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Supporting information for article:

Intermolecular Interaction Energies and Molecular Conformations in *N*-Substituted 4-Aryl-2-methylimidazoles with Promising *in vitro* Antifungal Activity

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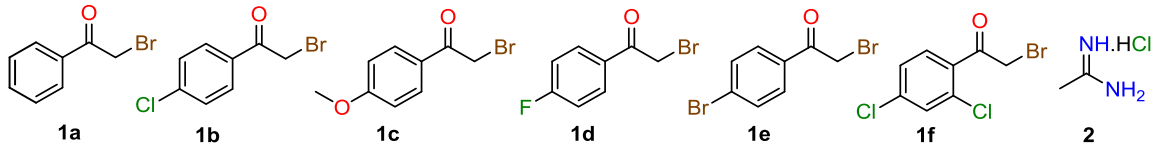
Content:

S1. Overview of reactants, substrates and products numbering

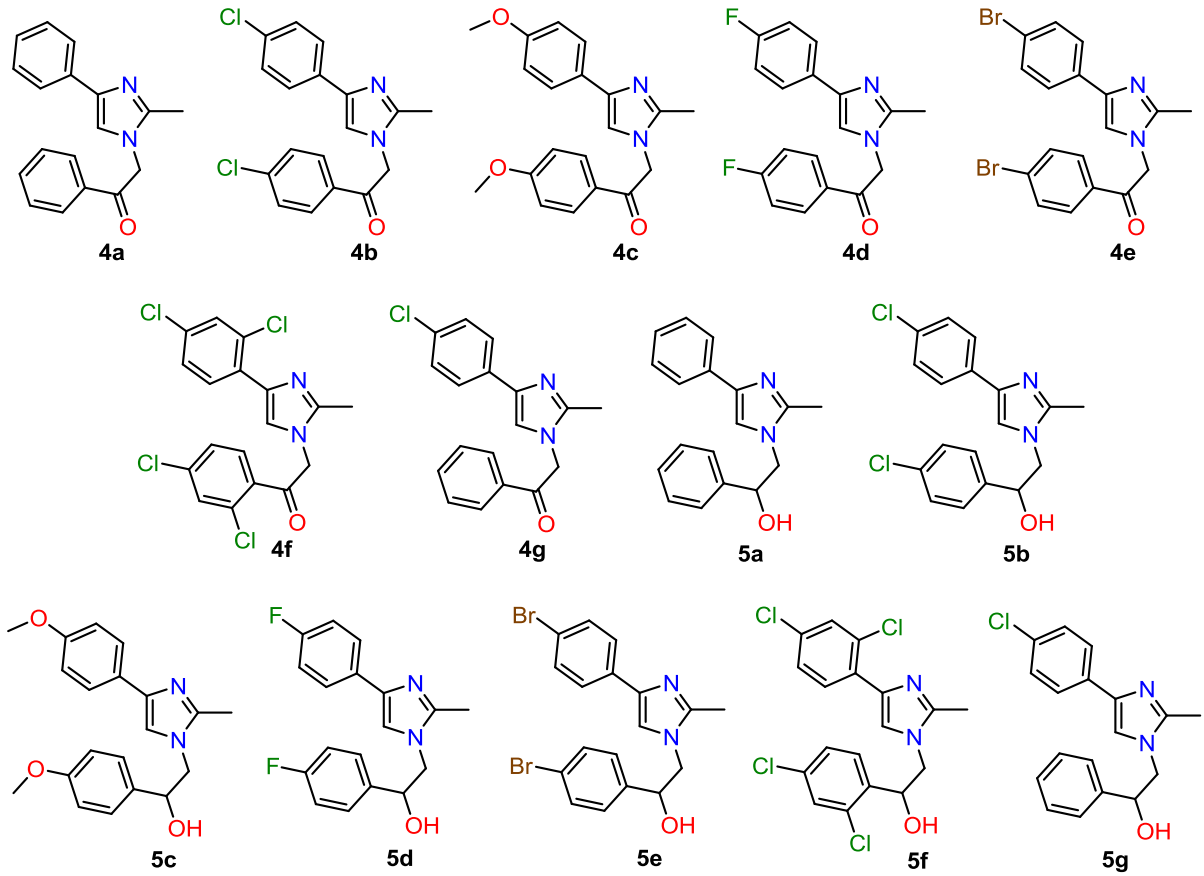
Reactants and substrates

α-Bromoacetophenones **1a**–**f** and acetamidine hydrochloride **2**



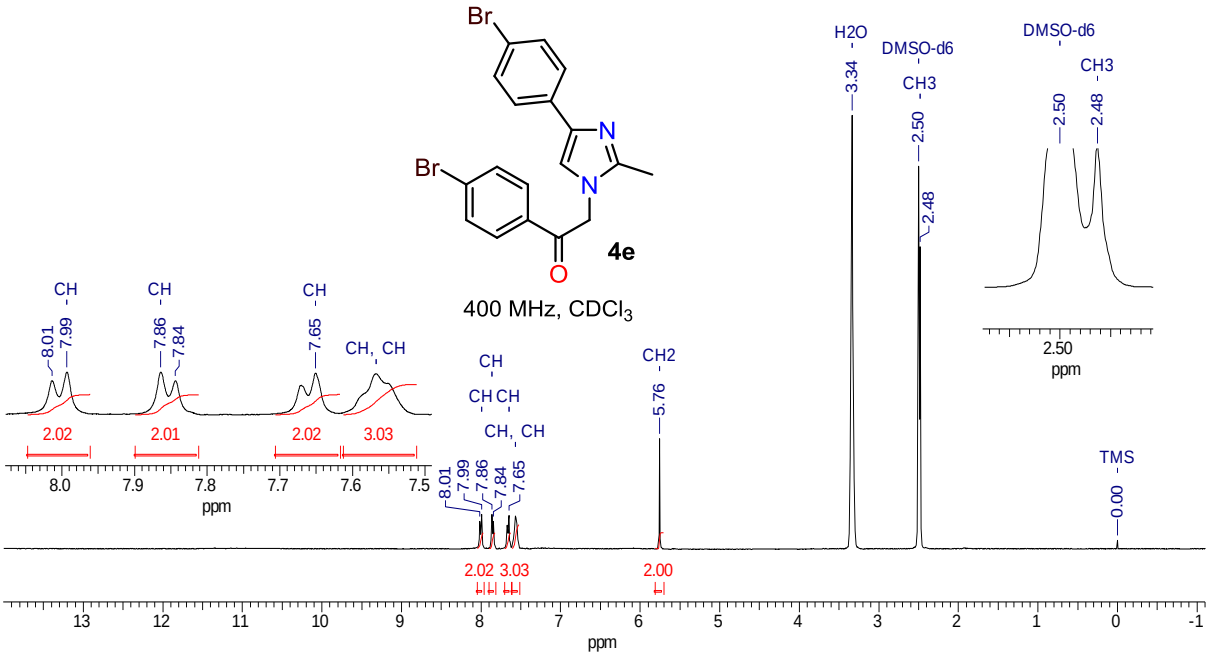
Products

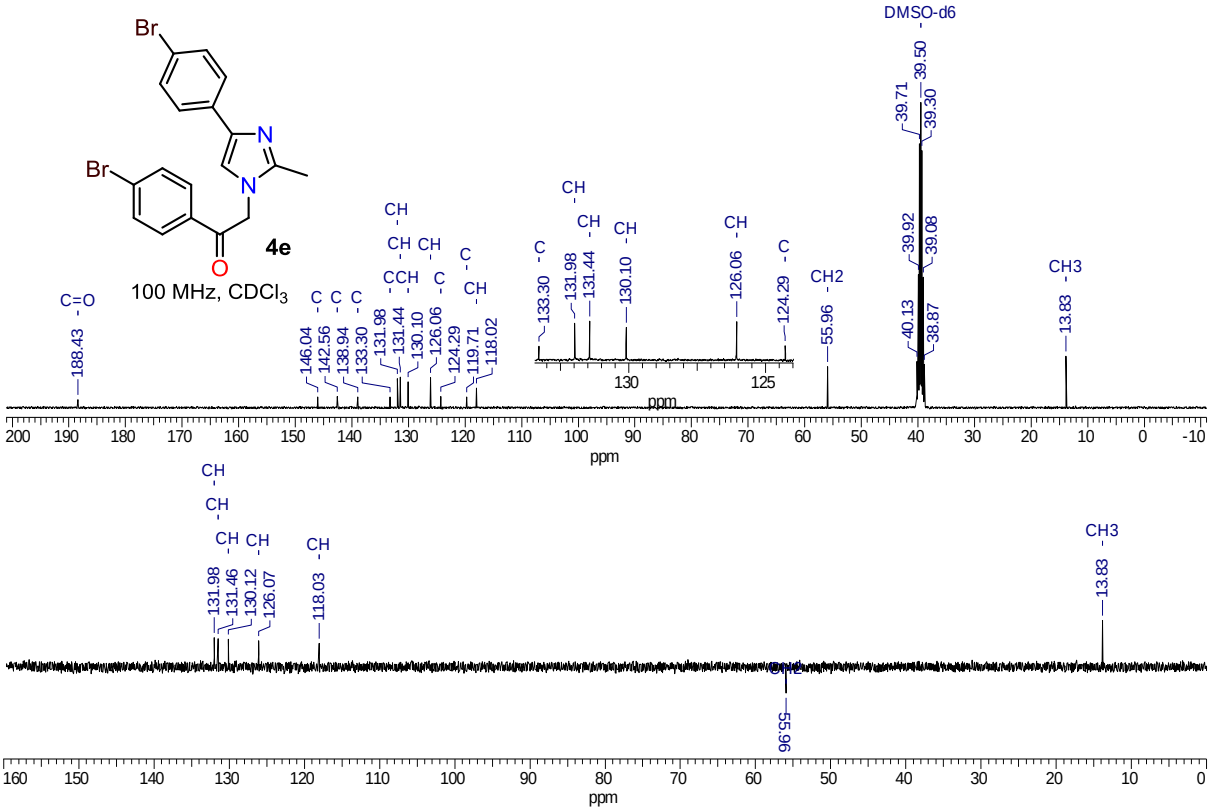
N-Phenacyl-2-methylimidazoles **4a-g** and *N*-(2-hydroxyethyl)-2-methylimidazoles **5a-g**



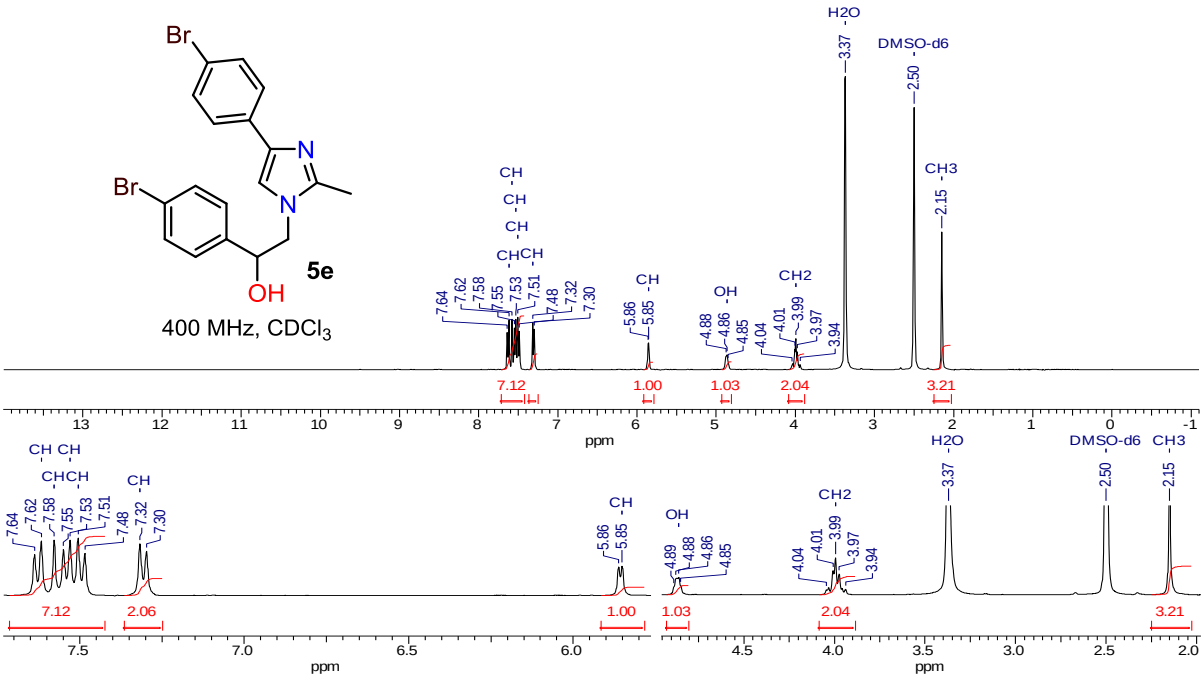
S2. Copies of NMR spectra of novel compounds 4e, 4f, 5e, and 5f

