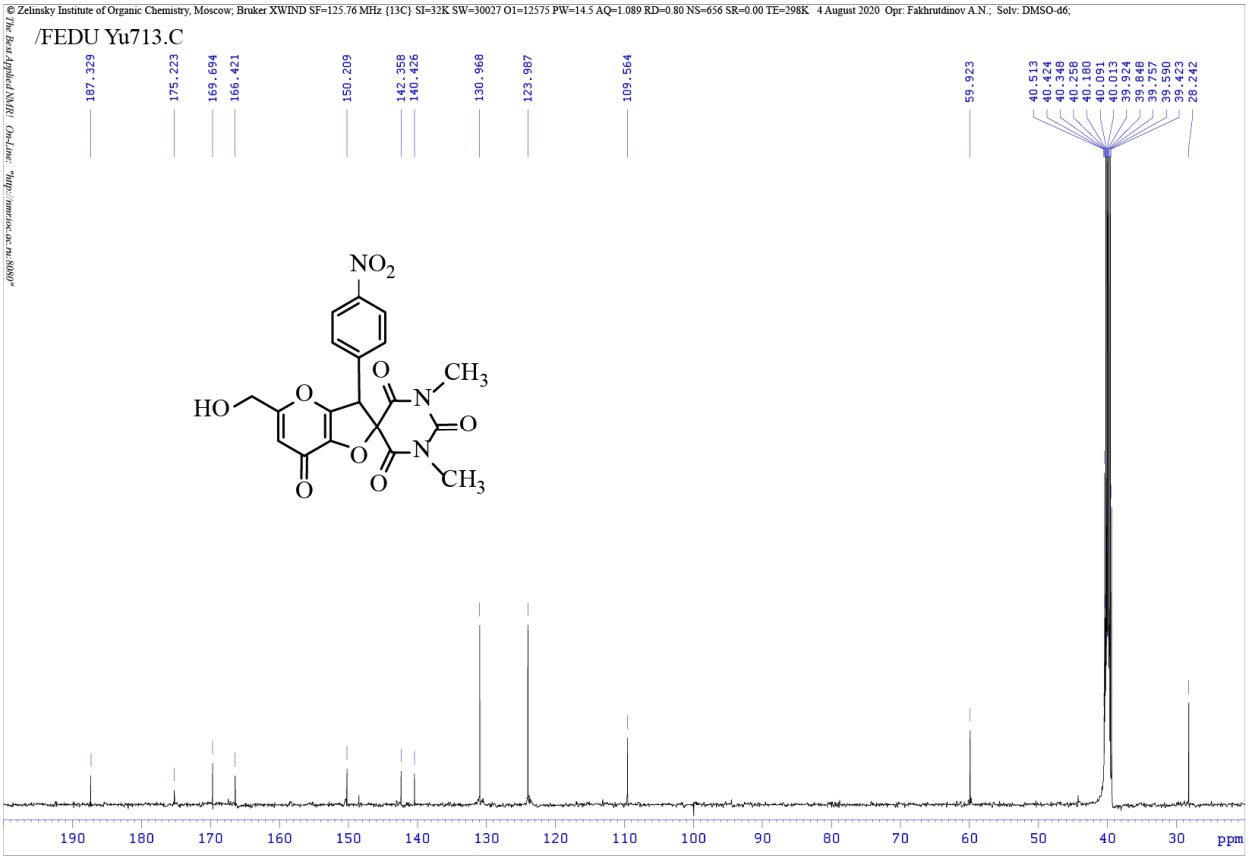

Figure S16. Compound **2h.**

Methyl 4-(5-(hydroxymethyl)-1',3'-dimethyl-2',4',6',7-tetraoxo-1',3,3',4',6',7-hexahydro-2'H-spiro[furo[3,2-b]pyran-2,5'-pyrimidin]-3-yl)benzoate 2i

