SUPPLEMENTARY MATERIAL

Novel Cyclam Multicomponent Crystal Forms: Synthesis, Characterization and Antimicrobial Activity

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*1) Synthesis and characterization data for compounds **3-6***

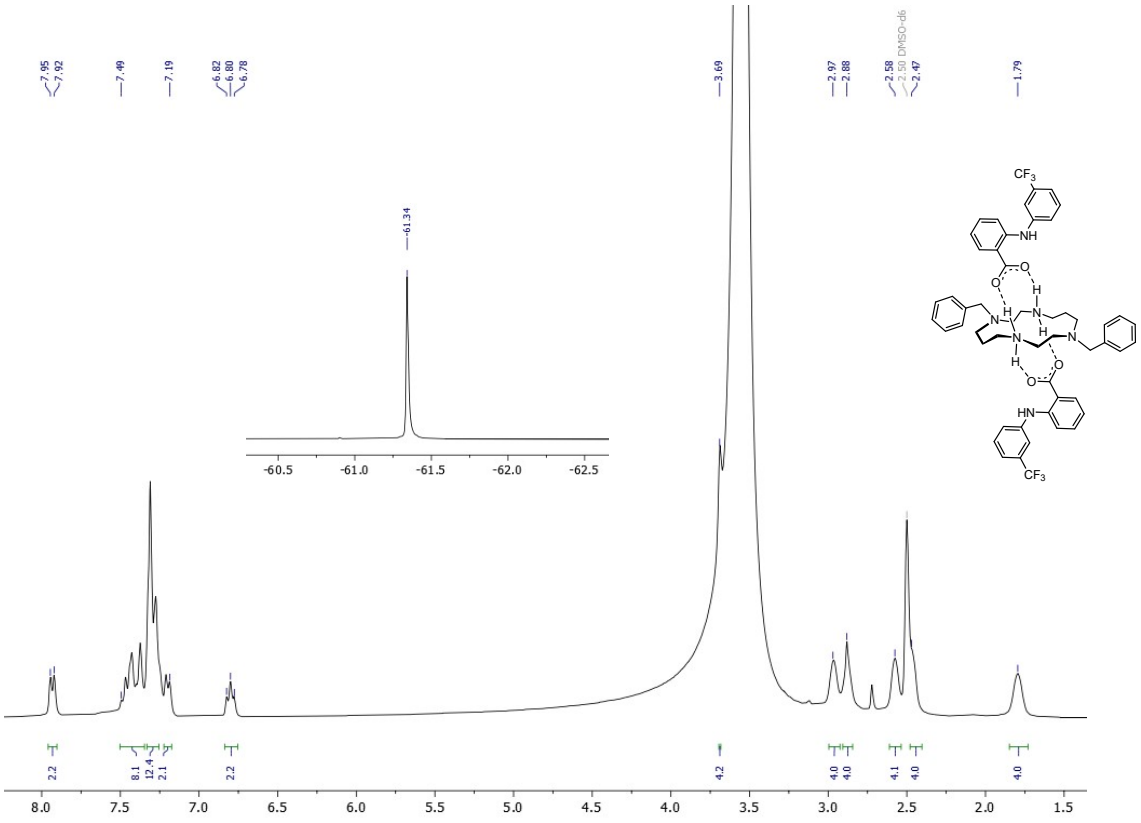

***Figure S1A**: ^{1}H and ^{19}F NMR spectra of **3** in $D_2O/(CD_3)_2SO$.