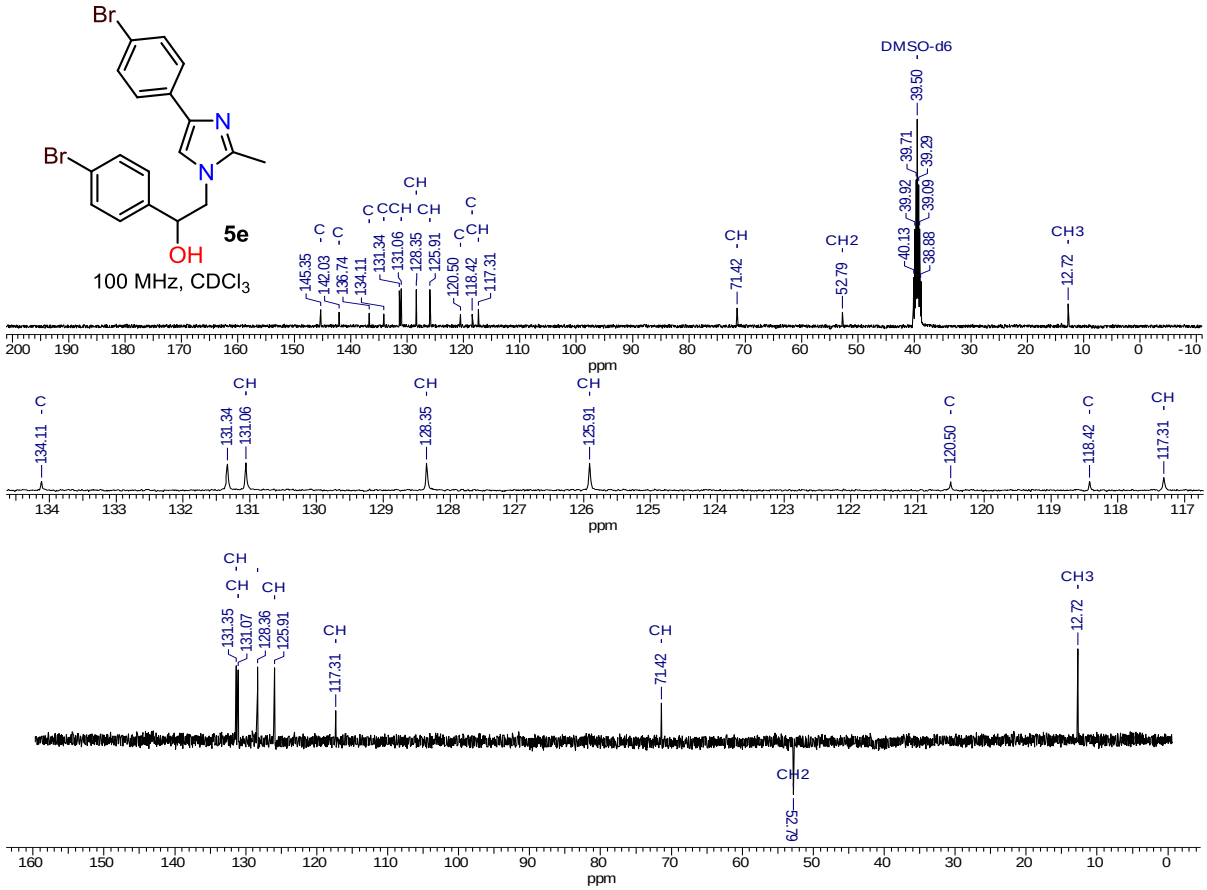
^{1}H, ^{13}C{^{1}H} NMR and DEPT-135 of 4-(2,4-dichlorophenyl)-1-(2-(2,4-dichlorophenyl)-2-etanone)-2-methyl-1*H*-imidazole (**4e**)



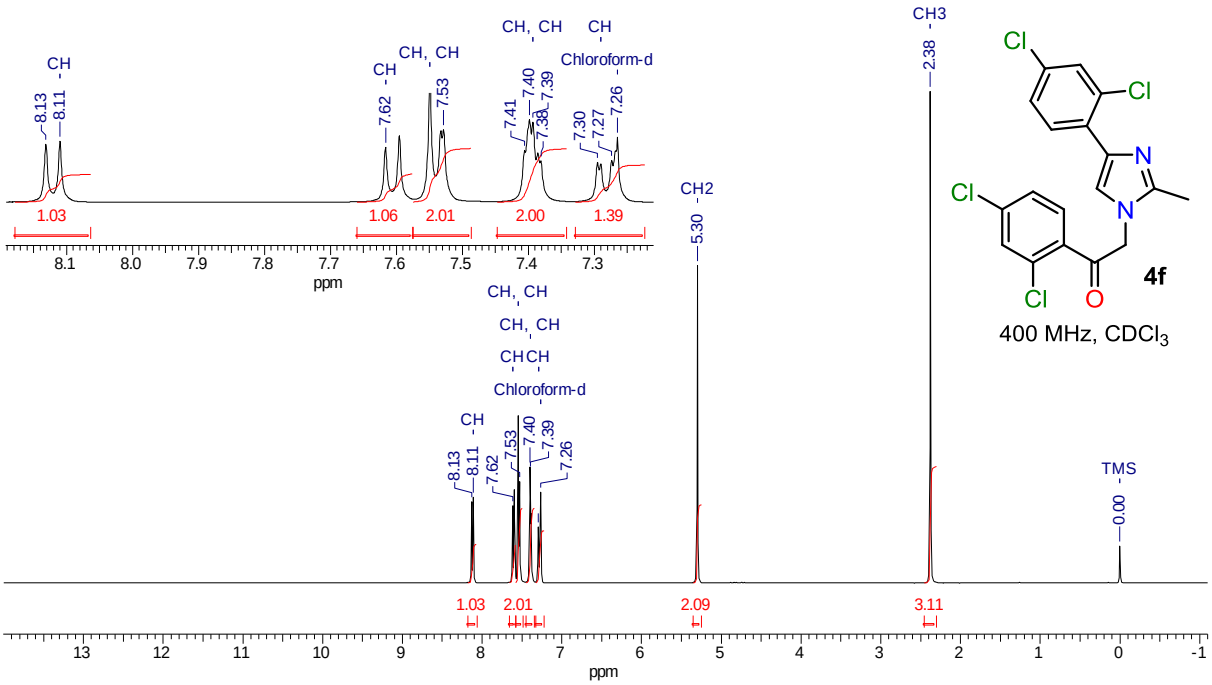


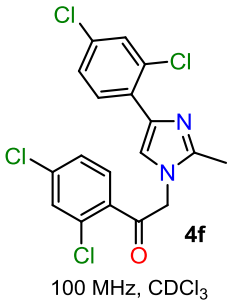
^{1}H, ^{13}C{^{1}H} NMR and DEPT-135 of 1-(4-bromophenyl)-2-(4-(4-bromophenyl)-2-methyl-1*H*-imidazol-1-yl)ethan-1-ol (**5e**)