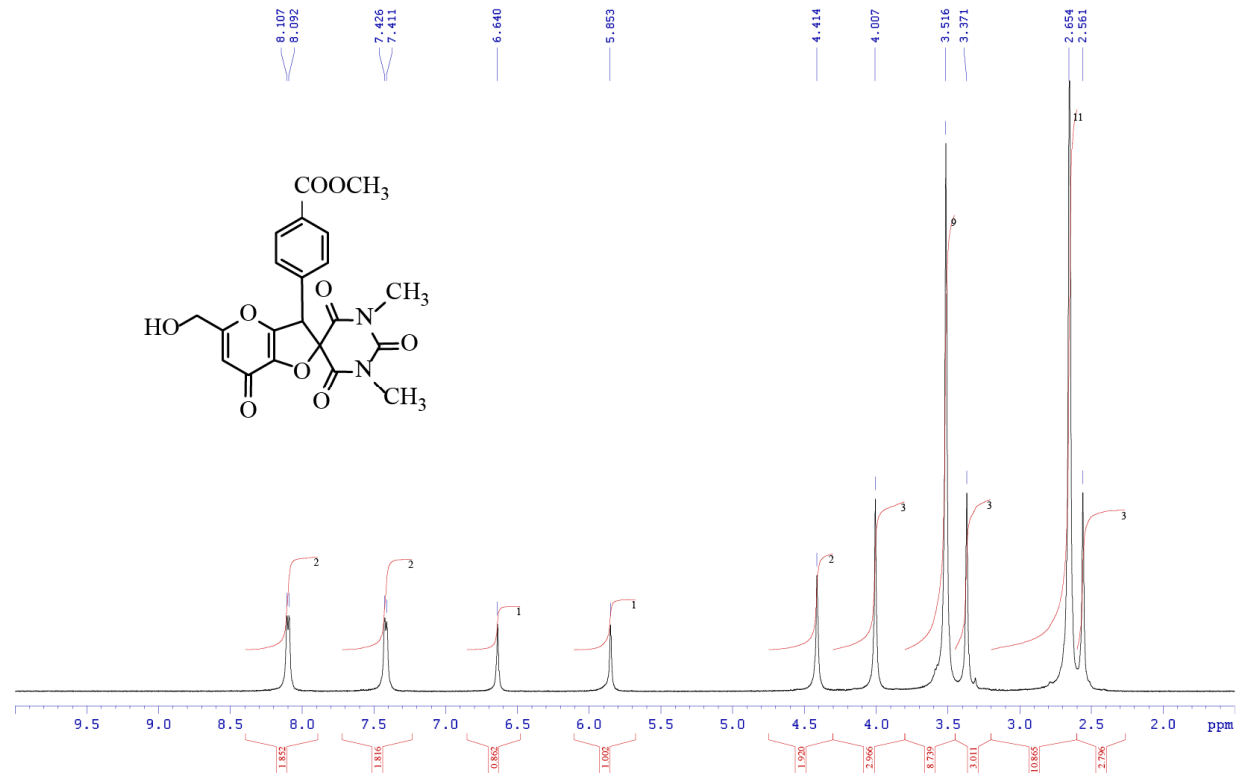

Figure S17. Compound **2i.**

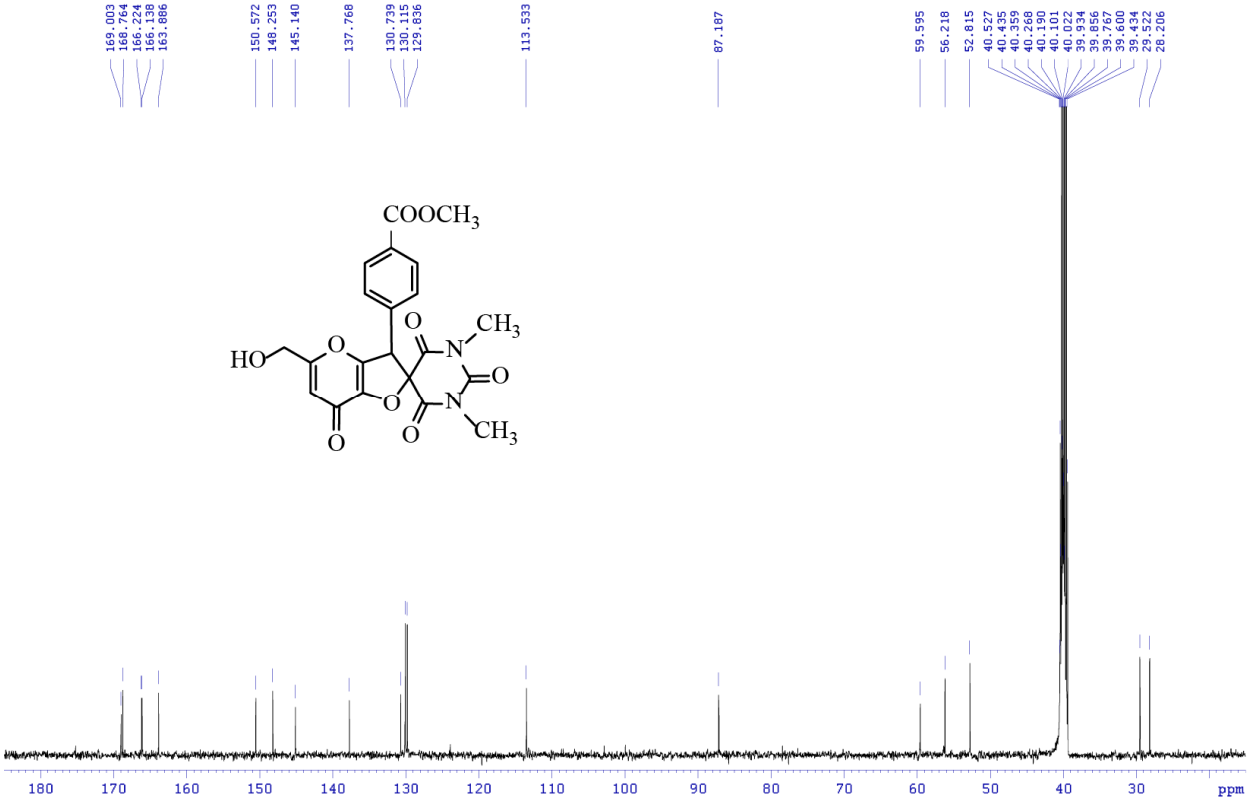

Figure S18. Compound **2i.**

2. 2D NMR Spectra of Compound 2a

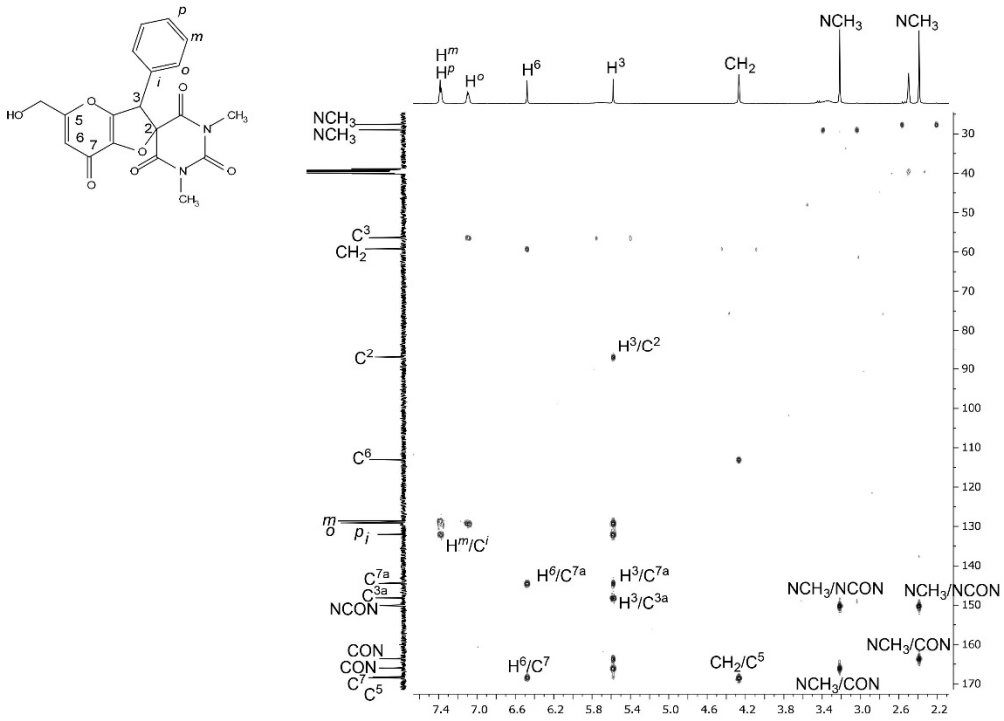

Figure S19. ^{1}H-^{13}C HMBC NMR spectrum of **2a.**

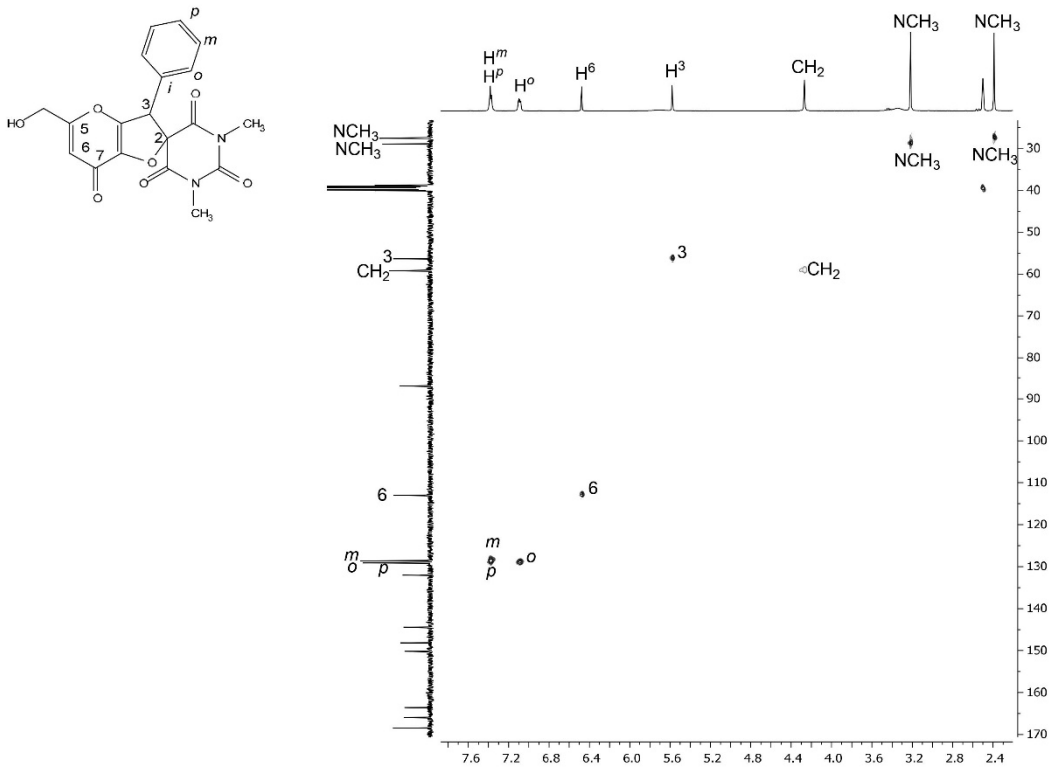

Figure S20. ^{1}H-^{13}C HSQC NMR spectrum of **2a.**

2. Single-crystal X-ray Diffraction Data for Compound 2f

Table S1. Crystal data and structure refinement for **2f**.

Identification code	**2f**	
Empirical formula	C19 H15 Cl N2 O7	
Formula weight	418.78	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 5.68820(10) Å	= 90°.
	b = 11.4345(2) Å	= 90°.
	c = 27.5456(6) Å	= 90°.
Volume	1791.61(6) $Å^3$	
Z	4	
Density (calculated)	1.553 g/cm^3	
Absorption coefficient	0.262 mm^{-1}	
F(000)	864	
Crystal size	0.170 x 0.150 x 0.130 mm^3	
Theta range for data collection	1.928 to 28.278°.	