*

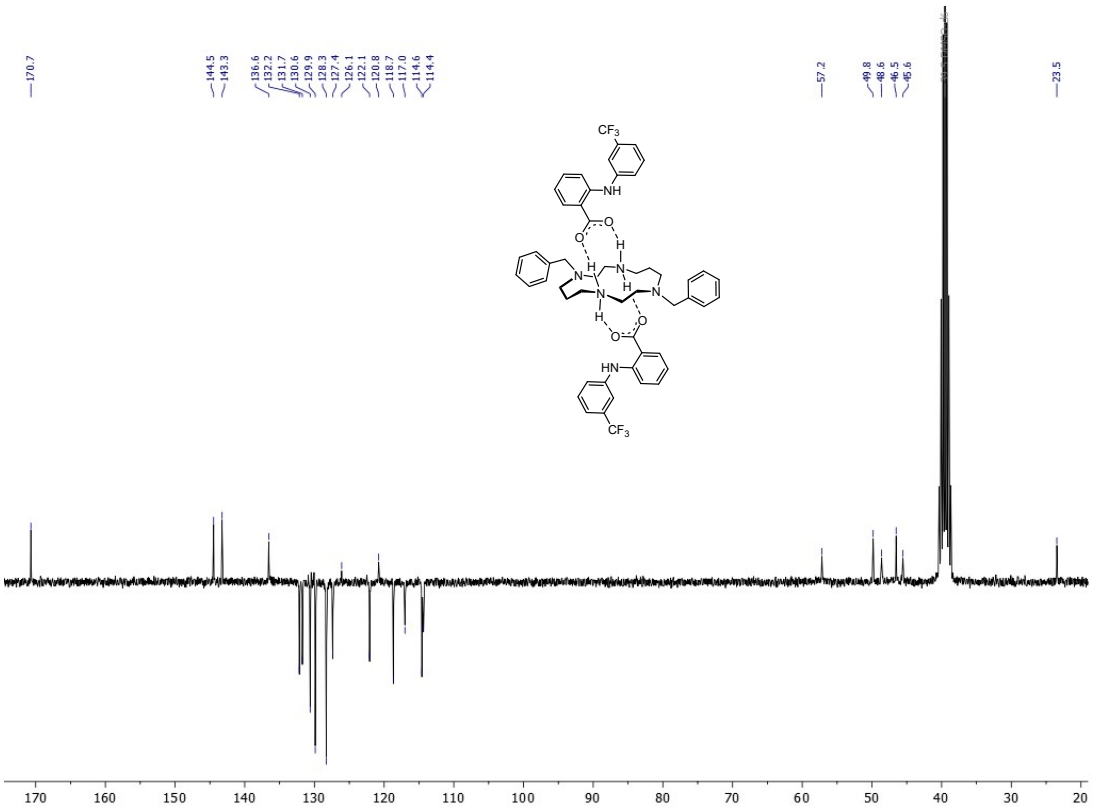

***Figure S1B**: $^{13}C\{^{1}H\}$ NMR spectrum of **3** in $D_2O/(CD_3)_2SO$.*

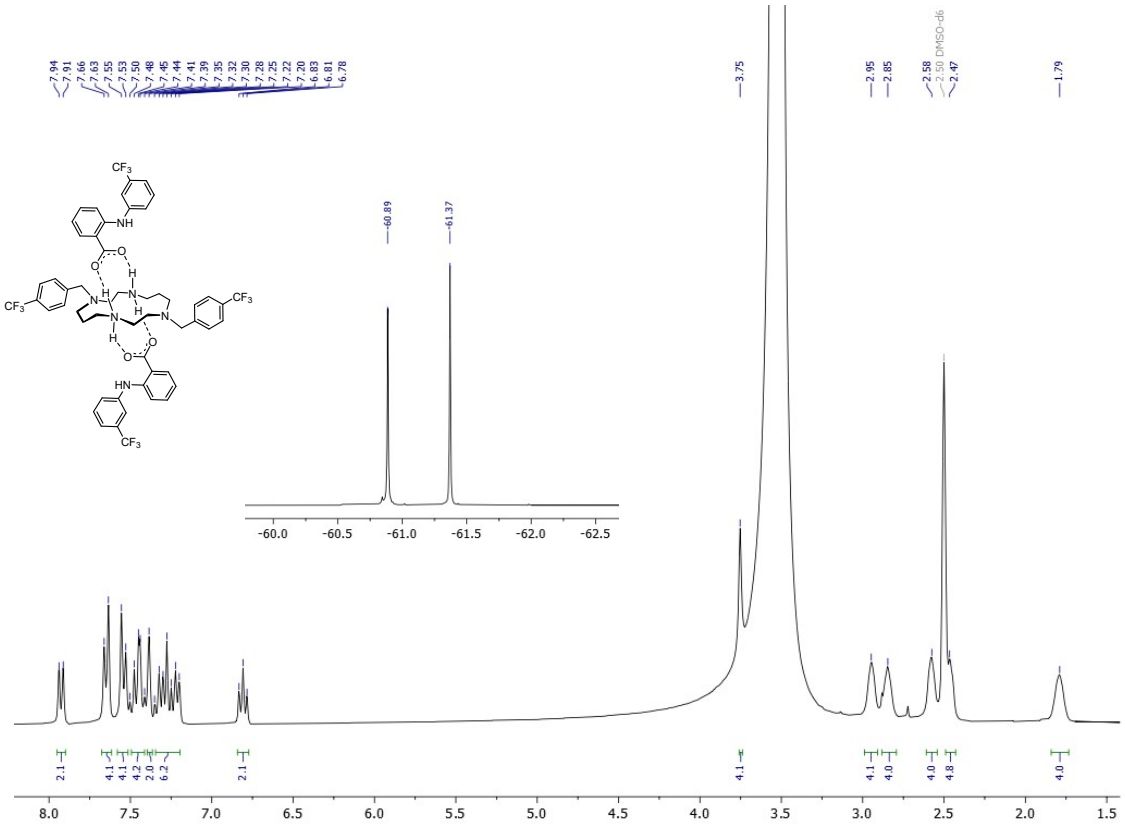

***Figure S2A**: ^{1}H and ^{19}F NMR spectra of **4** in $D_2O/(CD_3)_2SO$.*

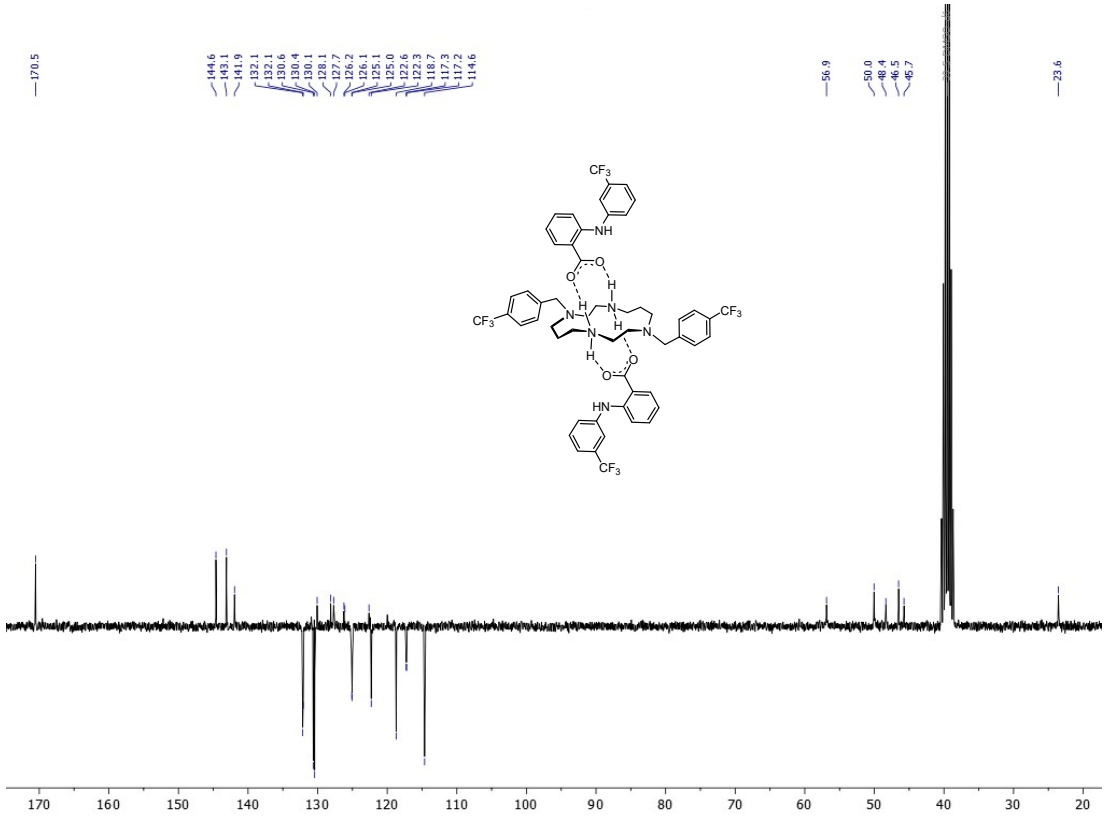