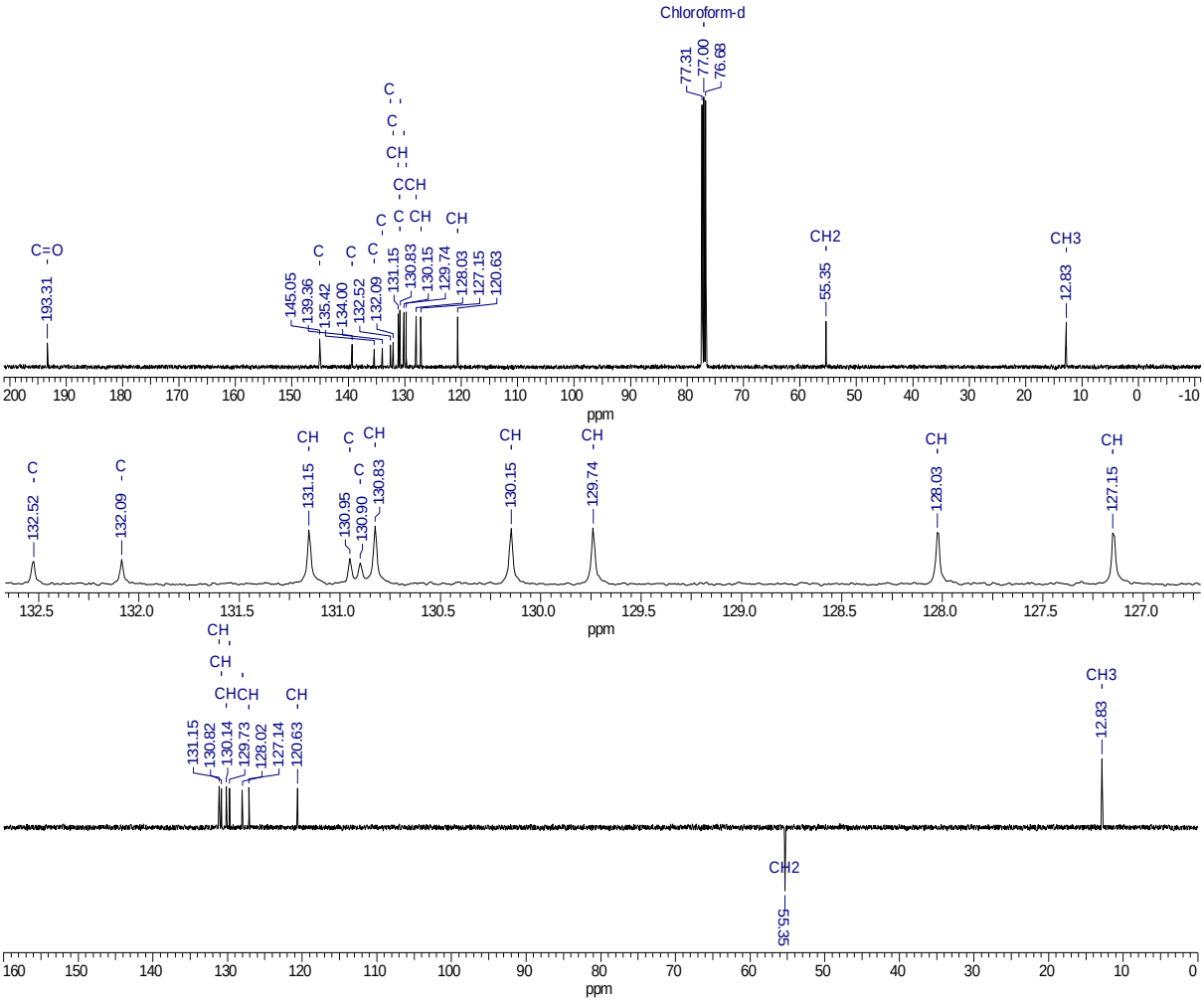




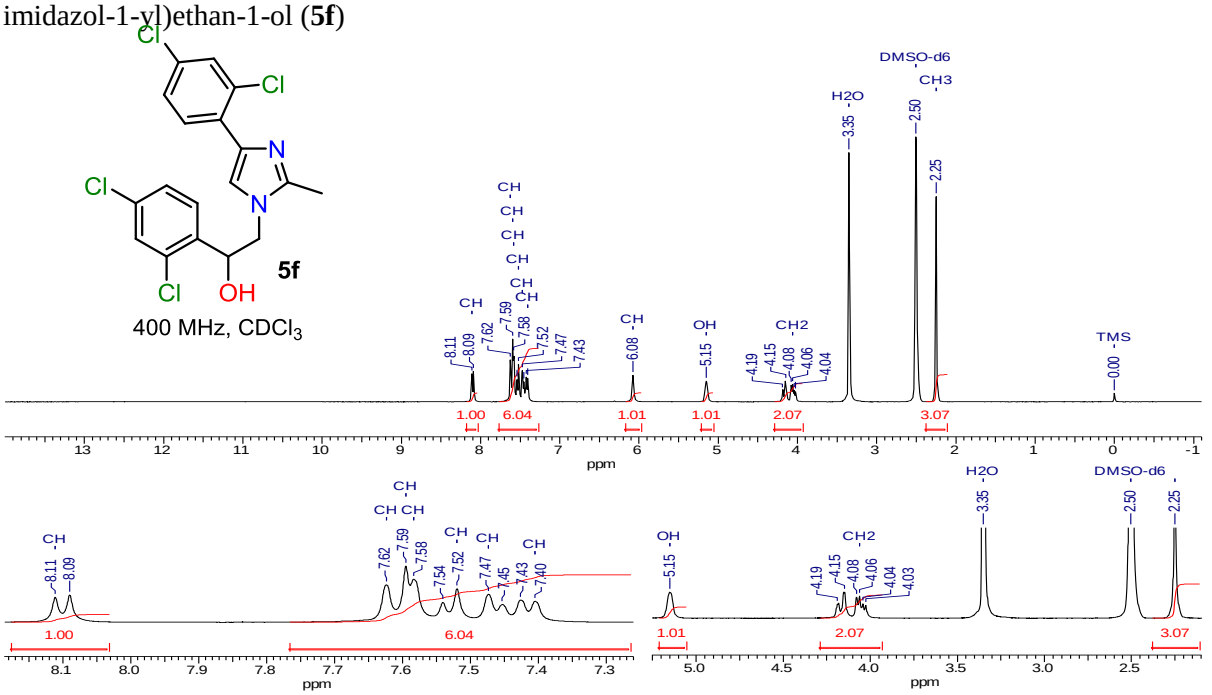
^{1}H, ^{13}C{^{1}H} NMR and DEPT-135 of 4-(2,4-dichlorophenyl)-1-(2-(2,4-dichlorophenyl)-2-etanone)-2-methyl-1*H*-imidazole (**4f**)

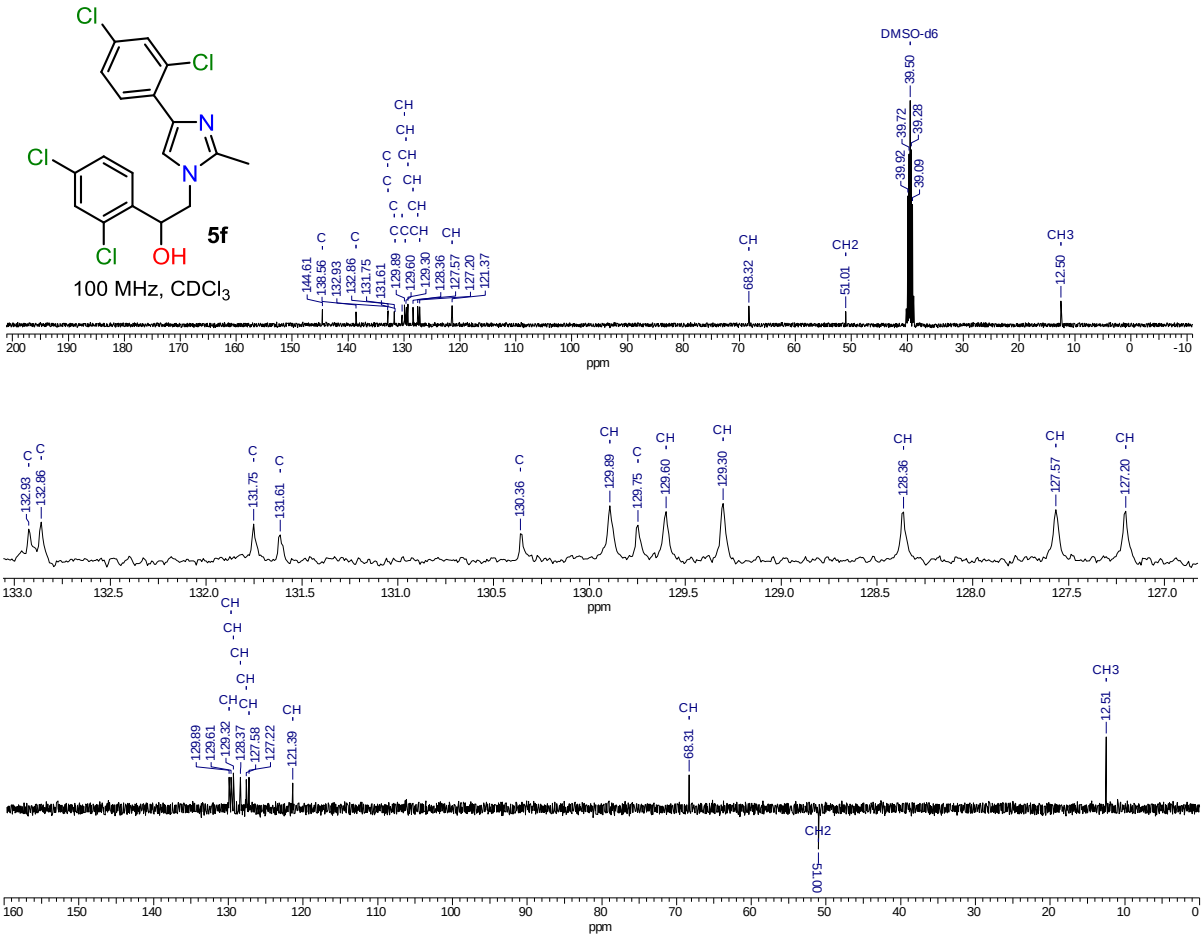






^{1}H, ^{13}C{^{1}H} NMR and DEPT-135 of 1-(2,4-dichlorophenyl)-2-(4-(2,4-dichlorophenyl)-2-methyl-1*H*-imidazol-1-yl)ethan-1-ol (**5f**)




Cl
Cl
N
Cl
N
5f
Cl
OH
100 MHz, CDCl3
DMSO-d6
39.50
39.72
39.28
39.92
39.09
CH
CH
C
CH
C
CH
C
CH
CCCH
CH
C
C
144.61
138.56
132.93
132.86
131.75
131.61
129.89
129.60
129.30
128.36
127.57
127.20
121.37
CH
68.32
CH2
51.01
CH3
12.50
ppm
C
C
132.93
132.86
C
C
131.75
131.61
C
130.36
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129.60
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129.30
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129.32
128.37
127.58
127.22
121.39
CH
68.31
CH3
12.51
CH2
51.00
ppm

S3. HRMS analysis data of novel compounds 4e, 4f, 5e, and 5f

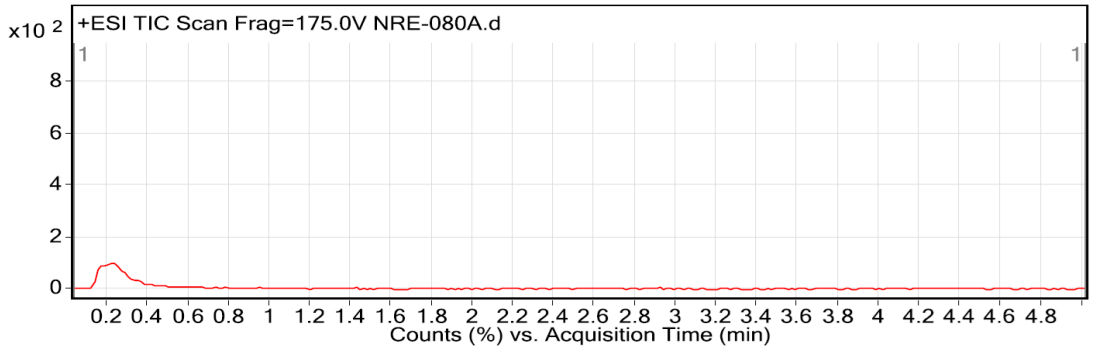
Qualitative Analysis Report

Data Filename	NRE-080A.d	**Sample Name**	NRE-080A
Sample Type	Sample	**Position**	P1-F9
Instrument Name	Instrument 1	**User Name**	
Acq Method	Default Method.m	**Acquired Time**	1/26/2018 4:50:01 PM
IRM Calibration Status	Success	**DA Method**	Metodo-analisis-signaltonoise.m
Comment			

Sample Group **Info.**

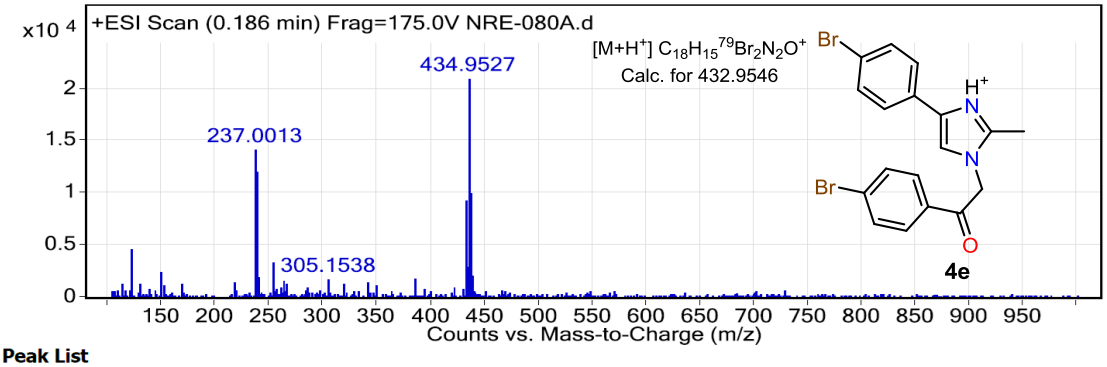
User Chromatograms

Fragmentor Voltage 175 **Collision Energy** 0 **Ionization Mode** ESI



User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
175	0	ESI



Peak List

m/z	z	Abund
122.0822		4635.9
237.0013	1	14186.1
237.0855		3029.3
238.9999	1	12102.9
253.0632		3368
432.9549	1	9334.9
433.9619	1	2957.5
434.9527	1	21008.3
435.9558	1	3716.5
436.9526	1	10015.2

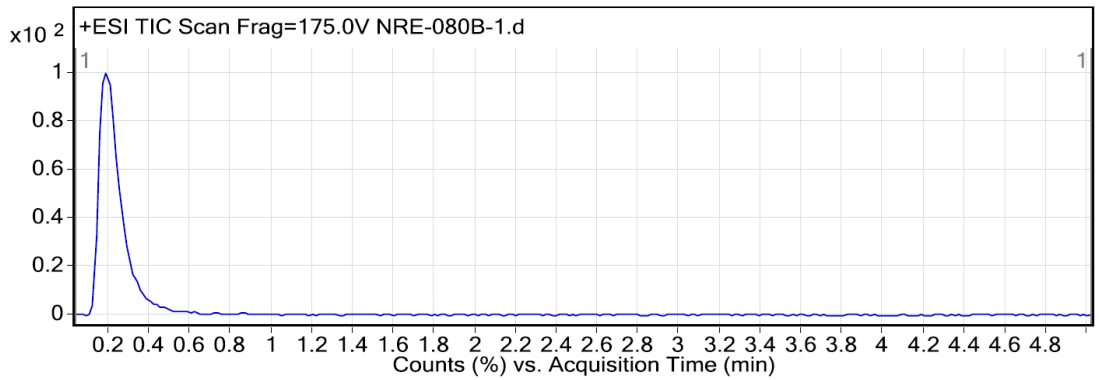
Qualitative Analysis Report

Data Filename	NRE-080B-1.d	**Sample Name**	NRE-080B
Sample Type	Sample	**Position**	P1-F1
Instrument Name	Instrument 1	**User Name**	
Acq Method	Default Method.m	**Acquired Time**	1/29/2018 1:33:02 PM
IRM Calibration Status	Success	**DA Method**	Metodo-analisis-signaltonoise.m
Comment			