Index ranges	-7<=h<=7, -15<=k<=15, -36<=l<=36
Reflections collected	35956
Independent reflections	4446 [R(int) = 0.0552]
Observed reflections	4004
Completeness to theta = 25.242°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7431 and 0.7180
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4446 / 0 / 268
Goodness-of-fit on F^2	1.061
Final R indices [I>2sigma(I)]	R1 = 0.0339, wR2 = 0.0727
R indices (all data)	R1 = 0.0423, wR2 = 0.0785
Absolute structure parameter	0.26(3)
Largest diff. peak and hole	0.232 and -0.248 e.$Å^{-3}$

Table S2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **2f**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	7794(1)	6058(1)	4128(1)	28(1)
O(1)	8292(3)	7886(1)	6502(1)	16(1)
O(2)	5515(3)	5255(2)	6871(1)	23(1)
O(3)	10579(3)	1869(2)	6050(1)	28(1)
O(4)	4108(3)	4177(2)	6062(1)	31(1)
O(5)	6570(4)	10824(2)	6793(1)	27(1)
O(6)	2661(4)	7005(2)	7364(1)	32(1)
O(7)	9535(3)	4437(2)	7293(1)	23(1)
N(1)	7415(4)	3077(2)	6021(1)	22(1)
N(2)	10128(3)	3143(2)	6678(1)	17(1)
C(1)	9478(4)	2649(2)	6236(1)	19(1)
C(2)	6086(4)	3967(2)	6203(1)	20(1)
C(3)	7308(4)	4740(2)	6571(1)	17(1)
C(4)	8729(4)	5771(2)	6307(1)	15(1)
C(5)	7623(4)	6769(2)	6572(1)	16(1)
C(6)	6998(4)	8724(2)	6736(1)	16(1)
C(7)	5112(4)	8470(2)	7012(1)	18(1)
C(8)	4354(4)	7276(2)	7105(1)	19(1)
C(9)	5846(4)	6445(2)	6856(1)	18(1)

C(10)	9045(4)	4090(2)	6894(1)	16(1)
C(11)	6464(6)	2431(3)	5601(1)	37(1)
C(12)	8450(4)	5851(2)	5759(1)	15(1)
C(13)	10213(4)	5417(2)	5459(1)	19(1)
C(14)	10004(4)	5471(2)	4957(1)	21(1)
C(15)	8013(4)	5963(2)	4756(1)	19(1)
C(16)	6232(4)	6405(2)	5045(1)	20(1)
C(17)	6459(4)	6348(2)	5546(1)	18(1)
C(18)	8008(4)	9907(2)	6628(1)	20(1)
C(19)	12056(5)	2588(2)	6946(1)	25(1)

Table S3. Bond lengths [Å] and angles [°] for **2f**.

Cl(1)-C(15)	1.738(2)
O(1)-C(5)	1.347(3)
O(1)-C(6)	1.369(3)
O(2)-C(9)	1.374(3)
O(2)-C(3)	1.439(3)
O(3)-C(1)	1.205(3)
O(4)-C(2)	1.215(3)
O(5)-C(18)	1.405(3)
O(5)-H(5)	0.78(3)
O(6)-C(8)	1.238(3)
O(7)-C(10)	1.202(3)
N(1)-C(2)	1.363(3)
N(1)-C(1)	1.402(3)
N(1)-C(11)	1.474(3)
N(2)-C(10)	1.380(3)
N(2)-C(1)	1.393(3)
N(2)-C(19)	1.467(3)
C(2)-C(3)	1.514(3)
C(3)-C(10)	1.523(3)
C(3)-C(4)	1.603(3)
C(4)-C(5)	1.494(3)
C(4)-C(12)	1.521(3)
C(4)-H(4)	1.0000
C(5)-C(9)	1.331(3)
C(6)-C(7)	1.348(3)
C(6)-C(18)	1.499(3)