***Figure S2B**: $^{13}C\{^{1}H\}$ NMR spectrum of **4** in $D_2O/(CD_3)_2SO$.*

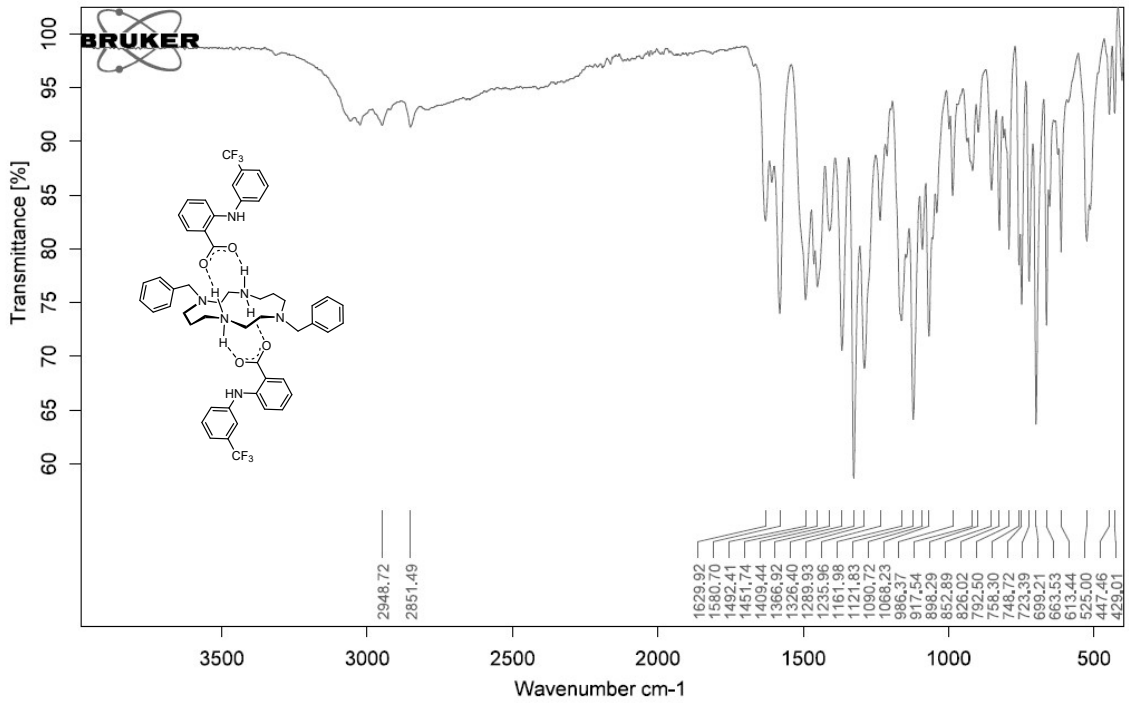

***Figure S3**: FT-IR spectra of **3**.*

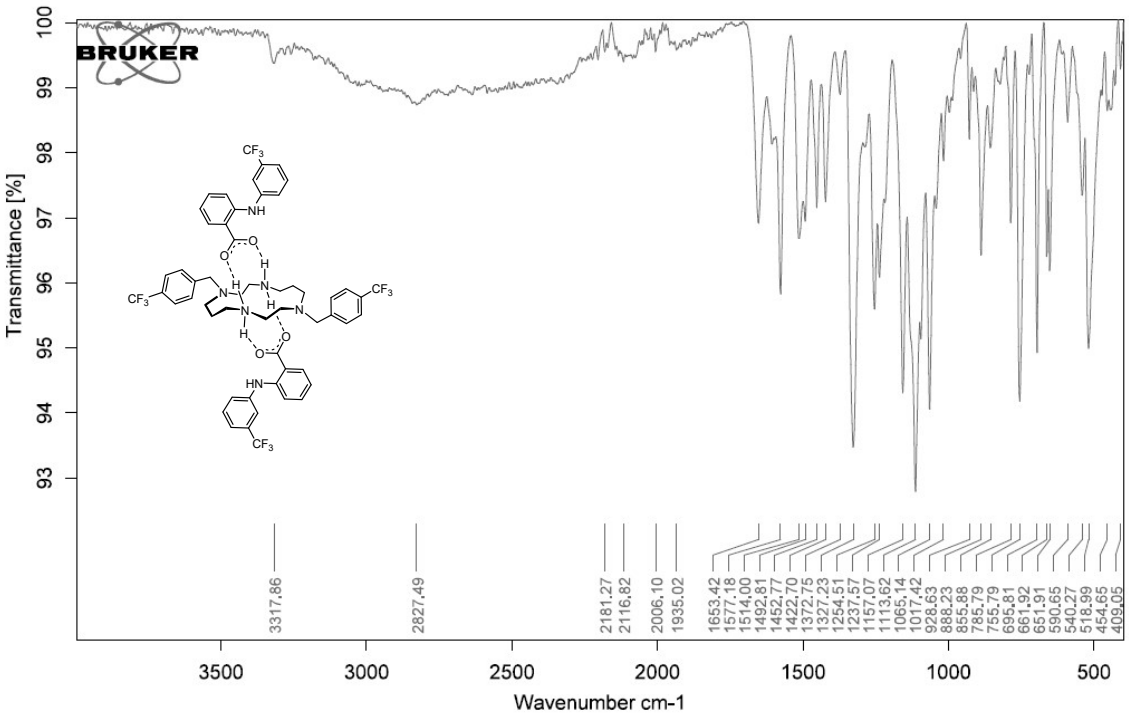

***Figure S4**: FT-IR spectra of **4**.*

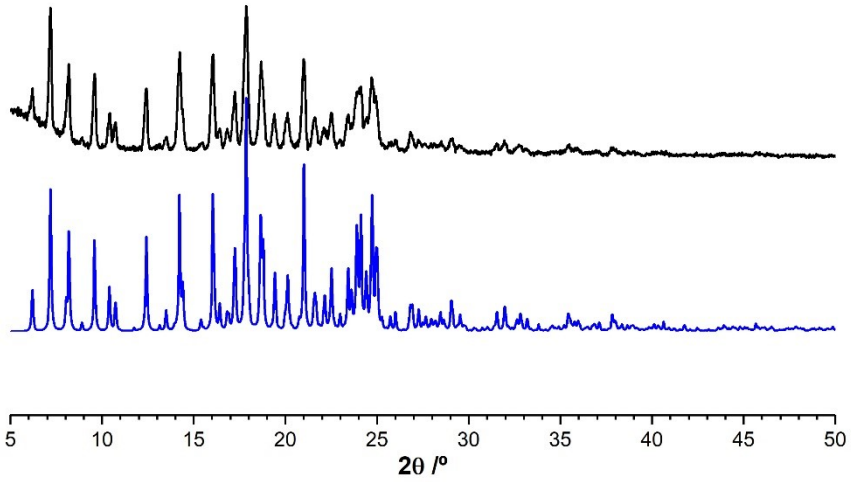

Figure S5: *Experimental (black) and theoretical (blue) PXRD patterns of* ***3****.*