Sample Group **Info.**

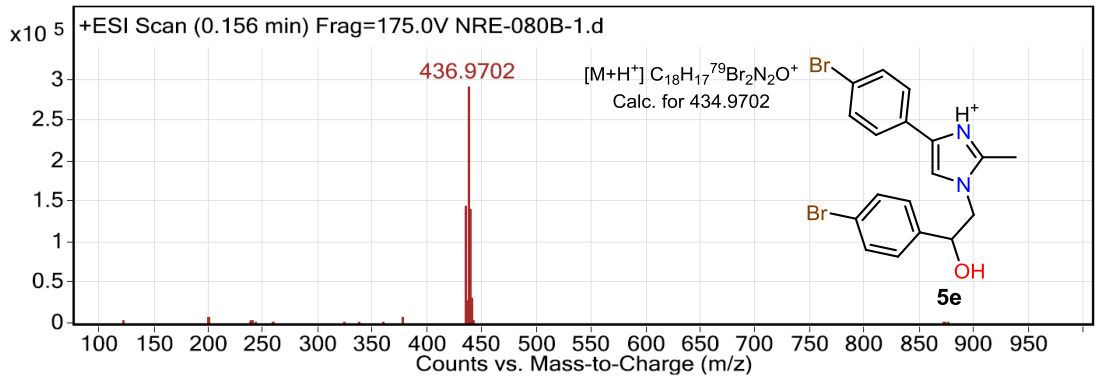
User Chromatograms

Fragmentor Voltage 175 **Collision Energy** 0 **Ionization Mode** ESI



User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
175	0	ESI



Peak List

m/z	z	Abund
434.9718	1	144858
435.9732	1	29615.1
436.9702	1	293207.7
437.0262		23875.3
437.0782		16226.3
437.1635		16520.1
437.9738	1	59808
438.968	1	142594.7
439.9696	1	32863.7

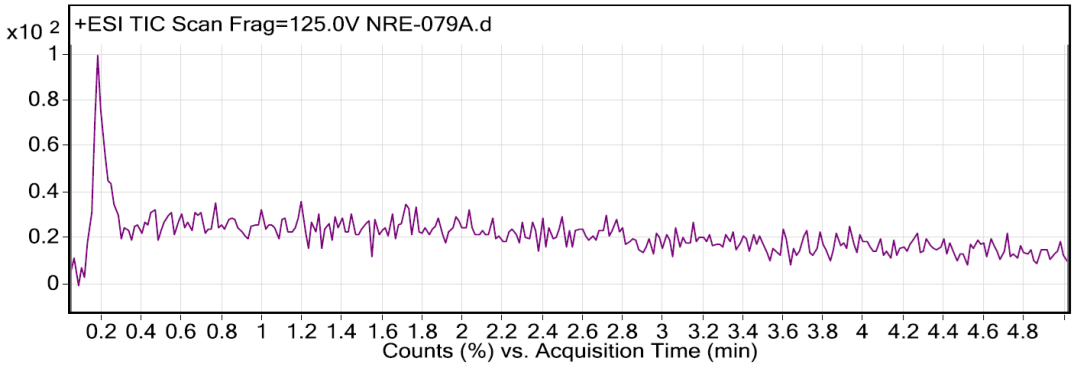
Qualitative Analysis Report

Data Filename	NRE-079A.d	**Sample Name**	NRE-079A
Sample Type	Sample	**Position**	P1-F4
Instrument Name	Instrument 1	**User Name**	
Acq Method	General +.m	**Acquired Time**	9/26/2017 10:53:55 AM
IRM Calibration Status	All Ions Missed	**DA Method**	Metodo-analisis-signaltonoise.m
Comment			

Sample Group **Info.**

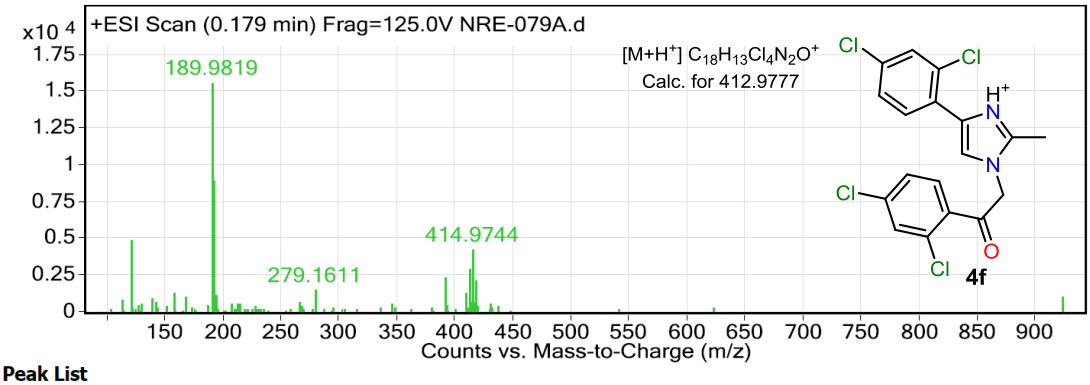
User Chromatograms

Fragmentor Voltage 125 **Collision Energy** 0 **Ionization Mode** ESI



User Spectra

Fragmentor Voltage	**Collision Energy**	**Ionization Mode**
125	0	ESI



Peak List

m/z	z	Abund
121.0859		4921.1
189.9819	1	15650.8
190.0214		1728.5
190.9866	1	1523.3
191.9796	1	9018.4
279.1611		1544.2
391.2846		2473.6
412.9789		3032
414.9744		4302.8
416.9715		2270.3

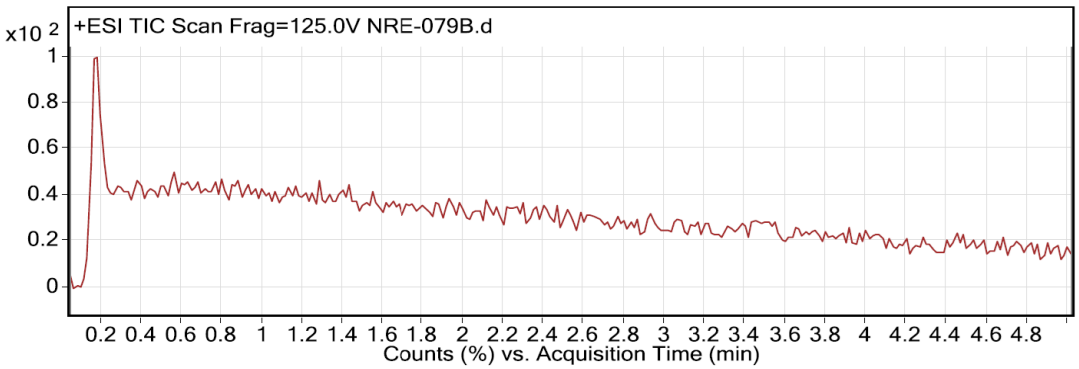
Qualitative Analysis Report

Data Filename	NRE-079B.d	**Sample Name**	NRE-079B
Sample Type	Sample	**Position**	P1-F5
Instrument Name	Instrument 1	**User Name**	
Acq Method	General +.m	**Acquired Time**	9/26/2017 10:59:20 AM
IRM Calibration Status	All Ions Missed	**DA Method**	Metodo-analisis-signaltonoise.m
Comment			

Sample Group **Info.**

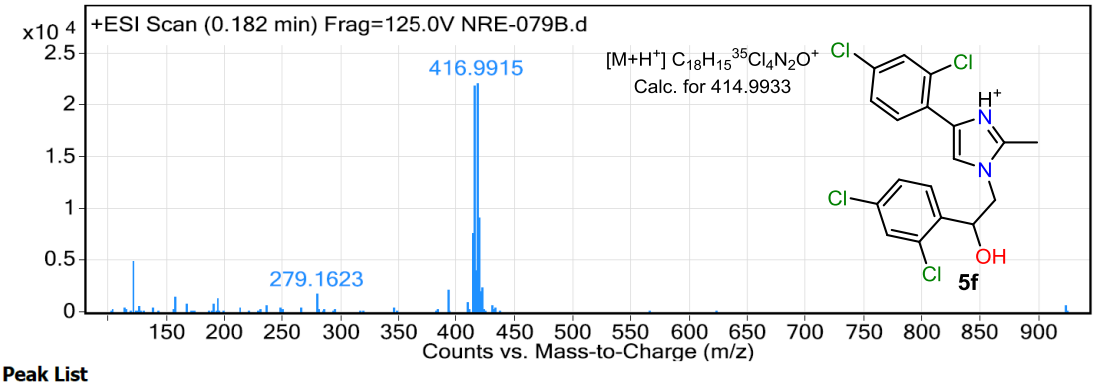
User Chromatograms

Fragmentor Voltage 125 **Collision Energy** 0 **Ionization Mode** ESI



User Spectra

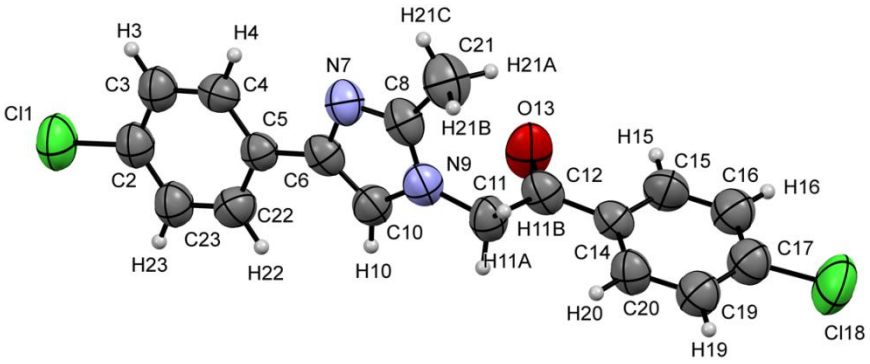
Fragmentor Voltage 125 **Collision Energy** 0 **Ionization Mode** ESI



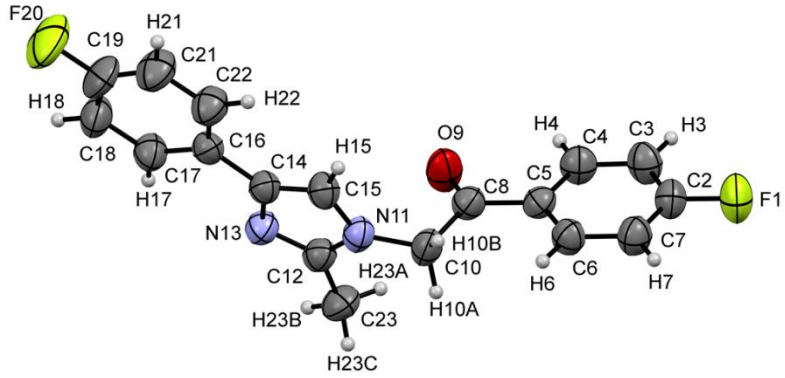
Peak List

m/z	z	Abund
121.0865		5023.8
391.2915		2287.6
412.9802	1	7694.8
414.9919	1	21886.9
415.993	1	4057
416.9915	1	22239.7
417.0477		4107.8
417.9935	1	4059.2
418.99	1	9201.4
420.9894	1	2553.3