C(7)-C(8)	1.454(3)
C(7)-H(7)	0.9500
C(8)-C(9)	1.446(3)
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(12)-C(13)	1.390(3)
C(12)-C(17)	1.396(3)
C(13)-C(14)	1.391(3)
C(13)-H(13)	0.9500
C(14)-C(15)	1.381(3)
C(14)-H(14)	0.9500
C(15)-C(16)	1.384(3)
C(16)-C(17)	1.389(4)
C(16)-H(16)	0.9500
C(17)-H(17)	0.9500
C(18)-H(18A)	0.9900
C(18)-H(18B)	0.9900
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(5)-O(1)-C(6)	116.36(18)
C(9)-O(2)-C(3)	106.90(18)
C(18)-O(5)-H(5)	111(3)
C(2)-N(1)-C(1)	124.6(2)
C(2)-N(1)-C(11)	117.3(2)
C(1)-N(1)-C(11)	117.6(2)
C(10)-N(2)-C(1)	125.1(2)
C(10)-N(2)-C(19)	117.2(2)
C(1)-N(2)-C(19)	117.6(2)
O(3)-C(1)-N(2)	122.3(2)
O(3)-C(1)-N(1)	120.9(2)
N(2)-C(1)-N(1)	116.8(2)
O(4)-C(2)-N(1)	123.0(2)
O(4)-C(2)-C(3)	121.5(2)
N(1)-C(2)-C(3)	115.4(2)
O(2)-C(3)-C(2)	107.38(19)
O(2)-C(3)-C(10)	108.85(18)
C(2)-C(3)-C(10)	113.8(2)

O(2)-C(3)-C(4)	108.50(18)
C(2)-C(3)-C(4)	110.97(19)
C(10)-C(3)-C(4)	107.25(18)
C(5)-C(4)-C(12)	113.29(19)
C(5)-C(4)-C(3)	97.35(17)
C(12)-C(4)-C(3)	116.19(18)
C(5)-C(4)-H(4)	109.8
C(12)-C(4)-H(4)	109.8
C(3)-C(4)-H(4)	109.8
C(9)-C(5)-O(1)	124.3(2)
C(9)-C(5)-C(4)	113.3(2)
O(1)-C(5)-C(4)	122.35(19)
C(7)-C(6)-O(1)	122.9(2)
C(7)-C(6)-C(18)	127.6(2)
O(1)-C(6)-C(18)	109.46(19)
C(6)-C(7)-C(8)	122.5(2)
C(6)-C(7)-H(7)	118.7
C(8)-C(7)-H(7)	118.7
O(6)-C(8)-C(9)	124.4(2)
O(6)-C(8)-C(7)	124.6(2)
C(9)-C(8)-C(7)	111.1(2)
C(5)-C(9)-O(2)	113.4(2)
C(5)-C(9)-C(8)	122.8(2)
O(2)-C(9)-C(8)	123.8(2)
O(7)-C(10)-N(2)	123.3(2)
O(7)-C(10)-C(3)	121.6(2)
N(2)-C(10)-C(3)	114.9(2)
N(1)-C(11)-H(11A)	109.5
N(1)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
N(1)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
C(13)-C(12)-C(17)	118.8(2)
C(13)-C(12)-C(4)	119.5(2)
C(17)-C(12)-C(4)	121.7(2)
C(12)-C(13)-C(14)	120.9(2)
C(12)-C(13)-H(13)	119.6
C(14)-C(13)-H(13)	119.6

C(15)-C(14)-C(13)	119.2(2)
C(15)-C(14)-H(14)	120.4
C(13)-C(14)-H(14)	120.4
C(14)-C(15)-C(16)	121.2(2)
C(14)-C(15)-Cl(1)	118.94(19)
C(16)-C(15)-Cl(1)	119.84(19)
C(15)-C(16)-C(17)	119.2(2)
C(15)-C(16)-H(16)	120.4
C(17)-C(16)-H(16)	120.4
C(16)-C(17)-C(12)	120.8(2)
C(16)-C(17)-H(17)	119.6
C(12)-C(17)-H(17)	119.6
O(5)-C(18)-C(6)	112.79(19)
O(5)-C(18)-H(18A)	109.0
C(6)-C(18)-H(18A)	109.0
O(5)-C(18)-H(18B)	109.0
C(6)-C(18)-H(18B)	109.0
H(18A)-C(18)-H(18B)	107.8
N(2)-C(19)-H(19A)	109.5
N(2)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
N(2)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table S4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **2f**. The anisotropic displacement factor exponent takes the form: $-2\ ^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	29(1)	36(1)	18(1)	0(1)	-4(1)	-6(1)
O(1)	20(1)	12(1)	18(1)	0(1)	5(1)	-2(1)
O(2)	19(1)	14(1)	34(1)	4(1)	12(1)	1(1)
O(3)	32(1)	19(1)	34(1)	-3(1)	10(1)	-1(1)
O(4)	20(1)	31(1)	42(1)	16(1)	-12(1)	-6(1)
O(5)	33(1)	17(1)	32(1)	-3(1)	8(1)	4(1)
O(6)	28(1)	22(1)	44(1)	11(1)	19(1)	6(1)