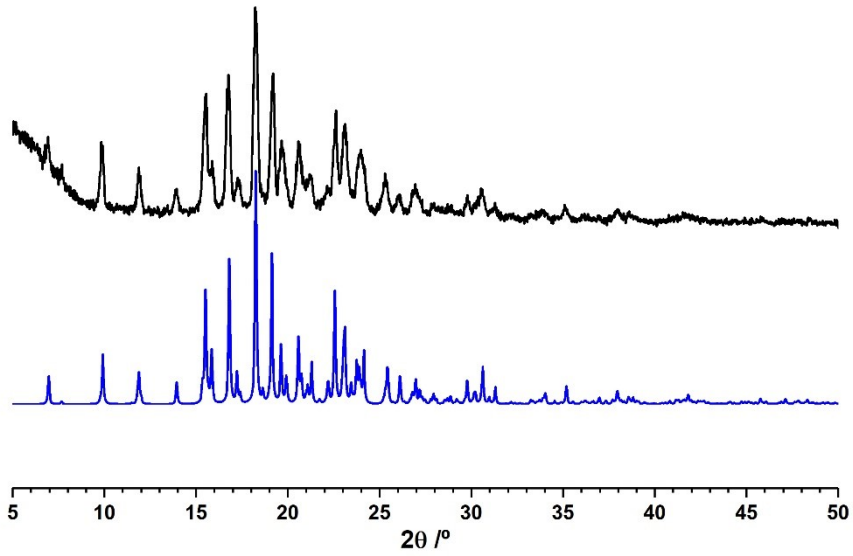

Figure S6: *Experimental (black) and theoretical (blue) PXRD patterns of* ***4****.*