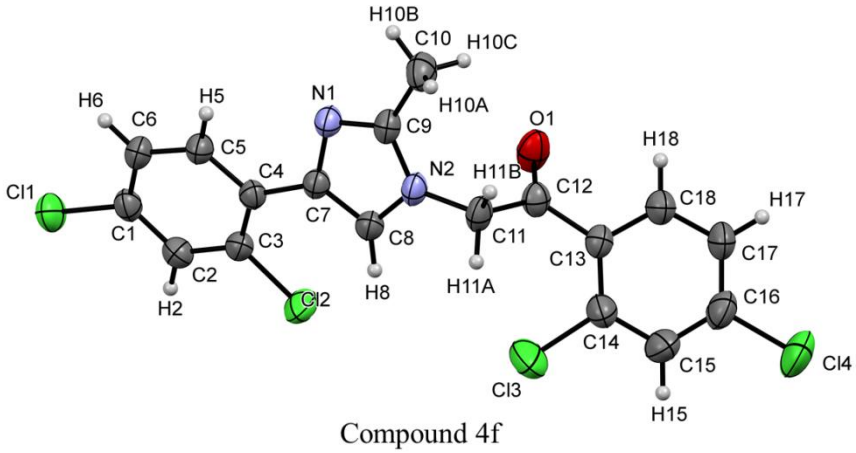
S4. ORTEP plots of compounds 4b, 4d, and 4f[a]



Compound 4b



Compound 4d

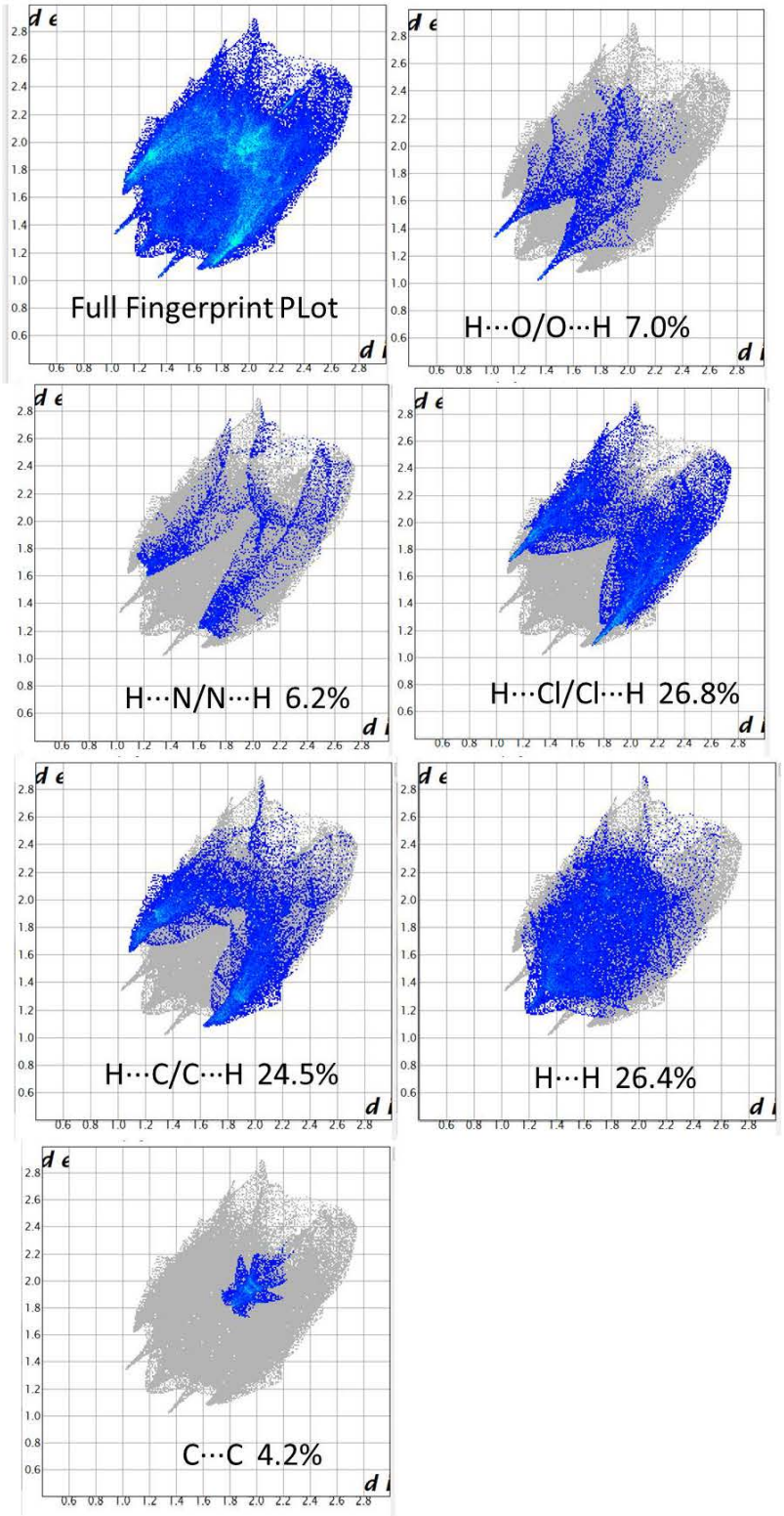


Compound 4f

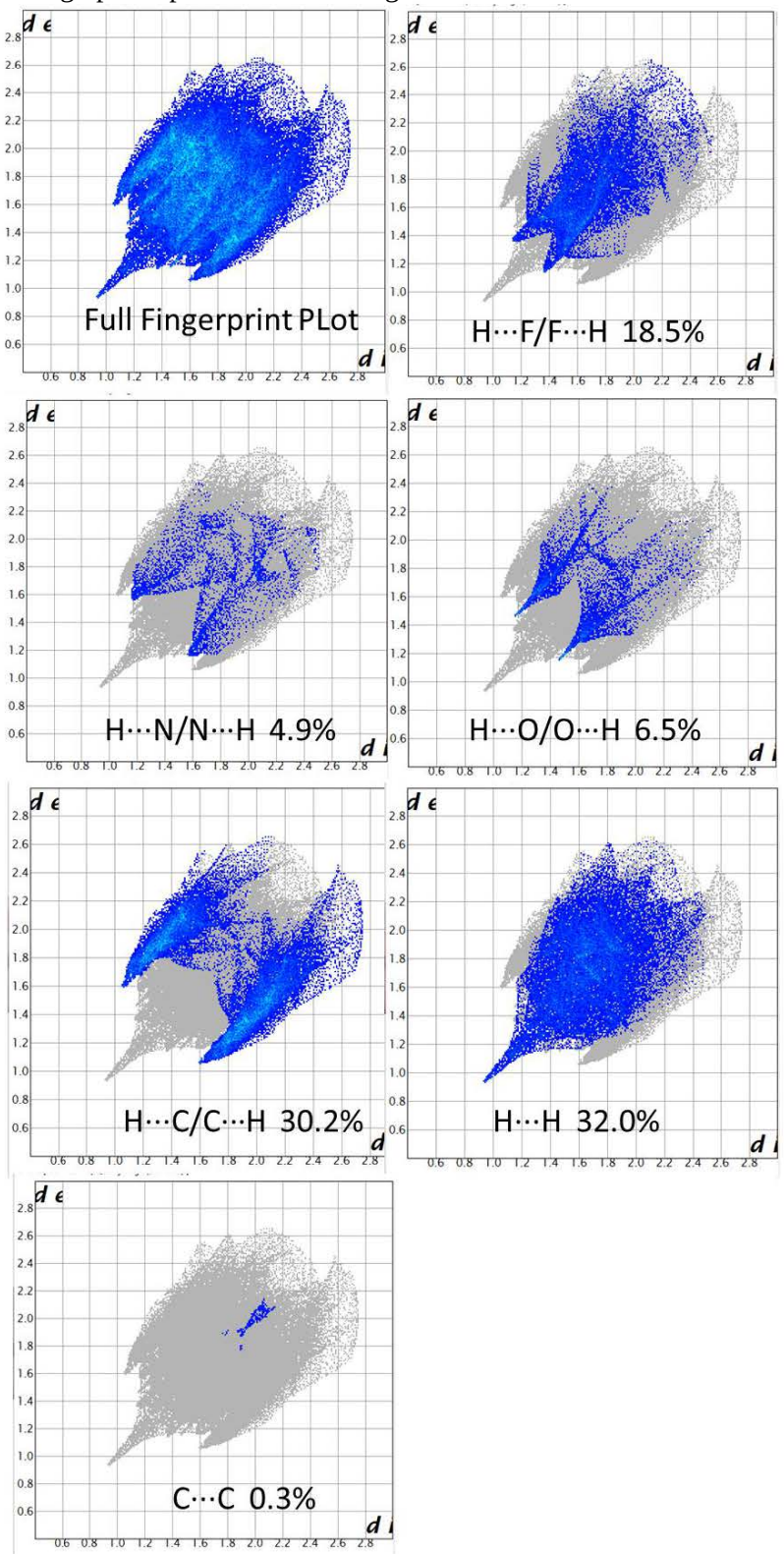
[a] Showing the numbering scheme and displacement ellipsoids drawn at the 50% probability level

S5. Two-dimensional fingerprints plots of 4b, 4d, and 4f[a]

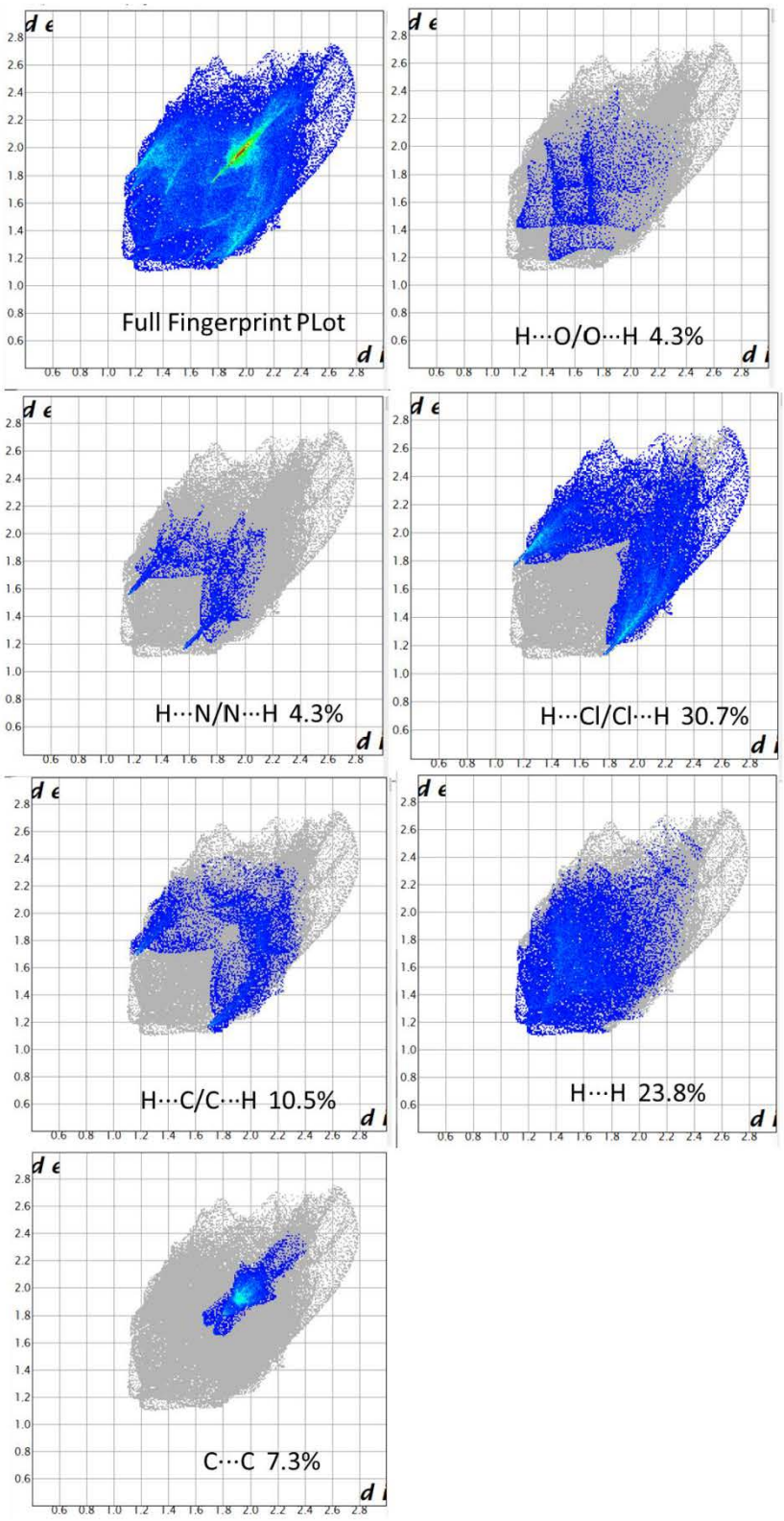
[a] Two-dimensional fingerprints plots of **4b** showing contributions from different contacts