O(7)	28(1)	23(1)	17(1)	1(1)	1(1)	-3(1)
N(1)	27(1)	18(1)	21(1)	0(1)	-4(1)	-4(1)
N(2)	15(1)	18(1)	19(1)	3(1)	-1(1)	2(1)
C(1)	22(1)	14(1)	21(1)	3(1)	3(1)	-3(1)
C(2)	19(1)	16(1)	25(1)	7(1)	-3(1)	-6(1)
C(3)	16(1)	14(1)	21(1)	2(1)	3(1)	0(1)
C(4)	13(1)	13(1)	18(1)	1(1)	1(1)	0(1)
C(5)	16(1)	15(1)	17(1)	2(1)	0(1)	0(1)
C(6)	19(1)	14(1)	15(1)	-1(1)	-1(1)	3(1)
C(7)	20(1)	16(1)	18(1)	2(1)	3(1)	4(1)
C(8)	18(1)	20(1)	21(1)	4(1)	5(1)	3(1)
C(9)	17(1)	14(1)	22(1)	3(1)	2(1)	1(1)
C(10)	16(1)	15(1)	18(1)	3(1)	1(1)	-3(1)
C(11)	46(2)	35(2)	30(2)	-11(1)	-11(1)	-12(1)
C(12)	15(1)	11(1)	18(1)	1(1)	0(1)	0(1)
C(13)	15(1)	19(1)	24(1)	1(1)	-1(1)	2(1)
C(14)	20(1)	22(1)	22(1)	-3(1)	3(1)	2(1)
C(15)	21(1)	19(1)	18(1)	-1(1)	-2(1)	-4(1)
C(16)	14(1)	20(1)	25(1)	2(1)	-3(1)	1(1)
C(17)	14(1)	17(1)	25(1)	0(1)	2(1)	2(1)
C(18)	22(1)	15(1)	21(1)	-1(1)	4(1)	0(1)
C(19)	18(1)	28(1)	28(1)	8(1)	-2(1)	4(1)

Table S5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **2f**.

	x	y	z	U(eq)
H(5)	6860(60)	10990(30)	7059(13)	39(10)
H(4)	10434	5719	6393	18
H(7)	4243	9095	7152	22
H(11A)	5195	1914	5709	56
H(11B)	7717	1963	5453	56
H(11C)	5850	2987	5362	56
H(13)	11579	5079	5600	23
H(14)	11217	5173	4755	25
H(16)	4873	6743	4902	24
H(17)	5244	6650	5747	22
H(18A)	9570	9972	6785	23
H(18B)	8234	9986	6274	23
H(19A)	13133	3190	7067	37
H(19B)	12909	2055	6731	37
H(19C)	11413	2147	7221	37

Table S6. Torsion angles [°] for **2f**.