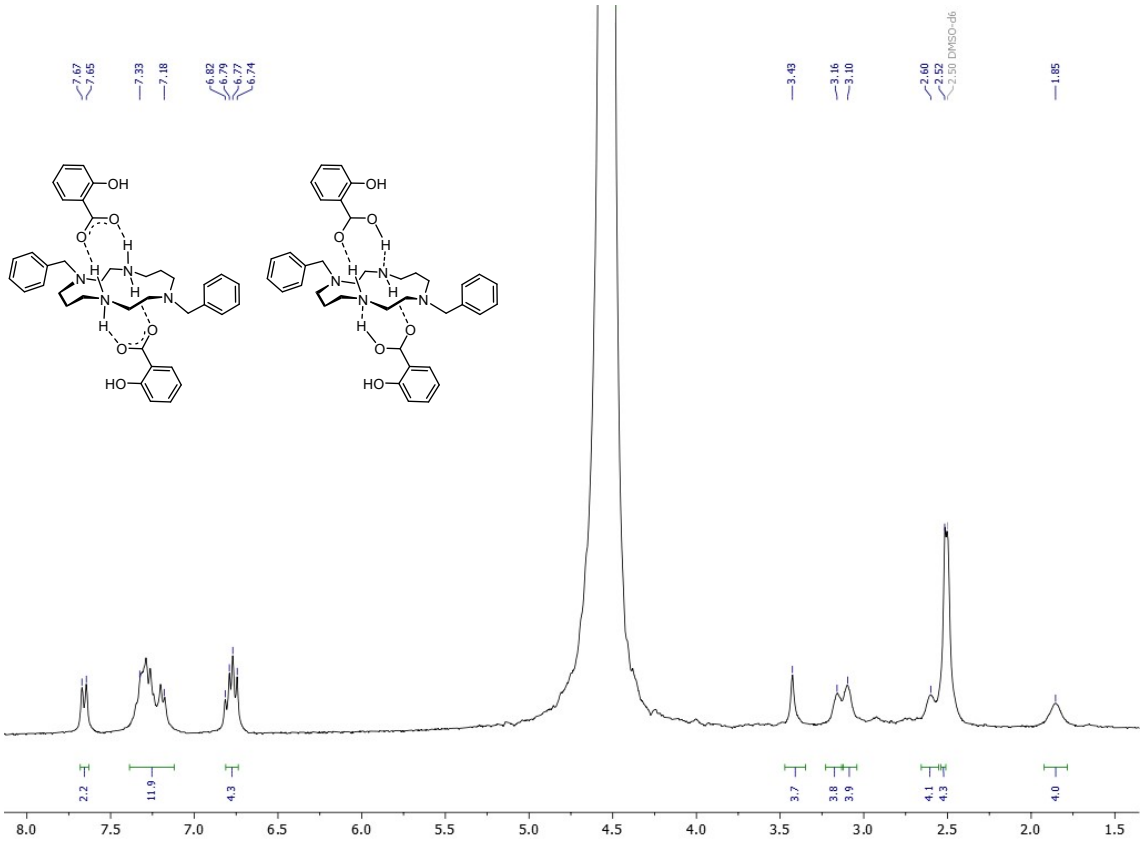

***Figure S7A**: [1]H and [19]F NMR spectra of **5** in $D_2O/(CD_3)_2SO$.*

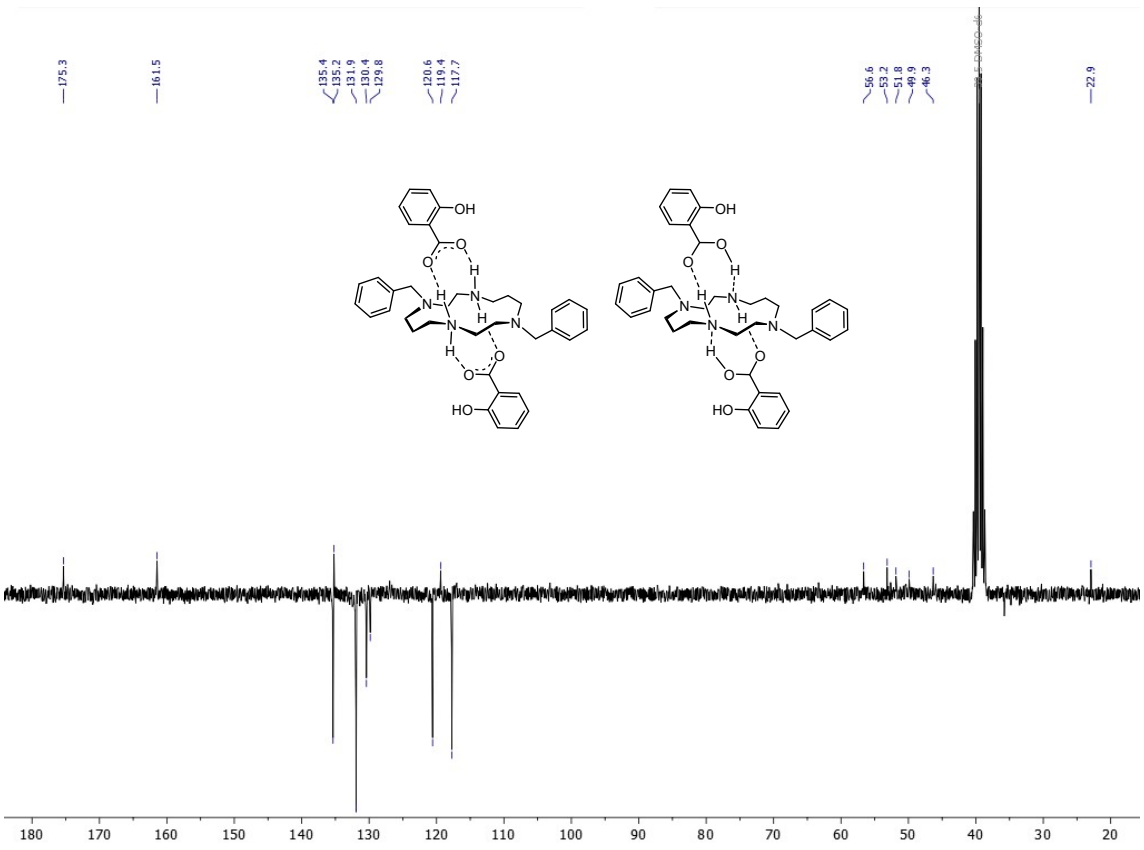

***Figure S7B**: [13]C{[1]H} NMR spectrum of **5** in $D_2O/(CD_3)_2SO$.*

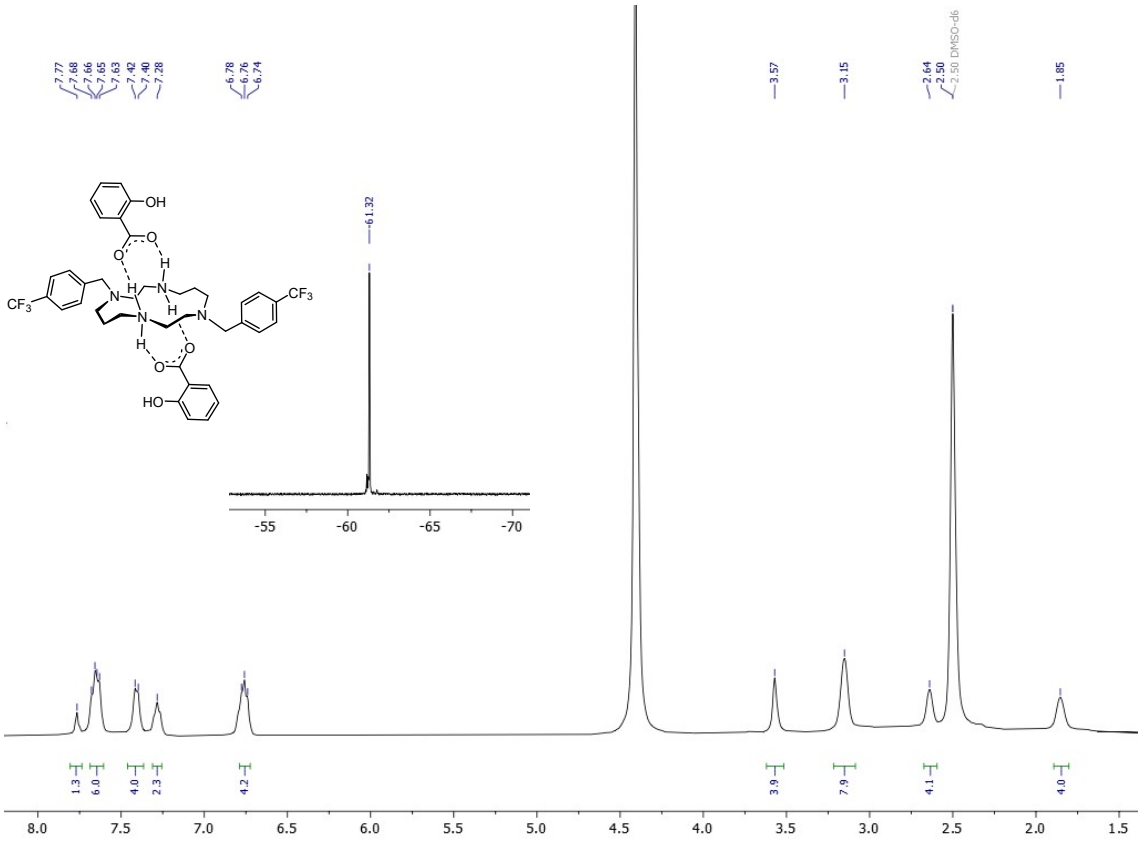