[a] Two-dimensional fingerprints plots of **4d** showing contributions from different contacts



[a] Two-dimensional fingerprints plots of **4f** showing contributions from different contacts

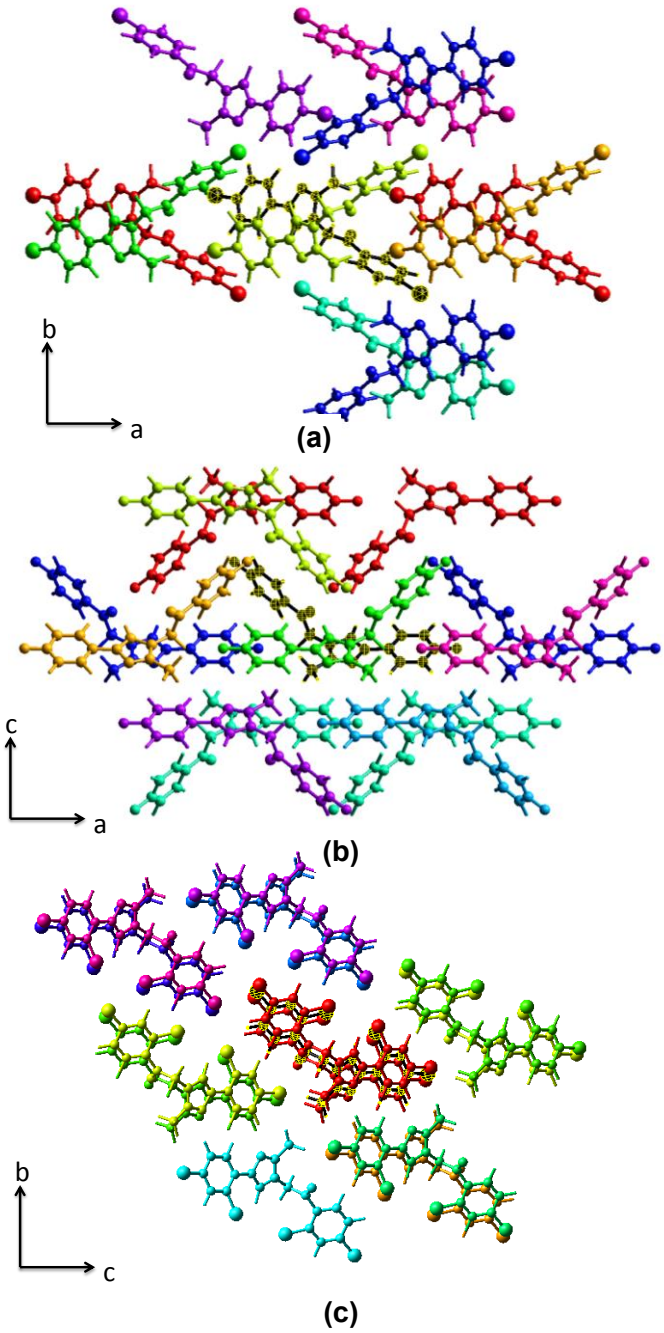


S6. CE-B3LYP interaction energies (kJ mol^{-1}) for 4b, 4d and 4f[a]

3	N	R	E_{ele}	E_{pol}	E_{dis}	E_{rep}	E_{tot}
4b							
	2	12.48	-5.9	-0.9	-19.8	13.6	-15.8
	2	15.45	-3.9	-0.5	-8.1	6.5	-7.6
	2	4.86	-22.3	-8.2	-60.8	36.1	-60.4
	2	10.95	-4.2	-1.9	-21.2	13.4	-16.0
	1	9.51	-4.5	-2.3	-40.6	22.3	-28.1
	2	9.66	-3.0	-0.6	-10.7	4.8	-10.0
	2	12.54	-0.1	-0.6	-7.0	4.2	-4.0
	1	11.01	-9.5	-2.9	-23.3	15.9	-22.7
	1	10.75	-1.6	-0.1	-2.0	0.1	-3.5
4d							
	2	8.63	-7.0	-1.8	-23.3	10.7	-22.4
	2	12.46	-2.4	-0.9	-12.4	9.4	-8.2
	2	9.58	2.5	-1.7	-14.6	5.2	-8.1
	2	4.79	-22.8	-7.0	-50.6	28.3	-55.9
	2	9.36	-3.9	-1.9	-20.0	11.2	-16.0
	1	10.85	-10.6	-3.4	-24.2	27.7	-17.7
	2	11.98	-7.8	-1.5	-19.0	11.4	-18.9
	1	10.31	-2.0	-0.2	-5.1	1.3	-6.0
	2	13.34	0.9	-0.5	-7.8	1.5	-5.3
4f							
	2	4.49	-17.3	-6.4	-97.0	55.0	-73.5
	1	11.96	-18.2	-3.3	-28.1	29.4	-27.9
	2	12.63	-7.6	-1.2	-20.5	14.6	-17.7
	2	10.97	-3.5	-1.9	-18.1	11.0	-14.0
	1	10.49	-4.2	-1.4	-27.3	11.6	-22.1
	1	11.53	-2.1	-0.3	-5.3	1.6	-6.1
	1	9.55	-5.7	-0.5	-20.4	16.0	-14.3
	1	16.65	-2.9	-0.4	-8.7	8.1	-6.0
	1	11.75	-1.2	-0.9	-13.4	10.3	-7.3
	1	18.52	0.0	-0.0	-3.6	3.6	-0.9

[a] N is the number of molecules with an R molecular centroid-to-centroid distance (Å) with an assigned C color-coded related to Figure 8. Electron density was calculated using B3LYP/6-31G(d,p) model energies. Note: (*) scale factors used to determine E_{tot}: E_{ele} = 1.057; E_{pol} = 0.740; E_{dis} = 0.871; E_{rep} = 0.618.

[a]Colored representation of the centroid-to-centroid interactions observed in Table 6 for (a) **4b**, (b) **4d** and (c) **4f**. Molecules in black and marked in the center of each figure correspond to the asymmetric unit and reference for the interactions.



S7. Hydrogen-bond geometry (Å, °) for 4b, 4d, and 4f

Table S1 **Table S1.** Selected hydrogen-bonds for **4b**, **4d**, and **4f**

Hydrogen-bond geometry (Å, °) for (4b)				
D—*H*···*A*	*D*—*H*	*H*···*A*	*D*···*A*	*D*—*H*···*A*
C4—H4···N7	0.93	2.57	2.903(5)	101.0
C11—H11B···O13^{i}	0.97	2.50	3.462(5)	170.1
C23–H23···Cg$_1$^{ii}	0.93	3.00	3.931(5)	174.5
	Cg···Cg	**Alpha***	**Gamma***	**mpd***
Cg$_1$···Cg$_1$^{iii}	3.863(3)	0.0(2)	18.7	-3.6583(19)

Symmetry code: (i) x, −y+3/2, z+1/2; (ii) -1+x,y,-1+z; (iii) 2-x,1-y,2-z
*Alpha: dihedral angle between planes I and J (°)
*mpd: perpendicular distance of Cg(I) on ring J (Å)
*Gamma: angle Cg(I)-->Cg(J) vector and normal to plane J (°)
Cg1 is the centroid of C14/C20 ring

Hydrogen-bond geometry (Å, °) for (4d)				
D—*H*···*A*	*D*—*H*	*H*···*A*	*D*···*A*	*D*—*H*···*A*
C17—H17···N13	0.93	2.57	2.903(5)	101.0
C3— H3···F1^{i}	0.93	2.59	3.212(5)	124.8
C6— H6···Cg$_1$^{ii}	0.93	2.94	3.717(3)	66.0
C23— H23C···Cg$_1$^{iii}	0.96	2.94	3.713(4)	66.0

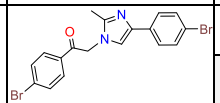
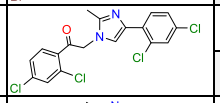
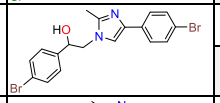
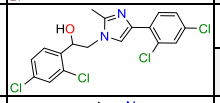
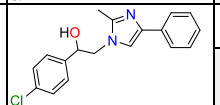
Symmetry code: (i) 1/2 − *x*, −1/2 + *y*, *z*; (ii) 3/2-x,-1/2+y,z; (iii) -1/2+x,1/2-y,1-z
Cg$_1$ is the centroid of C16/C22 ring

Hydrogen-bond geometry (Å, °) for (4f)				
D—*H*···*A*	*D*—*H*	*H*···*A*	*D*···*A*	*D*—*H*···*A*
C5—H5···N1	0.93	2.47	2.825(3)	103.0
C8—H8···Cl2	0.93	2.59	3.110(3)	116.0
C11—H11A···Cl3	0.97	2.57	3.268(3)	128.8
C6—H6···N1^{ii}	0.93	2.87	3.746(3)	157.6
	Cg···Cg	**Alpha***	**Gamma***	**mpd***
Cg$_1$···Cg$_1$^{i}	4.4932(17)	0.00(15)	42.6	3.3084(11)
Cg$_2$···Cg$_2$^{i}	4.4931(17)	0.00(12)	36.5	3.6103(11)
Cg$_3$···Cg$_3$^{i}	4.493(2)	0.03(16)	32.5	3.7900(14)

Symmetry code: (i) -1+x,y,z; (ii) −1 − *x*,-*y*,1 − z
*Alpha: dihedral angle between planes I and J (°)
*mpd: perpendicular distance of Cg(I) on ring J (Å)
*Gamma: angle Cg(I)-->Cg(J) vector and normal to plane J (°)
Cg$_1$, Cg$_2$ and Cg$_3$ are the centroids of N1/C9, C1/C6 and C13/C18 rings, respectively

S8. Percentages of inhibition of 4e, 4f, and 5e-g

Table S2 **Table S2.** Percentages of inhibition of **4e**, **4f**, and **5e-g** against *C. albicans* (*Ca*) and *C. neoformans* (*Cn*)[a]

	Structure	Fungi	250	125	62.5	31.2	15.6	7.8	3.9	IC_{50}
4e		*Ca*	12.8 ± 0.4	4.9 ± 1.5	4.2 ± 0.8	3.7 ± 0.1	2.4 ± 0.4	1.7 ± 0.5	2.0 ± 0.6	>250
		Cn	54.6 ± 1.0	27.2 ± 0.2	26.3 ± 0.4	18.4 ± 0.1	10.7 ± 0.2	6.6 ± 1.5	4.9 ± 1.4	250
4f		*Ca*	36.7 ± 0.2	26.9 ± 1.1	15.6 ± 0.1	6.4 ± 0.6	4.2 ± 0.7	4.1 ± 0.6	0 ± 0	>250
		Cn	65.3 ± 1.8	43.6 ± 1.5	25.9 ± 1.8	12.3 ± 1.2	9.8 ± 0.9	5.9 ± 0.5	2.8 ± 1.8	250
5e		*Ca*	31.5 ± 1.1	19.1 ± 1.1	11.1 ± 0.3	5.7 ± 0.2	6.3 ± 0.4	5.2 ± 0.9	0 ± 0	>250
		Cn	42.6 ± 1.4	34.2 ± 0.7	33.1 ± 0.4	29.6 ± 0.6	26.5 ± 0.2	23.3 ± 1.9	0 ± 0	>250
5f		*Ca*	55.1 ± 0.3	33.7 ± 0.1	21.1 ± 1.4	11.6 ± 0.5	10.4 ± 1.5	3.5 ± 0.3	0 ± 0	250
		Cn	100	100	100	100	83.3 ± 0.9	52.9 ± 0.4	40.4 ± 0.6	7.8
5g		*Ca*	49.9 ± 1.9	31.2 ± 0.7	19.1 ± 1.0	11.9 ± 1.5	8.9 ± 1.4	5.2 ± 0.2	0 ± 0	250
		Cn	38.6 ± 0.6	28.8 ± 0.5	21.4 ± 0.1	20.0 ± 1.2	15.9 ± 0.1	14.4 ± 0.5	11.0 ± 0.6	>250
AmpB		*Ca*	100	100	100	100	100	100	100	1.5
		Cn	100	100	100	100	100	100	100	1.0

[a] *Ca* ATCC 10231 and *Cn* ATCC 32264. Dilutions are at the range 250–3.9 µg/mL. IC_{50} value represents the concentration of each compound that inhibits 50 % of fungal growth. **AmpB**: Amphotericin B.