C(10)-N(2)-C(1)-O(3)	175.2(2)
C(19)-N(2)-C(1)-O(3)	-7.4(3)
C(10)-N(2)-C(1)-N(1)	-6.9(3)
C(19)-N(2)-C(1)-N(1)	170.5(2)
C(2)-N(1)-C(1)-O(3)	-179.0(2)
C(11)-N(1)-C(1)-O(3)	8.6(4)
C(2)-N(1)-C(1)-N(2)	3.1(3)
C(11)-N(1)-C(1)-N(2)	-169.3(2)
C(1)-N(1)-C(2)-O(4)	-166.1(2)
C(11)-N(1)-C(2)-O(4)	6.4(4)
C(1)-N(1)-C(2)-C(3)	18.2(3)
C(11)-N(1)-C(2)-C(3)	-169.4(2)
C(9)-O(2)-C(3)-C(2)	-125.8(2)
C(9)-O(2)-C(3)-C(10)	110.6(2)
C(9)-O(2)-C(3)-C(4)	-5.8(2)
O(4)-C(2)-C(3)-O(2)	29.2(3)
N(1)-C(2)-C(3)-O(2)	-155.0(2)
O(4)-C(2)-C(3)-C(10)	149.7(2)
N(1)-C(2)-C(3)-C(10)	-34.5(3)
O(4)-C(2)-C(3)-C(4)	-89.3(3)
N(1)-C(2)-C(3)-C(4)	86.6(2)
O(2)-C(3)-C(4)-C(5)	7.5(2)
C(2)-C(3)-C(4)-C(5)	125.3(2)
C(10)-C(3)-C(4)-C(5)	-109.9(2)
O(2)-C(3)-C(4)-C(12)	-113.0(2)
C(2)-C(3)-C(4)-C(12)	4.7(3)
C(10)-C(3)-C(4)-C(12)	129.6(2)
C(6)-O(1)-C(5)-C(9)	-1.2(3)
C(6)-O(1)-C(5)-C(4)	174.5(2)
C(12)-C(4)-C(5)-C(9)	115.6(2)
C(3)-C(4)-C(5)-C(9)	-7.0(2)
C(12)-C(4)-C(5)-O(1)	-60.5(3)
C(3)-C(4)-C(5)-O(1)	176.8(2)
C(5)-O(1)-C(6)-C(7)	-1.8(3)
C(5)-O(1)-C(6)-C(18)	178.63(19)
O(1)-C(6)-C(7)-C(8)	3.1(4)
C(18)-C(6)-C(7)-C(8)	-177.5(2)

C(6)-C(7)-C(8)-O(6)	178.5(2)
C(6)-C(7)-C(8)-C(9)	-1.2(3)
O(1)-C(5)-C(9)-O(2)	-179.7(2)
C(4)-C(5)-C(9)-O(2)	4.3(3)
O(1)-C(5)-C(9)-C(8)	3.0(4)
C(4)-C(5)-C(9)-C(8)	-173.0(2)
C(3)-O(2)-C(9)-C(5)	1.3(3)
C(3)-O(2)-C(9)-C(8)	178.5(2)
O(6)-C(8)-C(9)-C(5)	178.6(3)
C(7)-C(8)-C(9)-C(5)	-1.7(3)
O(6)-C(8)-C(9)-O(2)	1.5(4)
C(7)-C(8)-C(9)-O(2)	-178.7(2)
C(1)-N(2)-C(10)-O(7)	174.0(2)
C(19)-N(2)-C(10)-O(7)	-3.4(3)
C(1)-N(2)-C(10)-C(3)	-11.0(3)
C(19)-N(2)-C(10)-C(3)	171.5(2)
O(2)-C(3)-C(10)-O(7)	-34.3(3)
C(2)-C(3)-C(10)-O(7)	-154.0(2)
C(4)-C(3)-C(10)-O(7)	82.9(3)
O(2)-C(3)-C(10)-N(2)	150.71(19)
C(2)-C(3)-C(10)-N(2)	31.0(3)
C(4)-C(3)-C(10)-N(2)	-92.1(2)
C(5)-C(4)-C(12)-C(13)	147.2(2)
C(3)-C(4)-C(12)-C(13)	-101.3(2)
C(5)-C(4)-C(12)-C(17)	-33.0(3)
C(3)-C(4)-C(12)-C(17)	78.5(3)
C(17)-C(12)-C(13)-C(14)	-0.2(4)
C(4)-C(12)-C(13)-C(14)	179.6(2)
C(12)-C(13)-C(14)-C(15)	0.0(4)
C(13)-C(14)-C(15)-C(16)	0.2(4)
C(13)-C(14)-C(15)-Cl(1)	178.55(19)
C(14)-C(15)-C(16)-C(17)	-0.2(4)
Cl(1)-C(15)-C(16)-C(17)	-178.49(19)
C(15)-C(16)-C(17)-C(12)	-0.1(4)
C(13)-C(12)-C(17)-C(16)	0.2(4)
C(4)-C(12)-C(17)-C(16)	-179.6(2)
C(7)-C(6)-C(18)-O(5)	-8.8(4)
O(1)-C(6)-C(18)-O(5)	170.7(2)

Symmetry transformations used to generate equivalent atoms:

Table S7. Hydrogen bonds for **2f** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(5)-H(5)...O(6)#1	0.78(3)	1.99(4)	2.722(3)	158(3)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y+1/2,-z+3/2