***Figure S8A**: [1]H and [19]F NMR spectra of **6** in $D_2O/(CD_3)_2SO$.*

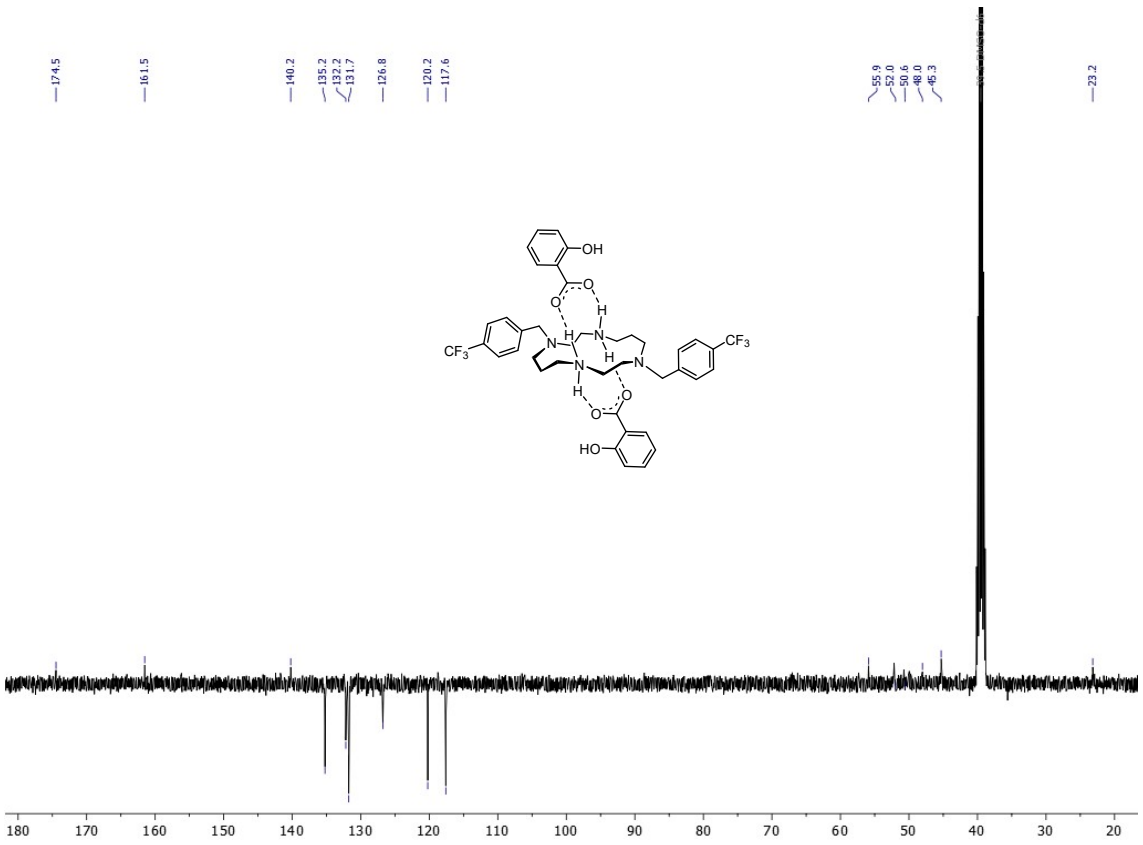

***Figure S8B**: [13]C{[1]H} NMR spectrum of **6** in $D_2O/(CD_3)_2SO$.*

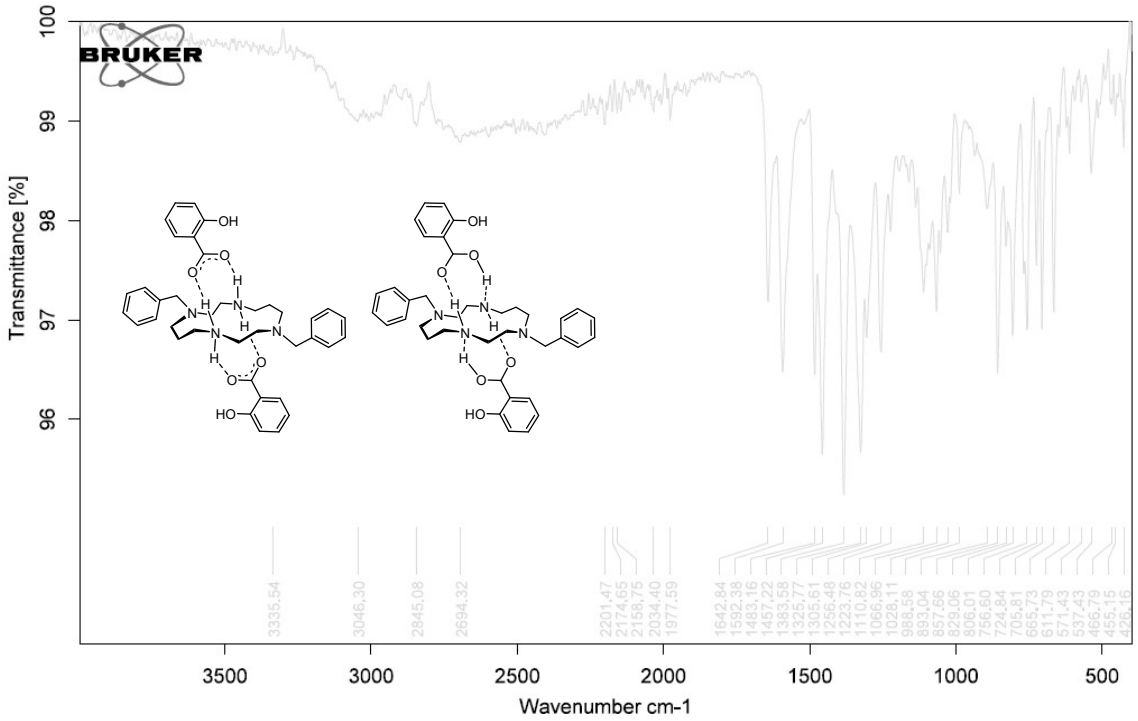

***Figure S9**: FT-IR spectra of **5**.*

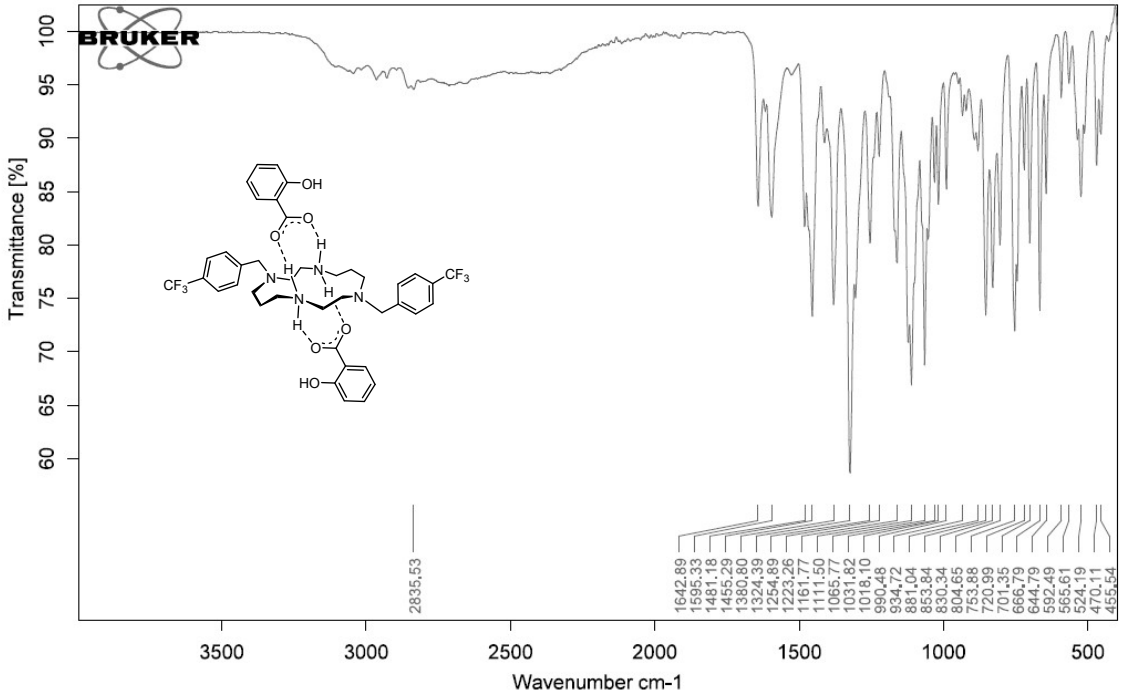