S9. HPLC analysis data of compounds 4e, 4f, and 5e−g

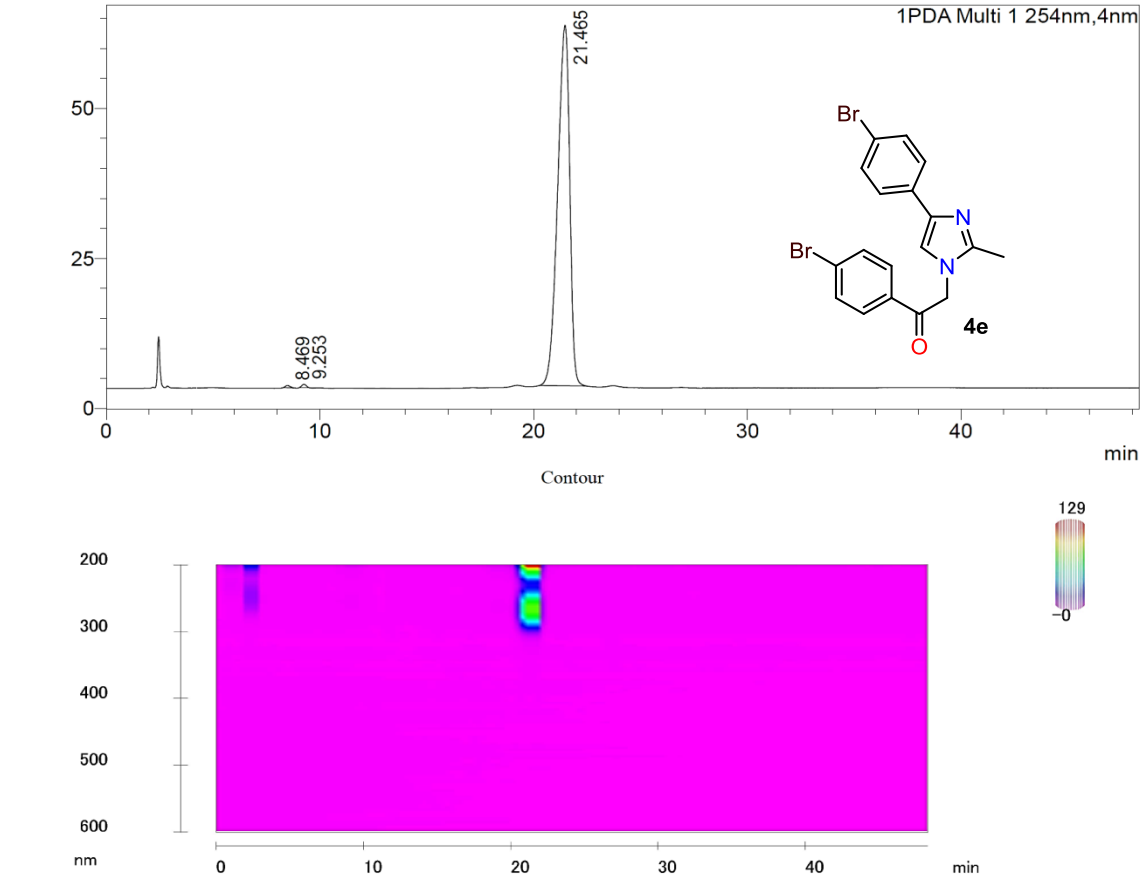
SHIMADZU LabSolutions

Analysis Report

<Sample Information>

Sample Name	: NRE-080A		
Sample ID	: NRE-080A		
Data Filename	: NRE-080A.lcd		
Method Filename	: a.lcm		
Batch Filename	:		
Vial #	: 1-1	Sample Type	: Unknown
Injection Volume	: 20 uL		
Date Acquired	: 12/04/2019 4:27:08 p. m.	Acquired by	: System Administrator
Date Processed	: 12/04/2019 5:15:32 p. m.	Processed by	: System Administrator

<Chromatogram>



<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Name	Area%
1	8.469	6346	418		0.240
2	9.253	10185	660		0.386
3	21.465	2624093	66785		99.374
Total		2640624	67863		100.000

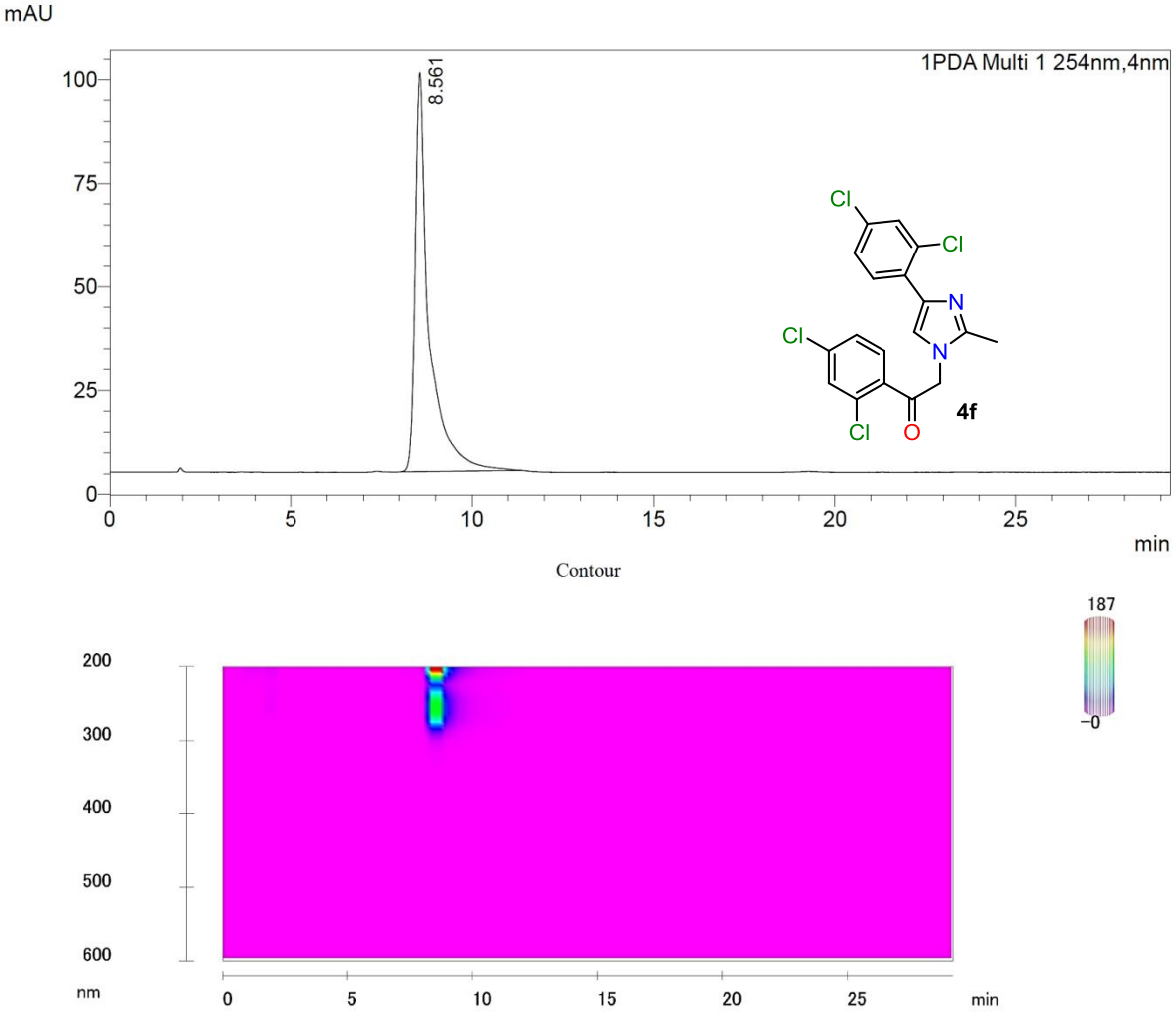
SHIMADZU LabSolutions

Analysis Report

<Sample Information>

Sample Name	: NRE-079A1		
Sample ID	: NRE-079A1		
Data Filename	: NRE-079A1.lcd		
Method Filename	: a.lcm		
Batch Filename	:		
Vial #	: 1-1	Sample Type	: Unknown
Injection Volume	: 20 uL		
Date Acquired	: 12/04/2019 3:06:59 p. m.	Acquired by	: System Administrator
Date Processed	: 12/04/2019 3:36:17 p. m.	Processed by	: System Administrator

<Chromatogram>



<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Name	Area%
1	8.561	2840002	106984		100.000
Total		2840002	106984		100.000