***Figure S10**: FT-IR spectra of **6**.*

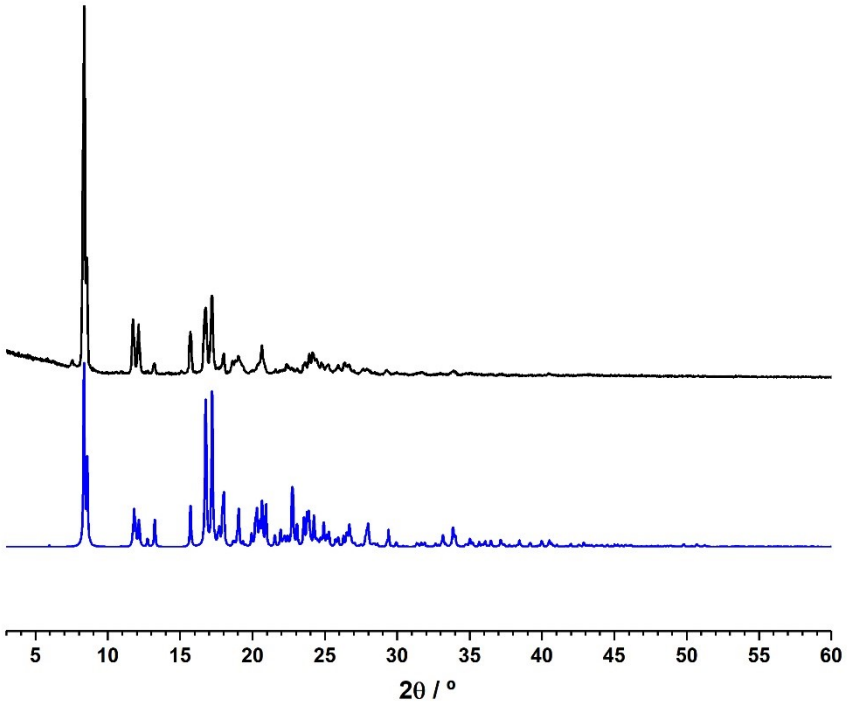

Figure S11: *Experimental (black) and theoretical (blue) PXRD patterns of* ***5****.*

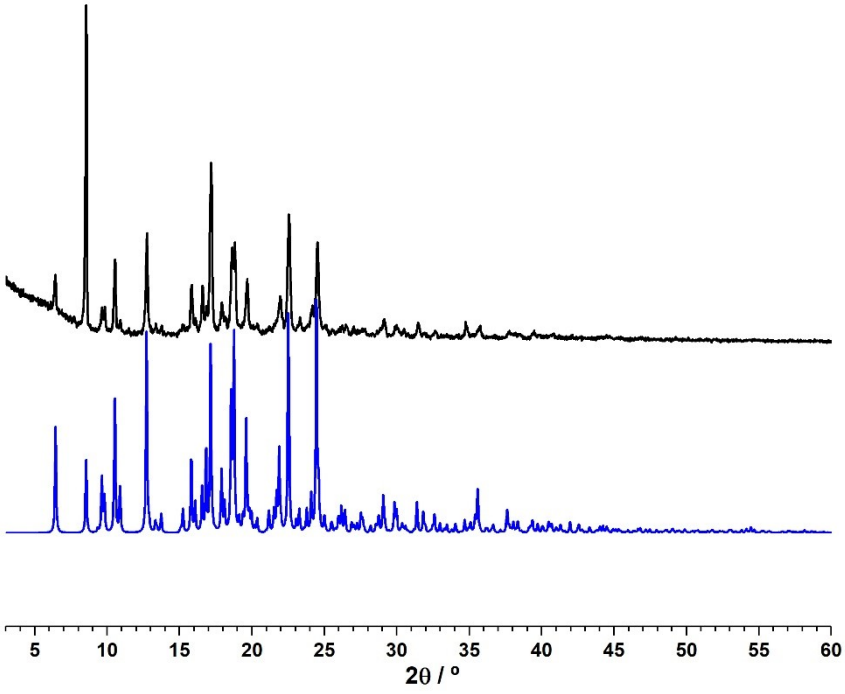

Figure S12: *Experimental (black) and theoretical (blue) PXRD patterns of* ***6****.*

*2) Hydrogen bond details for compounds **3-6***

Table S1:** List of the main hydrogen bonds found for **3

Sym. Op.	D–H···A	*d*(D–H) (Å)	*d*(H···A) (Å)	*d*(D···A) (Å)	(DHA) (°)
x, y, z	N_2– H_{1N}···O_1	0.91(3)	2.01(3)	2.853(3)	154(3)
x, y, z	N_2 –H_{1N}···O_2	0.91(3)	2.42(3)	3.151(3)	137(3)
1-x, -y, 1-z	N_2–H_{2N} ···O_2	0.83(3)	2.00(3)	2.766(3)	152(3)
x, y, z	N_3–H_{3N} ···O_1	0.95(4)	1.86(3)	2.652(3)	140(3)
x, y, z	N_5–H_{4N} ··· O_4	0.93(3)	1.85(3)	2.752(3)	163(3)
2-x, -y, 1-z	N_5–H_{5N}···O_3	0.90(3)	1.93(3)	2.759(3)	151(2)
x, y, z	N_6–H_{6N}··· O_4	0.85(4)	1.92(4)	2.617(4)	138(3)

Table S2:** List of the main hydrogen bonds found for **4

Sym. Op.	D–H···A	*d*(D–H) (Å)	*d*(H···A) (Å)	*d*(D···A) (Å)	(DHA) (°)
-x, 1-y, 1-z	N_2– H_{1N}···N_1	0.91(3)	2.54(3)	3.013(4)	113(3)
½-x, ½-y, 1-z	N_2 –H_{1N}···O_2	0.91(3)	1.99(4)	2.766(5)	143(3)
-½+x, ½+y, z	N_2–H_{2N} ···O_1	0.93(4)	1.84(4)	2.754(5)	169(4)
-½+x, ½+y, z	N_2– H_{2N} ···O_2	0.93(4)	2.54(4)	3.223(5)	131(3)
x, y, z	N_3–H_{3N} ··· O_1	0.76(4)	2.01(4)	2.653(5)	143(4)

Table S3: *List of the main hydrogen bonds found for compound* ***(5)***

Sym. Op.	D–H···A	*d*(D–H) (Å)	*d*(H···A) (Å)	*d*(D···A) (Å)	(DHA) (º)
x, y, z	O_1– H_{1O}··· O_3	0.82	1.81	2.531(7)	145
1-x, 2-y, -z	N_2– H_{1N} ··· O_2	0.92(5)	1.82(5)	2.741(5)	162(4)
1-x, -y, 1-z	N_4– H_{2N} ···O_6	0.73(5)	2.14(4)	2.807(6)	153(4)
x, y, z	O_3–H_{3O} ··· N_2	0.82	1.99	2.799(6)	169
x, y, z	N_4– H_{3N} ··· O_5	0.91(7)	1.89(6)	2.746(6)	157(6)
x, y, z	O_4– H_{4O} ··· O_5	0.82	1.77	2.497(5)	147

Table S4: *List of the main hydrogen bonds found for compound* ***6***

Sym. Op.	D–H···A	*d*(D–H) (Å)	*d*(H···A) (Å)	*d*(D···A) (Å)	(DHA) (º)
x, y, z	N_2– H_{1N}··· O_2	0.97(4)	1.92(3)	2.876(4)	166(3)
x, y, z	N_2 –H_{1N}···O_3	0.97(4)	2.52(4)	3.179(3)	125(2)
x, y, z	O_1–H_{1O} ··· O_2	0.82	1.83	2.558(3)	147
x, y, z	N_2– H_{2N} ···O_6	0.89(4)	2.07(3)	2.824(4)	143(3)
x, y, z	N_2–H_{2N} ··· N_3	0.89(3)	2.53(3)	3.051(3)	118(2)
x, y, z	N_4– H_{3N} ··· O_3	0.88(3)	2.09(3)	2.845(4)	143(3)
x, y, z	N_4–H_{3N} ··· N_1	0.88(3)	2.59(3)	3.071(4)	115(3)
x, y, z	N_4–H_{4N} ··· O_5	0.91(3)	1.89(3)	2.792(4)	169(3)
x, y, z	O_4–H_{4O} ··· O_5	0.82	1.83	2.557(3)	147

3) *Antimicrobial activity*

Table S5: *Minimum inhibitory concentration values (MIC, µg/mL) of compounds* ***1-6****, flufenamic acid (FA) as well as positive and negative controls Candida albicans and Saccharomyces cerevisiae (yeasts), Escherichia coli and Pseudomonas aeruginosa (Gram-negative bacteria) and Staphylococcus aureus, Enterococcus faecalis and Mycobacterium smegmatis (Gram-positive bacteria) after 24h for bacteria and after 48h for yeasts.*

Microorganisms		**FA**	**1**	**2**	**3**	**4**	**5**	**6**	**Positive control**	**Negative control**
Gram-positive Bacteria	***M. smegmatis***	>125.00	31.25	<0.49	40.63	<0.49	32.50	0.98	<0.49 (Van)	125.00
	E. faecalis	62.50	10.00	3.91	5.44	7.81	32.50	7.81	<0.49 (Van)	125.00
	S. aureus	62.50	10.00	7.81	10.88	7.81	62.00	7.81	3.91 (Van)	125.00
	***S. aureus* MRSA**	5.86	36.25	3.91	40.63	7.81	32.50	7.81	0.98 (Van)	125.00
Gram-negative Bacteria	***P. aeruginosa***	31.25	16.88	7.81	3.22	7.81	8.13	15.63	<0.49 (Nor)	62.50
	E. coli	>62.50	6.41	7.81	5.26	7.81	8.13	7.81	<0.49 (Nor)	62.50
Yeasts	***S. cerevisiae***	>62.50	10.00	15.63	5.44	15.63	16.25	31.25	15.63 (Nys)	62.50
	C. albicans	62.50	5.00	15.63	5.44	31.25	16.25	62.50	7.81 (Nys)	125.00

Positive controls: Nys – nystatin; Nor – norfloxacin; Van – vancomycin. Negative control: DMSO.

Note: The antimicrobial effect activity of flufenamic acid (FA) is limited by the effect of DMSO for *M. smegmatis, E. coli* and *S. cerevisiae*.