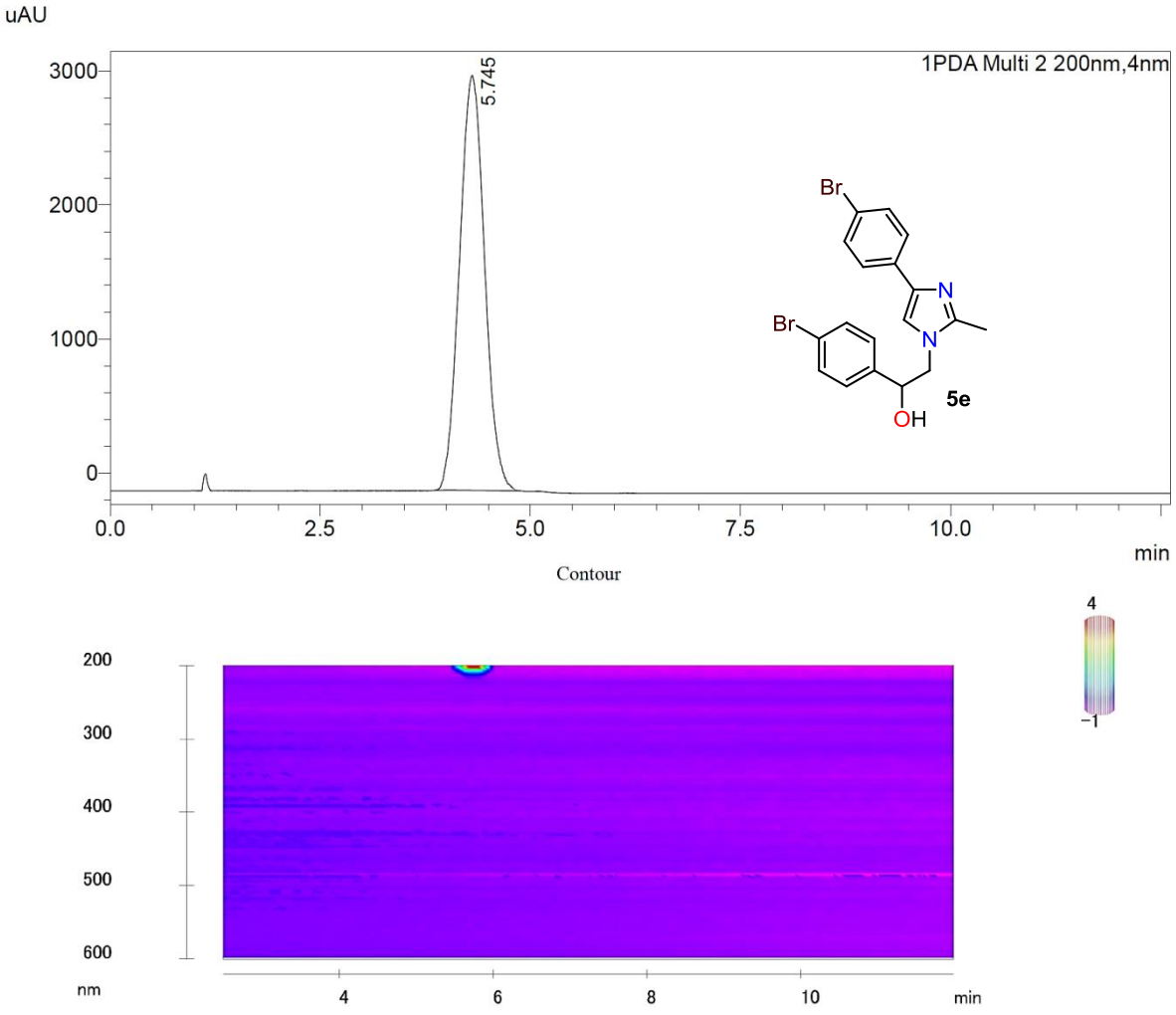
SHIMADZU LabSolutions

Analysis Report

<Sample Information>

Sample Name	: NRE-080B		
Sample ID	: NRE-080B		
Data Filename	: NRE-080B R2.lcd		
Method Filename	: a.lcm		
Batch Filename	:		
Vial #	: 1-1	Sample Type	: Unknown
Injection Volume	: 20 uL		
Date Acquired	: 10/05/2019 4:22:03 p. m.	Acquired by	: System Administrator
Date Processed	: 13/05/2019 12:51:39 p. m.	Processed by	: System Administrator

<Chromatogram>



<Peak Table>

PDA Ch2 200nm

Peak#	Ret. Time	Area	Height	Name	Area%
1	5.745	53798	3440		100.000
Total		53798	3440		100.000

SHIMADZU LabSolutions

Analysis Report

<Sample Information>

Sample Name	: NRE-079B-R2		
Sample ID	: NRE-079B-R2		
Data Filename	: NRE-079B-R2.lcd		
Method Filename	: a.lcm		
Batch Filename	:		
Vial #	: 1-1	Sample Type	: Unknown
Injection Volume	: 20 uL		
Date Acquired	: 10/05/2019 3:42:19 p. m.	Acquired by	: System Administrator
Date Processed	: 13/05/2019 12:53:44 p. m.	Processed by	: System Administrator

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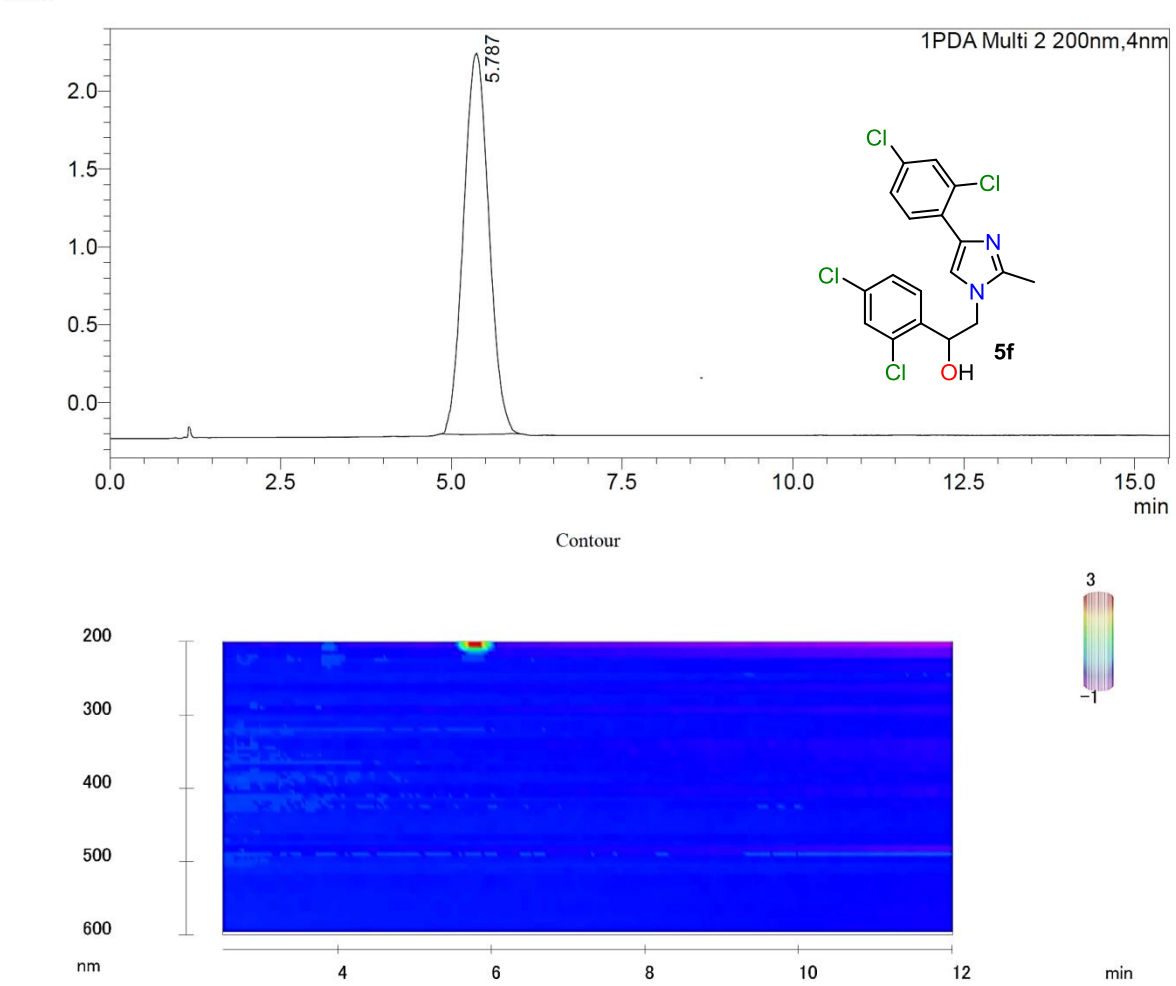


<Peak Table>

PDA Ch2 200nm

Peak#	Ret. Time	Area	Height	Name	Area%
1	5.787	41947	2689		100.000
Total		41947	2689		100.000

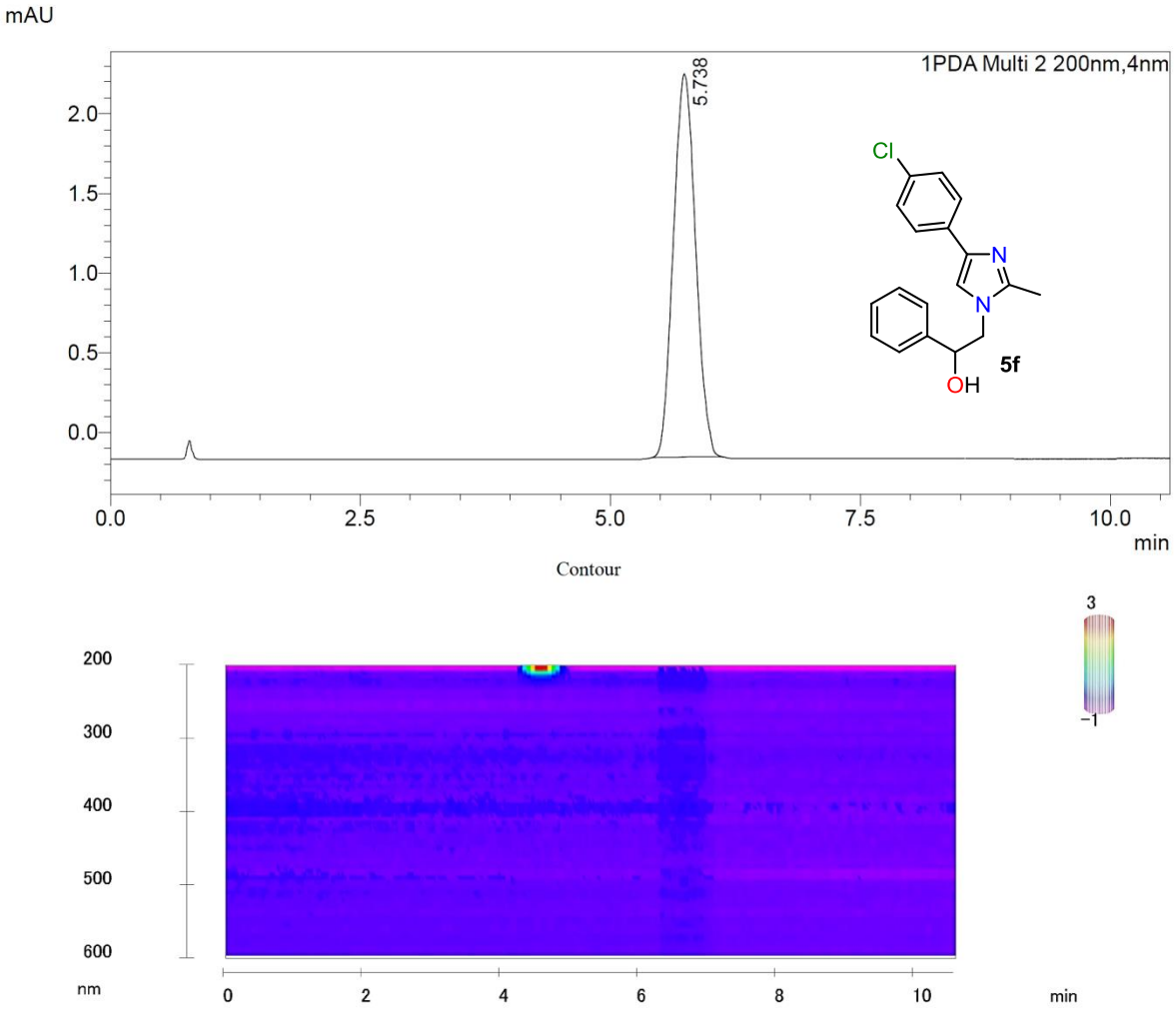
SHIMADZU LabSolutions

Analysis Report

<Sample Information>

Sample Name	: NRE-035E		
Sample ID	: NRE-035E		
Data Filename	: NRE-035E R2.lcd		
Method Filename	: a.lcm		
Batch Filename	:		
Vial #	: 1-1	Sample Type	: Unknown
Injection Volume	: 20 uL		
Date Acquired	: 10/05/2019 4:38:00 p. m.	Acquired by	: System Administrator
Date Processed	: 10/05/2019 4:48:39 p. m.	Processed by	: System Administrator

<Chromatogram>



<Peak Table>

PDA Ch2 200nm

Peak#	Ret. Time	Area	Height	Name	Area%
1	5.738	41059	2669		100.000
Total		41059	2669		100.000